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Altered patterns of cerebral activity during speech and language production in developmental stuttering

An $H_2{}^{15}O$ positron emission tomography study

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Summary

To assess dynamic brain function in adults who had stuttered since childhood, regional cerebral blood flow (rCBF) was measured with H_2O and PET during a series of speech and language tasks designed to evoke or attenuate stuttering. Speech samples were acquired simultaneously and quantitatively compared with the PET images. Both hierarchical task contrasts and correlational analyses (rCBF versus weighted measures of dysfluency) were performed. rCBF patterns in stuttering subjects differed markedly during the formulation and expression of language, failing to demonstrate left hemispheric lateralization typically observed in controls; instead, regional responses were either absent, bilateral or lateralized to the right hemisphere. Significant differences were detected between groups when all subjects were fluent—during both language formulation and non-linguistic oral motor tasks—demonstrating that cerebral function may be fundamentally different in persons who stutter, even in the absence of stuttering. Comparison of scans acquired during fluency versus dysfluency-evoking tasks suggested that during the production of stuttered speech, anterior forebrain regions—which play an a role in the regulation of motor function—are disproportionately active in stuttering subjects, while post-rolandic regions—which play a role in perception and decoding of sensory information—are relatively silent. Comparison of scans aqcuired during these conditions in control subjects, which provide information about the sensorimotor or cognitive features of the language tasks themselves, suggest a mechanism by which fluency-evoking manoeuvers might differentially affect activity in these anterior and posterior brain regions and may thus facilitate fluent speech production in individuals who stutter. Both correlational and contrast analyses suggest that right and left hemispheres play distinct and opposing roles in the generation of stuttering symptoms: activation of left hemispheric regions appears to be related to the production of stuttered speech, while activation of right hemispheric regions may represent compensatory processes associated with attenuation of stuttering symptoms.

Keywords: dysfluency; lateralization; auditory; frontal; paralimbic

Abbreviations: ACC = anterior cingulate cortex; rCBF = regional cerebral blood flow; SMA = supplementary motor cortex; SPM = statistical parametric mapping

Introduction

Stuttering is a common disorder of speech, recognized and well described since the advent of recorded history. Symptoms include involuntary sound or syllable repetitions, prolongations and blocks, and in its severest forms the disorder can be virtually incapacitating. It is estimated that 4% of children and 1% of the general population are affected (Andrews *et al*., 1983). The prevalence of stuttering, and its attendant impact on the quality of life, have prompted a century of concerted scientific research. Nevertheless, its pathophysiology remains obscure and the central mechanisms which underlie the generation of stuttering symptoms are unknown.

A number of causative factors have been proposed. One school of thought suggests that stuttering is best characterized as a speech motor control disorder and that symptoms represent breakdowns in the control, timing and coordination of the speech musculature. This view is supported by the fact that stuttering shares a number of characteristics with other motor control disorders (e.g. dysarthrias, dystonias and apraxias) such as differences in levels of muscle activity and the presence of tremor-like oscillations (Smith, 1995), worsening of symptoms with increasing task complexity (Jayaram, 1984) and improvement with repeated practice (Bruce and Adams, 1978) or with a slowed, rhythmically paced, rate of speech (Brady, 1969). Abnormalities have also been found using a variety of techniques which assess speech motor control—i. e. reaction time, perturbation and reflex studies (Smith and Luschei, 1983; Peters *et al*., 1989; McClean *et al*., 1990).

Although it can be characterized as a speech motor disorder, there is clearly a relationship between language and stuttering. Stuttering symptoms appear to be specifically related to the use of language, and there are characteristic syntactic locations where dysfluencies tend to occur (Brown, 1945; Soderberg, 1966; Silverman, 1972; Bernstein, 1981; Wall *et al*., 1981). Increasing syntactic complexity in the speech of children has been associated with increases in dysfluency (Gordon *et al*., 1986; Ratner and Sih, 1987; Wijnan, 1990), and the onset of stuttering can be traced to a time when significant increases in the development of language skills are taking place (Bernstein *et al*., 1995).

Another factor which may be associated with dysfluency is a perceptual one, related to auditory feedback of speech. Fluency can be improved when a person who stutters is talking under masking noise, with auditory feedback delayed, or with an external stimulus enabling them to pace their speech; a number of studies have demonstrated an abnormality in central auditory function in some persons who stutter (Hall and Jerger, 1978; Toscher and Rupp, 1978; Hannley and Dorman, 1982; Blood and Blood, 1984; Rosenfield and Jerger, 1984). These findings suggest that stuttering may involve an interruption in speech production because of centrally perceived errors due to distortion of auditory feedback (Quinn, 1972) or incorrect predictions about when speech sounds will be perceived relative to their production (Harrington, 1988).

The notion that incomplete or abnormal patterns of cerebral hemispheric dominance may characterize this disorder was first advanced in the 1920s (Orton, 1928; Travis, 1931). Since that time, evidence for altered lateralization patterns has accumulated in a number of studies (Moore, 1990) which have included evaluation of sequential motor task performance (Webster, 1986), dichotic listening paradigms (Curry, 1969; Quinn, 1972; Blood, 1985) and event related potential and other electrophysiological techniques (Zimmermann and Knott, 1974; Moore, 1990). A number of these studies have demonstrated greater right hemispheric activation in individuals who stutter. However, the implications of these findings have remained uncertain: does increased activity in the right hemisphere, for example, represent functional competition with intact left hemispheric mechanisms, or compensation for dysfunctional left hemispheric mechanisms? The issue has never been resolved. Results of the above studies have been consistent with either notion, and previous neuroimaging studies (Wood *et al*., 1980; Pool *et al*., 1991; Watson *et al*., 1992; Wu *et al*., 1995; Fox *et al*., 1996) have not been conclusive.

One of the most consistent observations in the evaluation of individuals who stutter has been that situation- or task-specific variations in symptom intensity represent a salient feature of the disorder (Andrews *et al*., 1983). Typically, stuttering occurs during spontaneous interpersonal communication and may be exacerbated by stress. Symptoms are most severe during situations such as speaking on the telephone or in front of an audience, yet may disappear when subjects are singing, acting, speaking alone, speaking to pets or to very young children. Symptoms are also reduced when speech production is paced, (thus slowing the rate), or when speech content is automatic or overlearned, rather than propositional.

Critical to any study that attempts to characterize the pathophysiology of stuttering would be the ability to manipulate these task-specific features in order to acquire data when stuttering subjects are both fluent and dysfluent. In the present study, we utilized such an approach; regional cerebral blood flow (rCBF) was estimated using $H_2{}^{15}O$ and PET in adults with deveolpmental stuttering and age and sex-matched control subjects during a series of speech, language and control tasks. In order to avoid complications inherent in the presentation of exogenous auditory or visual stimuli, only oral motor, language and speech production tasks were used. These were designed to differentiate the motor and linguistic elements of speech, and to modulate systematically the degree of dysfluent speech production using conditions known to evoke or ameliorate stuttering symptoms.

Both hierarchical (task contrast) and correlational approaches were used to address the following questions.

(i) Do stuttering subjects differ from controls during the execution of non-linguistic orolaryngeal motor tasks, when symptoms are not present? (ii) How do rCBF patterns in stuttering subjects differ from those of controls during formulation and expression of language, when stuttering symptoms are manifest? (iii) Which group differences manifest during the production of dysfluent speech are reduced or eliminated during fluency-evoking tasks, and may therefore be considered state-dependent? (iv) Which of these differences persist during fluency-evoking tasks, and are therefore likely to be trait-related? (v) Are differences in rCBF patterns manifest in control subjects during the performance of fluent versus dysfluent language tasks, and might these differences reflect task-specific cognitive demands that affect fluency in individuals who stutter? (vi) In which brain regions do rCBF rates correlate with quantitative measures of dysfluency, i.e. what are the functional and anatomical substrates of the speech disruptions (blocks, prolongations and repetitions) themselves?

Material and methods

Subjects

The study was approved by the Institutional Review Board of the National Institutes of Health, Bethesda. Informed consent was obtained from all subjects after the risks, hazards and discomfort associated with these studies were explained. Control subjects included eight females aged 36 ± 10 years (mean ± SD), range 24–50 years, and 12 males aged 33 ± 8 years, range 23–47 years. Developmental stuttering subjects included eight females aged 34 ± 11 years, range 23–51 years, and 10 males aged 37 ± 10 years, range 23–50 years. Each subject performed all skilled manual functions (writing, throwing a ball, combing, using scissors or other tools, etc.) with the right hand. All subjects were free of medical or neuropsychiatric illnesses which might affect brain function on the basis of history and physical examination, baseline laboratory evaluation, and MRI. The diagnosis of developmental stuttering conformed to DSM-IV criteria; symptom intensity ranged from mild to severe during the scanning sessions. None of the stuttering subjects were enrolled in speech therapy, and all subjects were free of medications at the time of the scan.

Scanning methods

PET scans were performed on a Scanditronix PC2048–15B tomograph (Uppsala, Sweden) which has an axial and in-plane resolution of 6.5 mm. Fifteen planes, offset by 6.5 mm (centre to centre), were acquired simultaneously. Subjects' eyes were patched, and head motion was restricted during the scans with a thermoplastic mask. For each scan, 30 mCi of $H_2{}^{15}O$ were injected intravenously. Speech tasks were initiated 30 s prior to injection of the radiotracer and were continued throughout the scanning period (Fig. 1). Scans commenced automatically when the count rate in the brain reached a threshold value (~20 s after injection) and continued for 4 min (Fig. 1). Studies were separated by 10-min intervals. Emission data were corrected for attenuation by means of a transmission scan. Arterial blood was sampled automatically during this period, and PET scans and arterial time–activity data were used to calculate cerebral blood flow images with a rapid least squares method (Koeppe *et al*., 1985).

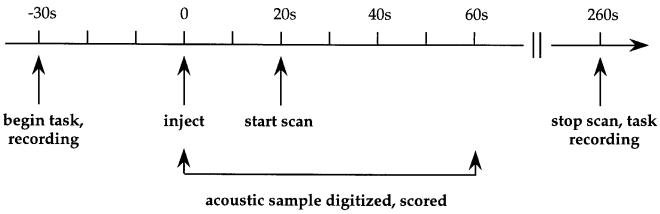

Fig. 1 A timeline illustrating the relationships between acoustic sampling, $H_2{}^{15}O$ injection and PET data collection.

Speech and language tasks

Tasks were presented in a counterbalanced order and consisted of a motor control condition (non-linguistic oromotor-laryngeal movements), two dysfluency-evoking language tasks (spontaneous narrative speech; sentence construction), two fluency-evoking language tasks (automatic or overlearned speech; paced speech) and a resting scan. All subjects underwent at least 1 h of training and practice in the performance of these tasks prior to the PET study.

The motor control task was designed to produce laryngeal and oral articulatory movements and associated sounds utilizing all of the muscle groups activated during speech, but was devoid of linguistic content. Subjects produced vocal fold vibrations periodically interrupted by glottal stops at a rate consistent with speech production (~5 Hz), varying pitch throughout a range that approximated the prosody of spoken English. At the same time subjects moved the lips, tongue and mandible at a rate and range of movement which were qualitatively similar to those produced during speech. Subjects were instructed not to produce movements that are not typically seen during speech, such as lateral movements of the tongue or jaw, clenching of the teeth, protrusion of the tongue or hyperextension of the jaw.

Dysfluency-evoking conditions included narrative speech and sentence construction tasks. In the narrative speech task, subjects were instructed to recount spontaneously an event or series of events from memory, using normal speech rate, rhythm and intonation. In this task, semantic content was typically rich in visual episodic detail. In the sentence construction task, subjects were instructed to produce a series of novel sentences using a verb that was assigned shortly before the onset of the scan. Speech rate, rhythm and intonation were normal while semantic content was typically constrained compared with that produced during the narrative task.

Fluency-evoking conditions included paced and automatic speech tasks. In the paced speech task, subjects were again asked to recount an event or series of events from memory (different from those recounted in the narrative speech task). However, they were instructed to produce one syllable at a time, at a rate of ~92 syllables per minute. To enhance their proficiency on this task, subjects underwent training using a metronome. During the scan session, subjects began speaking in time with the metronome, which was then turned off at least 20 s prior to injection of $H_2{}^{15}O$, to avoid external auditory stimulation during image acquisition. In the automatic speech task, subjects spoke the words of a familiar song, e.g. 'Happy Birthday', keeping speech rate, rhythm and intonation normal.

Because each of the language tasks utilized has unique cognitive features, rCBF differences identified in a single task contrast (e.g. narrative or sentence construction alone versus baseline) are likely to be a function of both the cognitive properties of that task as well as processes associated with the production of fluent or dysfluent speech. To minimize this potential confound, the two dysfluency-evoking and the two fluency-evoking tasks were in each case averaged in order to minimize cognitive idiosyncrasies and maximize the common feature, i.e. the presence or absence of stuttering symptoms.

During execution of the language tasks, subjects were instructed to avoid using any behaviours (circumlocution, word substitution) which might prevent the expression of stuttering symptoms, except when these behaviours constituted an intrinsic component of task performance (e.g. lowered rate during paced speech).

Speech recording and derivation of weighted dysfluency scores

The subjects' speech output was recorded along with a computer generated signal, identifying the start of the $H_2{}^{15}O$ scan. The data were digitized (Fig. 1) with a sampling rate of 5000 Hz, using an antialiasing filter of 2000 Hz. Using MITSYN software, the leading edge of the computer generated signal was identified, and the digitized speech sample (from 20 s before to 40 s following the start of the scan) was played back and dysfluent symptoms were scored as present (+1) or absent (0), in 2-s epochs.

The temporal position of dysfluency episodes during each scan was used to derive weighted dysfluency scores which reflected the probable contribution of speech symptoms to each PET image. This approach, similar to that previously described by Silbersweig *et al*. (1994) is based on the postulate that transient dysfluent episodes are associated with discrete, transient changes in local CBF in relevant brain areas.

Because of the tracer kinetic behaviour of the $H_2{}^{15}O$ in brain tissue, the observed change in the PET signal depends upon when during data acquisition the dysfluencies occur. Thus, stuttering events occurring within the first 10 s following the arrival of the $H_2{}^{15}O$ bolus in brain will affect the final PET image to a greater extent than events occurring 40 s later. We therefore calculated a weighting function which describes these changes in the PET signal. It was derived by (i) solving the Kety flow model (Kety, 1951) for predicted tissue activity in the case of changing flow, (ii) calculating the sensitivity (derivative) of the predicted PET tissue activity to the flow at each second during the period sampled and (iii) normalizing the resultant sensitivity curve by setting this to an integral of 1.0. The sensitivity curves from 20 independently derived $H_2{}^{15}O$ scans were averaged to generate the final weighting function, which was then shifted –5 s from the start of scan to account for the approximate haemodynamic response time.

The subjects' scores during each scan were determined by summing the sensitivity values [dysfluency scores (0 or 1) × the associated weights at each point throughout the period during which speech was sampled and scored] and scaling such that maximal dysfluency (i.e. evident during each epoch of this period) would be associated with a maximum score of 1.0. These scores were used in the correlational analyses described below.

PET data analysis

Image averaging and spatial normalization

PET scans were registered and analysed using statistical parametric mapping (SPM) software (MRC Cyclotron Unit, Hammersmith Hospital, London, UK). The 15 original PET slices were interpolated and spatially registered in order to minimize the effects of head movement. Images were smoothed with a Gaussian filter (20×20×12 mm in the x, y and z axes) to accommodate intersubject differences in anatomy, and stereotaxically normalized to produce images of 26 planes parallel to the anterior–posterior commissural line in a common stereotaxic space (Friston *et al*., 1989) cross-referenced with a standard anatomical atlas (Talairach and Tournoux, 1988). Differences in global activity were controlled for by analysis of covariance (Friston *et al*., 1990).

Hierarchical task contrasts

In the task contrast approach, it is postulated that differences in the cognitive or physiological properties of two task conditions result in associated differences in rCBF rates, and that these differences can be identified by contrasts of the corresponding PET images. In this study, paired comparisons were performed within each group individually, and between stuttering and control groups.

The following contrasts were made. (i) The resting scans for each group were compared in order to evaluate baseline group differences in the absence of oral motor activity or language production. (ii) The motor task was contrasted with rest for each group, and then compared between groups, to identify differences in orolaryngeal motor function in

stuttering and control subjects. (iii) Fluent and dysfluent language tasks were then compared with the motor task in both stuttering and control groups. These contrasts were designed to isolate the motor and linguistic elements of speech, in order to identify within- and between-group differences in language processing under fluency-enhancing and dysfluency-evoking conditions. (iv) Finally, averaged dysfluent and fluent language tasks were compared with each other. In this comparison, no attempt was made to isolate the motor and linguistic elements of speech; the aim was to identify any and all differences which may be related to the production or amelioration of stuttering symptoms.

Using SPM, activation was evaluated using the t statistic calculated for all voxels in parallel (Friston *et al*., 1991). The resulting set of values, transformed to Z-scores, constitutes a statistical parametric map (SPM{Z}). Maps were generated for both within- and between-group contrasts. For within-group comparisons, the profile of significant rCBF increases or activation was defined as the subset of voxels with Z-scores >3 in absolute value. This threshold has previously been shown to protect against false positives using phantom simulations (Bailey *et al*., 1991).

Between-group differences were evaluated only for brain regions in which significant differences were detected in at least one of the within-group comparisons. For example, differences between patient and control groups for the motor control–rest contrast are reported only for regions which showed significant activation in at least one of the groups when this contrast was evaluated independently in patients and controls. This restriction was applied to limit type I error. For between-group comparisons, voxels with Z-scores >2 in absolute value are reported; this Z-score threshold results in a conjoint significance level of $P < 0.0005$. The sole exception was the comparison of resting images in controls versus stuttering subjects. In this case, because no prior within-group comparisons existed, significant changes in rCBF in this between-group contrast were identified as voxels with Z-scores with an absolute value >3.

Correlation analyses

The correlational technique takes into account intersubject variations in fluency, while the contrast technique does not. When this variability is unaccounted for, significant differences are more difficult to detect. Therefore, assuming a linear relationship between weighted dysfluency scores and rCBF responses, the correlational technique may represent a more sensitive approach.

PET images were processed according to methods outlined without ANCOVA (analysis of covariance) correction. Global flow rates were calculated by averaging within-brain pixel values, and the images were normalized by generating reference ratios (regional/global CBF) on a pixel by pixel basis. The resulting normalized rCBF images were correlated with individuals' dysfluency scores within the stuttering group only, utilizing a modification of the SPM software (Horwitz *et al*., 1993; Horwitz and McIntosh, 1994) which produces a Pearson product-moment correlation coefficient assigned to each pixel in the image. Correlation coefficients were arbitrarily thresholded at a level of 0.5 (equivalent to a pairwise value of $P < 0.025$, $n = 18$). These uncorrected values, although not meaningful in themselves, can be treated as discrete, dichotomous variables and their hemispheric distribution evaluated using non-parametric methods. The proportions of positive and negative correlations in right and left hemispheres were compared using the χ^2 statistic.

Results

Resting studies

No significant differences were detected when resting scans of controls and stuttering subjects were compared.

Orolaryngeal motor–rest contrast

The motor control task minus rest was used to evaluate differences between stuttering subjects and controls during the production of laryngeal and oral articulatory movements which are devoid of linguistic content, a condition in which stuttering subjects are invariably asymptomatic.

In both groups, execution of these movements was associated with bilateral activation of an equivalent set of regions, including cerebellum, posterior putamen, ventral thalamus, primary motor, premotor, somatosensory, and auditory cortices (data not shown). Significant differences between stuttering and control subjects were apparent, however, in the magnitude of rCBF increases (ΔrCBF) over baseline (Table 1).

Significantly greater activations were seen in stuttering subjects in left hemispheral regions, including premotor (posterior supplementary motor area and posterior frontal operculum, pars opercularis) and inferior perirolandic cortices (primary somatomotor and primary somatosensory areas). In the perirolandic regions, stuttering subjects' rCBF responses were more variable as well (associated with greater coefficients of variation) in the left hemisphere. At the same time, rCBF responses were significantly larger in stuttering subjects in the right hemisphere in auditory cortices (primary auditory and anterior auditory association areas).

Language–motor contrasts

Dysfluent language–motor contrast

The dysfluent language minus motor task contrast was designed to evaluate how rCBF patterns in stuttering subjects differ from controls in the formulation and expression of language during conditions in which they were dysfluent—the expectation being that resulting differences would bear a relationship to stuttering behaviour. Increases in rCBF in controls were in this instance consistently lateralized to the left hemisphere. In stuttering subjects, left hemispheral

Table 1 *Within- and between-group contrasts in control and stuttering subjects, orolaryngeal motor task versus rest*

Region (Brodmann)	Control subjects										Stuttering subjects									
	Left hemisphere					Right hemisphere					Left hemisphere					Right hemisphere				
	Z	ΔrCBF	*x*,	*y*,	*z*	Z	ΔrCBF	*x*,	*y*,	*z*	Z	ΔrCBF	*x*,	*y*	*z*	Z	ΔrCBF	*x*,	*y*,	*z*
Premotor																				
Posterior SMA (6)	–	–	–	–	–	–	–	–	–	–	4.65	7.80	−2	−4	48*	4.93	7.65	6,	−4,	48
Posterior frontal operculum (44)	3.24	2.84	−52,	6,	24	3.24	3.59	52,	6,	24	4.54	5.30	−54	5,	24*	4.32	4.35	48,	8,	24
Peri-rolandic																				
Precentral gyrus (4, 6)	5.38	8.32	−46,	−6,	20	4.82	7.44	48,	−6,	20	4.80	10.89	−48	−6	20*	5.09	8.49	46,	−6,	20
Postcentral gyrus (3, 1, 2)	7.98	8.37	−48,	−16,	28	4.70	7.41	44,	−16,	28	4.54	10.95	−48,	−16	28*	4.45	7.50	44,	−16,	28
Auditory																				
Anterior auditory association cortex (22)	6.00	5.17	−50,	−18,	4	5.50	4.58	58,	−18,	4	7.98	5.10	−58,	−8,	4	5.37	7.74	54,	−8,	4*
Primary auditory area (42)	7.98	5.76	−52,	−22,	8	5.44	5.80	54,	−10,	8	7.98	7.22	−56,	−6,	8	5.26	8.41	46,	−14,	8*

Regions in which rCBF responses in stutterers and controls differed significantly are tabluated, asterisks indicating the higher value (conjoint significance of $P < 0.0005$ in each case). Z-scores (Z), rCBF differences (ΔrCBF; ml/100g/min normalized to a mean of 50) and associated Talaraich coordinates (*x*, *y*, *z*) identify increases in rCBF from baseline values for each group independently.

regions were not activated in this fashion. Instead, regional responses were either absent, bilateral, or lateralized to the right hemisphere (Table 2A; Fig. 2).

Stuttering subjects' failure to activate left hemispheral regions entirely was more common in posterior (post-rolandic) sensory and associated ventrolateral (paleocortical) paralimbic regions.

Specifically, in post-rolandic sensory cortices, stuttering subjects failed to activate the central portion of Wernicke's area in the left posterior superior temporal gyrus (Brodmann area 22); they also failed to activate the adjacent portion of left inferior angular gyrus (Brodmann 39) and the left middle temporal gyrus (Brodmann 21). While control subjects activated visual areas in the left occipital cortex (Brodmann 17 and 18), stuttering subjects did not.

In paleocortical paralimbic areas, control subjects activated the left inferior insular cortex, while stuttering subjects did not, and in the caudal orbital cortex (Brodmann 25) bilateral increases in rCBF were observed in stuttering subjects but not in controls.

On the other hand, the pattern of bilateral or right hemispheric activation seen in stuttering subjects was more common anteriorly, in premotor, prefrontal and associated dorsomedial (archicortical) paralimbic regions, and in subcortical structures.

Specifically, in prefrontal cortices, the dorsolateral regions (Brodmann 8 and 9), in which significant increases in rCBF were confined to the left hemisphere in controls, were bilaterally activated by stuttering subjects. The medial orbital (Brodmann 11) and medial prefrontal cortices (Brodmann 10) were also bilaterally activated, while in controls, significant increases in rCBF were found only in the left hemisphere.

In frontal motor cortices, control subjects activated the left anterior frontal operculum throughout its dorsoventral extent, from inferior (pars orbitalis, Brodmann 47) to superior levels (pars triangularis, Brodmann 44 and 45), while stuttering subjects activated a more circumscribed region (Fig. 2a and b). Increases in CBF in the anterior supplementary motor cortex (SMA) (medial Brodmann 6) were restricted to the left hemisphere in both groups; however, the lateral premotor area (lateral Brodmann 6) was activated bilaterally by stuttering subjects, but only the left hemisphere was activated by controls.

In archicortical paralimbic areas, the anterior-most portion of the anterior cingulate cortex (ACC) (Brodmann 32/24) was activated by both groups during these language tasks. However, rCBF responses in both dorsal and ventral portions of the ACC were lateralized to the left in controls, but were seen bilaterally in stuttering subjects.

In subcortical regions, stuttering subjects activated the right caudate nucleus, while control subjects did not. The mesencephalic periaqueductal grey and midline cerebellum were activated bilaterally in stuttering subjects but not in controls.

Patterns which emerged from the within-group contrasts were reflected and confirmed in the statistical comparisons between stuttering and control groups. Thus, between-group contrasts demonstrated that left hemispheral post-rolandic sensory and paleocortical paralimbic regions were more active in controls, while right hemispheral subcortical, frontal and archicocortical paralimbic regions were more active in stuttering subjects (Table 2A).

Fluent language–motor contrast

The fluent language minus motor task contrast was designed to evaluate language formulation and expression under conditions in which stutterers are fluent. The results of this contrast can then be compared with those outlined above. The findings (Table 2A and B), can be parsed into two categories: (i) group differences identified during dysfluent language tasks which persist when stuttering subjects are fluent, and may therefore be considered trait-related, i.e. associated with the diagnosis of stuttering *per se*, independent of symptom production; and (ii) differences which are no longer manifest under fluency-evoking conditions, and may therefore be considered condition-dependent, i.e. associated with symptom production (when observed in stuttering subjects) or somehow

Table 2 *Results of within-group contrasts in control and stuttering subjects: dysfluent language contrasts (A) and fluent language contrasts (B)*

Region (Brodmann)	Control subjects										Stuttering subjects									
	Left hemisphere					Right hemisphere					Left hemisphere					Right hemisphere				
	Z	ΔrCBF	*x,*	*y,*	*z*	*Z*	ΔrCBF	*x,*	*y,*	*z*	*Z*	ΔrCBF	*x,*	*y*	*z*	*Z*	ΔrCBF	*x,*	*y,*	*z*
(A) Dysfluent language contrasts																				
Subcortical																				
Caudate nucleus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.55	2.18	8,	10,	−4*
Midline cerebellum	–	–	–	–	–	–	–	–	–	–	3.50	2.46	−2,	−48,	−8	3.29	2.11	6,	−46,	−8
Periaqueductal grey	–	–	–	–	–	–	–	–	–	–	3.23	1.86	−6,	−34,	−4	3.34	2.25	2,	−36,	−4
Prefrontal																				
Medial orbital cortex (11)	–	–	–	–	–	–	–	–	–	–	3.74	2.72	−4	36	12*	3.91	2.67	4,	36,	−12*
Medial prefrontal cortex (10)	3.28	1.93	−14,	54,	12	–	–	–	–	–	3.68	3.30	−16	52	12*	4.61	2.35	12,	56,	12*
Dorsolateral prefront. cortex (8, 9)	4.20	3.43	−24,	24,	40	–	–	–	–	–	4.83	3.22	−20,	24,	40	3.77	2.39	22,	24,	40*
Frontal motor																				
Inferior anterior frontal operculum (47)	4.39	3.59	−38,	22,	−8	–	–	–	–	–	3.13	2.14	−40,	24,	−8	–	–	–	–	–
Mid anterior frontal operculum (45)	3.63	1.91	−44,	30,	8	–	–	–	–	–	3.39	2.36	−44,	24,	8	–	–	–	–	–
Superior anterior frontal operculum (44, 45)	3.99	2.99	−38,	18,	20	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Anterior SMA (6)	4.44	5.17	−12,	14,	48	–	–	–	–	–	3.69	3.48	−14,	14,	48	–	–	–	–	–
Lateral premotor cortex (6)	3.81	3.51	−26,	10,	48	–	–	–	–	–	4.01	3.01	−34,	12,	48	3.47	2.45	28,	14,	48*
Unimodal sensory																				
Lateral occipital cortex (18)	3.23	1.79	−18	−96,	4*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Posterior superior temporal gyrus (22)	4.30	2.82	−48,	−56	16*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Heteromodal sensory																				
Middle temporal gyrus (21)	3.62	2.03	−58,	−40	−4*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Inferior angular gyrus (39)	3.81	3.57	−40,	−68	24*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Paralimbic																				
Inferior anterior cingulate cortex (32)	3.18	2.74	−10,	44,	12	–	–	–	–	–	4.40	2.98	−10,	44,	12	3.98	3.01	6,	44,	12*
Superior anterior cingulate cortex (32)	5.43	3.43	−12,	28,	36	–	–	–	–	–	4.53	3.05	−12,	26,	36	4.43	3.18	4,	24,	36*
Inferior insula	3.67	2.89	−34	16	−4*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Caudal orbital cortex (24, 25)	–	–	–	–	–	–	–	–	–	–	3.56	2.88	−4,	22,	−8	3.65	2.99	4,	20,	−8*
(B) Fluent language contrasts																				
Subcortical																				
Caudate nucleus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.08	1.71	8,	12,	−4*
Prefrontal																				
Medial prefrontal cortex (10)	–	–	–	–	–	–	–	–	–	–	3.68	1.95	−16,	52,	12	3.25	1.81	10,	52,	12*
Dorsolateral prefrontal cortex (8, 9)	3.09	2.18	−20,	30,	40	–	–	–	–	–	3.10	1.83	−20,	32,	40	3.25	2.03	20,	30,	40
Frontal motor																				
Anterior SMA (6)	3.23	3.70	−14,	16,	48	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Lateral premotor cortex (6)	3.16	2.22	−26,	14,	48	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Unimodal sensory																				
Lateral occipital cortex (18)	3.20	2.14	−14,	−88	24*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Heteromodal sensory																				
Middle temporal gyrus (21)	3.31	2.80	−54,	−32	−4*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Inferior angular gyrus (39)	3.42	2.32	−40	−68	24*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Paralimbic																				
Inferior anterior cingulate cortex (32)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.25	2.28	4,	44,	12*
Superior anterior cingulate cortex (32)	3.09	2.17	−14	28	36*	–	–	–	–	–	3.60	2.48	−2,	24,	36	3.68	2.45	2,	22,	36*
Caudal orbital cortex (24, 25)	–	–	–	–	–	–	–	–	–	–	3.02	2.15	−8,	22,	−8	3.02	2.38	4,	20,	−8

The oral motor task is compared to dysfluent (A) and fluent (B) language formulation tasks. Regions in which rCBF responses differ from baseline are tabulated along with *Z*-scores representing local maxima or minima (*Z*), followed by magnitude of rCBF differences (ΔrCRF; ml/100g/min normalized to a mean of 50) and associated Talaraich coordinates (*x, y, z*). Instances in which rCBF responses in stutterers and controls differed in between-group contrasts are identified by asterisks, indicating the higher values (conjoint significance of $P < 0.0005$ in each case).

related to cognitive features of the language tasks themselves (when observed in controls).

A number of trait-related group differences were indicated by patterns of cerebral activity which differentiated stuttering subjects and controls even during the production of fluent speech. Thus, during fluent language tasks, increases in CBF were again lateralized to the left hemisphere in controls, but were absent, bilateral or lateralized to the right hemisphere in stuttering subjects. Stuttering subjects persistently failed to activate post-rolandic sensory association areas, including the left middle temporal and inferior angular gyri and left lateral occipital cortices. The

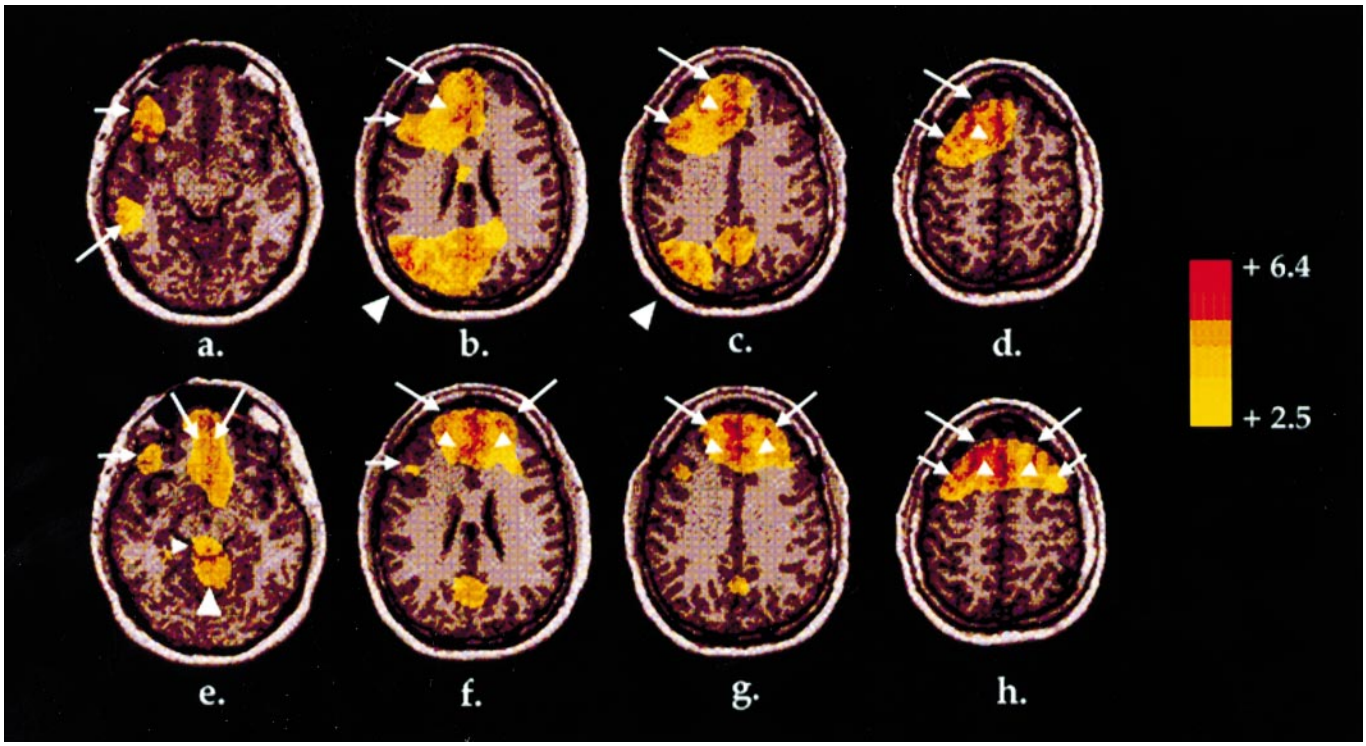

Fig. 2 Brain map illustrating focal rCBF activation during the formulation and expression of language in controls (**a**–**d**) and stuttering subjects (**e**–**h**) during tasks in which stuttering subjects were dysfluent. Language tasks are contrasted with the oral motor task as a baseline, in order to highlight regions involved in linguistic processing. The statistical parametric (SPM{Z}) map illustrating changes in rCBF is displayed on a standardized MRI scan. The MR image was transformed linearly into the same stereotaxic (Talairach) space as the SPM{Z} data. Using Voxel View Ultra (Vital Images, Fairfield, IA, USA), SPM and MR data were volume-rendered into a single three-dimensional image for each group. The volume sets are resliced and displayed at selected planes of interest. Data for control subjects are displayed in the top row (**a**–**d**), and for stuttering subjects in the bottom row (**e**–**h**). Planes of section are located at –8 mm (**a** and **e**), +21 mm (**b** and **f**), +30 mm (**c** and **g**), and +48 mm (**d** and **h**) relative to the anterior commissural–posterior commissural line. Values are *Z*-scores representing the significance level of increases in normalized rCBF in each voxel; the range of scores is coded in the colour table. Significant regional CBF responses in both stuttering subjects and controls are highlighted (*see* text for details). Control subjects activated post-Rolandic unimodal and heteromodal sensory cortices in the left hemisphere including middle temporal gyrus (**a**, long arrow), posterior superior temporal gyrus and inferior angular gyrus (**b** and **c**, large arrowheads), while stuttering subjects did not. In control subjects a larger spatial extent of the frontal operculum (**a**–**c**, short arrows) was activated than in stuttering subjects (**e** and **f**, short arrows). Significant increases in rCBF in medial and dorsolateral prefrontal (**b** and **c**, long arrows; **d** long and short arrows) and anterior cingulate cortices (**b**–**d** small arrowheads) were confined to the left hemisphere in control subjects, but were observed bilaterally in stuttering subjects (**f** and **g**, long arrows; h, long and short arrows) and anterior cingulate cortices (**f**–**h** small arrowheads). Activation of the caudal orbital cortices (**e**, long arrows) mesencephalic periacqueductal grey (**e**, small arrowhead) and cerebellar vermis (**e**, large arrowhead), was observed in stuttering subjects, but not in controls.

medial and dorsolateral prefrontal cortices, superior anterior cingulate cortex and caudal orbital cortices were bilaterally activated in stuttering subjects, while activation in controls, if present, was lateralized to the left hemisphere. Stuttering subjects continued to activate the right caudate nucleus and right inferior anterior cingulate cortex, while control subjects did not. Between-group contrasts again showed that left hemispheral sensory and paleocortical paralimbic regions were more active in control subjects, and right hemispheral subcortical, frontal and archicocortical paralimbic regions more active in stutterers (Table 2A and B).

Two types of condition-dependent differences were detected when fluent and dysfluent language conditions were compared with the motor baseline (Table 2A and B). The first included regions which had been activated by controls but not by stuttering subjects during dysfluency-evoking tasks (resulting in significant group differences), but which controls no longer activated under fluency-evoking conditions. These differences were evident in classical neocortical language areas of the left hemisphere. During fluency-evoking conditions, control subjects no longer activated Wernicke's area in the posterior superior temporal gyrus nor did they activate the left anterior frontal operculum.

The second set of condition-dependent differences included regions which had been activated by stuttering subjects during dysfluency-evoking tasks (regardless of whether these regions were also activated by controls) but which were no longer activated under fluency-evoking conditions. These differences were evident in a number of regions related to motor function. Increases in rCBF in both the left lateral premotor cortex

and anterior SMA were seen in control subjects during both sets of language tasks (the rCBF increases within these premotor regions were lower during fluent language tasks, but still significantly exceeded baseline values). On the other hand, these premotor areas were activated by stuttering subjects only under conditions in which they were dysfluent. The right lateral premotor cortex was also no longer activated by stutterers under fluency-evoking conditions.

Similarly, the left lateral portion of the superior ACC, the motor area deep within the cingulate sulcus (Morecraft and Van Hoesen, 1992), was activated by control subjects during both fluency and dysfluency-evoking tasks, but only during dysfluency-evoking tasks by stuttering subjects. Activation maxima in the superior portions of the left ACC during fluent language tasks were instead located in the medial, non-motor cingulate, while the inferior portions of the left ACC were activated by stuttering subjects only during production of dysfluent speech. In stuttering subjects, rCBF rates in the midline cerebellum and periaqueductal grey matter were significantly increased above baseline only during dysfluency-evoking tasks.

Fluent–dysfluent language contrasts

While the fluent and dysfluent language versus motor task contrasts were designed to isolate the sensorimotor and cognitive-linguistic elements of speech, the direct comparison of fluent and dysfluent tasks does not segregate motor and linguistic function, but instead should identify any differences in cerebral activity associated with fluent and dysfluent language tasks. When these tasks were compared directly, significant differences were detected, some common to both control and stuttering groups, and others observed in stuttering or control subjects only.

In both stuttering and control subjects, regions in which rCBF rates were significantly higher under dysfluency-evoking conditions were located predominantly in anterior brain regions, in premotor and association cortices and related (archicortical) paralimbic areas, where they were lateralized to the left hemisphere (Table 3A and B; Fig. 3). Relative elevations during dysfluent language tasks common to both groups were found in the medial (Brodmann 10) and dorsolateral (Brodmann 9) prefrontal cortices, superior frontal operculum (pars triangularis and opercularis, Brodmann 44 and 45), and in the superior portion of the ACC (Brodmann 32). In the dorsolateral prefrontal and opercular cortices, these condition-dependent differences were significantly greater in controls than in stuttering subjects.

In contrast, regions in which rCBF was higher under fluency-evoking conditions tended to be located posteriorly, in post-rolandic sensory and related (paleocortical) paralimbic areas (Table 3A and B; Fig. 3). Relative increases during fluent language tasks common to both groups were found in primary auditory (Brodmann 42), anterior and posterior auditory association cortices (Brodmann 22), and in the posterior insular cortex. In the auditory cortices, relative elevations during fluent language tasks were lateralized to the left hemisphere in controls but were observed bilaterally in stuttering subjects. In the posterior insula, relative elevations were lateralized to the right hemisphere in controls but were again observed bilaterally in the individuals who stuttered.

In stuttering subjects alone, rCBF rates were significantly higher during dysfluency-evoking language tasks in the left lateral orbital cortex (Brodmann 11), right and left medial orbital cortices (Brodmann 11), in the left orbital operculum (pars orbitalis, Brodmann 47) and in the midline cerebellum and periacqueductal grey bilaterally. Regional CBF rates were significantly higher during fluency-evoking tasks in stuttering subjects alone, in the right supramarginal gyrus and, as outlined above, in primary auditory, and both anterior and posterior auditory association cortices of the right hemisphere (Table 3A; Fig. 3).

In control subjects alone, rCBF rates were significantly higher during dysfluency-evoking language tasks in the left inferior angular gyrus, and significantly higher during fluency-evoking in the left superior parietal lobule, right parahippocampal gyrus and in the fusiform gyri bilaterally (Table 3B; Fig. 3).

Correlation of dysfluency scores and rCBF

From the acoustic analysis of speech recorded during each scan, the following weighted dysfluency scores (mean ± SD) were calculated for each of the five speech tasks: spontaneous narrative (0.60 ± 0.25); sentence construction (0.27 ± 0.35); automatic speech (0.02 ± 0.09); and paced speech and motor control tasks (0 ± 0.00). Dysfluency scores associated with the sentence construction task had the widest dynamic range, making it most appropriate for the use of correlational techniques, and this task was therefore selected for analysis. Results are summarized in Table 4. The hemispheric distribution of positive and negative correlation coefficients exceeding ± 0.5 was non-random [$\chi^2(1) = 7.67$, $P < 0.01$].

Dysfluency scores were positively correlated with cerebral activity in anterior brain regions, in subcortical motor areas, frontal association cortices and related (archicortical) paralimbic regions, located principally in the left hemisphere (Table 4, Fig. 4). These included the left ventral thalamus and posterior putamen, and areas in the left medial (Brodmann 10) and dorsolateral (Brodmann 9 and 46) prefrontal cortices. Dysfluency scores were also positively correlated with rCBF in both inferior (in the left hemisphere) and superior (in both right and left hemispheres) portions of the ACC. Significant correlations were, in each case, associated with anterior regions of the ACC (Brodmann 32/24), and maxima were located deep within the cingulate sulcus, which, as noted above, appears to constitute a cingulate motor region. Dysfluency scores were also positively correlated with rCBF in the posterior cingulate cortex (Brodmann 31).

Dysfluency scores were negatively correlated with regional cerebral activity in posterior brain regions, i.e. unimodal

Table 3 *Relative differences in rCBF under fluency and dysfluency evoking conditions in stuttering and control subjects*

Region (Brodmann)	Left hemisphere					Right hemisphere				
	Z	ΔrCBF	*x*,	*y*,	*z*	Z	ΔrCBF	*x*,	*y*,	*z*
(A) Stuttering subjects										
Relative increases, dysfluent conditions										
Subcortical										
Midline cerebellum	3.39	1.90	−6,	−46,	−8*	3.12	1.42	4	−46,	−8*
Periaqueductal grey	3.39	1.79	−2	−28,	−4*	3.34	1.96	2,	−24,	−4*
Prefrontal										
Medial orbital cortex (11)	4.12	2.66	−8,	50,	−12*	3.63	2.08	6	50,	−12*
Lateral orbital cortex (11)	4.67	2.90	−38	40,	−12*	–	–	–	–	–
Medial prefrontal cortex (10)	3.56	1.75	−8,	60,	12	–	–	–	–	–
Dorsolateral prefrontal cortex (8, 9)	3.56	1.70	−20,	32,	44	–	–	–	–	–
Frontal motor										
Inferior anterior frontal operculum (47)	4.26	2.24	−40	38,	−8*	–	–	–	–	–
Superior anterior frontal operculum (44, 45)	3.22	1.78	−52,	20,	16	–	–	–	–	–
Paralimbic										
Superior anterior cingulate cortex (32)	3.08	1.78	−10,	36,	28	–	–	–	–	–
Relative decreases, dysfluent conditions										
Unimodal sensory										
Primary auditory cortex (42)	−3.21	−2.00	−50,	−24,	8	−3.39	−1.95	50,	−20,	8
Anterior auditory association cortex (22)	−3.28	−1.92	−48,	−18,	4	−3.10	−1.80	52,	−18,	4
Posterior auditory association (22)	−3.79	−2.50	−46,	−32,	12*	−3.02	−1.62	50,	−30,	12
Heteromodal sensory										
Supramarginal gyrus (40)	–	–	–	–	–	−3.61	−1.76	54,	−38,	32
Paralimbic										
Posterior insula	−3.63	−2.10	−42,	−14,	4	−3.70	−2.07	42,	−22,	4
(B) Control subjects										
Relative increases, dysfluent conditions										
Prefrontal										
Medial prefrontal cortex (10)	3.18	1.38	−16,	56,	12	–	–	–	–	–
Dorsolateral prefrontal cortex (9)	4.36	2.23	−32,	20,	36*	–	–	–	–	–
Frontal motor										
Superior anterior frontal operculum (45)	3.63	2.38	−38,	18,	20*	–	–	–	–	–
Heteromodal sensory										
Inferior angular gyrus (39)	3.05	1.48	−44,	−62,	24*	–	–	–	–	–
Paralimbic										
Superior anterior cingulate cortex (32)	3.81	2.13	−6,	26,	36	–	–	–	–	–
Relative decreases, dysfluent conditions										
Unimodal sensory										
Primary auditory cortex (42)	−4.27	−2.67	−52,	−10,	8*	–	–	–	–	–
Anterior auditory association cortex (22)	−3.24	−2.10	−54,	−20,	4	–	–	–	–	–
Posterior auditory association (22)	−3.87	−1.81	−60,	−28,	12	–	–	–	–	–
Medial superior parietal lobule (7)	−3.13	−2.05	−2,	−32,	44*	–	–	–	–	–
Fusiform gyrus (37)	−3.24	−1.57	−34,	−68,	−12*	−3.35	−1.45	42,	−60,	−12*
Paralimbic										
Parahippocampal gyrus (35, 36)	–	–	–	–	–	−3.64	−1.73	36,	−22,	−16
Posterior insula	–	–	–	–	–	−4.64	−2.70	42,	0,	4

Regions in which rCBF responses differ between conditions are tabulated along with Z-scores representing local maxima or minima (Z), followed by magnitude of rCBF differences (ΔrCRF; ml/100g/min normalized to a mean of 50) and associated talaraich coordinates. Instances in which the magnitude of rCBF differences were themselves significantly different in between-group contrasts are identified by asterisks, indicating the greater absolute differences (conjoint significance of $P < 0.0005$ in each case).

sensory areas, parietal association cortices and related (paleocortical) paralimbic regions, located principally in the right hemisphere (Table 4; Fig. 4). These included the primary auditory (Brodmann 42), anterior, and posterior auditory association cortices (Brodmann 22), somatosensory areas (Brodmann 43, 3, 1 and 2) and supramarginal gyrus (Brodmann 40) within the right hemisphere. Dysfluency scores were also negatively correlated with activity in the right posterior insula, anterior insular and temporal polar cortices. Dysfluent speech was negatively correlated with rCBF in the right frontal operculum (pars opercularis and triangularis, Brodmann 47 and 45) as well as the caudal brainstem and limbic regions of the mesial temporal cortex in both right and left hemispheres.

Discussion

After a century of clinical investigation, utilizing a variety of techniques, the pathophysiology of stuttering remains a mystery. The nature of stuttering symptoms—evanescent yet condition-dependent and amenable to manipulation—makes this disorder an ideal one for study using $H_2{}^{15}O$

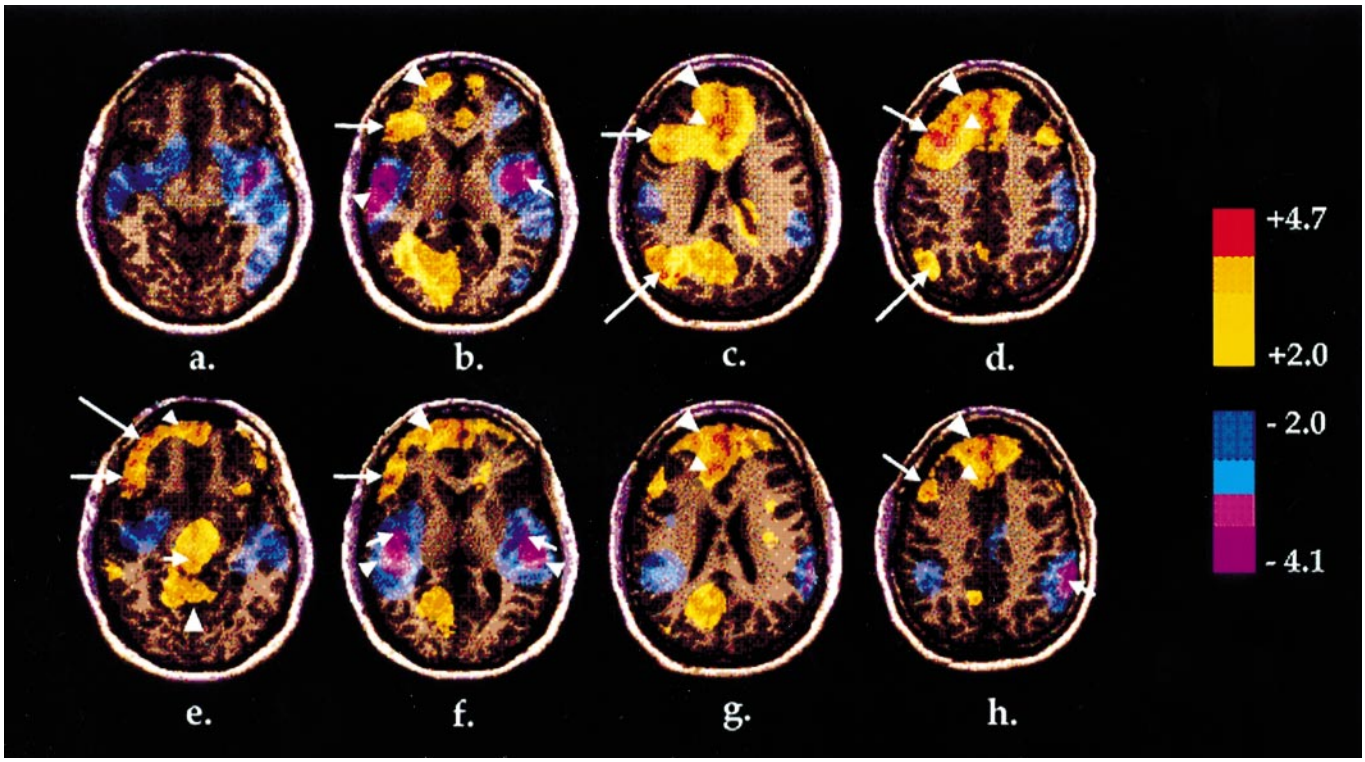

Fig. 3 Brain map illustrating differences in rCBF when fluency-evoking and disfluency-evoking tasks are compared directly, prepared using methods outlined in the legend to Fig. 2. Differences observed in stuttering subjects (**e**–**h**) highlight regional increases and decreases in CBF related to the production of dysfluent speech. Differences observed in control subjects (**a**–**d**) highlight increases and decreases in rCBF related to the sensorimotor or cognitive features of the language tasks themselves (which could account for their effects upon fluency in developmental stutterers). Planes of section are located at –8 mm (**a** and **e**), +12 mm (**b** and **f**), +20 mm (**c** and **g**), and +32 mm (**d** and **h**) relative to the anterior commissural, posterior commissural line. Values are *Z*-scores representing the significance level of increases and decreases in normalized rCBF in each voxel; the range of scores is coded in the accompanying color table. Significant regional CBF responses showing differences between conditions in both stuttering subjects and controls are highlighted (*see* text for details). In both stuttering and controls groups, rCBF rates were significantly higher under dysfluency-evoking conditions and lower under fluency-evoking conditions (associated with positive *Z*-scores in this instance) in anterior brain regions including medial and dorsolateral prefrontal cortices (**b**–**d** and **f**–**h**, large arrowheads; d and h, medium arrows), superior frontal operculum (**b**, **d** and **f**, medium arrows), and ACC (**c**, **d**, **g** and **h**, small arrowheads) in the left hemisphere. In both groups, rCBF rates were significantly higher under fluency-evoking conditions, and lower under dysfluency-evoking conditions (associated with negative *Z*-scores in this instance) in posterior brain regions, including primary auditory, and anterior and posterior auditory association cortices (**b** and **f**, small arrowheads); in control subjects, these differences were detected in the left hemisphere; in stuttering subjects they were bilateral. In both groups, rCBF rates were significantly higher under fluency-evoking conditions in the posterior insular cortices (**b** and **f**, small arrows); in control subjects, these differences were detected in the right hemisphere; in stuttering subjects they were bilateral. In control subjects alone, rCBF rates were significantly higher during dysfluency-evoking conditions in the left angular gyrus (**c** and **d**, long arrows). In stuttering subjects alone, rCBF rates were significantly higher during dysfluency-evoking conditions in the left and right medial (**e**, small arrowhead indicates changes in the left hemisphere) and left lateral orbital cortices (**e**, long arrow), left inferior frontal operculum (**e**, medium arrow), as well as the midline cerebellum (**e**, large arrowhead) and mesencephalic periacqueductal grey (**e**, small arrow). In stuttering subjects alone, rCBF rates were significantly higher under fluency-evoking conditions in the right supramarginal gyrus (**h**, small arrow).

PET techniques. Although the express purpose of the present study was exploratory, results at each level of analysis clearly indicate that cerebral activity in adults with developmental stuttering can be characterized by a constellation of state- and trait-dependent patterns. These findings provide the rudiments of a pathophysiological model for stuttering and serve as a springboard for further study of this disorder.

Oral motor activity (orolaryngeal motor–rest contrast)

Differences in rCBF patterns in stuttering versus control subjects were most pronounced during conditions in which stuttering symptoms are regularly manifest, i.e. during tasks which involve the production of language. However, group differences were also apparent during the execution of nonlinguistic laryngeal and oral articulatory movements,

Table 4 *Correlations between weighted measures of dysfluency and normalized regional cerebral blood flow*

Region (Brodmann)	Left hemisphere				*Right hemisphere*			
	r	*x*,	y,	*z*	*r*	*x*,	y,	z
Positive correlations								
Subcortical								
Putamen	0.780	−22,	−2,	12***	–	–	–	–
Ventral thalamus	0.617	−12	−20	12*	–	–	–	–
Prefrontal								
Medial prefrontal cortex (10)	0.500	−18,	52,	4	–	–	–	–
Mid dorsolateral prefrontal cortex (9, 46)	0.529	−32,	32,	24	–	–	–	–
Paralimbic								
Inferior anterior cingulate cortex (32)	0.655	−18,	48,	)*	–	–	–	–
Superior anterior cingulate cortex (32)	0.545	−16,	36,	28	0.576	14,	40,	28
Posterior cingulate cortex (31)	0.576	−8,	−66,	24	0.600	6	−62	16*
Negative correlations								
Subcortical								
Pons	−0.561	−10,	−16,	−20	–	–	–	–
Caudal midbrain	−0.680	−12	−12	−12*	−0.506	12,	−18,	−12
Frontal motor								
Inferior anterior frontal operculum (47)	–	–	–	–	−0.561	46,	22,	−8
Mid anterior frontal operculum (45)	–	–	–	–	−0.514	50,	20,	4
Unimodal sensory								
Second somatosensory area (43)	–	–	–	–	−0.639	56	−18	16*
Inferior postcentral gyrus (3, 1, 2)	–	–	–	–	−0.514	56,	−22,	24
Primary auditory cortex (42)	–	–	–	–	−0.561	58,	−22,	8
Anterior auditory association cortex (22)	–	–	–	–	−0.741	48	4	)**
Posterior auditory association cortex (22)	–	–	–	–	−0.545	52,	−30,	12
Heteromodal sensory								
Supramarginal gyrus (40)	–	–	–	–	−0.520	38,	−36,	40
Paralimbic/limbic								
Inferior insula, temporal pole	–	–	–	–	−0.773	40	4	−8***
Anterior insula	–	–	–	–	−0.694	40	6	−4*
Posterior insula	–	–	–	–	−0.631	40	−22	4*
Hippocampus	−0.608	−22	−18	−12*	−0.576	22,	−20,	−12
Amygdala	−0.529	−22,	−6,	−16	−0.553	24,	−6,	−16

r = correlation coefficients; *x*, *y*, *z* = Talaraich coordinates. Values represent local maxima and minima. *$P < 0.01$; **$P < 0.001$; ***$P < 0.0001$; otherwise $P < 0.025$.

a complex praxic task in which stuttering subjects are invariably asymptomatic (Table 1).

While there were no qualitative differences in the nature and anatomical distribution of regions activated during this task, the magnitude of rCBF increases over baseline in a subset of these regions was significantly greater in stuttering subjects than in controls (Table 1). In the neocortex, rCBF responses were larger in premotor, primary motor and somatosensory cortices, suggesting that these regions may be more active in both the generation and proprioceptive, or tactile, perception of movement of the lips, tongue, jaw and larynx. Increases in rCBF in primary and secondary auditory cortices were similarly augmented, suggesting that responses to the sounds generated may be relatively exaggerated in these regions. Hemispheral differences were also apparent at this level of the analysis. Significant differences in premotor and perirolandic areas were confined to the left hemisphere; significant differences in the auditory areas, on the other hand, were clustered to the right.

Taken together, these findings imply that there are differences in brain function in stuttering subjects which are present even in the absence of stuttering. These could represent secondary or compensatory processes related to the subjects' stuttering history, manifest as increased attention to, or effort exerted in the control of, oral motor activity. However, they may also represent fundamental differences in motor, somatosensory and auditory processing which underlie the appearance of symptoms, and constitute a diathesis upon which the use of language, acting as a stressor, precipitates the emergence of stuttered speech.

Language processing and paralinguistic mechanisms (language–motor contrasts)

The rest, and oral motor and language tasks represent a hierarchical set of conditions which serve to differentiate the motor from the linguistic elements of speech. Contrasts

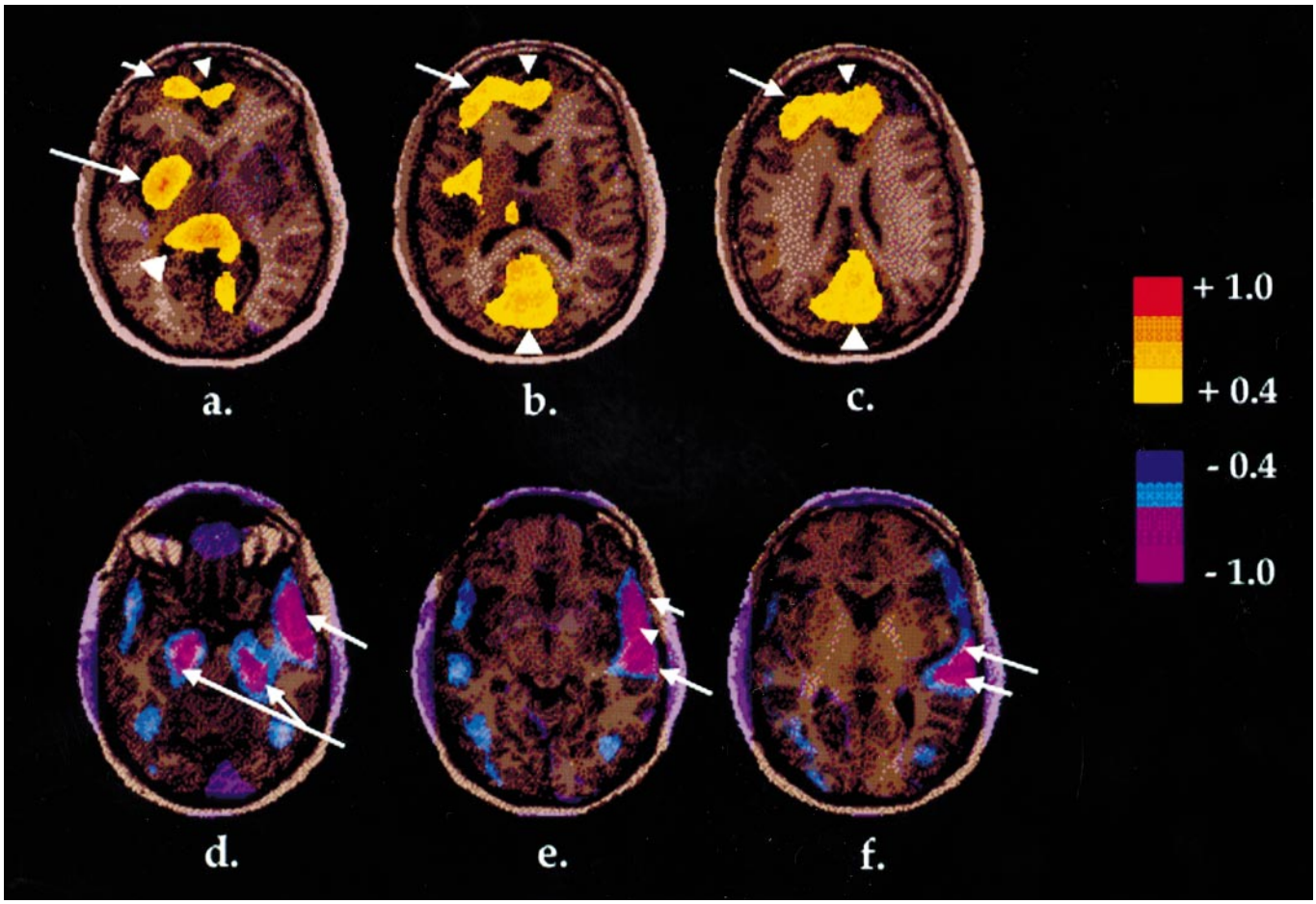

Fig. 4 Brain map illustrating correlations between rCBF and severity of stuttered speech. Normalized rCBF images were correlated with individual dysfluency scores within the stuttering group only, utilizing a modification of the SPM software (*see* Material and methods) which produces a Pearson product-moment correlation coefficient assigned to each pixel in the image. The map illustrating these correlation coefficients is displayed on a standardized MRI scan using the methods outlined in the legend to Fig. 2. The range of positive and negative coefficients is coded in the accompanying color table. Positive correlations are illustrated in the top row; planes of section are located at +8 mm (**a**), +16 mm (**b**), +24 mm (**c**) relative to the anterior commissural–posterior commissural line. rCBF was positively correlated with dysfluency scores in (**a**) putamen (long arrow), ventral thalamus (large arrowhead), medial prefrontal cortex (short arrow) and inferior ACC (small arrowhead) in the left hemisphere, and (**b**) and (**c**) ACC (small arrowheads) and posterior cingulate cortex (large arrowheads) bilaterally, and medial and dorsolateral prefrontal cortices (medium arrows) in the left hemisphere. Negative correlations are illustrated in the bottom row; planes of section are located at –10 mm (**d**), 0 mm (**e**), and +12 mm (**f**) relative to the anterior commissural–posterior commissural line. rCBF was negatively correlated with dysfluency scores in (**d**) left and right hippocampus and parahippocampal gyri (double arrow), and right temporal pole-inferior insula (medium arrow); (**e**) inferior frontal operculum (short arrow), anterior insula (small arrowhead), and anterior auditory association cortices (medium arrow) in the right hemisphere; (**f**) primary auditory and posterior auditory association cortices (short arrow) and posterior insula (medium arrow) in the right hemisphere.

in which language were compared with the oral motor task were performed to highlight regions involved in linguistic processing, independent of motor execution. Evaluation of these contrasts, both within and between groups, suggests that cerebral organization for language, particularly as it relates to hemispheric lateralization, is fundamentally altered in adults with developmental stuttering (Table 2A and B; Fig. 2).

As expected, during the formulation and expression of language, increases in rCBF in controls were consistently lateralized to the left hemisphere. In contrast, rCBF responses in stuttering subjects were absent, spatially constricted, bilateral or lateralized to the right hemisphere (Table 2A; Fig. 2).

In the dysfluent language–motor task contrast, group differences were conspicuous in those neocortical regions constituting the central elements of the classical Wernicke–Geshwind model of language processing (Geschwind, 1965, 1979) (Table 2A; Fig. 2), in both anterior (or expressive) and posterior (or receptive) areas. Although activation of the left anterior frontal operculum was evident in both groups, these increases in rCBF were less robust and more spatially constricted in stuttering subjects. Furthermore, stuttering subjects failed to activate left temporoparietal

regions (posterior superior temporal and inferior angular gyri) which constitute the conventional boundaries of Wernicke's area (Penfield and Roberts, 1959; Ojemann *et al.*, 1989).

In previous PET studies in normal subjects (Petersen *et al.*, 1988; Wise *et al.*, 1991; Démonet *et al.*, 1992; Zatorre *et al.*, 1992) it has been shown that Wernicke's area and contiguous portions of the temporal and parietal lobes may be involved in both phonological and semantic processing of speech and language. In light of this, our results suggest that when they are dysfluent, stuttering subjects may not be monitoring speech-language output effectively in the same fashion as controls. Perhaps an inability to monitor rapid, spontaneous speech output may be related, at some level, to the production of stuttered speech.

In stuttering subjects, distorted lateralization patterns were evident not only in classical neocortical language areas, but also in association areas, i.e. in dorsolateral prefrontal cortices, middle temporal gyrus and ACC (Table 2A; Fig. 2), which are also thought to play a significant role in language processing, but for which precise linguistic functions are less well characterized. Both the left dorsolateral prefrontal and anterior cingulate cortices, for example, appear to be activated during word finding or verbal fluency tasks (Frith *et al.*, 1991*a*; Yetkin *et al.*, 1995), and the left middle temporal gyrus is selectively activated during the processing of meaningful narrative (Mazoyer *et al.*, 1993). In the present study, left lateralized activation of these regions was evident in controls but not in stuttering subjects. Lateralized activation was also evident in controls, but not in stuttering subjects, in visual association areas (Table 2A), which may be involved in the processing of visual imagery during discourse formulation (Lüders *et al.*, 1986; Sakai and Miyashita, 1993).

Thus, under conditions which precipitate dysfluent speech, stuttering subjects show a striking distortion of the normal pattern of left hemispheral dominance for language, either not activating left hemisphere neocortical areas which are normally engaged in language processing or activating these regions bilaterally.

Failure to activate left hemispheral regions entirely was seen in post-rolandic sensory (auditory, visual and higher order sensory association) areas and related paleocortical (insular) paralimbic regions of the brain (Table 2A; Fig. 2), while bilateral activation was more common in anterior premotor, prefrontal and associated archicortical (cingulate) paralimbic areas (Table 2A; Fig. 2) (Sanides, 1975). The latter finding is consistent with reports of greater right hemispheric activity in some stuttering subjects during the processing of meaningful linguistic stimuli (Curry, 1969; Zimmermann and Knott, 1974; Moore, 1986).

The notion that stuttering involves a disordered activation of neocortical language areas is consistent with the observations that symptoms are wedded to the use of language, and that the onset of stuttering occurs in childhood during the acquisition of complex linguistic skills (Ratner and Sih, 1995).

While normal neocortical activation patterns were absent during dysfluent speech production, stuttering subjects activated regions which constitute elements of an ancillary communication system, i.e. the intermediate portion of the ACC and mesencephalic periaqueductal grey (Table 2A; Fig. 2). This is a phylogenetically older system related to vocalization rather than language production (Sutton *et al.*, 1974; Jurgens, 1976). The idea that stuttering may, in part, result from an antagonistic relationship between a primitive paralinguistic signalling system and neocortical regions involved in formal language processing has been suggested previously (Perkins *et al.*, 1991). However, whether such activity is compensatory or antagonistic is unclear in the present contrast.

Indeed, it is not clear whether any of the differences in hemispheral lateralization, evident when stuttering subjects were dysfluent, represent causative features, compensatory manoeuvres, trait-related features associated with the diagnosis of stuttering (but unrelated to symptom production), or simply epiphenomena. Comparisons including tasks in which stuttering subjects were fluent were performed to help differentiate these possibilities.

When fluency-evoking language tasks were contrasted with the motor baseline, certain essential differences which were detected in the dysfluent language–motor contrast persisted, i.e. group differences were manifest (Table 2B) that could not be attributed to the presence or absence of dysfluent symptoms.

Thus, during the execution of fluent language tasks, increases in rCBF in control subjects were again lateralized to the left hemisphere, while in stuttering subjects they were either absent, bilateral, or lateralized to the right. Between-group contrasts again showed that left hemispheral sensory and paleocortical paralimbic regions were activated to a greater extent in controls, whereas right hemispheral subcortical, frontal and archicocortical paralimbic regions were activated to a greater extent in stuttering subjects (Table 2B). Because this pattern of group differences is evident during both fluent and dysfluent language production, it constitutes a trait, i.e. a consistent and fundamental difference in the pattern of cerebral activity in stuttering subjects, even in the absence of overt symptoms.

On the other hand, while patterns of activity in the neocortical language areas remained distorted, activation of the inferior portion of the left ACC and the mesencephalic periaqueductal grey to which it projects, was no longer evident when stuttering subjects were able to speak fluently. This raises the previously mentioned possibility that elements of this archaic paralinguistic system may have been interfering with the production of fluent speech during dysfluency-evoking tasks. If this is the case, it is possible that such interference is no longer manifest during fluency-evoking conditions. On the other hand, these paralinguistic regions may have been enlisted as part of a compensatory

response to stuttered speech, and are no longer activated as speech becomes fluent.

Cerebral activation patterns related to dysfluent speech production

Condition dependent differences in stuttering subjects (language–motor contrasts: fluent–dysfluent language contrasts)

Comparison of fluent and dysfluent language tasks in stuttering subjects—when these were contrasted with the oral motor baseline or compared directly—should pinpoint brain regions or networks of regions associated with the expression of stuttering symptoms (Tables 2A and B and 3A; Figs 2 and 3). These contrasts demonstrated both increases and decreases in rCBF which appeared to be related to the production of dysfluent speech.

Regional CBF rates were significantly elevated during dysfluent speech production in an array of regions which appear to share certain characteristic features. They are regions, located for the most part in the anterior forebrain, which play an executive rather than evaluative role—in linguistic parlance, closer to expressive than to receptive in function. Whether formally classified as association (prefrontal, orbital), paralimbic (cingulate) or motor (opercular, lateral premotor, SMA or cerebellar), each of these regions is involved at some level with intention, initiation, or on-line regulation of motor activity, and each depends upon integrated sensory input from posterior systems in order to function properly.

For example, the prefrontal cortices—in which increased rCBF rates during stuttered speech were demonstrated by the direct contrast of fluent and dysfluent language tasks (Table 3A; Fig. 3)—are involved in the organization of complex goal-directed behavioural responses to input from sensory, paralimbic and other higher order association areas of the brain (Pandya and Yeterian, 1985). The dorsolateral portions of the prefrontal cortex utilize integrated input from posterior brain regions in the planning and temporal sequencing of behaviour (Shallice and Burgess, 1991; Dubois *et al.*, 1994) and, via projections to premotor areas, may play a role in the highest order execution of voluntary action (Frith *et al.*, 1991*b*). The dorsolateral regions of the left hemisphere play a cardinal role in language formulation (Petersen *et al.*, 1988; Ojemann *et al.*, 1989).

The orbitofrontal cortices analyse input from post-rolandic sensory association areas (Pandya and Yeterian, 1985) and play a role in inhibiting competing or inappropriate responses during the execution of ongoing behaviours (Passingham, 1972; Blumer and Benson, 1975; Deuel and Mishkin, 1977). Dysfunction of inhibitory or regulatory mechanisms carried out by this region could play a role in the generation of stuttering symptoms.

Increased activity in the left ACC during dysfluent speech production was identified in both fluent–dysfluent language (superior ACC, Table 3A) and language–motor contrasts (inferior ACC, Table 2A and B); in the direct fluent–dysfluent language contrast, dysfluent task-related elevations in rCBF in the inferior ACC approached but did not reach the criteria set for significance (Z-score = 2.68, ΔrCBF = 1.23; Talaraich coordinates x = –14, y = 48, z = 12).

While frequently considered a region mediating affective behaviours, vigilance or autonomic processes (Maclean, 1993), the dorsal portion of the ACC also plays a well-defined role in the initiation and on-line selection of motor responses, and is considered by some to constitute a premotor region in itself (Morecraft and Van Hoesen, 1993). The ACC is the recipient of widespread afferent input from other association areas in addition to direct projections from sensory, especially auditory, cortices (Vogt, 1985; Vogt *et al.*, 1992; Van Hoesen *et al.*, 1993) and is involved in the control of speech and movement of the lower facial musculature in humans (Muakkassa and Strick, 1979; Morecraft and Van Hoesen, 1992; Paus *et al.*, 1993). The region which represents the source of this efferent outflow, i.e. the lateral ACC, origin of motor efferents deep within the cingulate sulcus (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992), was activated by controls during all language tasks, but by stuttering subjects only when they were dysfluent, providing a possible anatomical substrate for the ACC's role in the generation of stuttering symptoms.

Condition dependent differences in stuttering subjects were also observed in regions which are more immediately associated with motor control, i.e. areas one synapse removed from the primary motor cortex. These premotor regions—the left frontal operculum and the two principal subdivisions of the neocortical premotor system, anterior SMA and lateral premotor cortex—have access to complex information from all sensory modalities (Pandya and Kuypers, 1969; Jones and Powell, 1970) and use such information in the organization, initiation, sensory guidance and smooth execution of complex sequences of movements (Brinkman and Porter, 1983). Each of these regions has been shown to play a role in speech and language production (Freedman *et al.*, 1984; Fried *et al.*, 1991; Lim *et al.*, 1994).

Language–motor contrasts alone implicated the lateral premotor cortex and anterior SMA, which were activated in control subjects during both sets of language tasks, but by stuttering subjects only when speech was dysfluent. [In the direct comparison of fluent and dysfluent tasks, relative elevations in rCBF in these regions approached, but did not reach, the criteria set for significance (in the left lateral premotor cortex, Z-score = 2.60, ΔrCBF = 1.54, Talaraich coordinates x = –40, y = 16, z = 44; in the anterior or SMA Z-score = 2.32, ΔrCBF = 1.16, Talaraich coordinates x = –6, y = 24, z = 44).]

Both language–motor and fluent–dysfluent task contrasts indicated that rCBF rates in superior and anteroventral

regions of the left frontal operculum were selectively elevated during the production of dysfluent speech (Tables 2A and B and3A; Fig. 3). The involvement of the opercular regions in the generation of stuttering symptoms would not be unexpected. The superior opercular regions (Brodmann 44/45), constituting the classical 'Broca's area', are traditionally considered to participate in the generation of speech-related motor programmes (Freedman *et al*., 1984); the anteroventral regions of the frontal operculum (Brodmann 47) may be more closely related to syntactic processing and language expression (McCarthy *et al*., 1993).

In addition, both language–motor and fluent–dysfluent language contrasts indicated that rCBF rates in the midline cerebellum were significantly elevated in stuttering subjects during the production of dysfluent speech (Tables 2A and 3A; Figs 2 and 3). The cerebellum is known to play a role in the control of speech (Holmes, 1939; Brown *et al*., 1970), and the midline cerebellum or vermis is specifically involved in ongoing error detection and correction of motor activity initiated by neocortical systems (Thach *et al*., 1992). This region contains neurons which are both responsive to auditory stimuli and are coupled to activity in the auditory cortex (Snider and Stowell, 1944; Hampson, 1949; Aitkin and Boyd, 1975; Huang and Liu, 1985), placing the midline cerebellum in position to monitor speech output and, via its ascending efferents, to modulate speech motor activity. Task-specific increases in rCBF in this region may reflect a disruption of this process, which could play a role in the production of stuttered speech. Thus, like the prefrontal, cingulate and premotor cortices, the midline cerebellum constitutes a region which uses sensory information to regulate motor function, and depends upon ordered, integrated sensory feedback in order to function properly. All of these regions, increased rCBF responses were categorically associated with the production of dysfluent speech.

In contrast, regions in which rCBF rates were significantly lower during dysfluent speech production were clustered in post-rolandic brain regions, which are involved in more proximate reception and decoding of sensory information (Table 3A; Fig. 3).

These areas were located, furthest upstream, in primary auditory and auditory association cortices, regions engaged in first and second order processing of auditory information, which is then transmitted to frontal, parietotemporal, paralimbic and subcortical areas (Pandya and Yeterian, 1985). Results from a previous neuroimaging study suggest that rCBF in these areas is relatively lower in adults with developmental stuttering, even at rest (Pool *et al*., 1991).

Regional CBF in the contiguous portion of the posterior granular insula was also attenuated during tasks in which speech was dysfluent. This portion of the insula is reciprocally connected with primary auditory and auditory association cortices, and may be involved in relatively direct processing of auditory input (Pandya *et al*., 1969; Mesulam and Mufson, 1982; Mufson and Mesulam, 1982), serving as a parallel relay to prefrontal, motor, somatosensory and cingulate regions of the brain. The insula is activated by acoustic stimulation in normal subjects (Kushner *et al*., 1987), and selective damage to this region can result in a relatively specific disorder of auditory processing (Fifer, 1993).

Activity in the right supramarginal gyrus was also reduced in stuttering subjects during dysfluent speech production (Table 3A). This portion of the inferior parietal lobule plays a role in auditory-linguistic processing which is distinct from that played by the contiguous angular gyrus. While the latter is involved in lexico-semantic decoding, the supramarginal gyrus may be selectively involved in lower level acoustic-phonological processing of auditory stimuli (Roeltgen and Heilman, 1984; Démonet *et al*., 1994).

All of these regions may therefore belong to a system which carries out relatively elemental processing of auditory information, at a lower level than that carried out, for example, by the temporoparietal regions that constitute Wernicke's area, which are dependent upon the unimodal cortices and related regions for their auditory input. Indeed, defective processing at this more elemental level might account for the fact that the posterior superior temporal gyrus and inferior angular gyrus were not effectively activated by stuttering subjects during dysfluent language tasks. Decreased activation of this network of regions would be consistent with the notion that a disturbance of central auditory function may underlie symptom production in developmental stutterers (Hall and Jerger, 1978; Toscher and Rupp, 1978; Hannley and Dorman, 1982; Blood and Blood, 1984; Rosenfield and Jerger, 1984).

Taken together, these results suggest a tentative hypothesis: that dysfluent speech production may be associated with a functional imbalance between anterior forebrain and cerebellar regions which mediate the organization, initiation and regulation of motor activity, and post-rolandic regions involved in reception and decoding of sensory information. It is possible that the posterior regions fail to provide the integrated sensory input upon which anterior regions depend for accurate regulation of motor function. Such a dissociation may underlie the production of stuttering symptoms.

Condition-dependent differences in control subjects (language–motor contrasts: fluent–dysfluent language contrasts)

In the above contrasts, condition-dependent changes in cerebral activity observed in stuttering subjects may clearly reflect mechanisms which either underly the production of dysfluent speech or are manifest as a reaction to it. However, a number of condition-dependent differences were observed in control subjects as well. These differences may provide information about the sensorimotor or cognitive

features of the language tasks themselves, which might account for their differing effects upon fluency in developmental stutterers.

One of the more striking findings, evident both in language–motor (Table 2A and B) and fluent–dysfluent language contrasts (Table 3B; Fig. 3), involved task-related activation of classical anterior and posterior neocortical language areas, namely the posterior superior temporal gyrus, inferior angular gyrus and anterior frontal operculum of the left hemisphere. These areas were robustly activated in control subjects during narrative speech and sentence construction task, but CBF rates in these regions were either not significantly elevated above baseline values or were significantly attenuated during the automatic or paced speech tasks, i.e. under conditions in which people who stutter were able to speak fluently (Tables 2A and B, and 3B; Fig. 3). [While rCBF rates in the posterior superior temporal gyrus were not elevated above baseline values during fluent language tasks, relative attenuations versus dysfluent language tasks approached, but did not reach the criteria set for statistical significance (Z-score = –2.59, ΔrCBF = –1.15, Talaraich coordinates x = –50, y = –60, z = 20).]

It is possible that when speech is paced (and the rate is therefore slower), or when speech content is overlearned rather than spontaneous, language formulation demands may be fewer, or phonological or semantic monitoring may be less critical, to the degree that significant engagement of the neocortical language areas is no longer ‘essential’. This may account for the ability of stuttering subjects, who had unsuccessfully or incompletely activated these areas previously, to produce fluent speech under such conditions.

Fluent–dysfluent task contrasts (Table 3B; Fig. 3) also identified an array of condition-dependent differences in control subjects which extended beyond the traditional language areas, which appear to be similar in their essential distribution to the patterns observed in stuttering subjects.

Thus, during fluency-evoking language tasks, rCBF responses were significantly attenuated in control subjects in anterior regions of the left hemisphere, including dorsolateral and medial prefrontal association cortices and related archicortical paralimbic areas. At the same time, responses in post-rolandic sensory cortices, namely auditory, visual, somatosensory association and related paleocortical paralimbic areas, were significantly augmented. Certain of the latter findings might be due, at least in the case of paced speech, to an internally imaged or remembered sound of the metronome, which although no longer active, might account for augmented rCBF in the auditory regions. On the other hand, primary perception of a subject’s own voice may be enhanced when speech is paced (and the rate is slower), than during free narrative or sentence construction.

If a functional dissociation between anterior and posterior regions—i.e. increased activity in effector regions, under-activation of sensory areas—underlies the production of stuttered speech, the fluency-evoking conditions themselves may provide a cognitive set which reduces or corrects such an imbalance. The recitation of overlearned material or the production of paced, slow speech may place less ‘demand’ upon left hemispheral mechanisms involved in executive or effector function, while enabling activity within post-rolandic regions that are involved in reception and processing of sensory information.

It is tempting to speculate that this pattern may represent a generalizable mechanism by which fluency-evoking manoeuvres affect sensorimotor or cognitive demand and thus facilitate fluent speech production in people who stutter. It will be interesting, in future studies, to see if such a pattern manifests itself during other, cognitively distinct, fluency-evoking tasks.

Correlations between rCBF and weighted measures of dysfluency in stuttering subjects

In the foregoing contrasts, stuttering behaviours themselves are only partially taken into account, i.e. differences in rCBF that may underlie the production of stuttered speech are mixed with differences that may be related to cognitive properties of the fluent or dysfluent language tasks themselves. As we have just seen, the latter may be entirely independent of symptom production, since condition-dependent differences are observed in control subjects (in whom symptoms are never present).

On the other hand, the correlational analysis, carried out only in the stuttering cohort, evaluating the direct relationship between rCBF and measures of dysfluency, should reflect differences exclusively related to the production of stuttered speech (either underlying the production of dysfluent speech, expressed in response to it, or associated with a parametric increase in motor activity accompanying stuttering). In addition, since the correlational technique takes into account intersubject variations in fluency, it may represent a more sensitive approach. As such, the results of the correlation analysis were expected to overlap and corroborate, to some degree, those generated by the task contrasts and to help identify regions which were not detected using the latter technique. This was indeed the case.

Findings from the two approaches converged in a number of meaningful ways (Tables 3A and 4; Figs 3 and 4). Paralleling the results of the fluent–dysfluent language contrasts, positive correlations between rCBF and stuttering symptoms were chiefly located in anterior brain regions, in prefrontal association cortices, related (archicortical) paralimbic areas and subcortical structures, strongly lateralized to the left hemisphere. These results support the notion that stuttered speech may be associated with disproportionate increases in activity in anterior-effector regions of the brain.

Medial prefrontal, dorsolateral prefrontal and anterior cingulate cortices represent explicit overlaps, i.e. rCBF rates in these regions were both positively correlated with stuttering symptoms and significantly higher during dysfluent language tasks. In the ACC, the tightest correlations between rCBF and stuttered speech were found in the sulcal regions, the motor portion of the ACC similarly identified by the task contrasts (Tables 3A and 4).

In contrast, paralleling the results of fluent–dysfluent language contrasts, regions which were negatively correlated with stuttering symptoms were chiefly located posteriorly, in post-rolandic unimodal and heteromodal sensory and related (paleocortical) paralimbic areas (Table 4; Fig. 4), supporting the idea that dysfluent speech production is associated with decreased activity in regions that are involved in the more proximate processing of sensory information.

The primary auditory and auditory association cortices, supramarginal gyrus and posterior insula also represent explicit ovelaps, i.e. rCBF rates in these regions were both negatively correlated with stuttering symptoms and significantly lower during the performance of dysfluent language tasks. Identification of the insula by both techniques reinforces the notion that the paleocortical paralimbic system may play a central role in developmental stuttering.

The correlational analysis also identified a number of brain regions that were not detected by the task contrast method (Table 4; Fig. 4). Those in which rCBF rates were positively correlated with measures of dysfluency were areas once again known to be involved in the initiation or regulation of motor activity. For example, dysfluency scores were positively correlated with activity in the left posterior putamen and ventral thalamus, areas which are richly connected with anterior effector regions of the neocortex. These regions constitute the subcortical elements of a well-defined motor circuit, one of a family of parallel circuits (Alexander *et al*., 1986; Parent and Hazrati, 1995) connecting discrete regions of the basal ganglia, diencephalon and frontal cortex, in this instance the SMA. [Dysfluency scores were positively correlated with activity in the left anterior SMA, but the correlation coefficient in this instance did not exceed the threshold set for tabulation ($r = 0.41$, Talaraich coordinates $x = -2$, $y = 4$, $z = 52$).] The basal ganglia and their projections also play a well-documented role in speech motor control and language processing (Naeser *et al*., 1982; Klein *et al*., 1994).

In addition, the putamen, dorsolateral prefrontal and anterior cingulate cortices each represent primary targets of the mesostriatal and mesocortical dopamine projections. This is intriguing since a number of studies have reported the successful use of haloperidol or other drugs which block dopamine transmission in the treatment of stuttering symptoms (Quinn and Peachey, 1973; Murray *et al*., 1977; Prins *et al*., 1980).

Dysfluency scores were also positively correlated with activity in the posterior cingulate cortex (Table 4; Fig. 4). This region has strong reciprocal connections with the anterior cingulate (Baleydier and Mauguiere, 1980) with which it interacts as part of a highly coordinated feed forward system, gating and regulating anterior cingulate outflow (Van Hoesen *et al*., 1993) and thus modulating the effects of the ACC on motor function. Involvement of both anterior and posterior elements of the cingulate cortex again suggests that activity in the archicortical paralimbic system may play a central role in developmental stuttering.

On the other hand, rCBF rates in the hippocampus, amygdala, the inferior, agranular portion of the insula and temporal pole, were negatively correlated with measures of dysfluent speech production. The notion that activity in these limbic and paralimbic structures may be in some way related to the generation of stuttering symptoms is not unexpected in a disorder in which symptoms are frequently coupled to stress or other emotional features. Future studies, in which quantified measures of anxiety or other affective parameters are correlated with rCBF rates during dysfluent speech production will help clarify the role played by these regions in the pathophysiology of stuttering.

Altered patterns of hemispheral lateralization

Ultimately, the contrast and correlational approaches converge in a broader fashion. Results from both suggest that the left and right hemispheres may play distinct and opposing roles in the generation of stuttering symptoms.

The notion of altered hemispheric dominance and proposed differences in the roles played by left and right hemispheres in the pathophysiology of stuttering have been the subject controversy since the concept was first advanced early in the 20th century (Orton, 1928; Travis, 1931). As noted previously, increased activity in the right hemisphere has been documented in developmental stutterers (for review *see* Moore, 1990), a finding which has been confirmed in the present study.

However, it has never been clear whether increased activity in the right hemisphere might be interfering with normal left hemispheric processing or compensating for left hemispheric dysfunction. The results of previous studies which utilized electrophysiological techniques or lower resolution blood-flow methods (Wood *et al*., 1980; Boberg *et al*., 1983) have been interpreted as suggesting that right hemispheric activity may be causally related to dysfluent speech production, and that activity in the left hemisphere may be augmented when stuttering is suppressed. However, such results have not been universally encountered (Pinsky and McAdam, 1980; Prescott and Andrews, 1984), and the present results rather strongly suggest the alternative.

In our study, both contrast and correlational analyses suggest left hemisphere dysfunction in this disorder (Tables 3A and 4; Figs 3 and 4); regions in which rCBF rates were positively coupled to the production of dysfluent

speech (i.e. orbital, cingulate, opercular as well as dorsolateral prefrontal cortices, striatum and ventral thalamus) were located almost exclusively within the left hemisphere. Activity in these regions increased, in our subjects, as speech became more dysfluent. Even in dorsolateral and medial prefrontal cortices, where bilateral increases over baseline motor activity were evident during both fluent and dysfluent language tasks (Table 2A and B), fluent–dysfluent contrasts and correlational analyses indicate that activity in the left hemisphere is exclusively related to stuttering (Table 3A and 4; Figs 3 and 4).

In addition, stuttering subjects never effectively activated sensory cortices within the temporal, parietal and occipital lobes (Table 2A and B), regions in which activity in control subjects was consistently and robustly lateralized to the left hemisphere. The functional dissociation, proposed above, between anterior regions involved in regulation of motor activity and posterior regions involved in sensory processing, may represent selective dysfunction of left hemispheric mechanisms in stuttering subjects.

On the other hand, rCBF rates in regions located almost exclusively in the right hemisphere (Table 4; Fig. 4) were negatively correlated with stuttering symptoms, i.e. activity in these regions increased, in our subjects, as speech became more fluent. It is therefore possible that activity in these regions may represent compensatory processes related to the production of fluent speech. In the auditory and posterior insular cortices, where bilateral increases were evident during fluent language tasks (Table 3A; Fig. 3), correlation analyses indicated that only activity in the right hemisphere was unequivocally related to fluent speech production (Table 4; Fig. 4).

As noted previously, primary auditory and auditory association cortices, insula and supramarginal gyrus each function at elementary levels of auditory processing, which may be carried out more effectively by stuttering subjects under fluency-evoking conditions. However, these regions also constitute the elements of a more widespread collateral system centred upon the posterior insula and extending along the anterior and posterior banks of the sylvian fissure. All of the elements of this distributed system (i.e. insular, auditory, somatosensory, and opercular cortices) were increasingly active in our stuttering subjects as their speech became more fluent. The interconnections of these regions (Mesulam and Mufson, 1985) suggest a mechanism by which their activation may bring about such an effect.

Auditory and somatosensory cortices (primary and secondary areas) project directly to the posterior insula, which appears to function as a parallel waystation for the integration of acoustic and somaesthetic information (Pandya *et al*., 1969; Mesulam and Mufson, 1982; Mufson and Mesulam, 1982). From there, projections carry information to premotor and higher order frontal association regions of the brain (Mesulam and Mufson, 1982). One such projection, to the frontal operculum, may provide an alternative neural relay between the temporoparietal cortices and anterior language regions (Mesulam and Mufson, 1985), and may subserve the roles proposed for the insula in language processing (Mazzocchi and Vignolo, 1979; Augustine, 1985) and the initiation of speech (Shuren, 1993). Indeed, even within the non-dominant hemisphere, an intact insula may be necessary for normal expressive speech production (Starkstein *et al*., 1988).

It is possible that, in individuals who stutter, these right hemispheric perisylvian regions constitute an auxiliary system which integrates auditory and orolingual-laryngeal somaesthetic information and provides a alternative relay to anterior forebrain areas. Once again, if stuttering symptoms are predicated on a dissociation of anterior motor and posterior sensory mechanisms, this system may effectively couple anterior and posterior regions within the right hemisphere during, and perhaps enabling, the production of fluent speech.

Previous neuroimaging studies in developmental stuttering

Four groups have reported results of functional neuroimaging studies in developmental stuttering, which in some instances overlap, and in other instances differ from our own. Wood *et al*. (1980), in an early activation study, estimated cortical blood flow in stuttering subjects using ^{133}Xe. Subjects were studied while reading aloud, on both placebo and the medication haloperidol, which was used to induce fluency. The results of this study differed from ours, as these investigators reported that increases in blood flow in the left hemisphere were associated with fluent speech production. These differences could be due to the fact that Wood *et al*. (1980) were studying fluency induced by a drug, i.e. they were evaluating a drug effect, and thus the results are not entirely comparable. In addition, their study was carried out in a small number of subjects, using a relatively low resolution technique.

Pool *et al*. (1991) reported asymmetries in rCBF in stuttering individuals in some of the same regions in which significant group differences were identified in the present study, i.e. ACC and superior temporal gyrus. However, theirs was a resting study, using SPECT (single photon emission computed tomography), so the results are again not directly comparable with our PET activation study. We did not detect any group differences in these or any other regions when stuttering subjects and controls were studied at rest.

The PET study by Wu *et al*. (1995) was also methodologically different from ours, utilizing fluorodeoxyglucose to estimate regional cerebral glucose metabolism with a significantly different temporal resolution. This group used a chorus reading task to induce fluency in order to compare stuttered with nonstuttered speech. They saw some condition dependent differences which paralleled our own: decreased activity in Wernicke's area and in the

frontal operculum during the stuttering condition when affected subjects were compared with controls. We did not see decreases in the frontal pole that were also reported. Wu *et al*. (1995) also reported reduced metabolic rates in the left caudate as a trait related feature in stuttering subjects, i.e. these decreases were observed whether subjects were fluent or dysfluent. While we did not see this precisely, we found similarly lateralized changes in the basal ganglia, i.e. increased activation of right caudate, which appeared to be trait related.

The study by Fox *et al*. (1996), an $H_2{}^{15}O$ activation study, is the most directly comparable with ours in terms of technique. Like Wu *et al*. (1995) this group used a chorus reading task to compare stuttered and nonstuttered speech. The most signifcant consistency in the findings of Fox *et al*. (1996) and the present study is the demonstration, in both instances, of right lateralized brain activity during stuttered speech, which did not normalize during fluent speech production. Some differences were also apparent. Fox found decreased activity in auditory cortices in stutterers when dysfluent, which reversed when they were fluent. However, we found the same pattern in control subjects when dysfluency-evoking tasks were compared with fluency-evoking tasks, suggesting that such changes may reflect differences in the cognitive or sensorimotor properties of the tasks themselves. In the Fox study, activation of the right auditory cortices was indeed observed in control subjects during the fluency-evoking (chorus reading) but not the dysfluency-evoking (solo reading) task. However, it was attributed, in this instance, to left ear auditory stimulation used during the chorus procedure. Fox also reported relative hyperactivity of the primary and extraprimary motor regions in stuttering subjects versus controls during the production of stuttered speech. However, we saw such differences during the performance of nonlanguage oral motor tasks, when stutterers were asymptomatic, suggesting that such changes may not be related to stuttering *per se*. Further studies may help clarify these issues.

Indeed, it will be by putting together and comparing the results from all of these studies, as well as those currently in progress, in essence as a qualitative meta-analysis, that a truly comprehensive picture of brain function in developmental stuttering may emerge.

Conclusions

The results of the present study provide the rudiments of a pathophysiological model for developmental stuttering.

Differences in rCBF between stuttering and control subjects in brain regions mediating motor activity in the left hemisphere, and sensory processing in the right, were evident even during the performance of a non-linguistic oral motor task, when subjects were symptom-free. These results suggest that there are underlying differences in sensorimotor function in stuttering subjects, a diathesis which may precede the development of overt stuttering symptoms.

Superimposed on this diathesis, propositional language, acting as a stressing, may precipitate stuttering symptoms, and it is only when speech content is linguistically meaningful that the major changes in regional cerebral activity are manifest. Cerebral organization for language, particularly as it relates to hemispheral lateralization, appears to be fundamentally altered in stuttering subjects. The normal pattern of left hemispheral dominance for language is not seen in these individuals, who either fail to activate left hemisphere neocortical areas which are normally engaged in language processing, or activate these regions bilaterally.

Viewed from another angle, the data suggest that, during the production of stuttered speech, there appears to be a functional dissociation between activity in post-rolandic regions, which play a role in perception and decoding of sensory (particularly auditory) information, and anterior forebrain regions, which play an a role in the regulation of motor function. Anterior regions were disproportionately active in stuttering subjects while post-rolandic regions were relatively silent. The posterior regions may somehow fail to provide the integrated sensory feedback upon which the anterior regions depend for efficient coordination of speech output.

Fluency-evoking tasks may attenuate the hypothesized imbalance by reducing ‘demand’ upon left hemispheric language areas and frontocingulate motor regions, while enhancing effective sensory processing within post-rolandic regions.

The right and left hemispheres appear to play distinct and opposing roles in the generation of stuttering symptoms. Both contrast and correlation analyses indicated that symptom production was associated with activation of anterior forebrain regions located almost exclusively in the left hemisphere. On the other hand, both anterior and posterior perisylvian areas of the right hemisphere were activated as subjects’ speech became more fluent, suggesting right hemisphere-mediated compensatory processes may be associated with the attenuation of stuttered speech—perhaps effectively coupling motor and sensory areas within the right hemisphere in subjects who were able to speak fluently, even under dysfluency-evoking conditions.

Taken together the foregoing may constitute a model in which a number of existing theories of stuttering, including those which have implicated language processing, hemispheral asymmetry, motor planning or sequencing and auditory feedback, can be integrated. All of these conclusions will require independent confirmation and further investigation driven by hypotheses generated in the present study.

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