Published in final edited form as:

Brain Lang. 2010 July ; 114(1): 43–51. doi:10.1016/j.bandl.2010.03.007.

Longitudinal cerebral blood flow changes during speech in hereditary ataxia

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Abstract

The hereditary ataxias constitute a group of degenerative diseases that progress over years or decades. With principal pathology involving the cerebellum, dysarthria is an early feature of many of the ataxias. Positron Emission Tomography was used to study regional cerebral blood flow changes during speech production over a 21 month period in a group of seven right-handed subjects with hereditary ataxia (6 females and 1 male, 3 SCA1 and 4 SCA5, aged 38.3 $\pm$ 18.9 years). The decline in blood flow was greatest in cerebellar regions. In contrast, blood flow actually increased during speech production in the classic speech area (Broca's area) but not in its right hemisphere homologue at the second evaluation. This increase in cortical flow may have been compensatory for cerebellar degeneration as speech intelligibility did not decline significantly during this period. Compensation was not complete, though, as syllable timing shifted in the direction of equal syllable duration, one of the characteristics of ataxic dysarthria. These results are consistent with previous functional imaging studies of ataxia demonstrating a pattern of brain activity that reflects both loss of function and relative compensation when clinical signs and symptoms are still mild. The combination of disease-relevant tasks, behavioral measurement, and functional imaging may provide insight into the early changes associated with neurodegenerative disease.

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Keywords

Ataxia; Speech; Dysarthria; Broca's area; Positron emission tomography; Cerebral blood flow; Cerebellum; Disease progression; Functional imaging

Introduction

The hereditary ataxias are a class of neurodegenerative diseases that progress over years or decades. As such, they present an opportunity to study functional reorganization in the central nervous system that may reflect both loss and compensation, a combination that can alter the relationship between clinical status and neuropathological change (Gilman *et al.* 1988; Rosenthal *et al.* 1988; Ormerod *et al.* 1994). Functional imaging techniques offer the possibility of studying brain changes associated with neurodegenerative disease progression, with the potential for new insights into brain-behavior relationships involving areas of primary neuropathology as well as secondary changes in other brain regions.

The limited number of functional imaging studies in ataxia demonstrate changes in patterns of regional cerebral metabolic rates for glucose (rCMRglu) and regional cerebral blood flow (rCBF) in both cerebellar and supratentorial regions. Regional cerebral glucose metabolism was studied as a function of disease stage in seven affected and seven individuals at risk for developing hereditary ataxia (Matthew *et al.* 1993) from a kindred subsequently identified as carrying the spino-cerebellar ataxia type 1 (SCA1) mutation (Orr *et al.* 1993). Compared to normal controls and at-risk subjects, there were significant reductions in cerebellar rCMRglu (30-40%) in the affected group (mean disease duration 7.7 years), and smaller reductions (approximately 10%) in the frontal lobes. Increases of 6-9% were found in temporal lobe regions, which may have been related to the use of an auditory attention task during scanning. A pattern of reduced cerebellar and increased cerebral metabolism was also reported in a mixed group of hereditary and ideopathic ataxic subjects as a function of disease progression (Rudolf *et al.* 2000). Both studies demonstrated that the early stages of progressive cerebellar ataxia reflect diminished cerebellar metabolism and regional changes in supratentorial function.

One of the common features of the hereditary ataxias is a progressive loss of motor speech control leading to dysarthria. A recent positron emission tomography (PET) study of speech production in hereditary ataxia (Sidtis *et al.* 2006) demonstrated that compared to normals, ataxic subjects had significant reductions in cerebellar blood flow during a speech production task (syllable repetition). Further, the flow increases during syllable repetition were significantly smaller in the ataxic group suggesting a diminished functional response range. When a performance-based analysis (PBA) was used to predict syllable rate from regional blood flow, the ataxic subjects had the same basic relationship between rate and blood flow: as rate increased, blood flow increased in Broca's area and decreased in the right caudate nucleus. In addition, the PBA also revealed that higher speech rates in ataxic subjects were associated with increased flow in the right cerebellum and decreased flow in the left superior temporal lobe.

When performance was taken into account, ataxia amplified the right cerebellum's role in speech production, which is evident in lesion studies (Ackermann *et al.* 1992; Amarenco *et al.* 1993; Urban *et al.* 2001; Urban *et al.* 2003) but not in average cerebral blood flow measured with PET or in hemodynamic activation responses measured by functional magnetic resonance imaging (fMRI) studies. When blood flow or hemodynamic responses are considered alone, bilateral responses are typical (Riecker *et al.* 2002a; Riecker *et al.* 2005, 2006; Sidtis *et al.* 2006; Urban *et al.* 2003). A rate analysis of the BOLD activation responses during syllable repetition in normal speakers demonstrated an increase in cerebellar response with rate like

that found with the PBA applied to PET data from the ataxic speakers, but the BOLD response was bilateral (Riecker *et al.* 2006). A similar discrepancy between the results of task contrasts and the PBA has also been found for the inferior frontal gyrus and is attributed to differences in image processing in the two approaches (Sidtis, 2007). The notion that neurological disease can amplify a functionally relevant imaging signal derives, in part, from discrepancies between the results of lesion studies and the results of functional imaging studies of specific behaviors in normal subjects. The amplification notion is also derived from the assumption that specialized brain systems operate with levels of biologic efficiency that make all of the constituent elements difficult to detect with functional imaging in normal situations. The result is that functional brain maps provide simplified accounts of complicated systems (Sidtis, 2007).

Increased speech rate in ataxic speakers was also associated with decreased flow in the left transverse temporal region. A meta-analysis of activation effects in speakers who stutter (Brown *et al.* 2005) suggested reduced activation in the superior temporal region in this population (e.g., Watson *et al.* 1992; Braun *et al.* 1997; De Nil *et al.* 2000; Fox *et al.* 2000; Van Borsel *et al.* 2003). Although brain regions identified in activation results do not necessarily reflect those identified by lesion studies (Sidtis *et al.* 1999) or PBA (Sidtis *et al.* 2003), both ataxic and stuttering speakers demonstrated reduced temporal lobe activity during speech. However, in the ataxic speakers, temporal lobe flow increased as speech rate decreased and higher blood flow in the left superior and transverse temporal areas was associated with more severe dysarthria. The latter finding suggests an increased role in auditory feedback in ataxic speakers. It may well be that the motor difficulties reflected in stuttering and ataxic dysarthria reflect different roles for auditory feedback and/or different brain responses during speech.

The present study was conducted to evaluate the effects of disease progression on the functional anatomy of speech in hereditary ataxia in the SCAs previously studied (Sidtis *et al.* 2006). A group of subjects with mild- to-moderate SCA1 or SCA5 (Ranum *et al.* 1994) were studied twice. Both SCA types are progressive, and both present with dysarthria as an early sign.

Methods

Subjects

This study was approved by the institutional review boards for studies involving human subjects at the University of Minnesota and the Minneapolis Veterans Affairs Medical Center. Subjects participated in this study as part of a multidisciplinary study of hereditary ataxia. Disordered speech was not a prerequisite for entry into the study. After research procedures and their possible consequences were explained, informed consent was obtained for each study. A group of seven right-handed volunteers with hereditary ataxia (6 females and 1 male, aged 38.3 ± 18.9 years) were studied twice over an average period of 20.9 months; there were three SCA1 subjects and four SCA5 subjects. All participants were native speakers of English. Subjects were screened to exclude confounding neurologic, psychiatric, and medical disorders, and to exclude current psychotropic medication or recreational drug use. Table 1 presents mean age, gender, speech rate (diadochokinetic or alternating movement rate, AMR) during syllable production while scanning, and dysarthria severity rating for both studies. Table 2 presents summary scores for upper and lower limb coordination, gait, and station from a standardized neurological examination. Disease duration is a difficult concept in the age of genotyping. Genetic testing allows SCA classification prior to the onset of clinical signs and symptoms that would warrant a diagnosis of idiopathic ataxia. For example, one of the SCA1 subjects entered the study at the time she underwent her initial genetic testing. Her neurological signs at the time were subtle, but notable given her familial risk for ataxia. She did not report significant symptoms. If hers was a case of idiopathic ataxia, she would likely not have come to medical

attention for several years. Additionally, disease progression and severity is not simply a function of duration of symptoms in SCA, as the time course varies with SCA type and the extent of genetic abnormality (e.g. number of trinucleotide repeats in SCA1). For severity of disease, it is most useful to consider the neurological findings in Table 2.

Behavioral Task

Subjects were studied with eyes covered, room lights dimmed, and insert earphones placed in each auditory canal. During each rest scan, subjects were required to remain awake, quiet, and still. The speech task consisted of the repetition of the syllable sequence /pa-ta-ka/, produced as quickly and clearly as possible, as performed in standard polysyllabic diadochokinesis (DDK) motor speech examination (Kent et al., 1987). DDK is sensitive to disordered speech performance in subjects with ataxic dysarthria when conducted using the repetition of a single syllable (Kent et al., 2000; Ziegler & Wessel, 1996) or the polysyllabic syllable sequence /pa-ta-ka/ (Schalling et al., 2008). The polysyllabic syllable sequence form has been used previously to develop a performance based model of functional image analysis (Sidtis et al., 2003, 2007), to describe the relationship between repetition rate and regional cerebral blood flow in hereditary ataxic speakers (Sidtis et al., 2006) and was sensitive to disease progression in spinocerebellar ataxia whereas the single syllable versions were not (Schalling et al., 2008). Subjects were instructed to take a deep breath, then produce as many syllable sequences as possible during expiration. Subjects repeated this process for 60 seconds. Syllable sequence repetitions were recorded during the scans for subsequent analyses.

Behavioral Measures

Speech recorded during each scan was used to determine syllable repetition rates. Dysarthria ratings were based on perceptual ratings of 10 masters students in speech pathology based on speech samples recorded during a standard examination performed prior to each scanning session (Sidtis et al., submitted). Perceptual rating scores had a possible range of 1 (normal) to 5 (most severe). There was a high degree of agreement between across the raters (Cronbach's $\alpha = 0.81$). The most prominent abnormal feature of the speech samples was articulation, followed by rate, rhythm, and prosody. Secondary features were articulatory breakdown, imprecise consonants, excessive and equal stress, and prolonged phonation. These were mild, but consistent with ataxic dysarthria. Recordings were digitized and measurements were made from waveforms (Mertus, 1984). Syllables were counted by identifying the initial bursts (confirmed by the onset of the subsequent vowels). Rates were determined by dividing the number of syllables produced in the 60 s period by the speaking time (60 s – pause time). Syllable duration was determined from the onset of the initial burst to the end of phonation or the onset of the initial burst of the subsequent syllable. Mean syllable durations and standard deviations were calculated for each syllable type separately across all repetitions during the 60 s production period.

PET Scanning

Bolus injection of [^{15}O] water was used as a marker of rCBF (Silbersweig et al. 1993). A Siemens-ECAT 953B tomograph acquired the images in 3D mode. Each study consisted of eight 90-second scans (four rest scans alternating with four speech scans) separated by an inter-scan interval of approximately 9 minutes. The speech task was performed for 60 seconds beginning at tracer injection. Subjects were thus engaged in the task for 10 to 15 seconds prior to the initiation of each scan, which was triggered when radioactivity reached the brain. This procedure has been reported in previous studies (e.g., Sidtis et al. 1999, 2003, 2004, 2006) and is based on the Silbersweig et al. (1993) technique. A detailed description of the image preprocessing, including intra- and intersubject alignment has been previously published (Strother et al. 1995).

Functional Imaging Measure

A set of 22 standard regions-of-interest (ROIs) was used for this protocol. This set was previously generated based on evidence of a significant regional change during this task or either of two other speech tasks (sustained phonation, repetitive lip closure) performed by a group of normal subjects (Sidtis *et al.* 1999). Homologous left/right pairs of regions were drawn to capture the anatomical regions in which signal changes occurred in any of the three tasks using an anatomical template generated from a multi-subject composite PET image superimposed on a reference anatomical MRI image. The ROI's were larger than the area of signal change, but did not extend beyond the anatomical region (e.g., head of the caudate). Several anatomic atlases were used as reference material in establishing the ROI boundaries (Maat *et al.* 1981; Matsui & Hirano, 1978; Ono *et al.* 1990; Tailairach & Tournoux, 1988). A threshold was applied to each ROI such that ROI values represented the mean of the upper 25% of voxel values (Rottenberg *et al.* 1991; Sidtis *et al.* 2003, 2006). Thresholding reduces the partial volume error in measuring blood flow but more importantly, allows for intrasubject variation in the locus of thresholded voxels within an anatomical region. The following regions (left and right) were examined: inferior, mid (including the dentate nucleus), and superior portions of cerebellum in horizontal planes, superior temporal gyrus (Brodmann's area 22, anterior and inferior to the transverse temporal gyrus), transverse temporal gyrus (Brodmann's area 41, Heschl's gyrus), putamen, caudate nucleus (head), thalamus, inferior frontal lobe (Brodmann's areas 44 and 45, including Broca's area), sensorimotor cortex (Brodmann's areas 3 and 4), and supplementary motor area (Brodmann's area 6). This region set has been used previously with this protocol (Sidtis *et al.* 1999; 2003; 2004; 2006). The set of ROIs were applied interactively to the PET images for each subject, allowing the automatically applied ROIs to be adjusted to conform to individual anatomical differences. The mean global activity (all voxels) from each scan was used to create volume-mean normalized measures of regional cerebral blood flow (vnrCBF). A set of ROI values and a volume mean were determined for each scan for each subject. Normalization factors were obtained by dividing the highest volume mean in the dataset by the volume mean of each scan; each subject's ROI values were then multiplied by his or her normalization factor for that scan. The use of volume normalized rCBF reduces irrelevant inter-subject variability due to global differences (Arnt *et al.* 1996; Sidtis *et al.* 2003). The reliability of these measures with the present task was assessed previously in a group of normal subjects who were studied twice (Sidtis *et al.*, 1999). The test-re-test correlations for blood flow changes during syllable repetition were significant [$r = 0.8$; $p < 0.001$]. Further, the relationship between syllable repetition rates and regional cerebral blood flow found in normal speakers using these methods (Sidtis *et al.*, 2003) was replicated in a group of ataxic speakers (Sidtis *et al.*, 2006).

Statistical Analyses

In order to compare regional activity across the first and second studies, an omnibus analysis of variance (ANOVA) was performed with time (first vs. second study), task (speech vs. rest), side (left vs. right), and regions as factors. Because of the large number of regions, separate ANOVAs were conducted with the rest and speech data for each left-right pair of ROIs with time and side as factors. Although these comparisons were planned, F -statistics with probabilities < 0.01 were considered significant. Pair-wise comparisons were conducted with appropriate t -tests.

Results

Subject Changes

The mean interval between studies was 20.9 months. Consequently, subjects were significantly older at their second study [$t(27) = -19.44$; $p < 0.001$]. Except for mild dysarthria and saccadic visual pursuit, two subjects (SCA1.2 and SCA1.3) had essentially normal neurological

examinations at each evaluation. Both were confirmed as SCA1 by genetic testing. In one subject (SCA1.1), finger-to-nose performance progressed from mild inaccuracy on left-sided testing to a bilateral abnormality. Two subjects (SCA5.2, SCA5.3) progressed to mild or moderate upper or lower limb incoordination.

Speech Changes

Summary measures for dysarthria ratings and syllable production rates are presented in Table 1. Only one subject (SCA5.3) had a higher dysarthria rating at the second evaluation than at the first (a change from 1 to 2). Analysis of the recorded speech samples revealed a 6% increase in average syllable rate from the first to the second study, a non-significant trend. For syllable duration, there was a significant interaction between evaluation time and place of articulation/position in the syllable sequence [$F(2,52) = 25.09$; $p < 0.001$]. This interaction is presented in Figure 1 (top), which depicts a significant reduction in the duration of the syllable /ka/ at the second evaluation [$t(26) = 5.31$; $p < 0.001$]. Comparable results were observed for the variability (standard deviations) of the syllable durations across repetitions (Figure 1, bottom), with a significant interaction between evaluation time and place of articulation/position in the syllable sequence [$F(2,52) = 17.99$; $p < 0.001$].

Regional Blood Flow Changes

An omnibus analysis of variance revealed main effects of evaluation time [$F(1,27) = 55.68$; $p < 0.001$], of speech vs. rest [$F(1,27) = 294.99$; $p < 0.001$], of side [$F(1,27) = 44.93$; $p < 0.001$], and of region [$F(10,270) = 53.08$; $p < 0.001$]. These main effects revealed that across all regions and both tasks, normalized flow was reduced by 1.5% at the second evaluation. Normalized flow was 2.6% higher during speech compared to rest and 2.2% higher across left-sided side regions compared to right-sided regions. There was also a significant interaction between time and side (across tasks) [$F(1,27) = 30.297$; $p < 0.001$] such that the decrease in flow over time on the right side (−2.1%) was significantly greater [$t(27) = -5.504$; $p < 0.001$] than the decrease on the left side (−0.9%). To clarify the effects of disease progression on regional flow, separate analyses were performed for each region with time and side as factors. The results were comparable for the speech and rest scans. This is consistent with our previous observations in normal speakers (Sidtis *et al.* 2004) demonstrating significant correlations between regional cerebral blood flow during a range of behavioral tasks, including the speech task used in this study, and their associated resting control states. Accordingly, the descriptions will focus on the speech data. For reference, regional flow values during speech for both evaluations are presented in Table 3. Figure 2 depicts the blood flow differences between the first and second evaluations during speech production for regions in which time was a significant factor.

Cerebellum—There were significant declines in flow during speech production between the first and second evaluations in the inferior [$F(1,27) = 21.92$; $p < 0.001$], mid [$F(1,27) = 14.41$; $p < 0.002$], and superior cerebellum [$F(1,27) = 15.09$; $p < 0.002$]. These results are presented in Figure 3. All seven subjects showed declines in cerebellar blood flow at the second evaluation. All individual differences between the first and second evaluations are significant ($p < 0.001$ except for left mid-cerebellum where $p < 0.01$). Flow was higher on the left than the right for the inferior [$F(1,27) = 16.55$; $p < 0.001$] and mid-cerebellar regions [$F(1,27) = 44.38$; $p < 0.001$], but there were no significant interactions between study time and asymmetry.

Inferior Frontal Region—Flow in this region, which includes Broca's area on the left side, has been shown to have a significant role in speaking rate in this task in both normal (Sidtis *et al.* 2003) and ataxic speakers (Sidtis *et al.* 2006). The effect of time alone was not significant, but it did interact with side [$F(1,27) = 66.64$; $p < 0.001$]. The left and right normalized CBF values for this region during speech at the first and second evaluations are presented in Figure 4. The interaction reflected opposite changes over time in the left and right inferior frontal

regions. Flow in the left inferior frontal region increased significantly from the first to the second evaluation during speech [$+3.6\%$; $t(27) = -3.27$; $p < 0.004$]. In contrast, normalized CBF in the right inferior frontal region decreased significantly over the same time period [-3.5% ; $t(27) = 4.32$; $p < 0.001$]. Six of the seven subjects demonstrated increased CBF in Broca's area.

Caudate Nucleus and Putamen—Normalized CBF in the right caudate nucleus has also been shown to have a significant role in speaking rate in this task in both normal (Sidtis *et al.* 2003) and ataxic speakers (Sidtis *et al.* 2006), but neither time nor side nor the interaction of time and side produced a significant effect on blood flow in the caudate nucleus. For the putamen, however, normalized CBF was greater on the left side compared to the right [$F(1,27) = 33.6$; $p < 0.001$]. There was also a significant interaction between side and time [$F(1,27) = 12.81$; $p < 0.002$] such that flow increased slightly over time in the left putamen and decreased slightly in the right putamen. These changes mimicked the changes in the inferior frontal region, but the changes in neither the left nor right putamen alone were significant.

Thalamus—There was a trend toward lower flow during the second evaluation in the thalamus [$F(1,27) = 5.03$; $p = 0.03$].

Superior Temporal Regions—Flow in the left transverse temporal region is associated with speech rate in ataxic speakers (Sidtis *et al.* 2006). Flow was greater on the left side than on the right side [$F(1,27) = 62.12$; $p < 0.001$] across evaluations, but there was no effect of time, nor did time interact with side. A similar pattern was observed for the superior temporal region [$F(1,27) = 14.29$; $p < 0.002$].

Sensorimotor Cortex—Flow was significantly greater on the left side across time [$F(1,27) = 194.92$; $p < 0.001$]. There was also a trend toward increased flow during the second evaluation [$F(1,27) = 5.93$; $p = 0.02$], but time did not interact with side.

Supplementary Motor Area—As with the sensorimotor cortex, normalized CBF was significantly greater on the left side across time [$F(1,27) = 24.30$; $p < 0.001$]. There was no significant effect of time, but there was a trend toward an interaction between time and side [$F(1,27) = 6.68$; $p < 0.015$]. This trend suggested that flow increases tended to be greater on the right side than on the left side during the second session [$t(27) = -2.34$; $p = 0.027$].

Performance Based Analysis: The Relationship Between Syllable Rate and Blood Flow

In a larger group of ataxic subjects, a PBA (Sidtis, 2006) found that syllable repetition rate was predicted by a linear combination of blood flow in the left inferior frontal gyrus, the left transverse temporal gyrus, the right caudate, and the right inferior cerebellar region. Flow increased with rate in the left inferior frontal and right cerebellar regions and decreased with rate in the left temporal and right caudate regions in this model. In the present study, syllable rates increased 6% from the first to second evaluations. In the brain areas related to speech rate, the right inferior cerebellum flow decreased 7%, the right caudate nucleus flow decreased 2%, the left transverse temporal gyrus flow was essentially unchanged (-0.5%), and the left inferior frontal gyrus flow increased 3.6%. Given these changes, the syllable rate model derived for ataxic speakers by the PBA (Sidtis *et al.* 2006) was applied to the relevant regional values for the first and second evaluations to determine if the predictive relationships were maintained.

Syllable rate = $(2.95 * \text{left inferior frontal gyrus}) + (-2.65 * \text{right caudate nucleus}) + (-2.47 * \text{left transverse temporal gyrus}) + (3.21 * \text{right inferior cerebellum})$

An ANOVA compared the actual and predicted syllable rates for the first and second evaluations and found no significant differences. For the first evaluation, the predicted rate was 4.1 syllables/sec while the actual rate was 4.0. For the second evaluation, the predicted rate was 4.0 while the actual rate was 4.2. Using the ataxic PBA model, it appears that the blood flow increases in Broca's area at the second evaluation compensated for the decreases in cerebellar blood flow. The possibility that the relationship between blood flow in the left inferior frontal gyrus and the right cerebellum was altered in ataxia was examined by comparing the relationship between these two areas in normal speakers (Sidtis *et al.*, 2003) and in the present group of ataxic subjects. Using a partial correlation to control for syllable rate, there was a significant inverse relationship between blood flow in the left inferior frontal gyrus and the right cerebellum [$r = -0.727$; $p < 0.001$] in normal speakers. This relationship was absent in the ataxic subjects at both evaluations. The normal cortical-cerebellar relationship during speech was altered by cerebellar degeneration.

Discussion

Over a 21 month interval, a group of seven subjects with hereditary ataxia experienced little change in motor function but manifested a small increase in syllable repetition rate and a change in syllable timing in the direction of equating syllable duration across syllable types, consistent with one of the characteristics of commonly used to describe ataxic dysarthria (Ackermann & Hertrich, 1994; Hartelius *et al.* 2000). In the subjects in this study, who were suffering from relatively early stages of cerebellar disease, the changes in speech timing and rhythm were reflected in an increased syllable rate. Schalling *et al.* (2008) studied progressive speech changes in nine Swedish ataxic speakers (1 SCA2, 3 SCA3, 2 SCA7, 3 unspecified) who were clinically more affected than the subjects in the present study. The Swedish study examined changes over an average of 33 months. As in the present study, the speech changes were also small. A 14% increase in syllable repetition rate over the study period did not reach significance but there was a significant 10% reduction in the duration of /pa-ta-ka/ and a significant change in the stress pattern. While the classic descriptions of ataxic dysarthria include slowing and irregular syllable repetition rates (Kent *et al.*, 2000), the study of genotyped SCA subjects undoubtedly provides a perspective on earlier, more subtle neuropathology than was possible in earlier studies in which the subjects suffered from a wide range of pathologies such as stroke, neurosurgical tumor resection, paraneoplastic syndrome, and multiple sclerosis (Kent *et al.*, 2000). It is conceivable from the various descriptions of ataxic dysarthria that progression moves from normal speech to speech in which syllables are produced with equal duration (Kent, Netsell & Abbs, 1979), to speech that contains irregular syllable timing (Kent *et al.*, 2000). Small increases in syllable rate, as observed in the present study and in the study by Schalling *et al.* may well occur as syllable durations equalize. The likelihood that as ataxia progresses, different features of dysarthria become prominent may account for some of the debate regarding the features of ataxic dysarthria (Ackermann & Hertrich, 1994; Hartelius, Runmarker, Andersen, & Nord, 2000). However, it may also be possible that the differences reflect the use of monosyllabic repetition versus polysyllabic repetition. Task effects can play a significant role in the assessment of disordered speech (D. Sidtis *et al.*, 2010).

Across all brain regions in this study, average blood flow was reduced by 1.5% at the second evaluation. Blood flow was generally higher during speech than rest and on the left side compared to the right. Reductions in blood flow over time were greater on the right side than the left. Blood flow was significantly reduced in all cerebellar regions during the second evaluation and all subjects showed cerebellar decreases. In contrast, there was a significant increase in flow in the left inferior frontal gyrus but a decrease in the homologous right-sided region during this time period. Six of the seven subjects showed increased flow in Broca's area at the second evaluation. This interaction between time and side was present to a lesser degree in the putamen. The sensorimotor cortex and supplementary motor areas showed trends

towards increased flow at the second evaluation, but the transverse and superior temporal regions did not. It should also be noted that the blood flow in the left inferior frontal gyrus and the right cerebellum during syllable repetition was abnormally uncoupled in the ataxic subjects at both evaluations.

The performance based analysis model relating syllable repetition rate and regional blood flow accurately predicted syllable rate at both evaluations. This raises the possibility that the increase in blood flow in Broca's area at the second evaluation was a compensatory response to the decreased blood flow in the right cerebellum. Consistent with the notion that ataxia affected the normal cortical-cerebellar relationship during speech, the significant relationship between blood flow in Broca's area and the right cerebellum found in normal speakers was absent in the ataxic speakers. In contrast, the absence of increased blood flow in the superior temporal region at the second evaluation, together with the previous observation that higher blood flow in this area on the left was associated with more severe dysarthria in ataxic speakers (Sidtis *et al.* 2006), suggests that auditory feedback was a limited compensatory mechanism in this task in progressive ataxia.

Changes in regional cerebral blood flow in areas not involved in primary pathology have been viewed as evidence of plasticity in functional brain organization. Such changes have been studied most often following stroke, but there is some uncertainty about their relationship to clinical status. Two types of changes have generally been reported: increased blood flow in areas adjacent to the damaged area and increased responses in the intact hemisphere in regions homotopic to the damaged area.

Recovery of hand function following unilateral striatocapsular motor stroke has provided some insights into functional plasticity. Recovery has been associated with normal blood flow in contralateral cortical motor areas and ipsilateral as well as contralateral cerebellum (Weiller *et al.* 1992), but bilateral blood flow changes may be the result of mirror-movements of the unaffected limb (Weiller *et al.* 1993). Unilateral movements of the recovered hand have also been associated with bilateral cerebral and cerebellar responses (Chollet *et al.* 1991; Cramer *et al.* 1997) as well as with bilateral flow increases in dorsolateral and medial premotor areas but not in the sensorimotor cortex of either hemisphere (Seitz *et al.* 1998). A crossed cerebral-cerebellar relationship was documented in a six month study of recovery from an acute stroke that caused unilateral arm weakness (Small *et al.* 2002). Good recovery of hand function was associated with a hemodynamic response in the cerebellum contralateral to the damaged cerebral hemisphere. This response was not found in patients with poor recovery. A transient hemodynamic response was also observed in the ipsilateral cerebellum, but this was independent of successful recovery. Although the data on bilateralization of function in limb recovery is mixed, motor recovery following stroke likely represents reorganization within a preexisting network rather than a radical substitution of function in different brain areas (Weiller, 1998).

Studies of recovery of language and speech function following stroke have generally been more positive about the possibility that recovery is due to bilateralization of function. Greater activation in the right inferior frontal region was found during word repetition in patients recovering from Wernicke's aphasia, but a similar asymmetry was also observed in the normal group (Weiller *et al.* 1995). A patient who recovered from dysarthria following a capsular infarction was described as having speech reorganized in the right-cerebral-hemisphere-left cerebellar system based on activations during covert speech, but bilateral inferior frontal gyrus and cerebellar responses during overt speech were observed both acutely and following recovery (Riecker *et al.* 2002b). A study of aphasic subjects with frontal, subcortical, or temporal lesions suggested that good language function was restored only if left hemisphere

areas were integrated into the functional network, but right hemisphere areas contributed to recovery if important left hemisphere regions were destroyed (Heiss *et al.* 1999).

The functional imaging data on plasticity remains somewhat mixed, but it does appear that a return to—or maintenance of—a relatively normal level of performance involves a restitution of the normal network with some degree of enhancement. The enhancement most commonly appears to consist of a larger area of activity near the areas normally involved in a behavior. The role of bilateralization is less clear. In the present study, it appears that an increase in activity in the left inferior frontal region compensated for decreased function in the right cerebellum, consistent with the claim that plasticity most often involves the normal network (Weiller, 1998). The plastic changes in the present study were not bilateral for speech production. This may indicate that a greater degree of lateralized cerebral specialization is required for speech production than for non-speech motor learning, or that different mechanisms compensate for losses of cerebellar versus striatal function (Jueptner & Weiller, 1998; Doyon *et al.* 2003).

Conclusion

In this study of progressive hereditary ataxias, blood flow during syllable repetition changed differentially over time in speech-related brain regions. As expected, the greatest declines in blood flow were in cerebellar regions; however, blood flow actually increased in Broca's area but not in its right-hemisphere homologue. Although speech intelligibility did not decline during this period, syllable timing changed in the direction of equal syllable durations, indicating that motor speech control was changing as well. These results are consistent with previous studies of progressive ataxia demonstrating that the pattern of brain activity reflects both loss of function and relative compensation at a time when clinical signs and symptoms are still mild. The plastic changes during syllable repetition occurred in left hemisphere motor areas and did not become bilateral. This may reflect the use of a strongly lateralized task, cerebellar degeneration, or both. The combination of disease-relevant tasks, behavioral measurement, and functional imaging may provide insight into the early changes associated with neurodegenerative diseases. This approach may also provide another perspective on the relative contributions of different brain areas in speech-motor control and on potential mechanisms of plasticity.

Acknowledgments

Support was provided by NIDCD R01 DC007658, PO1NS33718, P20 MH57180, the Parkinson's Disease Foundation, and the Bob Allison Ataxia Research Center. The helpful comments of Dr. D. Sidtis on earlier versions of this manuscript are gratefully acknowledged. The assistance of J. Anderson, D. Daly, M. Kneer, C. Farmer, D. Hamm, C. Erickson, K. Connaghan, M. Alberg, and J. Mahowald in scanning, data collection, acoustic analysis, and data processing is also gratefully acknowledged.

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Figure 1.

Group mean duration (top) and variability (standard deviation, bottom) $\pm$ one standard error of the mean (SEM) for the syllables /pa/, /ta/, and /ka/ repeated as the sequence /pa,ta,ka/ for the first and second evaluations. Means and standard deviations of durations for each syllable were calculated for each subject. Individual subject means and standard deviations were averaged to generate the group means and SEMs presented in this figure. Both the mean duration and variability for the syllable /ka/ were significantly reduced from the first to second evaluations.

Figure 2.

Percent difference scores for regions that changed significantly from the first to second evaluation as a main effect of time, in an interaction with time, or both. All of the cerebellar regions decreased over time while there were left sided increases and right sided decreases in the inferior frontal region and the putamen.

Figure 3.

Mean normalized CBF values (+ 1 SEM) in left and right cerebellar regions during speech production at the first and second evaluations. Note that if average blood flow alone is interpreted as an indicator of functional organization, the left greater than right flow values during speech are discordant with the results of lesion studies, which demonstrate a more significant role for the right cerebellum during speech production. In spite of the asymmetry in mean flow values, the right inferior cerebellum—but not the left—is a significant predictor of speech rate during syllable repetition.

Figure 4. Mean normalized CBF values (± 1 SEM) for the left and right inferior frontal regions during speech for the first and second evaluations. The interaction between time and side is reflected in a significant increase in left-sided CBF and a significant decrease in right-sided CBF in the inferior frontal gyrus.

Table 1

Subject characteristics, average perceptual ratings (dysarthria) of speech samples obtained during a clinical examination, and mean syllable (SYL) rates (mean syllables/sec $\pm$ 1 standard deviation) for the participants in this study. Perceptual ratings ranged from 1 (normal) to 5 (severe impairment). The subject identifier represents the SCA type, subject number, and visit number. The mean syllable rate increases slightly at the second evaluation, but three of the subjects have increased rates, three have decreased rates, and in one the rate was essentially unchanged.

SUBJECT ID	GENDER	AGE	DYSARTHRIA	MEAN SYL RATE
SCA1.1.1	F	21	1.3	4.65 $\pm$ 0.17
SCA1.1.2	-	23	1.4	4.68 $\pm$ 0.22
SCA1.2.1	F	22	1.2	3.75 $\pm$ 0.17
SCA1.2.2	-	23	1.2	4.95 $\pm$ 0.17
SCA1.3.1	F	18	1.1	3.83 $\pm$ 0.29
SCA1.3.2	-	21	1.1	3.68 $\pm$ 0.25
SCA5.1.1	M	66	2.6	3.38 $\pm$ 0.29
SCA5.1.2	-	68	2.4	3.25 $\pm$ 0.17
SCA5.2.1	F	64	1.9	3.75 $\pm$ 0.30
SCA5.2.2	-	66	2.0	4.08 $\pm$ 0.13
SCA5.3.1	F	37	1.2	5.03 $\pm$ 0.57
SCA5.3.2	-	39	2.0	4.90 $\pm$ 0.59
SCA5.4.1	F	40	1.3	3.20 $\pm$ 0.17
SCA5.4.2	-	42	1.3	3.93 $\pm$ 0.19
MEAN FIRST	6F/1M	38.3 $\pm$ 18.9	1.5 $\pm$ 0.5	3.97 $\pm$ 0.68
MEAN SECOND	-	40.3 $\pm$ 18.9	1.6 $\pm$ 0.5	4.21 $\pm$ 0.66

Table 2

Summary of features from the standard neurological examination performed at the first and second evaluations. Upper limb coordination was evaluated with the finger-to-nose test (F-to-N) and rapid alternating movements (RAM) of the hands. For the F-to-N test: 0 = normal, 1 = mildly inaccurate, 2 = mild tremor at endpoint, 3 = consistent tremor throughout movement. For the rapid alternating movement of the hands: 0 = normal, 1 = slow, 2 = irregular, 3 = slow and irregular. Lower limb coordination was assessed by having subjects move the heel of the foot down the shin (heel-knee-shin). For the heel-knee-shin test: 0 = normal, 1 = mild dysmetria with or without end tremor, 2 = moderate dysmetria (severe tremors before reaching the ankle), 3 = severe dysmetria (cannot place the ankle on the knee). For each rating, the number of subjects with that rating is followed by a letter indicating the more severely affected side: L (left), R (right), B (bilateral). Gait and station were characterized by assessing truncal stability and the width of the base during gait. Truncal stability was scored as follows: 0 = normal, 1 = mild-to-moderate oscillations of head/trunk, 2 = severe oscillations, 3 = unable to sit without support. Gait base was scored as follows: 0 = normal, 1 = mild widening (4 - 10 cm apart), 2 = moderate widening (10 - 30 cm apart), 3 = severe widening (> 30 cm apart).

ID	F-to-N		RAM		HEEL-KNEE-SHIN		TRUNCAL		GAIT	
	SIDE	SCORE	SIDE	SCORE	SIDE	SCORE	SIDE	SCORE	STABILITY	BASE
SCA1.1.1	L	1	L	1	-	0	-	0	1	0
SCA1.1.2	B	1	-	1	-	0	-	0	1	0
SCA1.2.1	-	0	-	0	-	0	-	0	0	0
SCA1.2.2	-	0	-	0	-	0	-	0	0	0
SCA1.3.1	-	0	-	0	-	0	-	0	0	0
SCA1.3.2	-	0	-	0	-	0	-	0	0	0
SCA5.1.1	B	2	B	2	B	1	B	1	2	3
SCA5.1.2	B	2	B	3	B	1	B	1	2	3
SCA5.2.1	-	0	L	2	B	1	B	1	0	1
SCA5.2.2	-	0	L	3	B	2	B	2	0	1
SCA5.3.1	-	0	-	0	B	1	B	1	0	0
SCA5.3.2	-	0	-	0	B	2	B	2	0	0
SCA5.4.1	-	0	-	0	B	1	B	1	1	1
SCA5.4.2	-	0	-	0	B	1	B	1	1	1

Table 3

Ataxic group mean normalized rCBF values (± 1 SD) for each region during speech production at the first and second evaluations. Each mean represents 28 observations.

REGION	FIRST SCAN		SECOND SCAN	
	LEFT	RIGHT	LEFT	RIGHT
inferior cerebellum	1.69 $\pm$ 0.12	1.67 $\pm$ 0.11	1.60 $\pm$ 0.06	1.55 $\pm$ 0.07
mid cerebellum	1.60 $\pm$ 0.12	1.57 $\pm$ 0.10	1.55 $\pm$ 0.11	1.50 $\pm$ 0.10
superior cerebellum	1.57 $\pm$ 0.12	1.56 $\pm$ 0.10	1.52 $\pm$ 0.12	1.51 $\pm$ 0.12
superior temporal	1.75 $\pm$ 0.07	1.70 $\pm$ 0.07	1.73 $\pm$ 0.12	1.69 $\pm$ 0.14
transverse temporal	1.73 $\pm$ 0.06	1.65 $\pm$ 0.06	1.72 $\pm$ 0.10	1.64 $\pm$ 0.08
putamen	1.74 $\pm$ 0.06	1.71 $\pm$ 0.05	1.75 $\pm$ 0.07	1.69 $\pm$ 0.09
caudate nucleus	1.65 $\pm$ 0.09	1.64 $\pm$ 0.09	1.63 $\pm$ 0.08	1.60 $\pm$ 0.10
thalamus	1.68 $\pm$ 0.07	1.68 $\pm$ 0.05	1.64 $\pm$ 0.08	1.67 $\pm$ 0.05
inferior frontal	1.65 $\pm$ 0.08	1.70 $\pm$ 0.07	1.71 $\pm$ 0.10	1.64 $\pm$ 0.07
sensorimotor	1.49 $\pm$ 0.06	1.44 $\pm$ 0.06	1.52 $\pm$ 0.06	1.46 $\pm$ 0.06
supplementary motor	1.54 $\pm$ 0.11	1.47 $\pm$ 0.10	1.56 $\pm$ 0.11	1.51 $\pm$ 0.07