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Short communication

Grey matter volume differences in the left caudate nucleus of people who stutter

Paul F. Sowman [a,b,c,*], Margaret Ryan [a,b], Blake W. Johnson [a,b], Greg Savage [b,e], Stephen Crain [b,d], Elisabeth Harrison [d], Erin Martin [a], Hana Burianová [f]

[a] Department of Cognitive Science, Macquarie University, New South Wales 2109, Australia
[b] Australian Research Council Centre of Excellence in Cognition and Its Disorders, Australia
[c] Perception and Action Research Centre, Faculty of Human Sciences, Macquarie University, New South Wales 2109, Australia
[d] Department of Linguistics, Macquarie University, New South Wales 2109, Australia
[e] Department of Psychology, Macquarie University, New South Wales 2109, Australia
[f] Centre for Advanced Imaging, The University of Queensland, Queensland 4072, Australia

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ABSTRACT

The cause of stuttering has many theoretical explanations. A number of research groups have suggested changes in the volume and/or function of the striatum as a causal agent. Two recent studies in children and one in adults who stutter (AWS) report differences in striatal volume compared that seen in controls; however, the laterality and nature of this anatomical volume difference is not consistent across studies. The current study investigated whether a reduction in striatal grey matter volume, comparable to that seen in children who stutter (CWS), would be found in AWS. Such a finding would support claims that an anatomical striatal anomaly plays a causal role in stuttering. We used voxel-based morphometry to examine the structure of the striatum in a group of AWS and compared it to that in a group of matched adult control subjects. Results showed a statistically significant group difference for the left caudate nucleus, with smaller mean volume in the group of AWS. The caudate nucleus, one of three main structures within the striatum, is thought to be critical for the planning and modulation of movement sequencing. The difference in striatal volume found here aligns with theoretical accounts of stuttering, which suggest it is a motor control disorder that arises from deficient articulatory movement selection and sequencing. Whilst the current study provides further evidence of a striatal volume difference in stuttering at the group level compared to controls, the significant overlap between AWS and controls suggests this difference is unlikely to be diagnostic of stuttering.

1. Introduction

An influential review by Alm (2004) puts forth a theoretical account of stuttering that has at its core a primary dysfunction in motoric cuing circuits subserved by the striatum – a significant subregion of the basal ganglia that consists of the caudate nucleus, putamen, and ventral striatum. More recently, in modeling the neural mechanisms of stuttering, the work of Civier, Bullock, Max, and Guenther (2013) posits a dysfunction in dopaminergic transmission mediated by the striatum. Such theoretical work builds on observations that lesions of the basal ganglia (BG) are associated with acquired stuttering (e.g. Carluer et al., 2000; Cipolotti, Bisiacchi, Denes, & Gallo, 1988; Kent & Rosenbek, 1982; Kono, Hirano, Ueda, & Nakajima, 1998; Ludlow, Rosenberg, Salazar, Grafman, & Smutok, 1987; Marsden, 1982; Marshall & Neuburger, 1987; Meyers, Hall, & Aram, 1990; Nebel, Reese, Deuschl, Mehdorn, & Volkmann, 2009; Soroker, Bar-Israel, Schechter, & Solzi, 1990; Tani & Sakai, 2011; Theys, De Nil, Thijs, van Wieringen, & Sunaert, 2013; Wallesch, 1990; Yoshida, 1989); and that there are commonalities between stuttering and other BG associated movement disorders such as Parkinson's disease (Anderson, Hughes, Rothi, Crucian, & Heilman, 1999) and Tourette syndrome (Ludlow & Loucks, 2003). Moreover, activations of the striatum correlate with measures of stuttering (Ingham et al., 2004; Toyomura, Fujii, & Kuriki, 2011), and functional imaging evidence suggests a critical role for the striatum in speech fluency (Ellfolk et al., 2014). Additional evidence of BG involvement in stuttering are the findings that the symptoms of stuttering may be alleviated by antidopaminergic drugs (Burns, Brady, & Kuruvilla, 1978; Rosenberger, Wheelden, & Kalotkin, 1976), and may be exacer-

* Corresponding author at: Department of Cognitive Science, Australian Hearing Hub, 16 University Avenue, Macquarie University, North Ryde, NSW 2109, Australia.
E-mail address: paul.sowman@mq.edu.au (P.F. Sowman).

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bated by dopamine agonists e.g. levodopa (Anderson et al., 1999). However, it is important to note that positive effects of amphetamine/methylphenidate administration (which enhance dopamine levels) in stuttering suggest that the relationship between stuttering and dopamine levels is not straightforward (e.g. see Devroey, Beerens, & Van De Vijver, 2012; Fish & Bowling, 1965; Rabaeys, Bijleveld, & Devroey, 2015). Furthermore, not all stutterers improve when taking dopamine antagonists (Brady, 1991).

When comparing brain activations during speech in adults who stutter (AWS) to those in adults who do not stutter (AWDS) using positron emission tomography, Wu et al. (1995) found that AWS exhibited less activity in the left caudate during both fluent and dysfluent speech. Furthermore, the same research group showed increased fluorodopa (a fluorinated form of L-DOPA used as a radiotracer to measure dopamine metabolism) uptake in the left caudate tail in AWS compared to AWDS (Wu, Riley, Maguire, Najafi, & Tang, 1997), albeit in a group of only three AWS. A number of more recent neuroimaging studies have also reported abnormal striatal activations or abnormal connections to/from striatal areas in AWS (e.g. Chang, Kenney, Loucks, & Ludlow, 2009; Chang & Zhu, 2013; Giraud et al., 2008; Lu, Chen, et al., 2010; Lu, Peng, et al., 2010; Lu et al., 2009).

Building on functional imaging evidence, three structural studies have uncovered alterations in striatal morphology that suggest a link between the aforementioned observations of abnormal striatal function, and striatal structure in stuttering. However, the laterality and nature of the abnormality reported varies between these studies. Two of these studies were conducted in children: Reduced grey matter volume relative to matched controls was found in the right caudate nuclei of right-handed boys who stutter (Foundas, Mock, Cindass, & Corey, 2013), and in the left putamen of children who stutter (CWS) (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2013). Lu, Peng, et al. (2010) also investigated grey matter volume (GMV) in the striatum and found increased GMV in the left putamen in AWS compared to AWDS.

While a study of children close to the onset of stuttering may provide the best indication of its cause, comparing differences in brain structure or function between child and adult studies can help elucidate whether and which differences in the adult brain are as a result of compensatory mechanisms and/or the stutter itself (Beal et al., 2013; Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Sato et al., 2011). Commonalities in volumetric deviations between CWS and AWS compared to controls would support the conclusion that such deviations might be causally related to stuttering. Conversely, if a volumetric change is found in CWS that is not seen in AWS, this would lend itself to the contention that either childhood stuttering can manifest as a different disorder to persistent developmental stuttering, or that neuroplasticity has compensated for the early abnormality in AWS. Such a situation may point to a different cause of stuttering than the striatal source proposed in the studies with children (e.g. Beal et al., 2013; Foundas et al., 2013). That Lu, Peng, et al. (2010) found an increase in GMV rather than the decrease found in the two studies with children raises the above concerns. Attempted replication of the Lu, Peng, et al. (2010) findings are therefore warranted.

The current study aimed to test the hypothesis that changes in striatal GMV, consistent with that seen in studies of CWS, will be seen in AWS. Such a finding would support a causal role for the striatum in stuttering. Using region-of-interest (ROI) voxel-based morphometry (VBM) we examined GMV in the striatum of both hemispheres in a group AWS, and compared them with a matched cohort of AWDS. We hypothesized that the striatum of AWS would exhibit a significant reduction in volume of grey matter, as was found in Foundas et al. (2013) and Beal et al. (2013).

2. Methods

Fifty-four adults (27 AWS and 27 AWDS) participated in the current study. The mean age (±SD) of the AWS was 45.9 ± 16 years and the AWDS 47.1 ± 15 years. There were seven female subjects and one left-handed male in each group. Control subjects (AWDS) had no history of stuttering.

Stuttering participants were recruited based on self-report as recommended by Guntupalli, Kalinowski, and Saltuklaroglu (2006), Guitar (2015), and Yairi and Seery (2015). Stuttering participants were asked to self-rate their current stuttering severity and the range of severities over which their stuttering could vary on a 10-point scale (1 = no stuttering, 10 = extremely severe). Age of stuttering onset, duration of stuttering, and information about any stuttering treatment was also recorded, along with any other relevant information offered by participants. 26 of the 27 stuttering participants had received a diagnosis of stuttering and 25 had undergone treatment for their stutter.[1] A ten-minute speech sample of conversational speech was audio-recorded to calculate stuttering severity (percent syllables stuttered) at the time of the investigation.[2] This sample was rated by a qualified speech pathologist. These data are summarized in Table 1. No participants (AWS or AWDS) had any history of any other speech, hearing, language or neurological illness.[3] All participants were fluent in English. Bilingual participants were included in the study and matched by languages spoken across experimental groups. All participants provided written informed consent and the research was approved by the Macquarie University Human Research Ethics Committee.

2.1. MRI data acquisition

Anatomical T1-weighted magnetic resonance images were acquired at Macquarie University Hospital, Sydney, using a 3 T Siemens Magnetom Verio scanner with a 12-channel head coil. Anatomical images were acquired using an MP-RAGE sequence (TR = 2000 ms, TE = 3.94 ms, FOV = 240 mm, voxel size = 0.94 mm^3, TI = 900, flip angle = 9°).

2.2. MRI preprocessing & data analysis

Structural images were processed using SPM8 (Wellcome Trust Centre for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm). All preprocessing steps were conducted using standard procedures implemented in the VBM toolbox of SPM8. All the steps for data processing were followed precisely as detailed by Ashburner (2010). Briefly, structural images were normalized, modulated, and smoothed with 8 mm full-width at half maximum (FWHM) kernel. This smoothing kernel has been used in recent VBM studies in stuttering (e.g. Beal et al., 2013; Chang et al., 2008) and is thought to represent the best balance between smoothness and the ability to facilitate inferences about regionally specific group

[1] The single participant who had not received a diagnosis of stuttering had presented as a control in another study. Substantial stutters were observed in his conversational speech by the three researchers present. This participant later reported a history of stuttering.

[2] In the percentage of syllables stuttered calculation, repetitions, prolongations and blocks were classed as stuttered syllables. Multiple repetitions on one syllable were classed as a single stutter, as per Guitar (2015).

[3] Participants were excluded if they had experienced, or were currently experiencing any other speech, hearing, language, cognitive, psychological or neurological disorder other than their stutter, or if they were on any neuroactive medication. 26 of the 27 participants can be classed as persistent developmental stutterers as their stuttering developed at age 12 or under. However, stuttering onset for one participant was at 19 years. It is possible that this participant's stutter was not developmental, but rather had a neurogenic or psychogenic cause (Guitar, 2015). Chang, Synnestvedt, Ostuni, and Ludlow (2010) found that similar neuroanatomical differences were seen in adult-onset stutterers as compared to persistent developmental stutterers.

Table 1
Subjects' information.

	Stuttering subjects	Non-stuttering subjects
Number	27	27
Male:Female	20:7	20:7
Chronological age	47.6 years	45.9 years

Detailed information about stuttering subjects

ID	Gender	Handedness	% Stuttered syllables	Usual SR	SR Range	Total no. syllables analysed	Speech rate (syllables/min.)	Age of onset (years)	Treatment
S1	F	R	3.9	*4*	*3–8*	1428	198	7	Y
S2	F	R	1.7	*3*	*1–9*	851	219	5	Y
S3	F	R	0	*2*	*2–5*	1960	273	3	Y
S4	F	R	0.8	*2–3*	*1–5*	2237	232	5	Y
S5	F	R	0.9	*2*	*2–4*	2311	258	5	Y
S6	F	R	3.4	*4*	*2–5*	1604	204	3	Y
S7	F	R	*4*	*4–5*	*3–10*	*a*	*a*	3	Y
S8	M	R	4.4	*6*	*4–7*	1477	221	5	Y
S9	M	R	0	*2*	*2–6*	1101	230	5	Y
S10	M	R	2.6	*3*	*2–4*	1862	220	5	Y
S11	M	R	4.8	*2*	*1–5*	2943	255	6	Y
S12	M	R	0.6	*2*	*1–4*	2351	264	5	Y
S13	M	R	2	*3.5*	*2–8*	1855	236	12	Y
S14	M	R	0.5	*2*	*2–4*	1650	212	9	Y
S15	M	R	3.1	*3*	*1–5*	1408	212	5	N
S16	M	R	0.6	*2*	*2–3*	2413	247	3	Y
S17	M	R	2.7	*4*	*2–6*	1184	236	5	Y
S18	M	R	0.7	*2–3*	*1–7*	2000	271	4	Y
S19	M	R	1 */2*	*1*	*1*	1897	227	5	N
S20	M	R	2.1	*4*	*1–7*	*a*	*a*	10	Y
S21	M	L	0.2	*2–3*	*1–6*	1689	231	5	Y
S22	M	R	9.4	*1–5*	*1–5*	1108	176	5	Y
S23	M	R	1	*3*	*1–7*	1668	241	7	Y
S24	M	R	3	*2–3*	*1–9*	2454	254	7	Y
S25	M	R	0.6	*3*	*2–6*	1422	270	5	Y
S26	M	R	1.1	*2–5*	*2–6*	1904	220	5	Y
S27	M	R	0.9	*1*	*1*	2258	278	19	Y

SR = severity rating. Severity ratings are italicised. *a* the speech pathologist did not, or was not able to record this data.

differences (Beal et al., 2013). Whilst smaller kernels (6 mm) enhance spatial specificity, such small kernel sizes are recommended for large groups ($n > 50$) and larger kernels (8–10 mm) are recommended as best for comparisons between groups of ~25 subjects each (Shen & Sterr, 2013).

The primary focus of the analyses was the effect of stuttering status on GMV within the striatum. We therefore defined an ROI to represent the bilateral striatum which included the body, head, and tail of the caudate nucleus, the putamen and the nucleus accumbens region of the ventral striatum. The ROI was constructed using the IBASPM parcellation atlas in the WFU PickAtlas Standard Atlases tool (Alemán-Gómez, Melie-García, & Valdés-Hernandez, 2006). Statistical tests were performed using SPM routines. An absolute threshold mask of 0.2 was applied and the striatal ROI was included as an explicit mask in the second level statistical analysis comparing AWS with AWDS. Independent two-sample *t*-tests were used to test for statistically significant differences between the categorical variable Group (AWS vs. AWDS). Subjects' ages (demeaned) and total GMV were modeled as nuisance covariates (Tae, Kim, Lee, & Nam, 2009). Statistical parametric maps thus derived were thresholded voxelwise at $p = 0.05$ [corrected by family-wise error (FWE)] level. A further exploratory whole-brain analysis was conducted at a relaxed, uncorrected threshold of $p = 0.001$.

3. Results

Overall total volume of grey matter was not different between groups: 710 mL for AWDS vs. 707 mL for AWS ($p = 0.86$). ROI analysis revealed a single significant cluster (extent = 201 voxels) of reduced GMV within the striatum of AWS compared with AWDS. The peak of this cluster ($p = 0.002$, $Z = 4.18$) was located in the left caudate body at −18, 12, 17 (MNI coordinates) (Fig. 1). There were no significant regions of increased grey matter for AWS compared with AWDS within the striatal ROI.

4. Discussion

The current study adds weight to the contention that stuttering is linked to striatal volume. We show that, on a group level, the left caudate nucleus, an area critical for movement sequencing and speech fluency (e.g., Gerardin et al., 2004), contains reduced GMV in AWS compared to a group of matched controls. That striatal dysfunction might underlie stuttering is a proposition that has long been favoured by some researchers (e.g. Alm, 2004; Maguire, Riley, & Yu, 2002). Alm (2004), introduced a theoretical framework for stuttering which claims that dysfunction in internal timing circuits that cue movements, (likely to also be important for prosody; see e.g. Schirmer, 2004; Schirmer, Alter, Kotz, & Friederici, 2001), is at the core of the disorder. Alm's theoretical work, recently extended by Etchell, Johnson, and Sowman (2014a), provides converging evidence from neuroimaging studies which show a significant degree of overlap between the structures that underpin internal timing of movement and those brain regions proposed to be causally involved in stuttering. Central to this proposed timing network is the striatum – albeit with a primary focus on the putamen which seems to be the most active part of the striatum during motoric timing tasks (Coull, Cheng, & Meck, 2011). The complex connections of the striatum mean its precise role in the control of speech fluency has not yet been completely elucidated, however, there is general agreement that it plays a central role in selection and sequencing of motor programs (e.g., Gerardin et al., 2004). A

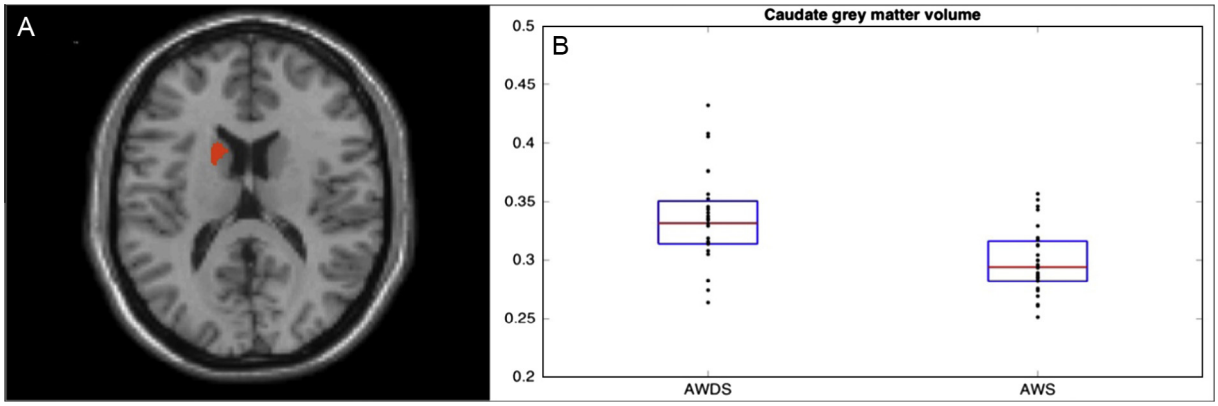

Fig. 1. A. Reduced striatal grey matter in stuttering. Red area indicates significantly reduced grey matter in AWS compared with AWDS. Image thresholded at t = 3.43 ($p < 0.05$, FWE-corrected) and overlaid on the single subject template brain (single_subj_T1) from the SPM8 toolbox. B. Individual subject GMV values extracted using the volume displayed in A as a mask. Black dots correspond to individual subject grey matter mean intensities within the mask, blue box represents the interquartile range and the red horizontal line the group mean. Considerable overlap between groups is evident.

deficit in striatally mediated timing circuits would be expected to manifest beyond the domain of speech and it is therefore important to note that a number of recent studies in CWS suggest that general temporal sequencing deficits are indeed evident in stuttering (Etchell, Ryan, Martin, Johnson, & Sowman, 2015; Falk, Muller, & Dalla Bella, 2015; Wieland, McAuley, Dilley, & Chang, 2015; for review see Etchell, Johnson, & Sowman, 2014b). Temporal sequencing is a defining feature of fluent speech production, and in this regard it has been shown that the striatum, and particularly the left caudate nucleus, is involved in the perception of prosody (Wittfoth et al., 2010), the suppression of irrelevant words (Ali, Green, Kherif, Devlin, & Price, 2010), the production of multisyllabic utterances (Soros et al., 2006), and speech rate (Riecker, Kassubek, Groschel, Grodd, & Ackermann, 2006; Riecker et al., 2005). Our finding that the grey matter in the left caudate nucleus may be compromised in AWS fits well with the proposed behavioural relevance of the caudate nucleus in speech (Bohland, Bullock, & Guenther, 2010) and the typical symptomatology of stuttering that includes failure of speech initiation (blocking) and sound and syllable repetition. Furthermore, a number of studies have implicated the left caudate in the development of stuttering acquired secondary to lesions (Caplan et al., 1990; Carluer et al., 2000; Ciabarra, Elkind, Roberts, & Marshall, 2000; Kono et al., 1998; Kumral, Evyapan, & Balkir, 1999; Theys et al., 2013) or in relationships between developmental stuttering and levels of functional activation (Giraud et al., 2008; Ingham, Grafton, Bothe, & Ingham, 2012; Toyomura et al., 2011; Wu et al., 1995, 1997). We know of only one other report of significantly reduced GMV in left caudate in AWS, however full details of this study are not available (Milford et al., 2012).

The striatal volume deviation reported in this study fits well with some theories of stuttering, and on the surface, seems to be consistent with previous findings. However, the inconsistency between the location of the difference between AWS and controls found here, and that reported in the previous studies needs to be discussed. Foundas et al. (2013) also found reduced caudate volume in their study of boys who stutter, but the reduction in their study was right lateralised compared to our finding of a left lateralised difference. Beal et al. (2013) found comparable left lateralized GMV reduction in their study of children who stutter, however this was located in the adjacent putamen, rather than the caudate. Lu, Peng et al.'s study of AWS found *increased* rather than *decreased* GMV in the putamen. Moreover, several studies of grey matter morphology have not found differences between groups in the striatum (Beal, Gracco, Lafaille, & De Nil, 2007; Chang et al., 2008; Kell et al., 2009; Song et al., 2007) and, in one instance, failed to find any difference in grey matter at all (Jancke, Hanggi, & Steinmetz, 2004). How then to explain these different findings? The most likely sources of such differing findings can be traced back to the significantly different profiles of the groups tested and also the different analytic methodologies used. For example, findings in the study by Foundas et al. show that more severe stutterers tend to show greater volume in their left caudate as compared to the right, whereas, milder stutterers and controls, tended to show a larger right caudate volume as compared to the left. As many of the subjects in the current study were at the milder end of the stuttering continuum, it is possible we have measured a more right-lateralized group on average. Perhaps differential levels of stuttering severity are reflected in the laterality of striatal volume differences. Methodology-wise, Foundas et al. (2013) present caudate volumes as a percentage of total hemispheric volume. It is therefore possible that reductions in other left hemisphere language areas (see e.g. Chang et al., 2008) might have mitigated the effects of any absolute volume reductions in the left caudate. Furthermore, the obvious differences in age and gender characteristics are a likely source of variation from our results (Raz et al., 2003). As noted by Beal et al. (2013), the relationship between gender and brain structure development is not well understood, but androgen exposure may have an impact on striatal grey matter volumes (Goddings et al., 2014; Herting et al., 2014; Mueller et al., 2011). This factor is important to consider when assessing the results of Lu, Peng, et al. (2010) whose study found increased GMV in the putamen of AWS compared to AWDS, as their stuttering cohort consisted of a higher proportion (5/6) of males than the control sample (3/4). Furthermore, only four of the participants (1/3) in the Lu, Peng, et al. (2010) study had received speech treatment. In contrast, almost all of the subjects in our study had received treatment, raising the possibility that compensatory techniques learned in speech therapy might have altered the distribution of grey matter in the striatum as a compensatory mechanism. Given that Beal et al. (2013) and Foundas et al. (2013) report on children and Lu, Peng, et al. (2010) on largely untreated AWS, this is another source of potential difference between theirs and our results. Foundas et al. (2013) did not report whether their participants had undergone stuttering treatment. However, their differential finding of reduced right caudate volume as compared to the left-lateralised reduction in this study may have been as a result of differential participant demographics. Foundas et al. (2013) calculated the degree of right-handedness of their participants, whereas only the dominant hand was recorded in this study. This study included one left-handed participant, albeit in both control and stuttering groups. It is therefore

Table 2
Regions of significantly different GMV for AWS relative to AWDS from the whole-brain voxel-based morphometry analysis at $p < 0.001$ uncorrected.

Contrast	Cluster	Peak MNI coordinate	Structures (AAL)	Associated Brodmann areas	Number of Voxels
AWS > AWDS	1	−34.5 −19.5 −24			648
			L Fusiform	36	434
			L Hippocampus	20	87
			L Parahippocampal		83
			L Inferior Temporal		5
	2	36 −22.5 −27			479
			R Fusiform	36	223
			R Parahippocampal	20	169
			R Hippocampus		39
			R Cerebellum		12
			Amygdala		1
	3	48 −22.5 −1.5			303
			R Superior Temporal	22	172
			R Middle Temporal	21	127
AWDS > AWS	1	−18 12 16.5			244
			L Caudate		208
			L Putamen		9

possible that the participants in Foundas et al.'s were slightly more left hemisphere dominant than our subjects. In fact, Foundas et al. found that nine of their fourteen children who stuttered had both atypical caudate asymmetry and atypical manual laterality. In addition, our study included seven females in both the stuttering and control groups, which may also have impacted on striatal laterality which is known to be functionally different in females compared to males (Martin-Soelch et al., 2011; Zaidi, 2010). As noted above, the relationship between gender and also handedness with brain structure development is not well understood (Beal et al., 2013).

Finally, the comparatively low numbers of subjects that tend to be reported in such studies is cause for a cautious approach when assessing the consistency or lack thereof in anatomical studies of stuttering. Shen and Sterr (2013) state that the results of their study demonstrate that a group size of 25 is the lower limit for finding a between group difference when two different groups of participants are compared (at least for studies that use the DARTEL method). Whilst the current study meets that criteria, the apparent heterogeneity of the subjects suggests that more subjects would be appropriate. Certainly, the comparatively small numbers reported in the studies of Lu, Peng, et al. (2010); 12 AWS vs. 12 AWDS, Foundas et al. (2013); 14 CWS vs. 14 CWDS, and Beal et al. (2013); 11 CWS vs. 11 CWDS, preclude any report to date from being the definitive description, and highlights the need for a more consistent methodological approach across studies such that data might be appropriately pooled in future meta-analyses. The data to date are methodologically inconsistent in a number of areas. Whilst most have used largely automated methods based on different flavours of the VBM approach (Beal et al., 2007, 2013; Chang et al., 2009; Jancke et al., 2004; Lu, Peng, et al., 2010; Milford et al., 2012; Song et al., 2007), notably Foundas et al. (2013), used a manual tracing approach. The automated methods include many parameters that may be varied and have the possibility of generating different outcomes. For example, the size of the kernels used to smooth the grey matter maps varies from 3 mm (Lu, Peng, et al., 2010) to 10 mm (Beal et al., 2007). Given that the spatial extent of significant findings generally increases with the size of the smoothing kernel, the difference in the location of grey matter volume reductions within small anatomical structures such as the striatum could be significantly affected by the choice of smoothing kernel. Shen and Sterr (2013), recommend that a small kernel of 6 mm is appropriate for studies comparing groups where there are approximate 50 subjects in each, but that studies at the lower limit (~25 in each group) should use a kernel of 8–10 mm. When assessing the results of uncorrected results in particular, this is of especial significance. Poldrack et al. (2008) caution that the risk of false-positives in uncorrected data depends on its smoothness. Therefore, whilst we present results of uncorrected whole-brain analysis primarily for comparison with other studies (see Table 2), we caution against any conclusions being drawn from these uncorrected results.

The findings of this study, that the reduction in GMV in the striatum seen in CWS, can also be seen in AWS, adds weight to evidence that nominates the area as playing a causal role in stuttering. This finding is supported by Beal et al.'s (2013) work, who showed that a group of young male AWS spanning from early in stuttering development at age 6, to a later age of 12, had reduced left striatal GMV. Whilst the degree to which these findings are in fact consistent with each other must be weighed carefully; the methodological inconsistencies between the studies could explain slight differences in precise anatomical locations between the studies. Our uncorrected results show that whilst the peak difference in the striatum was located in the caudate, the spatial extent of the cluster encroaches into the adjacent putamen. It is unknown the extent to which individual differences in gender, handedness, or extent of treatment impact on brain structure. Further studies engaging a longitudinal component that examine GMV in children early in stuttering development, then again periodically at later stages of adolescence and adulthood, could aid, not only in separating the causal from the reactive aspects of striatal differences in stuttering, but also control for these individual differences.

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