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Stuttering as a trait or state – an ALE meta-analysis of neuroimaging studies

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Abstract

Stuttering is a speech disorder characterised by repetitions, prolongations and blocks that disrupt the forward movement of speech. An earlier meta-analysis of brain imaging studies of stuttering (Brown *et al.*, 2005) revealed a general trend towards rightward lateralization of brain activations and hyperactivity in the larynx motor cortex bilaterally. The present study sought not only to update that meta-analysis with recent work but to introduce an important distinction not present in the first study, namely the difference between 'trait' and 'state' stuttering. The analysis of trait stuttering compares people who stutter (PWS) with people who do not stutter when behaviour is controlled for, i.e., when speech is fluent in both groups. In contrast, the analysis of state stuttering examines PWS during episodes of stuttered speech compared with episodes of fluent speech. Seventeen studies were analysed using activation likelihood estimation. Trait stuttering was characterised by the well-known rightward shift in lateralization for language and speech areas. State stuttering revealed a more diverse pattern. Abnormal activation of larynx and lip motor cortex was common to the two analyses. State stuttering was associated with overactivation in the right hemisphere larynx and lip motor cortex. Trait stuttering was associated with overactivation of lip motor cortex in the right hemisphere but underactivation of larynx motor cortex in the left hemisphere. These results support a large literature highlighting laryngeal and lip involvement in the symptomatology of stuttering, and disambiguate two possible sources of activation in neuroimaging studies of persistent developmental stuttering.

Introduction

Stuttering is a disorder characterised by speech with involuntary repetitions, prolongations, hesitations and blocks at the levels of syllables and words (Wingate, 1964). Theories of stuttering attribute its etiology to a wide variety of factors, including disordered sensory feedback (Max *et al.*, 2004), linguistic deficits (Postma & Kolk, 1993; Howell, 2004), anticipation of speech difficulties (Brocklehurst *et al.*, 2013), generalised motor deficits (Forster & Webster, 2001) and/or speech-specific motor deficits (Namasivayam & van Lieshout, 2011), including a strong genetic influence (see review by Kraft & Yairi, 2012). An activation likelihood estimation (ALE) meta-analysis of the neuroimaging literature on persistent developmental stuttering (Brown *et al.*, 2005) provided support for a diversity of underlying mechanisms, including overactivation of motor areas, underactivation of auditory areas, and anomalous right-hemisphere activation in regions not seen in fluent individuals.

However, research on stuttering frequently distinguishes between the person who stutters (i.e., 'trait' stuttering) and the act of stuttering (i.e., 'state' stuttering). An important question that comes from the observation of activation differences between people who stutter (PWS) and people who do not stutter (PWNS) is whether these differences are episodic, i.e., occurring only during bouts of stuttering, or whether they are stable features of the brains of PWS.

Stuttering is characterised not only by a propensity to produce stuttered speech but by abnormalities in speech motor control (Namasivayam & van Lieshout, 2011), non-speech motor skills (Neef *et al.*, 2011a), auditory-processing abilities (Toscher & Rupp, 1978) and possibly language abilities (Ntourou *et al.*, 2011; although see Nippold, 2012 for a refutation of this association). However, PWS do not always stutter. Stuttering occurs episodically, and the fluency state of a person who stutters is modulated by a broad array of contextual factors. PWS stutter more when speech difficulty is anticipated (Rappaport & Bloodstein, 1971), when using contrastive stress (Klouda & Cooper, 1988), and at the onset of voicing (Adams & Reis, 1971). PWS stutter less when they speak in a whisper (Commodore & Cooper, 1978), speak quietly, slowly (Johnson & Rosen, 1937) or with prior rehearsal (Brenner *et al.*, 1972), when they sing, speak rhythmically to a metronome or in chorus with a recording of the text they are reading aloud (Davidow *et al.*, 2009), when they speak in the presence of auditory noise (Garber & Martin, 1977), or when auditory feedback is altered (Stuart *et al.*, 1997). Stuttering,

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therefore, presents the paradoxical picture that, while a propensity to stutter is a relatively constant trait, a person's state of fluency can be modulated by a host of contextual factors that can provide immediate, although transient, remediation from stuttering.

We carried out an updated ALE meta-analysis of the neuroimaging literature on developmental stuttering that incorporated this important trait–state distinction. In particular, the analysis of trait stuttering compares PWS with PWNS when behaviour is controlled for, i.e., when speech is fluent in both groups. In contrast, the analysis of state stuttering examines PWS during episodes of stuttered speech compared with episodes of fluent speech.

Methods

Activation likelihood estimation is a meta-analytic technique for ascertaining the regions of concordant activation across a corpus of brain imaging studies (Turkeltaub *et al.*, 2002). Each activation focus is modeled as a three-dimensional Gaussian probability distribution whose width is determined by the size of the subject group so as to reflect increasing certainty with increasing sample size (Eickhoff *et al.*, 2009). Maps of activation likelihoods are created for each study by taking the maximum probability of activation at each voxel. A random-effects analysis then tests for the convergence of activations across studies vis-a-vis a null hypothesis of spatially independent brain activations.

General inclusion criteria

Published studies were searched using the Web of Knowledge and Pubmed databases with the search terms 'stuttering + fMRI' and 'stuttering + PET', where fMRI refers to functional magnetic resonance imaging and PET refers to positron emission tomography. The reference sections of the retrieved publications were searched for additional studies. To be included in the meta-analyses, studies had to (i) be published in a peer-reviewed scientific journal, (ii) report coordinate-based analyses of the data in a standard stereotaxic space, (iii) image the whole brain or nearly the whole brain, (iv) scan developmental stutterers and (v) have subjects perform overt speech tasks. The search returned 34 publications, 24 of which met our inclusion criteria. Several of the remaining articles reported previously published data and therefore did not contribute independent results to the data set. These data were combined according to subject group, as recommended by Turkeltaub *et al.* (2011). One study reported data for individual subjects but no group-level analysis (Wymbs *et al.*, 2013). Single-subject data were treated as individual experiments with $n = 1$. The present analysis included data from 21 unique subject groups reported across 18 publications, totaling 213 PWS and 186 PWNS. In all but one study, participants were audio-recorded during speech tasks in the scanner. The exception was Howell *et al.* (2012) who nonetheless determined the absence of stuttering by ear. MNI coordinates were transformed to Talairach coordinates (Talairach & Tournoux, 1988). ALE analyses were carried out using GingerALE 2.3, employing the False Discovery Rate correction for multiple comparisons ($P < 0.01$), with a cluster threshold $k > 10$.

Trait vs. state stuttering

Experiments were subdivided into those that examined stuttering as a stable trait and those that examined it as an episodic state (Fig. 1). The meta-analysis of trait stuttering included contrasts between PWS and PWNS when both spoke fluently. To be included in the analysis of trait stuttering, studies had to pass two additional criteria: (i) they had to confirm that all participants spoke fluently during image collection and (ii) they had to report either direct contrasts between brain images of PWS while they spoke fluently vs. PWNS speaking under matched conditions, or report correlations between brain imaging data and stuttering severity, as measured outside the scanner ($n = 8$ for overactivation and $n = 9$ for underactivation relative to PWNS). These studies reveal stable neural features of PWS during fluent speech.

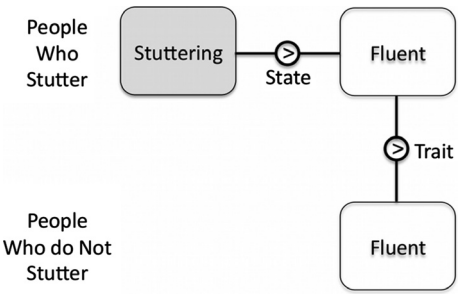

FIG. 1. Operational definitions of trait and state stuttering. Trait stuttering is revealed by contrasts between PWS and PWNS during fluent speech (PWS fluent > PWNS fluent). It is a between-group comparison. State stuttering is revealed by contrasts within PWS during stuttered vs. fluent speech (PWS stuttering > PWS fluent). It is a within-group comparison.

The meta-analysis of state stuttering included contrasts exclusively for PWS, and examined when PWS stuttered compared to when they spoke fluently. To be included in the analysis of state stuttering, studies had to pass two additional criteria: (i) confirm that PWS stuttered during image collection in stuttering conditions but not in fluent conditions and (ii) report direct contrasts between brain images while PWS stuttered vs. when they spoke fluently, or report correlations between brain images and rates of stuttering in the scanner. All state-stuttering contrasts included one scan in which PWS stuttered, although some of the earlier studies contained stutters embedded in otherwise fluent speech. Those studies might best be described as capturing speech that is prone to stuttering rather than stuttering *per se*. Nonetheless, to the extent that those stuttering scans were diluted by fluent speech, comparisons between these scans and scans containing only fluent speech are conservative in that they should underestimate differences between stuttered and fluent speech production. Table 1 lists the tasks performed in each study and the rate of stuttering for each study where applicable. These studies reveal the neural features associated with episodes of stuttering ($n = 10$ for overactivation and $n = 8$ for underactivation relative to fluent speech).

The analyses of both trait and state stuttering included brain-imaging data on PWS while they spoke fluently (see scheme in Fig. 1). In two studies contributing to these analyses, fluency was achieved by instructing participants to speak with a metronome (Braun *et al.*, 1997; Toyomura *et al.*, 2011), speak over-learned content (Braun *et al.*, 1997), or speak in chorus with another speaker (Toyomura *et al.*, 2011), all of which facilitated fluency (see Table 1). In these cases, experimental conditions and behaviour were matched between PWS and PWNS. However, in most of the studies contributing to our analyses, participants were spontaneously fluent. Spontaneous fluency may occur when speech tasks are restricted to short utterances or when scanner noise facilitates fluency. Some studies made no attempt to manipulate stuttering, but instead classified utterances as stuttered or fluent following data collection (i.e., den Ouden *et al.*, 2013; Wymbs *et al.*, 2013).

TABLE 1. Summary of studies included in the meta-analyses

Study	Trait +	Trait –	State +	State –	Stuttering task	Fluent task	Correlation
Trait stuttering							
Braun *et al.* (1997)	X	X			–	Overlearned, paced speech	–
Neumann *et al.* (2003)	X	X			–	Reading short sentences	–
Preibisch *et al.* (2003)	X	X			–	Reading short sentences	–
Giraud *et al.* (2008)	X	X			–	Reading short sentences	Severity
De Nil *et al.* (2008)	X	X			–	Word repetition	–
Chang *et al.* (2009)	X	X			–	Monosyllable repetition	–
Kell *et al.* (2009)	X	X			–	Reading short sentences	–
Sakai *et al.* (2009)		X			–	Reading short sentences	–
Lu *et al.* (2010)	X	X			–	Reading single words	–
Howell *et al.* (2012)	X	X			–	Reading single words	–
State stuttering							
Braun *et al.* (1997)			X	X	Recount narrative/sentence generation*	Overlearned/paced speech	Rate
Fox *et al.* (2000)			X		Reading paragraphs (62%)†	–	Rate
Ingham *et al.* (2004)			X	X	Reading paragraphs (73%)†	–	Rate
Toyomura *et al.* (2011)				X	Reading short sentences (2.5%)‡	Chorus/paced speech	–
Ingham *et al.* (2012b)			X	X	Paragraphs/narrative (9.75/8.84%)§	–	Rate
Jiang *et al.* (2012)			X	X	Sentence completion (100%)§	Sentence completion	–
Wymbs *et al.* (2013)			X	X	Reading words (100%)§	Reading words	–
den Ouden *et al.* (2013)			X	X	Reading words (100%)§	Reading words	–

This table lists the seventeen studies that contributed to the analyses of trait and/or state stuttering. Studies contributed to a positive association with trait stuttering if they reported the directional contrast [PWSfluent > PWNSfluent] and to a positive association with state stuttering if they reported the directional contrast [PWSstuttering > PWNSfluent]. Studies that reported contrasts in the opposite direction contributed to negative associations. The stuttering and fluent tasks columns list the tasks performed in each study. Rates of stuttering are reported in parentheses where applicable. The final column identifies studies that reported correlation with either (trait) severity of stuttering or (state) stuttering rate in the scanner in addition to or instead of high level contrasts. *Stuttering confirmed, but rates not reported. †Percentage of 4-s intervals which contained stuttering. ‡Percentage of Japanese morea which were stuttered. §Percentage of utterances which were stuttered.

The analyses of trait and state stuttering have a parallel structure in that both are based on contrasts with PWS while speaking fluently, as shown graphically in Fig. 1. In addition, the analysis of state stuttering may be interpreted as being additive with the analysis of trait stuttering. Trait stuttering reflects the fluent speech of PWS relative to PWNS and thus represents the background condition of PWS. State stuttering, then, reflects additional changes beyond that background state that occur during episodes of stuttering.

Results

Figure 2 presents the ALE results on axial slices, and Table 2 provides Talairach coordinates for the ALE foci. We examine trait and state stuttering in sequence. Trait stuttering showed increased likelihood of activation mainly in the right hemisphere, supportive of classic right-shift models of stuttering. The right hemisphere homologue of Broca's area, specifically the inferior frontal gyrus (IFG) pars opercularis or Brodmann Area (BA) 44, was more active in the brains of PWS than PWNS during fluent speech, as were other right-hemisphere premotor areas, including the pre-supplementary motor area (SMA), lateral premotor cortex in the precentral gyrus (BA 6), lip motor cortex (BA 4/6) and Rolandic operculum. Similar trends were observed in the right IFG pars orbitalis extending into the ventral insula, superior frontal gyrus (BA 6), superior frontal gyrus (BA 9), inferior parietal lobule (BA 40) and bilateral superior parietal lobule (BA 7).

Complementary to this result, trait stuttering showed decreased likelihood of activation exclusively in the left hemisphere. The most prominent decrease was seen in the left larynx motor cortex. Decreases were also observed in temporal lobe auditory areas, including the middle temporal gyrus (BA 21) and Heschl's gyrus (BA 41). Finally, a decrease was seen in the left cerebellar vermis. Overall, trait stuttering showed a strong right-shift pattern, with right-hemisphere increases and left-hemisphere decreases.

Looking now to the brain activations associated with bouts of stuttering in PWS (Fig. 2, lower panel), the pattern was more diverse, showing effects in both hemispheres. State stuttering was associated with increased likelihood of activation in right larynx motor cortex and lip motor cortex (BA 4) in the homologous location to the left-hemisphere underactivation seen for trait stuttering. Increases were also seen in the left SMA/Pre-SMA (BA 6), globus pallidus, precuneus (BA 7), Broca's area corresponding to both the IFG pars opercularis (BA 44) and pars triangularis (BA 45), bilateral cerebellum and right IFG pars orbitalis (BA 47).

State stuttering showed decreased likelihood of activation exclusively in the right hemisphere. Most notably, decreases were observed in right hemisphere auditory areas, including Heschl's gyrus (BA 41), the posterior superior temporal gyrus (BA 22) and middle temporal gyrus (BA 21). Decreases were also observed in the supramarginal gyrus (BA 40) and middle frontal gyrus (BA 46).

In order to assess the reliability of the data, we determined how many of the source studies reported activations in regions corresponding to each of the ALE foci. The results are shown in Table 2 as the proportion of the source-studies contributing to each peak. Among the most reliable ALE foci were: trait overactivation of the right precentral gyrus (0.50) and Broca's homologue (0.38); trait underactivation of left larynx motor cortex (0.44); state overactivation of the SMA (0.60), lip motor cortex (0.50), cerebellar vermis (0.50) and IFG pars orbitalis (0.40); and state underactivation of right auditory cortex (0.50).

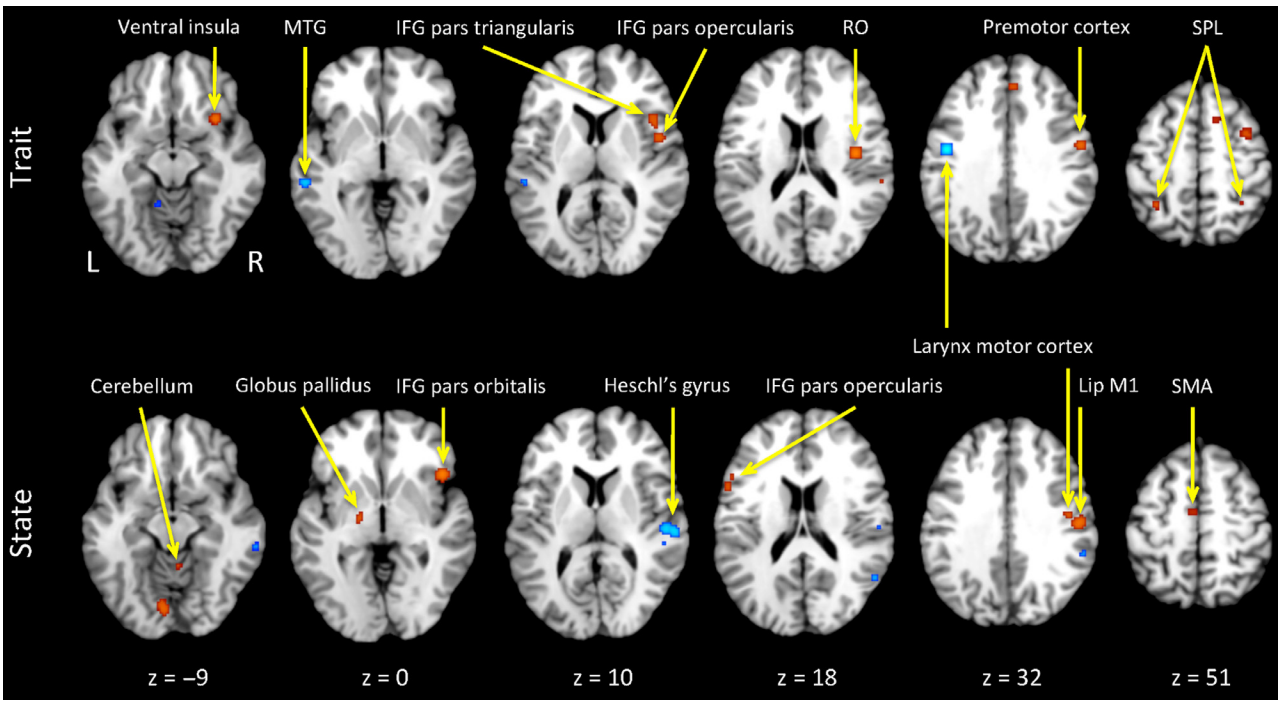

FIG. 2. Results of the ALE analyses. Axial slices in neurological convention showing regions consistently reported for trait and state stuttering. IFG, inferior frontal gyrus; MTG, middle temporal gyrus; RO, Rolandic operculum; SPL, superior parietal lobule; SMA, supplementary motor area.

Discussion

In the present study, we expanded upon an earlier meta-analysis of brain imaging studies of stuttering (Brown *et al.*, 2005) in order to examine the reliability of findings across the literature as well as to introduce a useful distinction not considered in the earlier analysis, namely that between stuttering as a stable trait and stuttering as a transient state. Overall, the findings were broadly consistent with the results of the earlier meta-analysis, showing overactivation in motor areas and underactivation in auditory areas. This argues for a general reliability of the findings of the last 10 years' worth of publications as well as a consistency in the analysis after switching to the more recent ALE methodology (Turkeltaub *et al.*, 2011).

A novel approach of this study was to partition the meta-analysis results into trait vs. state effects. We assess trait stuttering by a between-group comparison during fluent speech. In contrast, we assess state stuttering by a within-group comparison, looking at fluent vs. stuttered speech. This basic distinction is pervasive in the literature that we have reviewed. However, the literature must be interpreted with caution as it is unclear whether differences in brain activation are causes of stuttering or merely correlates. For example, studies of trait stuttering sometimes evoke fluency with task manipulations that may differentially affect activations in PWS and PWNS (although few studies that contributed to the current analysis did so). Furthermore, adult PWS have a lifetime of experience coping with their disorder. Trait stuttering could therefore reveal either brain abnormalities that cause the disorder or those that may compensate for it. Studies of children who stutter are few, but will be informative for this field (e.g., Chang *et al.*, 2008). Similarly, studies of state stuttering may reveal causes of the stuttering event, attempts to compensate for stuttering or the correlates of stuttering as a motor act. Nonetheless, the trait–state distinction provides a useful disambiguation of the neural correlates of stuttering.

The previous meta-analysis by Brown *et al.* (2005) identified three 'neural signatures' of stuttering, namely (i) overactivation of the right IFG/frontal operculum, (ii) underactivation of auditory cortex and (iii) overactivation of the cerebellar vermis. The current analysis elaborates on these findings by observing that (i) the right IFG/frontal operculum overactivation is restricted to trait stuttering, (ii) underactivation of auditory cortex is common to both trait and state stuttering and (iii) while the cerebellar vermis is overactivated during state stuttering, it is underactivated in trait stuttering, indicating that the relationship between the cerebellum and stuttering may be more complex than previously supposed. We further observed that the well-established right-shift for the brain activations of PWS (Travis, 1978; De Nil *et al.*, 2000) was more consistently found in the trait analysis than in the state analysis. Trait stuttering was associated with an increased likelihood of activation almost exclusively in the right hemisphere and a decreased likelihood of activation almost exclusively in the left hemisphere. The analysis of state stuttering, on the other hand, revealed increases in both hemispheres and decreases exclusively in the right hemisphere.

An important brain area that linked these two analyses was an area of primary motor cortex ($x = 44$, $y = -8$, $z = 32$) that matched the somatotopic location of the larynx motor cortex ($x = 44$, $y = -10$, $z = 34$) reported in Brown *et al.* (2008). State stuttering was associated with overactivation in the right hemisphere larynx motor cortex and trait stuttering with underactivation in the homologous region of the left hemisphere (see Fig. 2). The combination of the two results suggests a potential lack of coordination in the cortical control of the laryngeal muscles.

Before discussing the findings in detail, we would like to present a caveat. While an ALE meta-analysis detects brain regions that are commonly activated across studies, it is unable to detect differences between individuals. As previous research has demonstrated substantial individual differences in brain activations among PWS

TABLE 2. Cluster coordinates

Hemsiphere	Brain region	Brodmann	*x*	*y*	*z*	mm^3	ALE (10^3)	Prop.
Trait stuttering								
Positive associations								
Right	Precentral gyrus	BA 6	36	6	50	192	10.73	0.5
Right	Lip motor cortex	BA 4/6	54	−4	30	296	14.21	0.38
Right	Rolandic operculum	BA 13	38	−10	18	496	16.12	0.38
Right	IFG pars opercularis	BA 44	48	2	8	232	13.23	0.38
Right	IFG pars opercularis	BA 44	42	16	12	288	11.71	0.38
Right	IPL	BA 40	58	−30	22	184	13.07	0.38
Right	SPL	BA 7	32	−46	46	168	12.38	0.25
Right	Pre-SMA	BA 6	14	14	54	192	11.58	0.25
Right	Medial frontal gyrus	BA 9	4	38	32	80	10.57	0.25
Right	IFG pars orbitalis	BA 47/13	32	16	−8	264	13.91	0.38
Left	SPL	BA 7	−30	−48	50	96	10.79	0.25
Negative associations								
Left	Larynx motor cortex	BA 4	−44	−8	32	376	14.19	0.44
Left	MTG	BA 21	−56	−32	−2	280	11.88	0.33
Left	Heschle's gyrus	BA 41	−52	−30	10	24	8.74	0.22
Left	Cerebellar vermis		−12	−48	−6	128	9.83	0.11
State stuttering								
Positive associations								
Right	SMA	BA 6	2	−22	58	16	8.44	0.6
Right	Lip motor cortex	BA 4	54	−14	34	696	13.06	0.5
Right	Larynx motor cortex	BA 4	44	−8	32	136	9.33	0.3
Right	IFG pars orbitalis	BA 47	44	20	0	520	13.86	0.4
Right	Cerebellar vermis		4	−46	−8	32	8.89	0.2
Left	SMA	BA 6	−4	−8	56	432	11.75	0.6
Left	SMA	BA 6	0	0	54	L	8.62	0.6
Left	Cerebellar vermis		−6	−78	−10	440	11.01	0.5
Left	IFG pars opercularis	BA 44	−56	12	16	160	9.45	0.3
Left	IFG pars triangularis	BA 45	−52	20	16	L	8.88	0.2
Left	Globus pallidus		−18	−12	0	80	9.11	0.2
Left	Precuneus	BA 7	−6	−56	48	16	8.43	0.2
Negative associations								
Right	Heschl's gyrus	BA 41	58	−22	8	1128	14.82	0.5
Right	Heschl's gyrus	BA 41	52	−20	8	L	12.57	0.5
Right	Heschl's gyrus	BA 41	56	−18	14	L	11.82	0.5
Right	Heschl's gyrus	BA 41	50	−28	14	200	11.57	0.5
Right	IPL	BA 40	38	−36	40	16	9.49	0.38
Right	Posterior STG	BA 22	52	−56	22	352	12.13	0.38
Right	SMG	BA 40	54	−38	32	24	9.23	0.38
Right	MTG	BA 21	62	−32	−10	72	9.9	0.25
Right	Middle frontal gyrus	BA 46	42	16	24	240	12.85	0.13

The four sections of this table list brain regions that were either positively or negatively associated with trait and state stuttering. After each anatomical name in the brain region column, the Brodmann number for that region is listed. The columns labeled as *x*, *y*, and *z* contain the Talairach coordinates for the peak of each cluster. The mm^3 column lists the total volume of each cluster. 'L' indicates local maxima contained within the region listed directly above. The ALE column lists the peak ALE estimate for each region multiplied by 10^3. The final column lists the proportion of studies contributing to each analysis that reported foci of activation directly in each brain region. IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MTG, middle temporal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus.

(Wymbs *et al.*, 2013), we report a complementary analysis of the frequency of replication for each brain region that reached significance in our analysis (see Table 2). Hence we note that while our meta-analysis presents a unitary view of stuttering, PWS are a highly heterogeneous group of individuals, and stuttering as a syndrome may be comprised of multiple subtypes with distinct etiologies (Yairi, 2007). The results of individual neuroimaging studies may therefore reflect mixtures of neural correlates from different subtypes of stuttering found within particular groups of subjects. The ALE method, in turn, identifies regions of the brain that are consistently reported as part of this mixture. Any individual person who stutters may manifest abnormal activation in only a subset of the regions we identified, in none of these regions, or in regions not reported here, in accordance with the etiology of their particular case.

Basal ganglia and SMA

Alm (2004) proposed that dysfunction in the basal ganglia and corresponding cortical sites in the SMA may result in poor motor timing during speech production. Several neuroimaging studies have observed stuttering-related activation throughout the basal ganglia, including the caudate nucleus (Braun *et al.*, 1997), putamen (Kell *et al.*, 2009), globus pallidus (Ingham *et al.*, 2004), subthalamic nucleus (Loucks *et al.*, 2011), and substantia nigra (Wu *et al.*, 1995). The meta-analysis of Brown *et al.* (2005) revealed the involvement of the SMA in stuttering but failed to detect any ALE foci in the basal ganglia. The present analysis suggests that state stuttering is associated with overactivation of the SMA while trait stuttering is associated with overactivation of the pre-SMA. This is consistent with the observation of increased activity of the orofacial

muscles during stuttering, as the SMA has greater connectivity with cortical motor areas (Luppino *et al.*, 1993) and gives rise to more descending motor efferents (Dum & Strick, 1991) than does the pre-SMA. Both areas project to and receive projections from the basal ganglia (Inase *et al.*, 1999; Akkal *et al.*, 2007), although the present analysis observed overactivation in the globus pallidus of the basal ganglia for state stuttering only. However, this ALE focus was present in a relatively low proportion of studies, suggesting that this region is not reliably activated across studies of stuttering, as suggested previously by Brown *et al.* (2005). While it is clear that the basal ganglia are involved in stuttering, it is unclear as to which nucleus the abnormal activity is localised.

The potential for a causal role of the basal ganglia in stuttering is highlighted by the case study of a recovered person who stutters and who underwent deep brain stimulation as treatment for Parkinson's disease (Burghaus *et al.*, 2006). Stimulation of the subthalamic nucleus reduced Parkinsonian symptoms but caused a relapse of stuttering. Cessation of stimulation led to a return of Parkinsonian symptoms coupled with an abatement of stuttering. The pattern of brain activation in this subject in the presence vs. absence of deep brain stimulation revealed increased activation in many of the stutter-related regions reported in both Brown *et al.* (2005) and the current analysis, including the SMA, motor cortex and cerebellar vermis, as well as reduced activation in the auditory cortex.

Auditory cortex

There has been suggestive evidence since the earliest imaging studies of stuttering (Wu *et al.*, 1995; Fox *et al.*, 1996) that auditory areas are underactivated in PWS. The Brown *et al.* (2005) meta-analysis failed to detect auditory deactivations in the subtraction between PWS and PWNS, although there was a trend for reduced activity in PWS in the auditory cortex bilaterally. The present meta-analysis was able to shed new light on this bilateral trend by separating it into two hemisphere-specific effects. The strongest effect was an underactivation of the right primary auditory cortex during state stuttering. A weaker underactivation of the left primary auditory cortex was observed for trait stuttering. Because stuttered speech for some individuals includes frequent blocking, it is unclear whether auditory underactivation in state stuttering reflects abnormal auditory processing or simply reduced auditory self-stimulation resulting from the cessation of speech. Trait stuttering, by contrast, presents no such uncertainty as it only includes fluent speech that is matched in acoustic content to the speech of PWNS in the same analyses.

Auditory areas are connected with the vocal motor system through a projection to the inferior frontal gyrus via the arcuate fasciculus (Rilling *et al.*, 2008). This anatomical pathway is reduced bilaterally in PWS (Chang *et al.*, 2008; Connally *et al.*, 2014), which might be suggestive of a feed-forward deficiency. Given that the right IFG was not shown to be overactivated in state stuttering but the right larynx motor cortex was, this creates problems for a simple feed-forward pathway from auditory cortex via IFG to motor cortex. The fact that acoustic stimuli such as white noise can greatly enhance fluency in PWS suggests that the auditory system does indeed have an important feed-forward influence on the motor system. Regarding feedback, magnetoencephelography reveals that PWS have intact speech-induced suppression of auditory responses, although with somewhat more rapid auditory responses in the right hemisphere (Beal *et al.*, 2010). However, the fact that state stuttering was associated both with overactivation of the larynx motor cortex and with underactivation of the auditory cortex in the right hemisphere might suggest a causal connection between these two results through feedback suppression, although, as mentioned above, part of the underactivation of auditory areas in state stuttering may be due to reduced self-stimulation due to stuttering itself. Further work is needed to clarify the audio–motor relationship in stuttering, most especially disambiguating feed-forward vs. feedback contributions to stuttering. Importantly, the fact that acoustic stimuli alone can reduce the symptoms of stuttering suggests that there must be neural mechanisms for harnessing a motor system that is intrinsically overactive or discoordinated in PWS. One contributor to such a mechanism might be IFG pars orbitalis.

IFG pars orbitalis

The meta-analysis showed that the right IFG pars orbitalis (BA 47) was more likely to overactivate in PWS than in PWNS. A nearby, although non-overlapping, overactivation was also observed in the IFG pars orbitalis during stuttered speech compared to fluent speech in PWS. However, several studies have shown activation in this region to be negatively correlated with (trait) stuttering severity (Preibisch *et al.*, 2003; Kell *et al.*, 2009); the lesser the stuttering severity, the greater the activation in this region. Furthermore, activation of the IFG pars orbitalis is negatively correlated with the (state) quantity of stuttering in individual speech samples (Braun *et al.*, 1997). PWS engage the IFG pars orbitalis when stuttering is relatively light and fail to activate it during strong bouts of stuttering. These findings have led some researchers to speculate that activation of the IFG pars orbitalis may compensate for a dysfunction in adjacent Broca's area (Kell *et al.*, 2009). Indeed, we found that the right homologue of Broca's area in the frontal operculum was overactive in trait stuttering, an effect seen in the Brown *et al.* (2005) meta-analysis as well. Neumann *et al.* (2005) and Kell *et al.* (2009), in comparing the profiles of brain activation in PWS before and after speech therapy, found an increase in right IFG pars orbitalis activity after successful therapy. This region, therefore, might provide a suppressing mechanism to the vocal motor system in Broca's area and the primary motor cortex in PWS. Such a mechanism might shed light onto the mystery of how stuttering can be ameliorated instantaneously but transiently by a diverse array of seemingly unrelated environmental and contextual factors. Further research is required to elucidate the role of the IFG pars orbitalis as a protective factor against stuttering.

Lip motor cortex

We observed an increase in activation in a region of the motor cortex during stuttered speech ($x = 54$, $y = -14$, $z = 34$) near the somatotopic lip area ($x = 57$, $y = -10$, $z = 32$; Brown *et al.*, 2008) directly lateral to the larynx area. Electromyographical studies have demonstrated that, even during fluent speech, PWS are slow to articulate labial consonants (Zimmermann, 1980). The latency between initiating articulation and achieving maximal displacement of both the lower lip (van Lieshout *et al.*, 1993) and upper lip (van Lieshout *et al.*, 1996) is longer in the fluent speech of PWS than PWNS. During a stutter, a slow tremor is sometimes observed in the bottom lip, although antagonistic elevator and depressor muscles still activated reciprocally as they do during fluent speech (McClean & Goldsmith, 1984).

Larynx motor cortex

Given the general differences in activation profile observed between trait and state stuttering in our two meta-analyses, an important

commonality between the two analyses was the larynx motor cortex, the principal vocal center of the human brain (Brown *et al.*, 2008). As shown in Fig. 2, state stuttering was associated with overactivation in the right hemisphere and trait stuttering with underactivation in the homologous region of the left hemisphere.

Before discussing a laryngeal contribution to stuttering, it is important to note that motor theories of stuttering have presented evidence for disturbances at numerous levels in the speech production system, including motor timing (Alm, 2004), planning (Postma & Kolk, 1993; Howell, 2004) and articulatory control (Namasivayam & van Lieshout, 2011). In discussing a laryngeal mechanism for stuttering, we are in no way trying to discount other mechanisms or to prioritise laryngeal mechanisms over them. We are simply trying to interpret the ALE results in the most direct manner possible.

Research into the role of the larynx in stuttering declined after the 1980s when studies suggested that (i) stuttering is reduced but not eliminated when speaking in the absence of phonation, as in whispering (Perkins *et al.*, 1976; Bruce & Adams, 1978), (ii) paralysing the larynx by injecting botulinum toxin yields only a short-term reduction in stuttering (Ludlow, 1990; Brin *et al.*, 1994), although the timeframe is typical of botulinum toxin treatments of neuromuscular disorders (Blitzer & Sulica, 2001), and (iii) stuttering may still occur when the larynx is excised (Tuck, 1979; although see Wingate, 1981). Interestingly, larynx excision among PWNS can result in adult-onset stuttering (Freeman & Rosenfield, 1982; Rosenfield & Freeman, 1983). Together, these findings suggest that laryngeal dysfunction may be a sufficient, but not necessary, cause of stuttering. Indeed, 'prolonged speech' is a prominent stuttering therapy in which patterns of phonation are shaped to facilitate fluency (Goldiamond, 1965; Ingham, 1987). Similarly, speech conditions such as choral, rhythmic or whispered speech may induce fluency because they reduce alternations between voiced and unvoiced speech sounds (Ingham *et al.*, 2012a).

The larynx is a complex structure with many interdependent muscles whose coordinated operations are critical to both airway protection and speech. However, laryngeal function relevant to vocalisation involves two major dimensions of muscle control – on the one hand, adduction vs. abduction of the vocal folds and, on the other, tensing vs. relaxing. While the latter is intimately associated with vocalisation, the former occurs during other processes as well, most notably during respiration and swallowing. In analysing the cortical control of these muscles, Brown *et al.* (2008) had subjects perform both non-vocal (glottal stops) and vocal (phonation) laryngeal tasks, and showed that the same part of the motor cortex was activated by both types of tasks, leading to a characterization of a multi-functional larynx motor cortex (for a related set of observations, see Loucks *et al.*, 2007 and Belyk & Brown, 2014). Two distinct regions of activation were found, namely a ventromedial peak in the primary motor cortex (BA 4) and a dorsolateral peak in the premotor cortex (BA 6). The two meta-analyses performed in the current study specifically implicated the ventromedial primary motor peak in stuttering, consistent with the results of Brown *et al.* (2005).

The trait underactivation of the left larynx motor cortex among PWS may be associated with trait-related deficits in the operation of the larynx. PWS are slower to initiate phonation than PWNS (Adams & Hayden, 1976). Precise timing of voicing onset is important for conveying phonetic distinctions between particular consonants (Lisker & Abramson, 1966), and voice onset times are slower (Hillman & Gilber, 1977; Zimmermann, 1980) and more variable (Jäncke, 1994) in the speech of PWS than in the speech of PWNS. In addition, problems in initiating phonation represent a key deficit among PWS, one that may trigger instances of stuttering. PWS are more likely to stutter at the beginning of an utterance or after a pause (Wall *et al.*, 1981) as well as when speech requires alternations between voiced and unvoiced sounds, compared to when speech is voiced continuously (Adams & Reis, 1971) such as during singing. Rehearsing spoken material increases fluency, but only if the rehearsal is out loud and voiced (Brenner *et al.*, 1972), which suggests that rehearsal aids in phonation rather than articulation. These observations in no way exclude the possibility that PWS have disordered control of the articulators. Indeed, stuttering is associated with tremor in the jaw (Platt & Iwo, 1973) and lips (McClean & Goldsmith, 1984).

The state overactivation of the right larynx area during incidences of stuttering may be related to abnormal behaviour of the laryngeal muscles during stuttered speech. During part-word repetitions, the vocal folds are abducted more than during fluent speech (Conture *et al.*, 1977). Electromyography reveals that, during stuttered speech, the adductor and abductor muscles are overactivated and fail to coordinate as an antagonistic pair, as they do during fluent speech (Freeman & Ushijima, 1978). No abnormalities are observed in the muscles controlling laryngeal tension (Smith *et al.*, 1996). Laryngeal blocking, which is a common component of stuttering, might be related to the simultaneous contraction of the adductor and abductor muscles, resulting in high muscle tension but little movement. This specificity of physiological abnormalities to the adductor and abductor muscles is also consistent with the difficulty that PWS have in initiating phonation. Failure to initiate phonation may lead to repetitions as the speaker attempts to initiate a syllable repeatedly. Further research is required to determine whether there is a causal relationship between overactivation of the right larynx motor cortex and abnormal laryngeal-muscle physiology.

Unlike peripheral effectors, such as the hand, that can be controlled independently of the contralateral limb, a midline structure like the larynx requires symmetric and simultaneous control of the two vocal folds. For example, for phonation to occur, the vocal folds must be adducted by simultaneous bilateral contraction of the lateral cricoarytenoid muscles, the oblique arytenoid muscles and/or the unpaired transverse arytenoid muscle. Similarly, cessation of phonation requires abduction of the vocal folds via simulatenous bilateral contraction of the posterior cricoarytenoid muscles. Indeed, asymmetric operation of the laryngeal muscles is indicative of speech motor disorders, such as unilateral upper motor neuron dysarthria (Duffy, 2005). Well-coordinated activation of the upper motor neurons of the laryngeal system is all the more critical given the intrinsically asymmetric nature of the lower motor neurons. The left recurrent laryngeal nerve, which innervates both the abductor and adductor muscles, is twice the length of the right nerve (Prades *et al.*, 2012).

The reciproal activation–inhibition pattern in the larynx motor cortex seen in the two hemispheres might result from a process of interhemispheric inhibition, whereby a cortical region in one hemisphere inhibits its contralateral homologue by means of callosal projections. Neef *et al.* (2011b) found aberrant intracortical inhibition in the tongue motor cortex of PWS and our results may be indicative of a similar phenomenon in larynx motor cortex. The left larynx motor cortex is underactivated in trait stuttering which may in turn disinhibit the right larynx motor cortex resulting in overactivation. While the meta-analysis results cannot verify whether the two hemispheres are coupled in this way, further experiments could do so.

Neuroanatomical abnormalities among PWS further implicate the larynx motor cortex and its anatomical connections. Studies using diffusion tensor imaging have found reduced fractional anisotropy in the white matter adjacent to the larynx motor cortex bilaterally (Watkins *et al.*, 2008), indicating either reduced myelination or reduced coherence of the white matter tracts. The absence of

tractography data makes it unclear whether the affected fibres are derived from corticocortical connections, the descending corticobulbar tract, or some combination of the two. However, reduced fractional anisotropy among PWS has also been reported in both the motor cortical component of the corpus callosum (Cykowski *et al.*, 2010; Connally *et al.*, 2014) and the left corticobulbar–corticospinal tract (Chang *et al.*, 2008; Connally *et al.*, 2014), suggesting that both tracts may be affected.

Conclusions

We report an updated meta-analysis of neuroimaging studies of developmental stuttering, one that adds a new distinction between stuttering as a stable trait and stuttering as a episodic behavioural state. The results of these two analyses were remarkably divergent. Trait stuttering was characterised by the well-known rightward shift in lateralization for language and speech areas. State stuttering revealed a more diverse pattern. The larynx and lip motor cortex linked the two analyses. State stuttering was associated with overactivation in the right hemisphere lip and larynx motor cortex. Trait stuttering was associated with overactivation of lip motor cortex in the right hemisphere but underactivation of larynx motor cortex in the left hemisphere. These results suggest a potential lack of coordination in the cortical control of muscles relevant to speech.

Conflict of interests

The authors declare no conflict of interest.

Supporting Information

Additional supporting information can be found in the online version of this article:

Table S1. Literature meta-data. This table lists descriptive information about data and data handling for studies that contributed to the meta-analysis. Asterisks mark fMRI studies that utilised sparse or clustered event-related designs to eliminate scanner noise during speech tasks.

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Abbreviations

ALE, activation likelihood estimation; BA, Brodmann area; FMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; PET, position emission tomography; PWNS, people who do not stutter; PWS, people who stutter; SMA, supplementary motor area.

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