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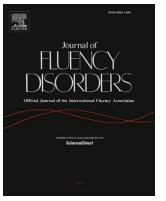

Evidence of different grey matter volume patterns in men and women who stutter – An explorative structural MRI study

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ABSTRACT

Developmental stuttering is a disorder with a high degree of heterogeneity, both behaviourally and neurologically. Research from different perspectives of stuttering indicates that sex is a potentially differentiating factor. In our study we explored if sex is related to variability of grey matter volume (GMV) patterns in adults with developmental stuttering. We used MRI to collect data on GMV from 24 righthanded adults who stutter (9 women and 15 men) and 29 righthanded fluent controls (10 women and 19 men). We analysed the following for 24 ROIs of the language system: 1) whole-group differences between the stuttering group and controls and 2) interaction between group (adults with stuttering versus controls) and sex. Our explorative results indicate that differences in grey matter volume between adults with stuttering and fluent adults are sex-specific for several areas involved in speech and language processing. We found an interaction between group and sex for the right BA45. The interaction indicates that men who stutter have larger GMV in this area compared to fluent men while women who stutter have smaller GMV compared to fluent women. Further, we found indications of sex-specific patterns in other areas of the bilateral inferior frontal cortex, but not the BA44, as well as in the cerebellum and the striatum.

1. Introduction

1.1. What is stuttering?

Developmental stuttering is a speech fluency disorder where speech sounds or syllables typically are repeated, prolonged, or stopped (Guitar, 2014; Wingate, 1964). For many who stutter, such dysfluent moments are associated with struggle that may give rise to other psychological or behavioural symptoms. There is a high degree of individual variability in all these aspects of developmental stuttering, as well as in the functional and structural neurological markers of the disorder. The origin of this heterogeneity though, remains unclear. In our study we wanted to explore if there are differences in grey matter volume (GMV) between adults with stuttering (AWS), and their fluent peers, and whether sex is a systematic influencing factor.

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1.2. Sex and stuttering

1.2.1. Sex differences in stuttering occurrence

The existence of sex differences in stuttering is clear from an epidemiological perspective. In the stuttering population there is a reported male to female ratio of stuttering in adulthood of around 4:1. This ratio is around 2:1 in the population of children who just experienced onset of stuttering (Yairi & Ambrose, 2013). One inference from this is that more girls than boys experience recovery from stuttering before reaching adulthood. There exists no unified explanation as to why girls and boys often demonstrate different trajectories of stuttering development.

There are also indications of sex differences in stuttering on a behavioural level. Studies have indicated that men and women tend to use different coping strategies to different degrees, as for instance avoidance behaviour (Russøy et al., 2021; Samson et al., 2022). There are also indications that men and women rate the impact of their stuttering differently (Samson et al., 2022).

1.2.2. Genetics, sex hormone levels and stuttering

Another sex difference in stuttering is reported by Drayna et al. (1999), who found greater heritability of stuttering in women than in men. This may imply that the aetiology of stuttering somehow differs between men and women. Recently, it has also been suggested that there is a relationship between sex hormones and developmental stuttering. Montag et al. (2015) found a positive correlation between prenatal testosterone exposure and stuttering severity. Also, Dönmez et al. (2019) found indications of higher prenatal testosterone exposure in a group of boys who stutter, as compared to a control group. They further linked this finding to theories stating that prenatal testosterone exposure may be a predecessor to atypical brain lateralization. Higher levels of testosterone in stuttering children were also found by Mohammadi et al. (2017). It has been hypothesized that variations in genes involved in regulating sex hormone levels may contribute to a risk of stuttering (Polikowsky et al., 2022).

1.2.3. Sex, speech development, and stuttering

Stuttering is, by nature, closely linked to speech development. Stuttering most often emerges at the time when a child starts to talk in sentences. Also, dysfluency more often occurs when producing phonetically complex and/or long words/sentences (Richels et al., 2010). There is a known sex difference in the early stages of language acquisition, with girls reaching developmental milestones earlier than boys (Adani & Cepanec, 2019).

There have also been reports of sex differences in the functional laterality of the language system (Shaywitz et al., 1995). Shaywitz et al. (1995) found that men had a typical left-lateralized activation pattern in the inferior frontal region during a phonological processing task. Women, on the other hand, had a more diffuse and bilateral activation pattern in the same region. Stuttering has, like sex, long been linked to differences in functional and structural laterality for language processing (Etchell et al., 2017). There are also indications of sex differences in two structures of the basal ganglia; globus pallidus and the putamen (Rijpkema et al., 2012). It should be mentioned that the notion of functional and structural sex differences in the brain's language system, in adults, have been questioned (Sommer et al., 2004; Wallentin, 2009, respectively). But, in a recent study, Xu et al. (2020) argued that a potential reason why some previous studies did not detect sex differences in language function is that such differences exist on a network level. Using advanced methods for studying network connectivity, they reported on sex differences in the integration of different parts of the language network. More specifically, they found that men had more inhibitory connections from the inferior frontal gyrus (IFG) to the superior temporal gyrus (STG). The women, on the other hand, had more inhibitory connections from the superior parietal lobule to the STG. The authors further suggested that such neurological differences may be part of the explanation for the sex difference in prevalence seen in e.g. the stuttering population.

Together, such findings indicate a complex relationship between stuttering, sex, and speech/language.

1.3. Neuroimaging research on stuttering

1.3.1. "The neural signatures of stuttering"

There is now convincing evidence in the literature supporting the notion that stuttering has neuroanatomical markers in the speech and language system of the brain. In an influential meta-analysis of functional neuroimaging research on speech production in fluent and stuttering subjects, Brown et al. (2005) postulated "the neural signatures of stuttering". Overall, the meta-analysis revealed a relative tendency towards a more right-lateralized activation pattern during speech. This elevated right hemisphere activation tended to be shown in a region around the motor and premotor cortices related to the pharynx and the mouth. Further, the auditory cortices, bilaterally, were less activated in the stuttering group. More recent meta-analyses have supplemented and refined these findings by, most notably, demonstrating differences in the activation of the supplementary motor area (SMA) and a differentiation between the roles of anterior and posterior portions of the superior temporal gyrus (Belyk et al., 2015; Budde et al., 2014; Zhang et al., 2022).

But even though there are some consistencies in the literature, there is also much diversity amongst both functional and structural brain imaging studies on stuttering (Etchell et al., 2017). A potential reason for varying results is that group differences between people who stutter, and controls might exist on a network level. One network that has received increasing attention in this context is the cortico-basal ganglia-thalamocortical (CBGTC-) motor circuit. This set of cortical and subcortical structures is proposed to function together as a feedforward control system during speech production (Guenther & Vladusich, 2012). The involvement of the basal ganglia in stuttering has been suspected for almost a century, and was proposed by e.g. Maguire et al. (2002). Further, it has been hypothesized that the CBGTC-circuits through the putamen are likely to play a key role in stuttering, and that the core dysfunction in stuttering is an impaired ability of the basal ganglia to produce cues for the initiation of the next motor segment in speech (Alm, 2004).

This model of involvement of the CBGTC-loop in developmental stuttering has gained cumulative support within the field (see e.g. Busan, 2020; Chang & Guenther, 2019; Chow et al., 2023a, 2023b; Civier et al., 2010; Craig-McQuaide et al., 2014; Jenson et al., 2019; Theys et al., 2024).

1.3.2. Research on grey matter volume in adults who stutter

1.3.2.1. Cortical areas. Given the explorative nature of our study, with e.g. small sample sizes, and our objective to elucidate tendencies for future research to study further, we have chosen to focus exclusively on grey matter volume. The most typical finding from stuttering research on GMV is widespread and diffuse group differences, in several areas throughout the speech and language network (Etchell et al., 2017). The most consistent results indicate higher GMV in AWS in the right superior temporal gyrus (STG) and the right premotor gyrus. There have also been reports of higher GMV in the left Brodmann area (BA) 44 (Beal et al., 2007) but also of lower cortical thickness (Cai et al., 2014; Lu et al., 2012) and GMV (Kell et al., 2009) in this area. Evidence for involvement of the prefrontal cortex in developmental stuttering also comes from two studies finding that the expected "brain torque", with protrusions of the right prefrontal lobe and the left occipital lobe, could not be demonstrated in the stuttering group (Foundas et al., 2003; Mock et al., 2012). In addition to these results, Lu et al. (2010) reported further differences, with larger GMV in the following cortical areas: the right medial frontal gyrus, the right precentral gyrus, the left superior parietal lobule, the left paracentral lobule, the right fusiform gyrus, the left middle occipital gyrus, and the bilateral cingulate gyri. In addition, they found lower GMV in the stuttering group in the left superior frontal gyrus, the bilateral medial frontal gyri, and the left superior and right middle temporal gyri.

1.3.2.2. Subcortical structures. Few studies have found structural differences in the basal ganglia in AWS (Deepa et al., 2022; Montag et al., 2019; Theys et al., 2024), despite functional neuroimaging studies supporting that the CBGTC-circuit is involved in stuttering (Chang & Guenther, 2019). Sowman et al. (2016) reported a smaller left caudate nucleus in AWS compared to the control group, and Montag et al. (2019) found a larger right caudate nucleus and putamen in the stuttering group. Lu et al. (2010) further found higher GMV in stuttering adults in the left putamen. Theys et al. (2024) found that lesions causing stuttering occurred in a network centred around the left putamen in the literature on acquired stuttering and, further, that this network was common with a cohort with stroke-induced stuttering. They also found positive associations between GMV of the left posteroventral putamen, ventral claustrum and transition to the amygdalostriatal area and impact of stuttering in a group of adults with developmental stuttering. The authors extend theories of the role of the putamen in stuttering and highlight the left posteroventral putamen as a key area. Foundas et al. (2013) reported reduced right caudate volume and atypical leftward asymmetry in a group of young boys with stuttering. Neef et al., (2018a), (2018b), on the other hand, found no group differences for the caudate nucleus or the putamen, but they found a small tendency towards AWS having a larger right nucleus accumbens in the ventral striatum. We have found two studies reporting on grey matter differences in the right cerebellar tonsil; Beal et al. (2007) reported higher GMV in this area for adults who stutter compared to controls, and Lu et al. (2010) found that this structure, as well as the right declive and culmen of vermis, was larger in controls.

1.3.2.3. Methodological quality and heterogeneity in grey matter studies. It should be underscored, that a high number of studies on GMV in stuttering report on results not corrected for multiple comparisons (as also noted by Etchell et al. 2017). Also, most studies on grey matter anatomy in AWS have included a relatively low number of participants and therefore have low power (Montag et al., 2019). There are also studies reporting no significant group differences in GMV (e.g. Jancke et al., 2004). Taken together, this shows that it is difficult to generalize on GMV in stuttering based on the studies available.

1.3.3. Neuroimaging research on sex differences in stuttering

The heterogeneity of results from neuroimaging studies on stuttering has led many researchers to strive to keep their group of stuttering participants as homogeneous as possible in the search for the origin of stuttering (Yairi, 2007). One consequence is that many studies have focused on righthanded men. In studies where women were included, results for women who stutter, as an isolated group, or sex differences, have seldom been presented (Etchell et al., 2017). In meta-analyses of functional brain imaging studies, sex is not a factor included in analysis (Belyk et al., 2015; Budde et al., 2014; Zhang et al., 2022)

Gough et al. (2018) is a rare example of a neuroimaging study reporting on sex differences in stuttering. In their study, they reported a tendency towards an interaction effect between group and sex on planum temporale asymmetry. Another example is Ingham et al. (2004), who presented sex differences in how brain activity correlated with stuttering rate. The two sexes both demonstrated positive correlates with stuttering rate in the right anterior insula and the right BA21/22. They further reported that the males in their stuttering group demonstrated increased right-hemispheric activation patterns with higher stuttering rate. The men also showed a male-specific positive correlate with stuttering rate in the left medial occipital lobe and the right medial cerebellum. The females had a more bilateral activation pattern in addition to a female specific correlate with stuttering rate in the left globus pallidus and the right caudate nucleus.

1.4. Aim of this study

The overarching objective of this study was to explore how GMV of the speech and language network of the brains of adults with and without developmental stuttering differ. Further, we focused on the potential influence of sex, with the intention to reveal factors that contribute to the diversity of results in the existing literature. We used magnetic resonance imaging (MRI) to explore GMV

differences between a group of adults with stuttering and fluent controls (FC) as well as interaction between group and sex. Our study is explorative and may serve as a starting point for further brain imaging research on the relationship between sex and stuttering.

2. Materials and methods

2.1. Participants

Twenty-four AWS (15 males, 9 females, mean age = 32.6) and 29 fluent controls (19 males, 10 females, mean age = 29.2) participated in the study. All participants were righthanded, defined as a handedness quotient $\geq$ 50 on the Edinburgh Handedness Inventory, short version (Veale, 2014). The participants in the stuttering group were recruited via the national interest organization for fluency disorders, local speech therapists, flyers in campuses for higher education and in medical offices. Inclusion criteria for the stuttering group were a clinical diagnosis of developmental stuttering and age above 18 years. The diagnosis was confirmed by the first author, who is an experienced speech therapist working in a specialized speech fluency team. AWS were excluded if they were engaged in speech therapy where the speech-related symptoms were the focus of the treatment at the time of participation or for 6 months prior to participation. For all participants exclusion criteria were neurological disease, medication that could affect cognition/brain function or blood flow, and the MR-related criteria pregnancy, ferromagnetic and non-MR compatible implants, or a history of claustrophobia. The study was approved by the Regional Committees for Medical and Health Research Ethics (2017/2096/REK vest), and each participant gave written informed consent prior to participation. Table 1 displays an overview of sex, age, and examiner-rated and self-rated measured stuttering severity for the group of participants with developmental stuttering.

2.1.1. Definition of sex used in this study

In our study we define sex in line with Heidari et al. (2016):

> *sex refers to a set of biological attributes in humans and animals that are associated with physical and physiological features including chromosomes, gene expression, hormone function and reproductive/sexual anatomy. Sex is usually categorized as female or male, although there is variation in the biological attributes that constitute sex and how those attributes are expressed (p. 1).*

We have aimed to follow the Sex and Gender Equity in Research (SAGER) guidelines when conducting and presenting this study (Van Epps et al., 2022).

2.2. Data collection

For the participants in the experimental group, data were collected as part of a full-day clinical assessment. For these participants,

Table 1
Characteristics of participants with developmental stuttering.

	Sex	Age	SSI4	WASSP
1	F	24	0	3.3
2	F	24	16	3.9
3	F	46	13	3.9
4	F	30	0	2.5
5	F	18	25	4.7
6	F	40	11	4.2
7	F	53	23	2.4
8	F	31	28	3.9
9	F	35	26	4.0
10	M	24	2	3.0
11	M	40	8	3.0
12	M	35	0	2.7
13	M	68	4	2.3
14	M	29	27	2.2
15	M	35	21	4.0
16	M	28	2	1.5
17	M	30	28	2.8
18	M	25	12	3.1
19	M	36	30	3.4
20	M	33	8	3.7
21	M	26	12	2.0
22	M	29	4	1.9
23	M	54	6	2.4
24	M	18	15	4.4

Note. F = female, M = male, SSI4 = total score from the Stuttering Severity Instrument 4. Total score < 17 has a severity equivalent of very mild stuttering and total score > 37 has a severity equivalent of very severe. Total score, rather than severity categories, were used in analyses in this study. WASSP = total score on Wright and Ayre Stuttering Self-rating Profile. This score is the mean score across all subscales and range from 1 (none) to 7 (very severe). See text for a more detailed description.

speech samples were collected at the start of the assessment, directly before MRI-scanning, and then assessment continued after scanning with the administration of stuttering severity assessment tools. The scanning itself took about one hour.

2.2.1. Stuttering severity

As we intended to investigate interaction effects between group and sex, and group differences per sex, we wanted to control for the potentially confounding effect of a sex difference in stuttering severity. We therefore collected data on self-rated and examiner-rated stuttering severity.

The Stuttering Severity Instrument, version 4 (SSI-4), was used for examiner-rated stuttering severity assessment (Riley, 1972). Total score on the SSI-4 is the sum of the scores from three subscales: (1) stuttering frequency measured as % stuttered syllables (% SS), (2) mean duration of the three longest dysfluent moments and (3) the degree of physical concomitants. The total score was used for the analyses in this study, rather than severity categories.

SSI-4-scores were based on video films from three speaking situations for each participant. The types of speaking situations were chosen to reflect the variability of speaking situations that a person might encounter in everyday life and were as follows: (1) Reading a text aloud; The total text is around 700 syllables long, and calculation of % SS was based on the 334 syllable-long mid-section of the text. (2) Written transcription of a 3–4-minute-long monologue, where the participant was instructed to talk about a topic of great interest to him or her. (3) A conversation with the experimenter, where the experimenter tried to make the conversation as realistic as possible by spontaneously, though carefully and empathically, interrupting the participant a few times during the conversation. All speech samples were collected in the same room where 1–3 persons involved in the study were present, in addition to the participant. Two independent raters assessed stuttering severity in accordance with the instructions given in the SSI-4 manual (Riley, 2009). These were speech therapy students in their last year of training. They then compared and discussed their ratings for each participant and agreed on a score. If they were unsure or could not reach agreement, they contacted the first author. She then conducted an independent severity rating from video tape and the scores were discussed before agreeing on a value. In addition to such few cases of ambiguity, several random participants' speech fluency was assessed by a set of three pairs of raters.

The Wright and Ayre Stuttering Self-rating Profile (WASSP) was used for self-rating of stuttering severity. Both the original English version of WASSP, and a recent Norwegian translation used in this study, have demonstrated good psychometric qualities (Ayre & Wright, 2009; Sævrøy et al., 2019; Wright et al., 1998). The total score from WASSP was used in statistical analyses and is based on the mean score across all subscales ('Stuttering behaviours' (8 items), 'Thoughts about stuttering' (3 items), 'Feelings about stuttering' (5 items), 'Avoidance due to stuttering' (4 items), and 'Disadvantage due to stuttering' (4 items)).

Table 2
Overview of all ROIs included in the study.

	ROI name	Voxel	Volume	X Y Z
Cortical ROIs				
1.	Left anterior insula	1630	5.50	- 36.22 10.26–3.87
2.	Right anterior insula	1679	5.67	37.41 11.29–3.96
3.	Left frontal operculum	752	2.54	- 41.37 17.67 1.47
4.	Right frontal operculum	788	2.66	43.22 17.71 2.06
5.	Left inferior frontal gyrus[a]	1486	5.02	- 51.16 15.39 15.73
6.	Right inferior frontal gyrus[a]	1600	5.40	51.95 16.75 16.38
7.	Left precentral gyrus	6250	21.09	- 38.23–9.07 49.91
8.	Right precentral gyrus	6283	21.21	40.18–6.73 49.01
9.	Left cerebrum and motor[b]	2860	9.65	- 3.91 4.13 54.69
10.	Right cerebrum and motor[b]	2644	8.92	5.21 5.14 55.01
11.	Left superior temporal gyrus	2966	10.01	- 59.40–25.81 2.6
12.	Right superior temporal gyrus	3341	11.28	60.28–21.06 2.16
13.	Left inferior frontal angular gyrus[c]	1419	4.79	- 49.62 32.76 4.67
14.	Right inferior frontal angular gyrus[c]	1521	5.13	50.62 33.27 5.01
Subcortical ROIs				
15.	Left nucleus accumbens	151	0.51	- 9.27 11.88–6.55
16.	Right nucleus accumbens	154	0.52	9.55 12.18–6.00
17.	Left caudate nucleus	1174	3.96	- 12.95 8.91 10.31
18.	Right caudate nucleus	1283	4.33	13.95 10.01 11.02
19.	Left pallidum	519	1.75	- 19.65–3.31–2.23
20.	Right pallidum	520	1.75	20.63–2.40–1.89
21.	Left putamen	1417	4.78	- 24.84 0.93 0.01
22.	Right putamen	1388	4.68	25.75 2.17 0.03
23.	Left cerebellar vermal lobules VI-VII	492	1.66	- 1.48–70.81–22.79
24.	Right cerebellar vermal lobules VI-VII	460	1.55	3.01–70.61–21.97

Note. This table lists all ROIs chosen for statistical analysis in this study. ROI name = the name of a region of interest as it appears in the Neuromorphometrics atlas, Voxel = the size of an ROI in number of voxels, Volume = size in mm^3 , X, Y & Z = MNI coordinates, centre of mass.

[a] The atlas area 'inferior frontal gyrus' corresponds to Brodmann area 44 and we will therefore designate it as BA44.

[b] The atlas area 'cerebrum and motor' corresponds to the supplementary motor area (SMA) and will therefore be designated as SMA.

[c] The atlas area 'inferior frontal angular gyrus' corresponds to Brodmann area 45 and we will therefore designate it as BA45

2.2.2. Brain imaging data

2.2.2.1. Image acquisition. The high-resolution T1-weighted images used in this study were acquired on a 3.0 T Siemens MAGNETOM Prisma MRI scanner as part of a larger multimodal scanning protocol. The full protocol included both functional and structural scanning and lasted for around an hour. The T1-weighted images were the first images acquired during the scanning, and they were collected with the use of an MP-RAGE sequence with the following imaging parameters: voxel size 1x1x1mm, Field of view (FOV) 256 mm, 192 slices, Repetition time (TR) = 1800 ms, Echo Time (TE) = 2.28 ms, flip angle= 8 degree.

2.2.2.2. Image processing and analysis. The acquired images were processed and analysed with the Matlab/SPM12 add-in toolbox CAT12 (Gaser & Dahnke, 2016). CAT12 has been shown to be an efficient, valid, and reliable tool for processing of structural data for different clinical populations (Farokhian et al., 2017; Seiger et al., 2018; Tavares et al., 2019).

The CAT12 default preprocessing pipeline was used for this study; the acquired T1-weighted images were first segmented into grey matter, white matter and cerebrospinal fluid and then spatially normalized to the standard Montreal Neurological Institute (MNI) space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) procedure. The images were then smoothed using an 8 mm Gaussian kernel for the analysis of GMV. Before smoothing, the images underwent a quality check in accordance with the procedures given by CAT12 to check for image artifacts. GMV has been shown to correlate strongly with brain size (Barnes et al., 2010) and total intracranial volume (TIV) was therefore calculated for all subjects and controlled for in the statistical analysis.

2.2.2.3. ROI-analysis. CAT12 has a function for calculating mean GMV values inside ROIs based on a number of different anatomical atlases. The atlas Neuromorphometrics (www.neuromorphometrics.com) was chosen for this study, as this was the most detailed and comprehensive atlas map of the speech and language system amongst the atlases included in CAT12.

GMV-values of 24 ROIs were transferred to IBM SPSS Statistics (version 25) (SPSS for further analysis. We chose ROIs which represent relevant cortical and subcortical areas of the speech and language network of the left and right hemisphere (Belyk et al., 2015; Brown et al., 2005; Budde et al., 2014; Chang et al., 2019; Etchell et al., 2017; Price, 2012). A detailed list can be found in Table 2.

2.3. Statistical analysis

2.3.1. Stuttering severity

We analysed differences between men and women who stutter in both examiner-rated and self-rated stuttering severity. This was done by running an independent group *t*-test between men who stutter ($n = 15$) and women who stutter ($n = 9$), with total SSI4-scores and total WASSP-scores as dependent variables.

We did not find any significant difference in examiner-rated stuttering severity (SSI4-scores) between men ($M = 11.9$, $SD = 10.1$) and women ($M = 15.8$, $SD = 10.7$) who stutter, $t(22) = 0.88$, $p = .39$. However, we found a significant sex difference in self-rated stuttering severity (WASSP-scores), $t(22) = 2.441$, $p = .023$. The women of the stuttering group rated their stuttering severity ($M = 3.6$, $SD = 0.8$) higher than men ($M = 2.8$, $SD = 0.8$).

See Table 1 for individual data on stuttering severity.

2.3.2. Grey matter volume

We first conducted a multivariate general linear model (GLM) analysis to investigate GMV-differences between the stuttering group and the control group, and possible interaction effects between group and sex. In addition to the fixed factors 'group' and 'sex', age and TIV were chosen as covariates since both factors have been demonstrated to covary highly with GMV. Previous research has demonstrated that the choice of method for controlling for total amount of the tissue of interest may affect results (Peelle et al., 2012). Two approaches, global scaling based on brain size and using TIV as a covariate in statistical analysis, were tested in our study with no apparent difference in the results. It was therefore decided to use TIV as a covariate across all data analysis as this is more applicable when doing ROI-analysis in IBM SPSS Statistics.

Effect size was calculated, based on estimated marginal means, for differences between AWS and FC, and interaction effects, across all 24 ROIs. Hedge's *g* was chosen as effect size measure for the group differences, as this is the most valid choice for study designs with uneven and/or small sample sizes (Lakens, 2013). Hedges' *g*, as Cohen's *d*, is positively biased when applied on small sample sizes (Durlak, 2009), and this was corrected for in the equation. Hedges' *g* was calculated using the following formula:

$$g = \frac{M_1 - M_2}{SD_{pooled}} \times \left(1 - \frac{3}{4n - 9}\right)$$

where M_1 = the mean value of the variable of interest for group 1, M_2 is the mean for group 2 and SD_{pooled} = pooled and weighted standard deviation.

Cohen's *f* was chosen as effect size measure for interaction effects.

In this study we interpret Hedges' g-values in line with Cohen's classification (Sullivan & Feinn, 2012); a large effect size/strong effect is where $g \geq 0.8$, a medium effect size is equivalent to $0.5 \leq g < 0.8$ and the group effect, or difference, is interpreted as small at $0.2 \leq g < 0.5$.

For the interaction effects, we also follow Cohen's classification. Hence, Cohen's $f > 0.40$ = large effect size/strong interaction effect, $0.25 \leq f < 0.40$ = medium effect size and $0.1 \leq f < 0.25$ = small effect size.

Bonferroni-correction was used to correct for multiple comparisons across the 24 analysed ROIs. However, we also performed explorative analyses and report also results that reached an uncorrected *p*-level of 0.05 to investigate and highlight tendencies for future studies to investigate further.

3. Results

3.1. Differences in GMV between the stuttering group and the control group

The GLM-analysis revealed no large group differences between adults with stuttering (AWS) and fluent controls (FC) as no differences survived Bonferroni-correction for multiple comparisons. We found a tendency towards the right BA44 being smaller in the stuttering group, on average ($p_{\text{uncorrected}} = .050$, $g = -0.55$). Further, there was a tendency towards a larger right putamen, on average, in AWS, with $p_{\text{uncorrected}} = .049$ ($g = 0.56$).

3.2. Interactions between group and sex for GMV

3.2.1. Cortical areas

The strongest interaction effect, and the only result surviving Bonferroni-correction, was found for the right inferior frontal gyrus pars triangularis, or BA45 ($F(1,47) = 17.64$, corrected $p = .003$, $f = 0.58$). This area was smaller in women who stutter (WWS) compared to fluent women (FW), but larger in men who stutter (MWS) compared to fluent men.

Further, we found interactions that were significant at an uncorrected level for other ventral frontal lobe areas; the frontal operculum demonstrated moderate interaction effects for both the left ($F(1,47) = 6.48$, $p_{\text{uncorrected}} = .014$, $f = 0.36$) and the right ($F(1,47) = 7.46$, $p_{\text{uncorrected}} = 0.009$, $f = 0.39$) hemisphere. The anterior insula also showed moderate interaction for the left hemisphere ($F(1,47) = 5.68$, $p_{\text{uncorrected}} = .021$, $f = 0.33$). Lastly, a smaller tendency towards interaction was also found for the right homologue area ($F(1,47) = 4.02$, $p_{\text{uncorrected}} = .051$, $f = 0.28$). The interaction effects for these cortical ROIs are displayed in Fig. 1.

In summary, our results indicate that, for all these frontal lobe speech and language areas, men who stutter tend to have larger GMV than fluent control men. For the women, there is overall a smaller difference between the groups in this region, but the trend is that women who stutter, on average, have slightly smaller GMV than female fluent controls.

Fig. 2 illustrates these results and summarises all areas where we saw tendencies towards a sex-specific pattern of GMV. These were for all areas adjacent to BA44, but not for BA44 itself. We have chosen to name the region close to BA44, showing similar interaction effects, the lateral posteroventral frontal cortex (LPVFC).

3.2.2. Subcortical ROIs

For the subcortical ROIs included in the GLM, the left and right caudate demonstrated the strongest interaction effects (left: $F(1,47) = 6.73$, $p_{\text{uncorrected}} = .013$, $f = 0.36$, right: $F(1,47) = 5.92$, $p_{\text{uncorrected}} = .019$, $f = 0.34$).

Further, we found interaction effects for the cerebellar vermal lobules 6–7 (left: $F(1,47) = 6.13$, $p_{\text{uncorrected}} = .017$, $f = 0.35$, right: $F(1,47) = 5.04$, $p_{\text{uncorrected}} = .030$, $f = 0.31$). No interaction effects survived Bonferroni-correction for the subcortical ROIs. The subcortical interaction effects are displayed in Fig. 3.

4. Discussion

Our aim was to explore if sex is a factor related to variation in GMV in adults who stutter. We found indications of group differences between AWS and fluent controls in two areas; the right BA44 was moderately smaller, and the right putamen was moderately larger in AWS. These results did not survive correction for multiple comparisons and should be interpreted with caution.

To further explore the relationship between sex, GMV and stuttering, we analysed interaction between group (AWS vs. controls) and sex. One interaction effect survived Bonferroni-correction for multiple comparisons; the right BA45 was smaller in the women in the stuttering group compared to female controls, but the tendency was clearly opposite when comparing the male stuttering group with male controls. We also found indications of interactions between group and sex, on an uncorrected level, for several areas of the inferior frontal cortex, the striatum and the cerebellum. Our explorative results suggest sex-specific GMV-patterns that have not previously been described. We hope that our findings may serve as guidance for future research on the relationship between sex and stuttering.

4.1. Group differences between AWS and fluent controls

The BA44 is a central area in prominent language models and is part of what is traditionally defined as Broca's area in the left hemisphere (Guenther & Vladusich, 2012; Hickok, Venezia, & Teghipco, 2023). A recent review highlighted the tendency towards stuttering adults activating areas of the right hemisphere homologue to speech production areas of the left hemisphere, when speaking (Etchell et al., 2017). In line with this notion, the right frontal operculum has been suggested to serve a compensating role in speech in adults who stutter (Preibisch et al., 2003). Our results do not indicate that this notion is also reflected on the structural level, as we found a tendency towards lower GMV in the right BA44 for the stuttering group. Also, our results do not support reports of lower GMV

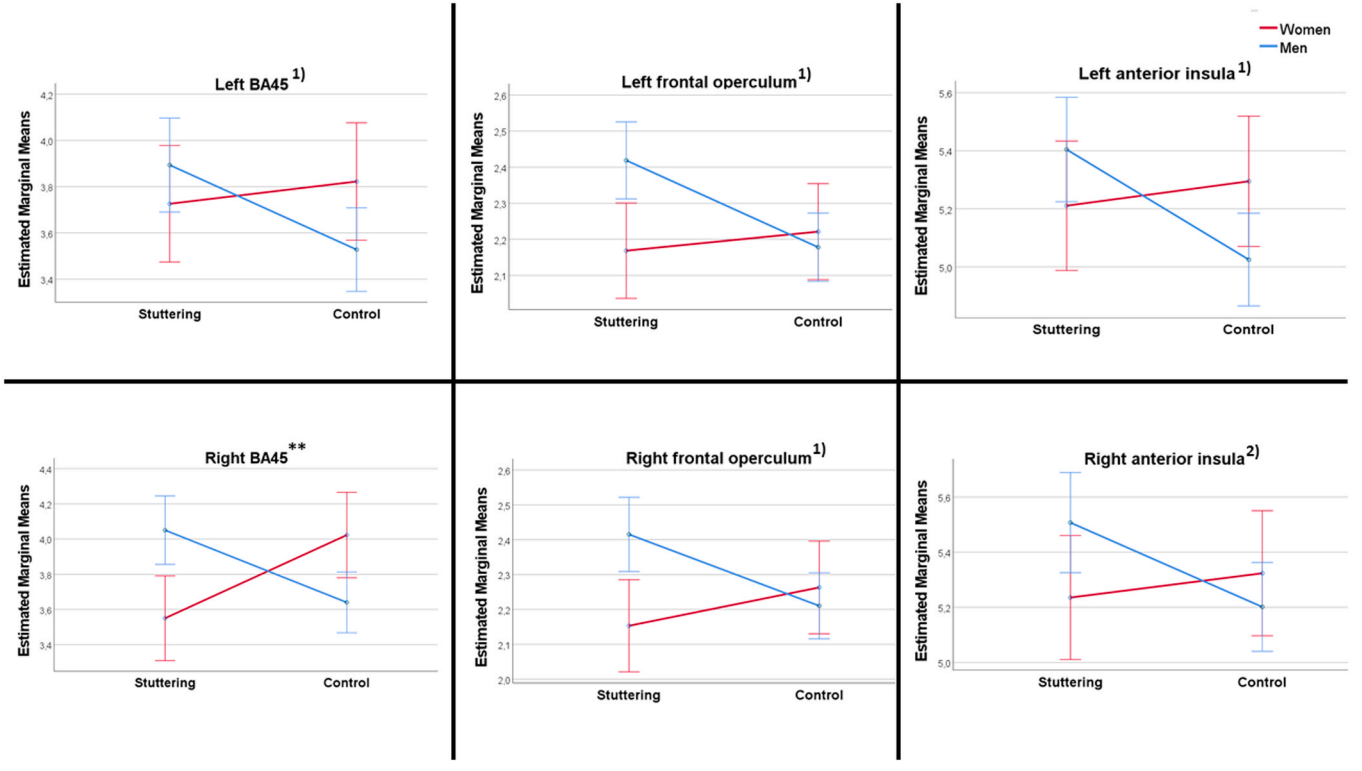

Fig. 1. *Group*Sex Interaction effects for Grey Matter Volume of Cortical ROIs. Note.* The figure show interactions between group (AWS vs. FC) and sex for ROIs of the left (top row) and right (bottom row) inferior frontal cortex. Estimated marginal means of grey matter volume, in number of voxels, is presented on the y-axis. Covariates appearing in the model are evaluated at the following values: Age = 31.3, total intracranial volume = 1640 mm^3 . Error bars: 95 % CI. $^{**}p < 0.01$, Cohen's $f > 0.5$. 1) = $p_{uncorrected} < 0.05$, Cohen's $f > 0.3$. 2) = not significant ($p_{uncorrected}$ =.051, Cohen's $f = 0.28$).

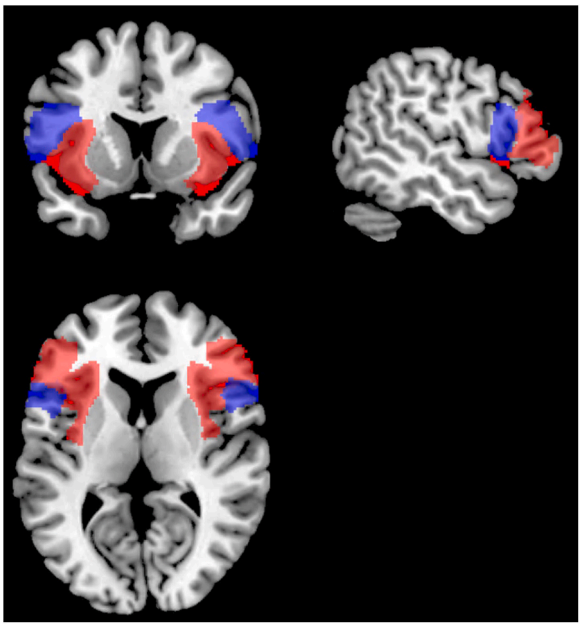

Fig. 2. *Results for the Lateral Posteroventral Frontal Cortex*, *Note.* The figure illustrates the location and boundaries for the region we have named the *lateral posteroventral frontal cortex* (LPVFC), i.e. the ROIs adjacent to the BA44 in the inferior frontal cortex showing similar interaction effects between sex and group (AWS vs. FC). The LPVFC includes the BA45, the frontal operculum and the anterior insula. Red area = bilateral LPVFC, blue area = bilateral BA44. The LPVFC is here superimposed on a standard MNI brain.

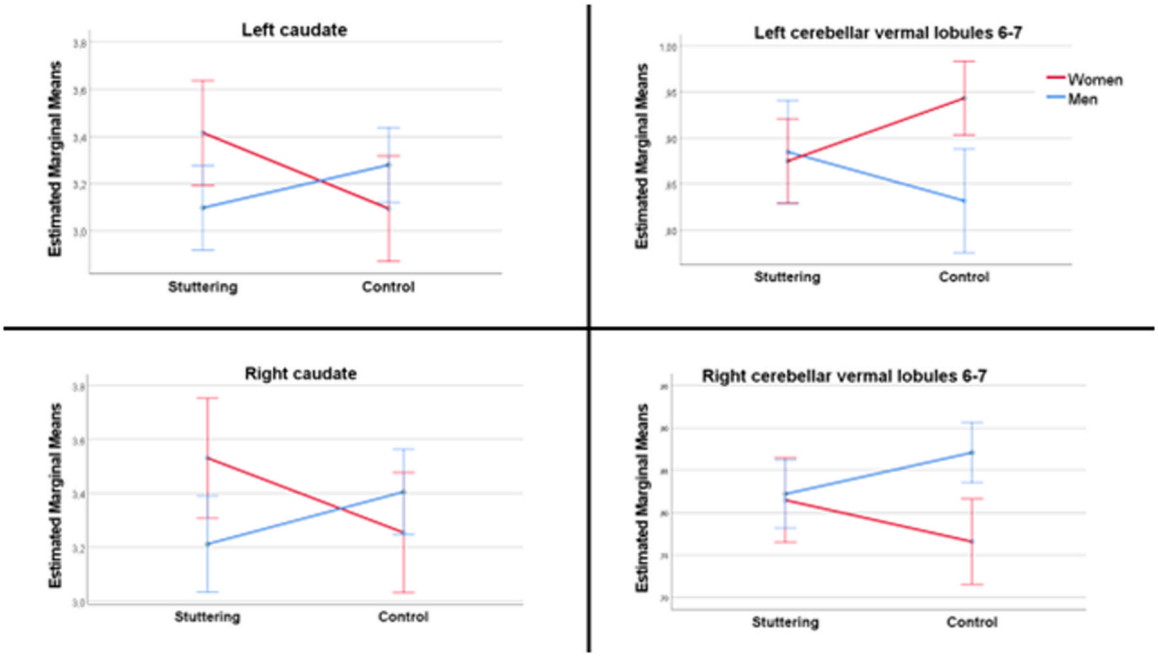

Fig. 3. *Group*Sex Interaction effects for Grey Matter Volume of Subcortical ROIs. Note.* The figure show interactions between group (AWS vs. FC) and sex for the subcortical ROIs included in analyses. Estimated marginal means of grey matter volume, in number of voxels, is presented on the y-axis. Covariates appearing in the model are evaluated at the following values: Age = 31.3, Total intracranial volume = 1640 mm^3. Error bars: 95 % CI. The subcortical interactions were significant at an uncorrected p-level < 0.03 (Cohen's $f > 0.3$).

in the left IFG in adults who stutter (Kell et al., 2009; Lu et al., 2010).

We also found indications towards larger GMV in the right putamen (and weaker indications of a larger left putamen) in the stuttering group. The putamen is suggested to be involved in feedforward speech motor control through its role in the BGTC-loop

(Guenther, 2015), and this circuit may seem to have a crucial role in dysfluent speech production in stuttering (see e.g. Chang & Guenther, 2019). The putamen is proposed to serve the role as an initiator of the next speech motor segment by giving a "go-signal" to the supplementary motor area (Alm, 2004, Theys et al., 2024) and is proposed to be a key neurological substrate in stuttering (Theys et al., 2024). Our group results for AWS vs. fluent controls support the theory of a relationship between the putamen and stuttering in adults but mainly for the right putamen. It should be underscored that these results did not survive correction for multiple comparisons and should only be interpreted as potential guidance for future research.

4.2. Interaction effects between group (AWS vs. controls) and sex

There are indications of a relationship between sex and stuttering when looking at developmental stuttering from an epidemiological, a genetic and a behavioural perspective, as discussed previously. We explored the potential role of sex by analysing interaction between sex and group (AWS vs. fluent controls).

4.2.1. Inferior frontal cortex

The strongest interaction effect was found for the right BA45. This was the only significant result after correction for multiple comparisons ($p < 0.01$, Cohen's $f > 0.5$). Further, we found interactions at an uncorrected level for the left BA45, the bilateral frontal operculum and the left anterior insula. Together, these interactions indicated that all these areas adjacent to the BA44, the region we have named the LPVFC, were smaller in stuttering females, compared to fluent females. For the males, this region showed a tendency towards being larger in the stuttering group. The exception is the BA44 where no interaction was detected. The inferior frontal cortex is known to be a main site for speech and language production, mainly in the left hemisphere (Flinker et al., 2015). The BA45 is part of Broca's area in the left hemisphere and is shown to be involved in several aspects of speech and language, e.g. in verbal fluency through its role in lexical retrieval and in the semantic aspects of language, like semantic decision-making tasks (see e.g. Heim et al., 2009). Together with the frontal operculum, BA45 is part of the ventral language pathway involved in semantic processing (Friederici & Gierhan, 2013). It is interesting in this context that research have found that stuttering is related to the dorsal, not the ventral, language pathway., i.e. that stuttering is related to the motor, or articulatory, aspects of speech production rather than semantics (Kronfeld-Duenias et al., 2016). Our results indicate that the relationship between the ventral language network and stuttering differs for men and women. Further, a study reports that inhibition of the right BA45 with repetitive transcranial magnetic stimulation (rTMS) influences stuttering severity for a group of men with stuttering (Tezel-Bayraktaroglu et al., 2020). It is interesting in relation to this that our results indicate that the right BA45 is larger in men who stutter than in fluent men, but the tendency is opposite for women. We hope that future research will further explore the role of the right BA45 in stuttering for both men and women.

4.2.2. Striatum and cerebellum

We found indications of interaction between sex and group for the bilateral caudate, at an uncorrected level; the tendency was that the caudate were larger in the women of the stuttering group, compared to fluent women. For the men, however, the difference was smaller, but with an opposite tendency. As mentioned, a few studies have found functional and structural differences in the caudate in people who stutter compared to fluent controls (Ingham et al., 2004, Montag et al., 2019). But, the results vary, and the picture is unclear at this point.

For the subcortical structures we also found indications of interactions (at an uncorrected level) between group and sex for the cerebellar vermal lobules 6–7 with opposite tendences for the left and right lobules. For the men who stutter, there was a tendency towards larger left lobules 6–7 compared to fluent men. For the men, the tendency was opposite for the right lobules 6–7 which were smaller in the male stuttering group. The difference between the female groups showed an opposite pattern; the left lobules 6–7 showed a tendency of being smaller in the female stuttering group compared to female controls but the tendency was opposite for the female groups for the right lobules 6–7. Several studies on brain function and structure in adults who stutter have demonstrated cerebellar involvement in stuttering (see reviews by Chang et al., 2019; Etchell et al., 2017). One explanation of the relationship between stuttering and the cerebellum has been that the level of activation of the cerebellum is linked to how fluent the speech of a person who stutters is, and their stuttering rate (i.e. Belyk et al., 2015; Fox et al., 1996). This is based on the cerebellum's proposed role in motor timing control, also in the timing of speech (Kotz & Schwartze, 2010). As mentioned, Ingham et al. (2004) found a sex difference with respect to correlations between brain activity and stuttering rate. More specifically, they reported a positive correlation for the medial cerebellum, for men only. In our study, we controlled for sex differences in both examiner-rated and self-rated stuttering severity and found a small sex difference for the latter. We cannot exclude that this has influenced the group results for the sex-wise analyses.

It has long been recognized that the basal ganglia loops and the cerebellar loops appear to work in parallel in the control of movements (Strick, 1985). For example, in basal ganglia disorders the cerebellar system may partially compensate for the basal ganglia impairments (Hanakawa et al., 1999). These two parallel systems seem to complement each other also in speech (Alm, 2004; Kotz & Schwartze, 2010). If there is a deficiency in the CBGTC-loop, this may lead to higher reliance on the loop involving the cerebellum, in a compensatory manner (Alm, 2004; Chang et al., 2019). Our results indicate that there might be a sex difference in how these areas are involved in stuttering.

4.3. Summary

Our explorative results give indications of regional sex-specific patterns of grey matter volume in cortical and subcortical areas

involved in speech and language processing.

One of several possible explanations for our tentative results is that men and women compensate for stuttering through different neural mechanisms. If so, our results for the subcortical ROIs might imply that women who stutter rely on pathways involving the striatum to a greater extent than men, and therefore these structures are larger in stuttering females than in controls. One may further speculate if women compensate through the use of a wider range of functions related to emotional regulation, cognition and/or motor control. It is interesting, in this context, that research has indicated that women tend to report that stuttering has a greater negative impact on their lives, compared to men (Samson et al., 2022). In our study we also found that the female participants rated their stuttering severity slightly higher than the male participants. Further, there are preliminary data indicating sex differences in the strategies AWS use to cope with dysfluencies (Russøy et al., 2021). More research is needed to explore the relationship between sex, coping strategies and brain structure and function, for adults who stutter.

One can further speculate that the role of the BA44 in stuttering is something men and women who stutter have in common, as this area shows little interaction between group and sex in our study, and a tendency towards a group difference between AWS and controls. The adjacent areas, on the other hand, show indications of sex-specific patterns, as discussed above. The left BA44 is part of Broca's area and has been described as the site for a "speech sound map" linking together auditory feedback and motor execution through connections with the auditory cortex and M1 (Guenther, 2015) i.e. forming an auditory motor integration pathway (Chang et al., 2019; Hickok & Poeppel, 2015). One hypothesis about the causes of stuttering is that this pathway is downregulated as a consequence of reward-based learning mechanisms. It is a known phenomenon that such downregulation happens because of repeated sensory feedback errors. This was demonstrated by Shannon et al. (2016) for hand movement controlled by visual feedback to the BA44. In the context of stuttering, it is possible that the person who stutters repeatedly receives auditory feedback from producing dysfluent speech, which does not match the expected speech outcome. When this happens over time, auditory pathways to the left BA44 might be downregulated.

In the context of compensation for stuttering, our data may indicate that women who stutter involve structures of the striatum to a greater extent than men. Further, one can speculate if, to a greater extent for men than women who stutter, the areas adjacent to the BA44 are upregulated as a form of compensatory mechanism. This hypothesis has previously been suggested by Kell et al. (2009) based on a study involving 13 male stutterers.

So far, we have speculated if sex differences in compensation strategies might explain our tentative results. One might also hypothesize if *the aetiology* of the disorder is sex specific. Support for this comes from the study by Drayna et al. (1999), indicating that stuttering "runs in families" to a greater extent for women who stutter than for men. If the genetic influence is different for men and women who stutter, then structural-/GMV-markers are likely to differ also (Chow et al., 2020). But the exact relationship between genes and the behavioural or neurological symptomatology of stuttering is still not well understood (Kraft & Yairi, 2011; Polikowsky et al., 2022).

Different aetiology of stuttering for men and women might be a reason in itself for sex differences in GMV, or it might be the predecessor to sex differences in compensation.

4.4. Strengths and weaknesses of our study

Our analyses are exploratory, and most results are not corrected for multiple comparisons. We suggest that our results are treated as a starting point for future research on the potential influence of sex on the structural neurology of stuttering in adults.

We only managed to recruit 9 stuttering women for this study, and even though that is a relatively high female representation compared to other neuroimaging studies on stuttering (Montag et al., 2019), the statistical power is relatively low. The results for females alone from this study should therefore be interpreted with particular caution.

Another factor that should be taken into consideration is the type and amount of treatment previously received by the stuttering participants. It has been demonstrated previously that fluency shaping can alter the activation patterns of both subcortical (Giraud et al., 2008) and cortical (Neumann et al., 2005) areas involved in speech production. Even though no participants in our study were involved in therapy targeting their speech for at least six months prior to participation, it can be argued that there may be long-term effects from fluency shaping therapy that were not controlled for, and that this might differ systematically between the men and women of our study.

A strength of our study is that we have managed to reveal tendencies towards patterns of sex differences in GMV related to stuttering, through an explorative design. This is a relevant approach if we are to increase our understanding of the aetiology of stuttering. Further, the reported effects may also provide hints as to why neuroimaging results from studies on persons who stutter are so heterogeneous.

4.5. Suggestions for future research

WE REMOVED THE FIRST SENTENCE HERE. We suggest that future studies have a greater focus on sex distributions of study groups. It is well-known that the grey matter of brain areas involved in networks that are of frequent use increase in volume. And that, conversely, networks that remain unused over time decrease in volume as a result of synaptic processes like long-term potentiation and long-term depression, as well as "synaptic pruning" (Sakai, 2020). But, the relationship between volume and specific behaviours, or skills, is not straightforward; as skills grow through practice, involved brain networks get increasingly connected and this connectivity gets more efficient over time. Hence, some involved brain areas may decrease in volume as a result of plasticity processes (Vaquero et al., 2016). This complex relationship makes it difficult to infer about behavioural or psychological factors related to stuttering from

research on grey matter volume. Research on structural and functional connectivity keeps giving us a deeper understanding of the relationship between structure and function. More research on connectivity, as well as combined functional and structural studies, on stuttering, is needed to further elucidate this in the future.

As mentioned, many studies on brain structure in stuttering have few participants and low power. If combining forces, the researchers in the field could build up the larger evidence base needed to detect factors differentiating between subgroups in stuttering, as for instance for the population of females who stutter. As highlighted also by Chang et al. (2019, p. 576), the individual variation in the neural markers of stuttering may be a result of compensatory strategies and strategies learned through therapy interacting with neural deficiencies. Such strategies may potentially vary systematically with sex.

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CRediT authorship contribution statement

Siv Andresen: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Alm Per:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Frøydis Morken:** Writing – review & editing, Supervision. **Karsten Specht:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Karsten Specht reports financial support was provided by Research Council of Norway. Co-author Per Alm is a member of the editorial board of the Journal of Fluency disorders. We do not believe this to have influenced our workor the publishing process, but thought it is still worth mentioning. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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