The neurobiological differences in the cerebrum between persons with developmental stuttering and their fluently speaking peers.

What are the functional and structural mysteries behind this speech disorder?

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Abstract

Developmental Stuttering (DS) is a speech disorder which is characterized by repetitions, prolongations, or pauses that disrupt the normal flow of speech. It occurs in approximately 5-8% of the pre-school children and recovers spontaneously in 70-80% of the cases, resulting in a prevalence of about 1% in adolescence. However, unrecovered people who stutter (PWS) can experience lifelong negative consequences, like participation restrictions, irritation and embarrassment. It is known that DS has a clear genetic basis, that PWS have increased dopamine activity, and that the severity of stuttering can be reduced by dopamine blockers. Here we describe functional and structural grey and white matter abnormalities that are present in PWS. It appears that the precentral gyrus (primary motor cortex), inferior frontal gyrus (IFG), superior temporal gyrus (STG), middle temporal gyrus (MTG), supplementary motor area (SMA), middle frontal gyrus (MFG), rolandic operculum (RO) and corpus callosum (CC) are important key players in DS. Although not all data support each other in all details, here we attempt to give a shared overview of current research and its directions, both in adults and children with DS. It has become clear that some brain differences already exist during childhood rather than resulting from compensatory attempts, and can therefore be used as markers for the development and monitoring of DS. Increased knowledge about DS could potentially open new ways for treatment of PWS, and may prevent the symptoms of persistent DS. This could results in less anxiety, shame, and irritation during social interaction, and would make the life of millions of stutterers a lot easier and more pleasant.

Keywords: speech disorder, developmental stuttering, neuroimaging, brain activity, brain anatomy, brain connectivity

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1. Introduction

In the past decades, research concerning the basis of developmental stuttering (DS) has revealed large amounts of information. Still, the underlying mechanisms behind this speech disorder are not clear. According to the International Classification of Diseases and Related Health Problems (ICD-10) of the World Health Organization (WHO), stuttering is defined as "speech that is characterized by involuntary frequent repetitions or prolongations of sounds, syllables or words as well as frequent involuntary hesitations or pauses that disrupt the rhythmic flow of speech" [1]. Secondary symptoms -such as eye blinking and head movement- are adapted in an attempt to minimize the severity of stuttering.

Stuttering is classified into 3 types: psychogenic, neurogenic, and developmental. Psychogenic stuttering is the rarest form of stuttering and is only seen in adults with a psychiatric history [2]. Neurogenic stuttering arises in adulthood as the result of injury or disease of the Central Nervous System (CNS), such as a stroke, head trauma, or neurodegenerative disease [3,4,5,6]. This chapter will focus on the last type of stuttering, which is developmental stuttering (DS). This type arises without apparent brain damage and is the most prevalent form of stuttering [5,7,8,9].

Previous research showed that speech therapy in an early phase contributes to the recovery of normal speech and prevents the development of moderate or severe stuttering [10]. If started within a year of onset of stuttering, a reduction of about 84-

96% of the stutter-related-behaviour was observed on a mid-long period. This percentage decreases to 47% when the stuttering already exists for 2 years [11]. It is therefore of great importance that a speech-language pathologist (SLP) is consulted early after the first symptoms of stuttering are observed, especially when these symptoms do not disappear within several months. Waiting too long in consulting a SLP may result in poor prospects.

Earlier research has shown that PWS have increased dopamine activity in specific brain regions [12]. Movsessian (2005) [13] hypothesized that the excitatory and inhibitory balance is disrupted by this dopamine increase, resulting in a possible hyperexcitation of the primary motor cortex, which could be important in DS. In addition, several other studies have shown that stuttering severity is reduced when dopamine blockers -like olanzapine, haloperidol, and risperidone- are administered [14,15,16]. Due to great side effects, however, dopamine blockers are not acceptable for treating secondary effects of DS at this moment.

Other studies have been focussing on the genetic background of stuttering. Most studies (some of them are several decades old) have shown that DS has a clear genetic basis [9,17,18,19,20,21,22]. For instance, it appears that the concordance rate in monozygotic twins is higher compared with dizygotic twins [23,24], and the heritability is about 70% [25]. Recently, Kang *et al.* (2010) [26] discovered that a mutation in the GNPTAB, GNPTG and NAGPA genes is associated with stuttering. These genes are crucial in the lysosome pathway and they found that a mutation in this route leads to lower enzyme activity, which is related to speech problems [9,26,27]. However, the exact mechanism behind this is still not known.

All these bewildering findings lead to the question in what way brain abnormalities are present in persons with DS. The main aim of this chapter is to discuss the brain regions which are involved in DS.

First of all, brain areas involved in the production of speech and hemispheric lateralization will be discussed (§2). In the subsequent paragraph, grey matter (GM) differences in brain anatomy (§3.1) and activity (§3.2) between people with DS and their fluently speaking peers will be discussed. Thereafter, the differences in white matter (WM) anatomy (§4.1) and connectivity (§4.2) between brain regions in DS will be discussed. Finally, the chapter will be completed with a conclusion.

2. The basis of speech production

For most people, the left hemisphere is language dominant: 70-75% in left-handed persons, and 90-95% in right-handed persons [28,29]. Also, men appear to be more left-lateralized for language than women [30]. Furthermore, it is known that language dominancy shifts to the right hemisphere after injury or lesions in the language-dominant left hemisphere [31,32]. So, when studying the brain regions involved in DS, confounding factors such as handedness, gender, and neurologic history should be taken into account.

Speech production is made up of four different stages which ensures that conceptual ideas of words or sentences are retrieved and pronounced in the correct way. It seems plausible that this process is somehow disrupted in PWS. The *first* stage in speech production is conceptual processing. Brain regions involved in this stage are seven left-lateralized brain regions: the (i) inferior frontal gyrus (IFG), (ii) medial prefrontal cortex (mPFC), (iii) inferior parietal lobe (IPL), (iv) middle temporal gyrus (MTG), (v) fusiform gyrus, (vi) parahippocampal gyri, and (vii) posterior cingulate gyrus [33,34]. These brain regions are also associated with single-word comprehension [34]. The *second* stage is word retrieval in which the left-lateralized (i) IFG (pars opercularis) and (ii) middle frontal cortex (MFC) are involved [34,35,36]. The *third* stage is articulation, with involved brain regions being the (i) left anterior insula, (ii) bilateral primary (pre)motor cortex, (iii) pre-supplementary motor area (pre-SMA), and (iv) the left putamen. The *fourth* and last stage in speech production involves feedback of the spoken response, which is important for the immediate correction of speech production and spoken language. Brain regions involved in this stage are (i) the cerebellum, (ii) superior temporal gyrus (STG) (planum temporale), and (iii) supra marginal gyrus (SMG) [33,37]. In PWS, the order of activation of these brain regions is altered during speech [38], but the exact causal factors remain unclear.

3. Grey matter alterations in DS.

In the past years, extensive neuroimaging research has been done to understand more about the mechanisms of DS. The main question discussed in this paragraph is in what way brain activity and anatomy in the grey matter is different in DS. There have been several studies in the last years which have tried to address this question using Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and functional MRI (fMRI) during rest, silent reading, stuttered speech, and fluent speech in PWS.

3.1 Anatomy

An early study investigating grey matter abnormalities in cortical brain regions involved in speech production in PWS was performed by Foundas *et al.* (2001) [39]. They studied the volumetric MRI scans of sixteen adults with DS and their matched controls and found several differences in the right and left STG (planum temporale). Increased grey matter volume (GMV) was observed in these regions in PWS compared with controls. Also, the degree of the planar asymmetry was decreased in adults with DS. Moreover, PWS had significantly more gyral variants in the speech production areas than their fluently speaking peers [39]. These results were one of the first that indicated a neuroanatomical abnormality in a speech-related area. The authors concluded that this abnormality is a risk factor and that the presence of it may put an individual at risk to develop DS.

In the healthy human brain, two consistent anatomic asymmetries can be found: a larger right than left prefrontal lobe, and a larger left than right occipital lobe [40,41]. An altered asymmetry in one or both of these regions is considered as atypical cerebral lateralization. This altered asymmetry was investigated using volumetric MRI scans on sixteen adults with DS and matched controls. No difference in total brain volume and hemispheric volume was observed between the two groups. Whereas in controls these prefrontal and occipital asymmetries were found, in adults with DS, however, these were lacking [42]. The lack of these asymmetries was even found in children with DS [43], indicating early abnormalities in this respect. So, these studies conclude that children and adults with DS have atypical brain asymmetries.

Beal *et al.* (2007) [45] investigated whether neuroanatomical differences in the auditory cortex are present in PWS. Twenty-six right-handed males with DS were tested using MRI. No difference was found in total GMV between PWS and their matched controls [45]. In PWS, however, increased GMV was found in several brain regions, including the right STG, two clusters of the left STG, left IFG, and right cerebellum (table 1) [45].

Table 1. Increased grey matter volume in PWS. *Displayed are five brain regions with increased grey matter volume in PWS relative to controls. x, y, z are coordinates in Montreal Neurological Institute (MNI) space; cluster size = size of voxels (table from Beal et al. (2007) [45].*

Anatomical region	Laterality	*x*	*y*	*z*	Z score	Cluster size
Grey matter						
Superior temporal gyrus	R	56	−12	−4	4.42	271
Superior temporal gyrus	L	−28	10	−28	3.78	95
Inferior frontal gyrus	L	−48	10	18	3.75	83
Cerebellum	R	16	−42	−46	3.63	73
Superior temporal gyrus	L	−54	−12	6	3.61	72

The greatest increases were found in both the right and left STG, which includes the primary auditory cortex and planum temporale area. Another study found overlapping results in PWS: increased GMV was observed in the bilateral STG, MTG, precentral gyrus (primary motor cortex), postcentral gyrus, inferior parietal lobes (IPL) and IFG compared with controls [46]. Additionally, a decrease in GMV was mainly observed in the bilateral posterior lobes of the cerebellum and dorsal part of

the medulla relative to fluent speakers [46]. Both studies [45,46] taken together with preceding studies [39,42,43], suggest that several brain structures are anatomically different in PWS.

The perisylvian region, which is an umbrella name for different brain areas located near the sylvian fissure, is important in speech. This region was studied in nineteen right-handed males with DS and sixteen right-handed controls using MRI by Cykowski *et al.* (2007) [47]. In the right perisylvian region (IFG), a greater number of sulci connecting the right Sylvian fissure (IFG) was observed in PWS [47]. This is in line with earlier research [39], although the neuroanatomical differences observed by Foundas *et al.* (2001) [39] were bilateral. The absence of a bilateral difference in asymmetry between PWS and controls in the study of Cykowski *et al.* (2007) [47] could be due the fact that only right-handed males participated in this study. In the study of Foundas *et al.* (2001) [39], both left- and right-handed males participated, as well as left-handed females. As we know, gender and handedness are factors which have an influence on the degree of asymmetry [29,30], and could have affected the results.

Until now, most neuroimaging research concerning DS was performed on adults. However, to find out whether abovementioned neurobiological differences observed in PWS are the cause or the consequence of the lifelong stuttering, studies are needed that investigate these differences during childhood, thereby resulting in a better understanding of the development of neurobiological brain differences in DS during life.

The first study which investigated brain anatomy differences in children with DS was performed by Chang *et al.* (2008) [48]. In this MRI study, GMV measured by voxel-based morphometry (VBM) was compared in eight children with DS, seven children who spontaneously recovered from DS, and seven controls. Reduced GMV was found in the left IFG, MTG and bilateral STG (planum temporale) in children with DS and children who recovered from DS, compared to controls. This is contradictory to previous findings [39,45], which observed an increase in GMV in these areas. Furthermore, Chang *et al.* (2008) [48] observed increased GMV in bilateral precentral gyrus (primary motor cortex) and STG in children with DS compared to children who recovered from DS and controls, which is consistent with previous findings in adults [45,46]. Finally, as in accordance with Cykowski *et al.* (2007) [47], the study of Chang *et al.* (2008) [48] found no left to right hemispheric asymmetry differences in children with DS, which has been observed in the study of Foundas *et al.* (2003) [42]. These results suggest that some neural differences observed in adults with DS are a compensatory effect rather than the underlying cause of the stuttering.

Kell *et al.* (2009) [49] studied the GMV and brain activity in adults with DS. In this study, thirteen PWS before and after speech therapy, thirteen persons who spontaneously recovered from DS, and thirteen controls were studied in an fMRI scanner while reading out loud. Speech therapy resulted in a decrease in overall

percentage stuttering from 7.4% to 0.6% in PWS, a percentage reached both in controls and in persons who spontaneously recovered from DS. Contradictory to findings of Beal *et al.* (2007) [45], reduced GMV was observed in the left IFG in PWS [49], which is an important area for the production of speech [33,34]. Stuttering severity correlated negatively with this decrease in GMV (figure 1).

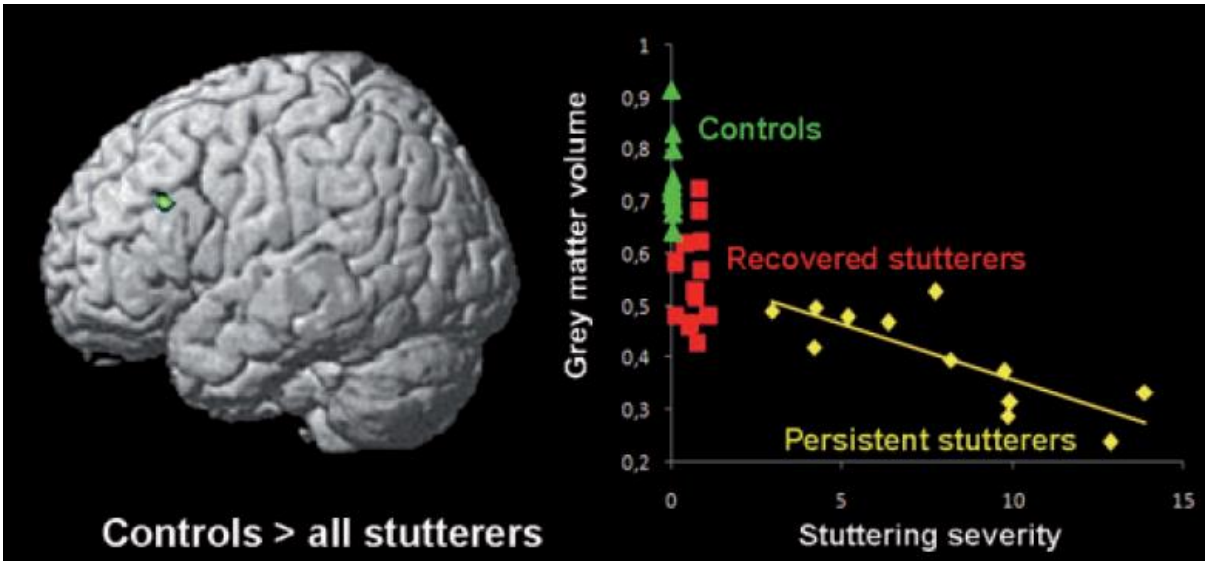

Figure 1. Decreased GMV in left IFG. *Decreased GMV was found in the superior part of the left IFG in PWS. This decrease correlated negatively with stuttering severity in persistent stutterers (figure from Kell et al., 2009 [49]).*

It is known that GMV in the brain can increase as a result of a certain expertise (for instance, navigation skills or yoga) [50,51]. Elaborating on this knowledge, the most recent study investigating grey matter differences in children with DS, found less GMV in the bilateral IFG in children with DS compared to controls [52]. Furthermore, a negative correlation was found between GMV in the right IFG and stutter severity (figure 2) [52]. These results are consistent with other studies on grey matter brain anatomy differences in both children [48] and adults [45,46] with DS. Furthermore, increased GMV was observed in the right rolandic operculum (RO), right MFG, and right STG compared to control children [52]. Again, these results are in line with the 2007-study of this group in adults with DS [45], and suggest that this is not a compensatory effect.

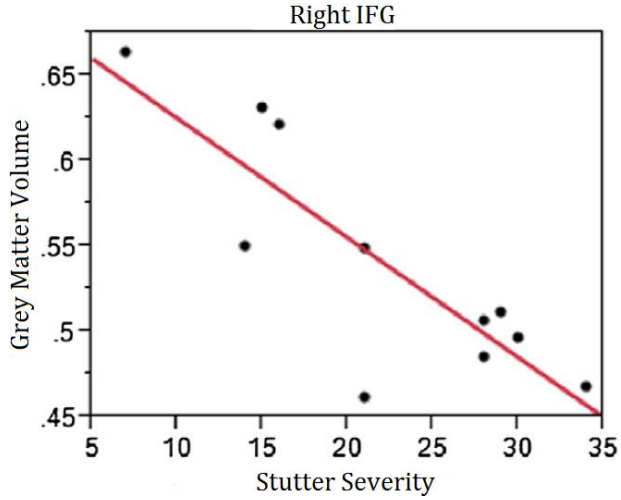

Figure 2. Correlation between right IFG and stutter severity. *Displayed is the correlation between GMV in the right IFG and stutter severity (image from Beal et al., 2013 [52]).*

3.2 Activity

The earliest neuroimaging study that investigated brain activity in PWS was performed in 1996 by Fox *et al.* (1996) [53]. Using PET-scanning, ten adults with DS and ten controls were measured during solo paragraph reading and chorus paragraph reading (to induce fluency in adults with DS). An increased consistent right-lateralized brain activity in either condition was observed in the premotor cortex, SMA, and cerebellum in PWS [53]. Left hemispheric activation of the superior and posterior temporal cortex and IFG was practically absent during speech in PWS [53].

Another old neuroimaging study that investigated brain activity in DS was performed by Braun *et al.* (1997) [54]. Just like Fox *et al.* (1996) [53], they found that the left-lateralized language dominancy is altered in PWS relative to fluent speakers. In this study, regional cerebral blood flow (rCBF) was measured during language tasks. rCBF is a derivative of brain activity, because active brain tissue needs more oxygen compared to less active brain tissue, so an increase in rCBF reflects activity. They found that increased rCBF rates of left hemispheric language regions in PWS is associated with stuttered speech, and increased rCBF rates of the right hemispheric brain regions is associated with fluent speech in adults with DS [54]. This was confirmed in a later study that found a negative correlation between brain activation in the right hemisphere and stutter severity (figure 3) [55]. Thus, it appears that fluent speech is associated with increased brain activation in the right hemisphere. Collectively, these results suggest a compensatory effect in the right hemisphere in PWS rather than a dysfunction in these regions.

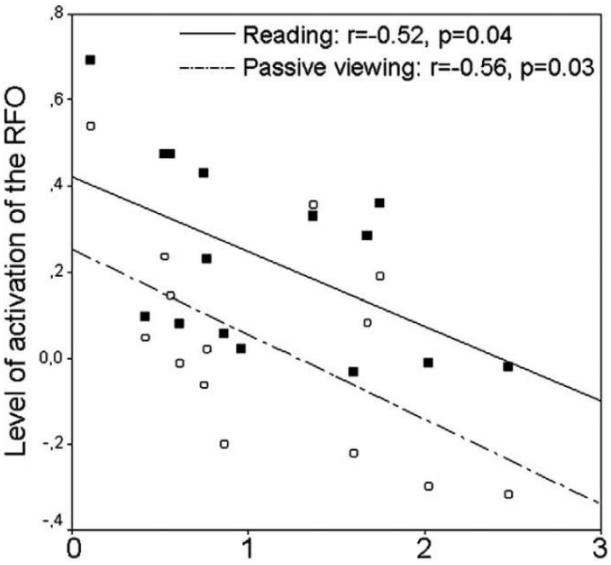

Figure 3. Correlation between BOLD activation in right hemisphere and stutter severity. *Stutter severity and mean Blood-Oxygen-Level Dependent (BOLD) response in the right hemisphere are negatively correlated with each other in PWS. Filled squares: reading; open symbols: passive viewing of meaningless signs; x-axis indicates stutter severity measured by stutter severity index; RFO = right frontal operculum (image from Preibisch et al., 2003 [55]).*

Another PET-study investigating the differences in lateralization between PWS and non-stutterers studied ten right-handed males with DS and ten matched controls during silent and oral single word reading tasks. As in accordance with Fox *et al.* (1996) [53] and Braun *et al.* (1997) [54], greater left lateralization was found in non-stutterers during oral reading and greater right lateralization was found in PWS during oral reading [56]. However, this difference in lateralization was not observed

during silent reading [56]. It could be that the underlying neural substrate for both tasks is different, or (as the authors of that paper already suggest) that the response of the neural substrate active during silent reading was not high enough to reveal a significant difference in the stuttering group. So, it appears that this study by De Nil *et al.* (2000) [56] supports the lateralization theory proposed by Fox *et al.* (1996) [53] and Braun *et al.* (1997) [54].

Beside the fact that Braun *et al.* (1997) [54] found left lateralization in fluent speakers and altered hemispheric lateralization during speech in persons with DS, some other differences were found between PWS and their fluently speaking peers. Firstly, more rCBF was observed in left-lateralized premotor, primary motor and somatosensory cortices in PWS during rest. Secondly, increased brain activity was found during stuttered speech in the premotor cortex, SMA, bilateral cerebellum, and bilateral association areas like the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) in adults with DS, which is in accordance with Fox *et al.* (1996) [53]. Moreover, it appeared that the degree of disfluency correlated positively with the rCBF in the left lateralized regions in the ACC, PFC, and posterior cingulate cortex (PCC) [54]. Ergo, this produces a feasible role for the ACC and PFC in the generation of stuttered speech. Finally, less activation was observed in the right supramarginal gyrus and post-rolandic areas -like the posterior STG- during stuttered speech in PWS [54]. Summarizing, these first neuroimaging studies suggest that –both during rest and stuttered speech- functional brain activity differences are present in PWS.

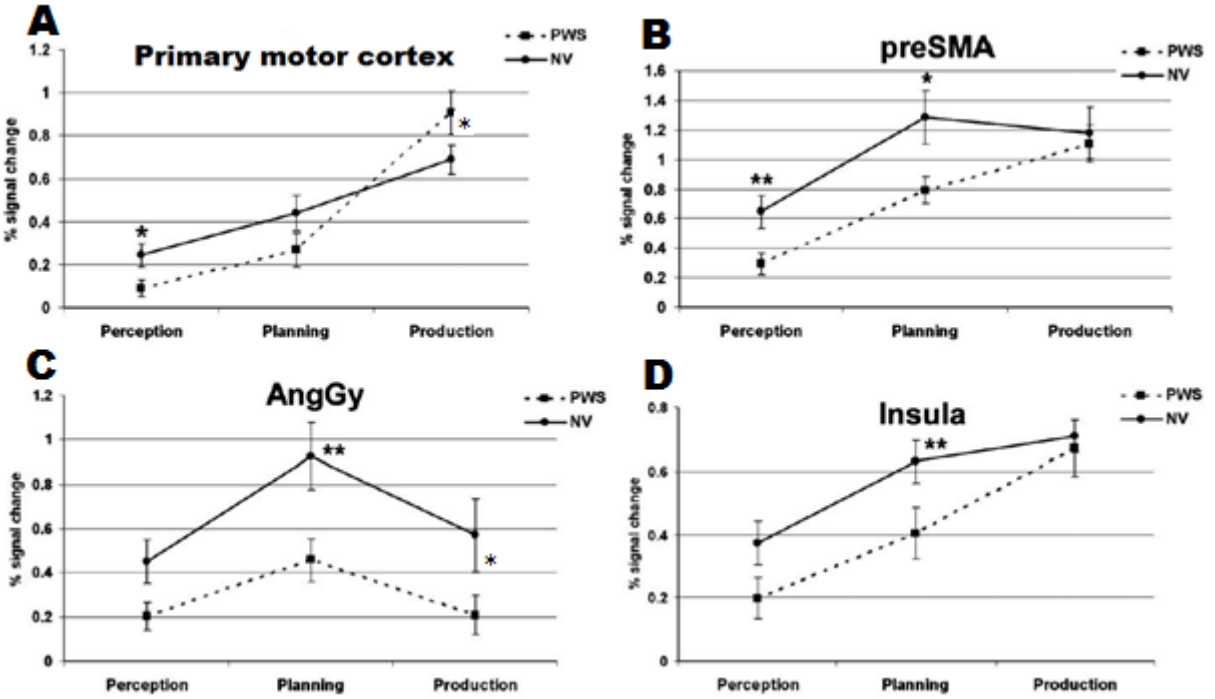

Figure 4. Group differences in mean BOLD signal change across the perception, planning, and production task. *Shown are the mean BOLD response changes for the (A) primary motor cortex, (B) pre-SMA, (C) angular gyrus, and (D) insula during the perception, planning and production task. * = p < 0.05, ** = p < 0.01 (figure from Chang et al., 2009 [57]).*

Chang *et al.* (2009) [57] specifically studied brain activation differences between PWS and controls during speak and non-speaking tasks. BOLD-responses were measured using fMRI in twenty right-handed adults with DS (nine females) and twenty right-handed controls (eleven females). Brain activation patterns were compared during speech perception (mechanism of receiving and the interpretation of speech), speech planning (initiation of speech), and speech production (generation of speech). Brain activation was reduced in the primary motor cortex (figure 4a), pre-SMA (figure 4b), angular gyrus (figure 4c), and insula (figure 4d) during speech perception and planning in PWS. During speech production, however, increased activation was observed in the primary motor cortex (figure 4a), auditory cortex, and angular gyrus (figure 4c) [57]. These results are largely in accordance with one of the first neuroimaging studies by Fox *et al.* (1996) [53].

Additionally, the study of Chang *et al.* (2009) [57] found a correlation between BOLD response and stuttering severity in the bilateral primary motor cortices (figure 5).

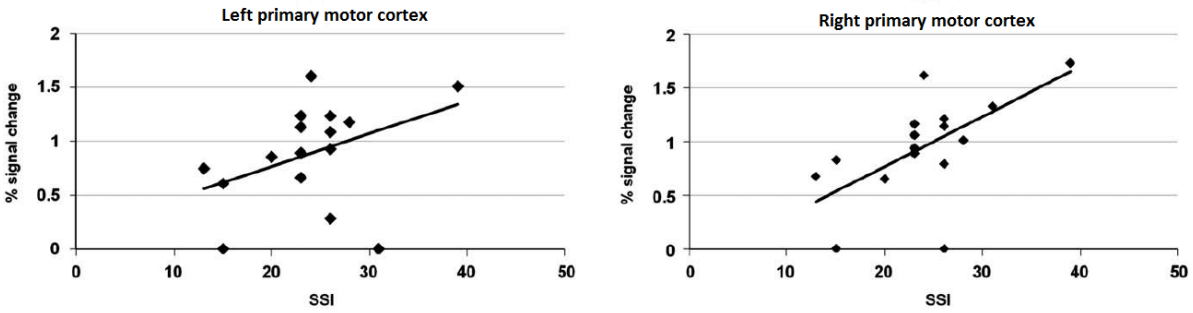

Figure 5. Correlation between BOLD response and stuttering severity. *Displayed are the correlations between brain activity in the left (r = 0.64) and right (r = 0.68) primary motor cortex and stuttering severity measured through the stuttering severity instrument 3 (SSI-3). Brain activity in the bilateral primary motor cortices show a positive correlation with stuttering severity (p < 0.005) (figure from Chang et al., 2009 [57]).*

Furthermore, three gender-specific differences were observed in the PWS-group. Firstly, during the speech perception phase, decreased activity was observed in the pre-SMA in males with DS compared to their matched male controls [57]. Secondly, during the planning of speech, decreased activity was observed in the angular gyrus and insula in females with DS relative to female controls. In the same phase, decreased activation was observed in the STG in males with DS compared to male controls. Finally, decreased activity in the angular gyrus was found during the production of speech phase in males with DS compared with male controls [57]. These findings confirm previous suggestions of gender-specific differences in the PWS-group [58].

In a recent study of Ingham *et al.* (2012) [59], brain activity was measured in eighteen male PWS and twelve male controls. Both groups completed three scanning trials: eyes-closed rest (ECR), oral reading task (reading out loud continuously)

(same task as in Fox *et al.* (1996) [53]), and monologue (continuous self-formulated speech on self-selected topic). In PWS, Ingham *et al.* (2012) [59] found increased brain activation in stutter related areas, like the bilateral primary motor cortex, left IFG, bilateral SMA, left pre-SMA, left STG, and bilateral cuneus, during speech and during ECR. This is partially consistent with previous reports [53,54,57], which also found increased activity in the primary motor cortex, as well as decreased activity in the left IFG. In controls, increased activation was observed in the left insula, right pre-SMA, and parts of bilateral cerebellum, both during speaking tasks and during rest [59].

Another study focused solely on resting-state brain activity using amplitude of low-frequency fluctuation (ALFF), which is a relatively new measurement to investigate resting-state brain activity [60]. Increased resting-state brain activity is represented as a larger ALFF value. In PWS, a higher ALFF was observed in the left STG (auditory cortex), left MTG, left IFG, left premotor cortex, and bilateral PFC [61]. Lower ALFF was observed in the bilateral SMA and left occipitotemporal region (OT) in PWS [61]. As we know, these brain areas are involved in speech production and auditory functions [33,34,35,36,37,62]. The results of Xuan *et al.* (2012) [61] are in accordance with previous results of e.g. Braun *et al.* (1997) [54] and Ingham *et al.* (2012) [59].

3.3 Summary

Much research has been done as yet and although not all data confirm all other in details, a general picture is emerging about grey matter brain activity and anatomy differences in people with DS. To this end, we can conclude that the primary motor cortex, IFG, STG, MTG, and SMA tend to be important key players in activity and anatomy differences in grey matter in PWS. Summarizing the so far discussed studies, altered hemispheric lateralization in PWS [53,54,55,56] and atypical prefrontal lobe and occipital lobe asymmetries are found in adults [42] and children [43] with DS. However, these observations were not found in other studies, neither in adults [47] nor children [48] with DS. Furthermore, increased brain activity was found in the primary motor cortex, SMA, cerebellum, IFG, STG, and MTG, both in rest and during speech, and in the left and right hemisphere in PWS [53,54,57,59,61]. It must be noted that not all studies support all results about grey matter brain activity differences in PWS, as some studies solely observed differences in specific brain regions [53,54,57] whereas others found opposite results [61]. Finally, increased GMV was observed in the bilateral STG (planum temporale), and IFG, both in adults [39,45] and children [48] with DS. However, not all results are fully supported [48], and earlier studies did not find a difference [44]. Some studies even found reduced GMV in the left IFG of adults with DS [49], or in the bilateral IFG, MTG, STG (planum temporale) of children with DS [48,52]. Thus, it is clear that grey matter brain activity and anatomy differences in DS are associated with abnormalities in the speech-related network of the brain. Also, it appears that silent reading and reading out loud activates different regions of the brain. It is therefore not easy to unravel the

neural correlates involved in DS, as multiple brain areas are involved in the four stages of speech production. Besides, possible confounding factors such as gender, age, and handedness should be taken into account when studying brain regions involved in DS [28,29,30].

4. White matter alterations in DS

Beside the fact that in the past years much research has been done concerning grey matter activity and anatomy differences in PWS, neuroimaging research has also been done on white matter anatomy and connectivity changes in PWS. The main question discussed in this paragraph is in what way white matter brain anatomy and connectivity is different in PWS compared to their fluently speaking peers. The most important findings will be discussed here.

4.1 Anatomy

The first known study investigating white matter anatomy in PWS found increased white matter volume (WMV) in right-lateralized speech related areas like the STG, IFG (pars opercularis), precentral gyrus (PrCG) (primary motor cortex), MFG, and somatosensory area (figure 6) using VBM in ten PWS compared with controls [44]. Most of these areas are important in speech production [33,34,37].

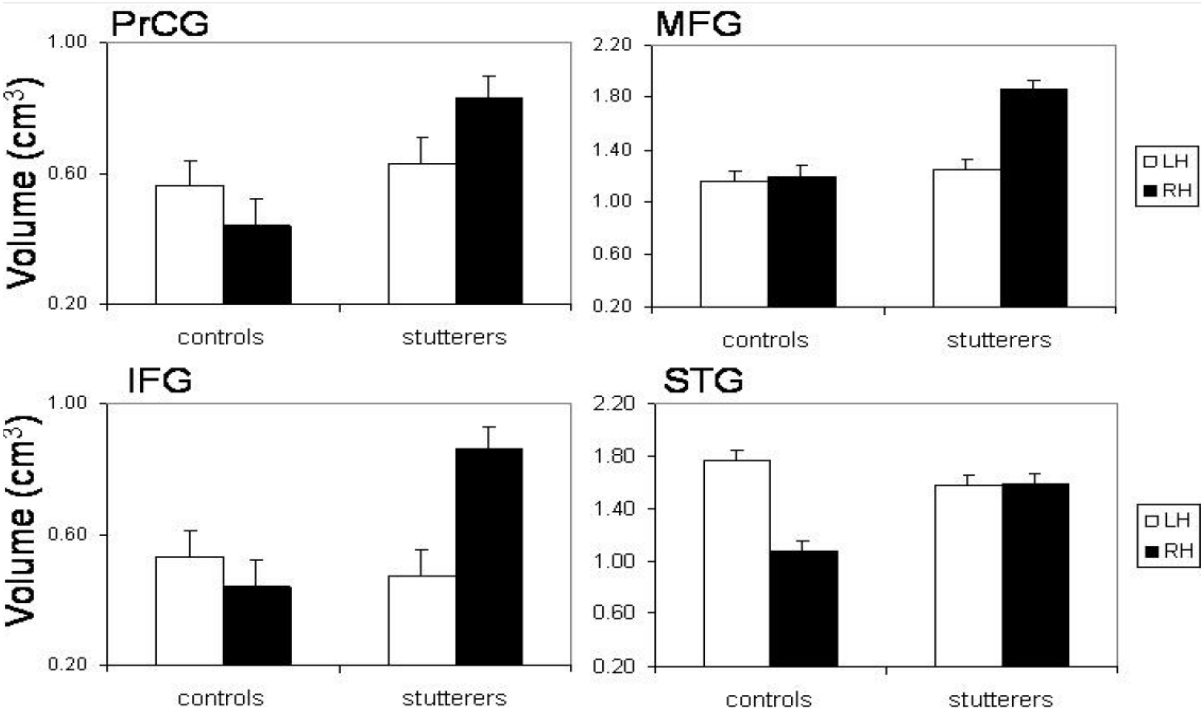

Figure 6. Increased WMV in PWS. *Displayed are mean WMV in right-lateralized precentral gyrus (PrCG) (primary motor cortex), middle frontal gyrus (MTG), inferior frontal gyrus (IFG), and superior temporal gyrus (STG) in controls and stutterers (PWS). LH = Left Hemisphere, RH = Right Hemisphere (image from Jäncke et al., 2004 [44]).*

Likewise, Beal *et al.* (2007) [45] found WMV differences in PWS as well, with an increase in white matter densities in the right precentral gyrus (primary motor cortex), IFG (pars opercularis and pars triangularis), insula, and left MTG (table 2). These findings are consistent with earlier findings of Jäncke *et al.* (2004) [44], and may indicate an asymmetry in white matter brain anatomy. Together with the results of Preibisch *et al.* (2003) [55], who found right lateralized brain activity in PWS, these findings indicate the presence of structural and functional white matter differences in the right hemisphere of PWS. These abnormalities may be involved in DS, however, whether this is a compensatory attempt or an underlying cause for DS remains unknown.

Table 2. Increased white matter volume in PWS relative to controls. *Displayed are five brain regions with increased grey matter volume in PWS relative to controls. x, y, z are coordinates in Montreal Neurological Institute (MNI) space; cluster size = size of voxels (table from Beal et al., 2007 [45]).*

Anatomical region	Laterality	*x*	*y*	*z*	Z score	Cluster size
White matter						
Insula	R	48	2	6	3.95	95
Inferior frontal gyrus	R	38	20	14	3.76	108
Middle temporal gyrus	L	−50	−22	−14	3.65	66

The corpus callosum (CC) is the largest and main interhemispheric white matter tract connecting the left and the right hemisphere with each other for communication [63] and is very important for written and oral language [64]. Sexual dimorphism is found in the CC [65], as well as differences in myelinisation between the sexes [66]. Choo *et al.* (2011) [67] studied CC differences between eleven right-handed male adults with DS and twelve right-handed control adults using MRI. An overall larger CC was found in adults with DS, especially in the rostrum and anterior midbody (figure 7).

Later, the CC anatomy was studied in children (Choo *et al.*, 2012) [68] which included eight right-handed boys with DS, six right-handed boys who spontaneously recovered DS, and seven right-handed age-matched controls. Strikingly, no morphological differences in CC anatomy was observed between the children (figure 8) [68]. Another similar study, however, observed a bilateral decrease in WMV in the forceps minor (anterior forceps) of the CC in children with DS [52]. These results indicate that CC abnormalities might be associated with DS and suggest that this is the result of a compensatory attempt related to the life-long stuttering.

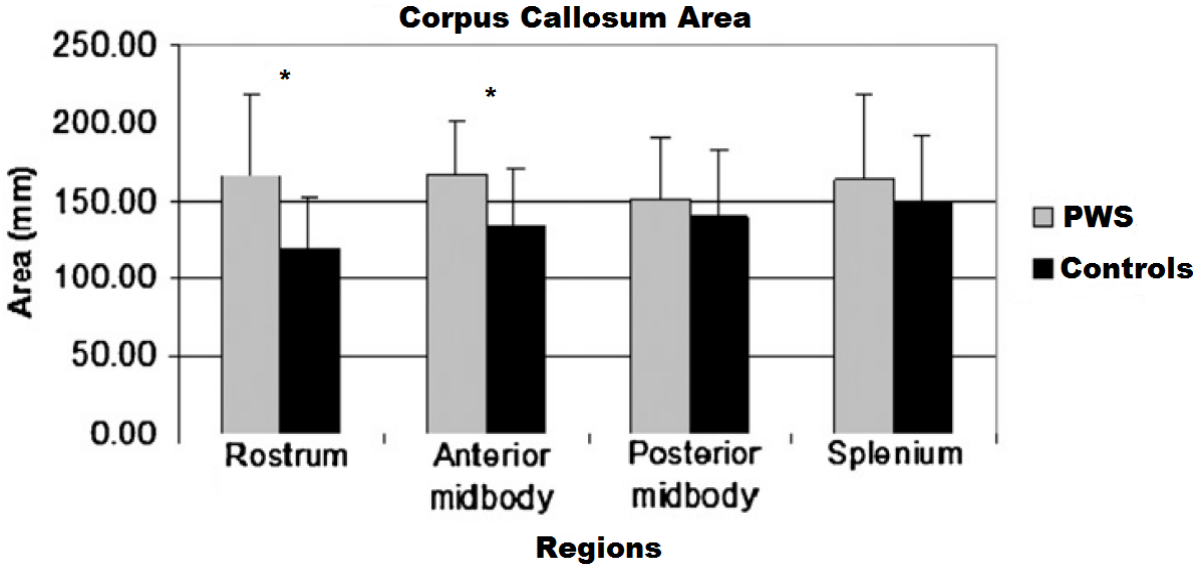

Figure 7. Mean corpus callosum (CC) volume in adults. *Displayed are the mean corpus callosum (CC) area of adult PWS and age-matched controls. Larger rostrum and anterior midbody of the CC was observed in PWS (image from Choo et al., 2011 [67]).*

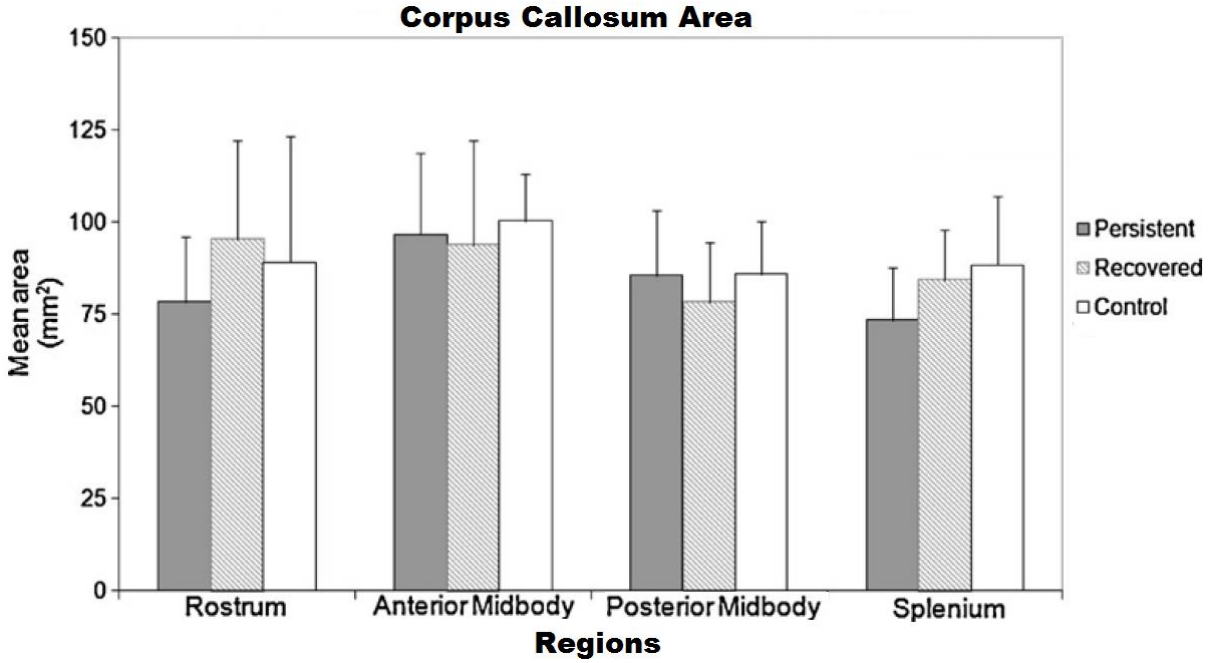

Figure 8. Mean corpus callosum (CC) volume in children. *Displayed are the mean corpus callosum (CC) area of persistent (children with DS), recovered (spontaneously recovered from DS), and control children. No differences in CC anatomy were observed between these three groups (image from Choo et al., 2012 [68]).*

Areas of increased WMV have been found in both the left and right hemisphere, as well as the CC of adults with DS [44,45,67]. In a study of Mock *et al.* (2012) [43], which investigated total brain and WMV in children with DS using VBM, no differences in total volume of the left and right hemispheres were found. However, children with DS did show increased WMV in both the left and right hemisphere

[43], which has also been observed in two other studies [44,45]. Moreover, increased WMV in the bilateral PFC correlated positively with stuttering severity [43].

4.2 Connectivity

Many studies focussing on white matter brain connectivity differences in PWS used Diffusion Tensor Imaging (DTI) to measure Fractional Anisotropy (FA) of diffusion. DTI is a MRI technique which is sensitive to diffusion properties of water protons, and in this way can reveal the orientation of white matter fibres [69,70]. FA is a measure of coherence in white matter tracts [71,72,73]. A low FA value means that diffusion of water protons is unrestricted, and a high FA value means that diffusion of water protons is restricted in a specific direction. Normally, white matter tracts are structured in a specific way, and are therefore expected to have high FA values. It is known that in white matter diseases (such as multiple sclerosis) abnormalities are observed in connectivity, and this is associated with reduced FA values [74,75].

The first known study investigating the white matter integrity (as measured by FA) in PWS was done by Sommer *et al.* (2002) [76] in fifteen adults with DS and fifteen age-matched controls. Reduced FA values were found in the left Rolandic operculum (RO) (figure 9) [76], a region involved in speech production [33,34,37]. More specifically, reduced white matter integrity was found in the left inferior arcuate fasciculus [76], which is a part of the superior longitudinal fasciculus that connects parts of the parietal and temporal cortex with the frontal and premotor cortex [77,78], and is a critical pathway in the speech production system [33,34,37,62]. Thus, it seems plausible that impaired signal transduction in the left superior longitudinal fasciculus may lead to speech problems.

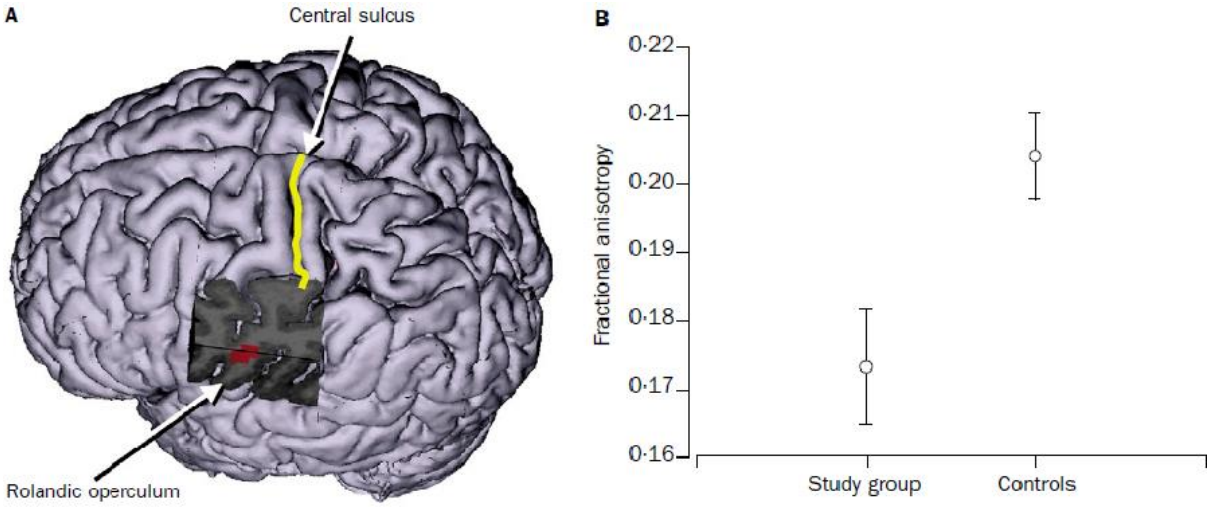

Figure 9. Decreased FA value in Rolandic operculum. *(A) In the Rolandic Operculum (RO), (B) decreased FA was observed in PWS (study group) compared with controls. Bars in (B) indicate SE (figure of Sommer et al., 2002 [76]).*

Echoing the study of Sommer *et al.* (2002) [76], Watkins *et al.* (2008) [79] also investigated white matter tracts in PWS. Using DTI to measure FA in seventeen PWS,

lower FA was observed in bilateral ventral premotor cortex, right IFG (including pars orbitalis), bilateral precentral gyrus (primary motor cortex), left supramarginal gyrus, and corticospinal tract in PWS. Higher FA was observed in the left posterior IFG, right postcentral gyrus, right supramarginal gyrus in PWS [79]. The decrease in white matter integrity in the premotor cortex ultimately results in decreased white matter integrity in the superior longitudinal fasciculus, as this white matter tract is anatomically situated in this region. This finding is in accordance with Sommer *et al.* (2002) [76], who found lower FA values for the left superior longitudinal fasciculus in PWS.

As already discussed in paragraph 3.1, the study of Chang *et al.* (2008) [48] was the first investigating the neural correlates of DS in children. Decreased white matter integrity was found in the left RO, which includes the left arcuate fasciculus (figure 10) [48]. This is consistent with previous data found in adults with DS [76,79]. So, these results in children with DS [48] together with the results in adults with DS [76,79] indicate that –regardless of age- a decreased white matter integrity in the left RO might be a morphological difference in brain anatomy in DS. It must be noted that such decreases in white matter integrity in PWS has not been found in all studies [49]. Contrarily, increased white matter integrity was observed in the left IFG, left orbitofrontal cortex (OFC), and left intraparietal sulcus in PWS relative to controls.

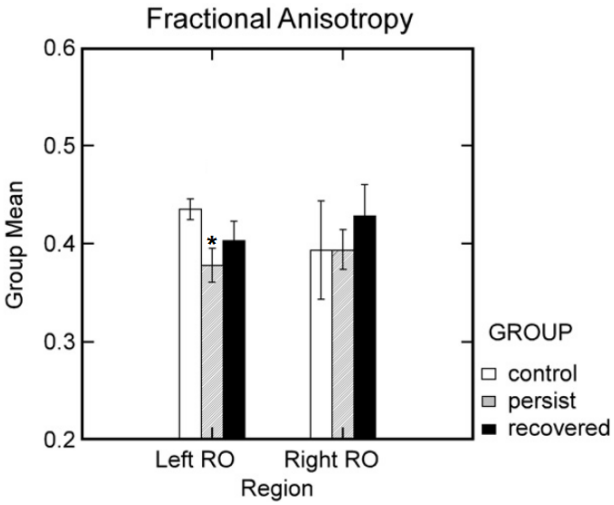

Figure 10. Mean FA values in RO. *Displayed are mean FA values and standard errors for the white matter tracts in the left and right RO in children with DS (persist; grey bars), children recovered from DS (recovered; black bars) and age-matched controls (control; white bars). Asterisk indicates only difference found in FA value in children with DS (image from Chang et al., 2008 [48]).*

In another study on white matter integrity in speech-related areas and the CC, reduced FA was found in parts of the left perisylvian region, like the superior corona radiata and superior longitudinal fasciculus. Also, reduced white matter integrity was found in the CC, including forceps minor and callosal body (figure 11) [80]. These findings are in accordance with previous results (48,76,79) that also found decreased white matter integrity, e.g. in the superior longitudinal fasciculus in adults and children with DS (figure 12.) However, Kell *et al.* (2009) [49] did not find these results in adults with DS.

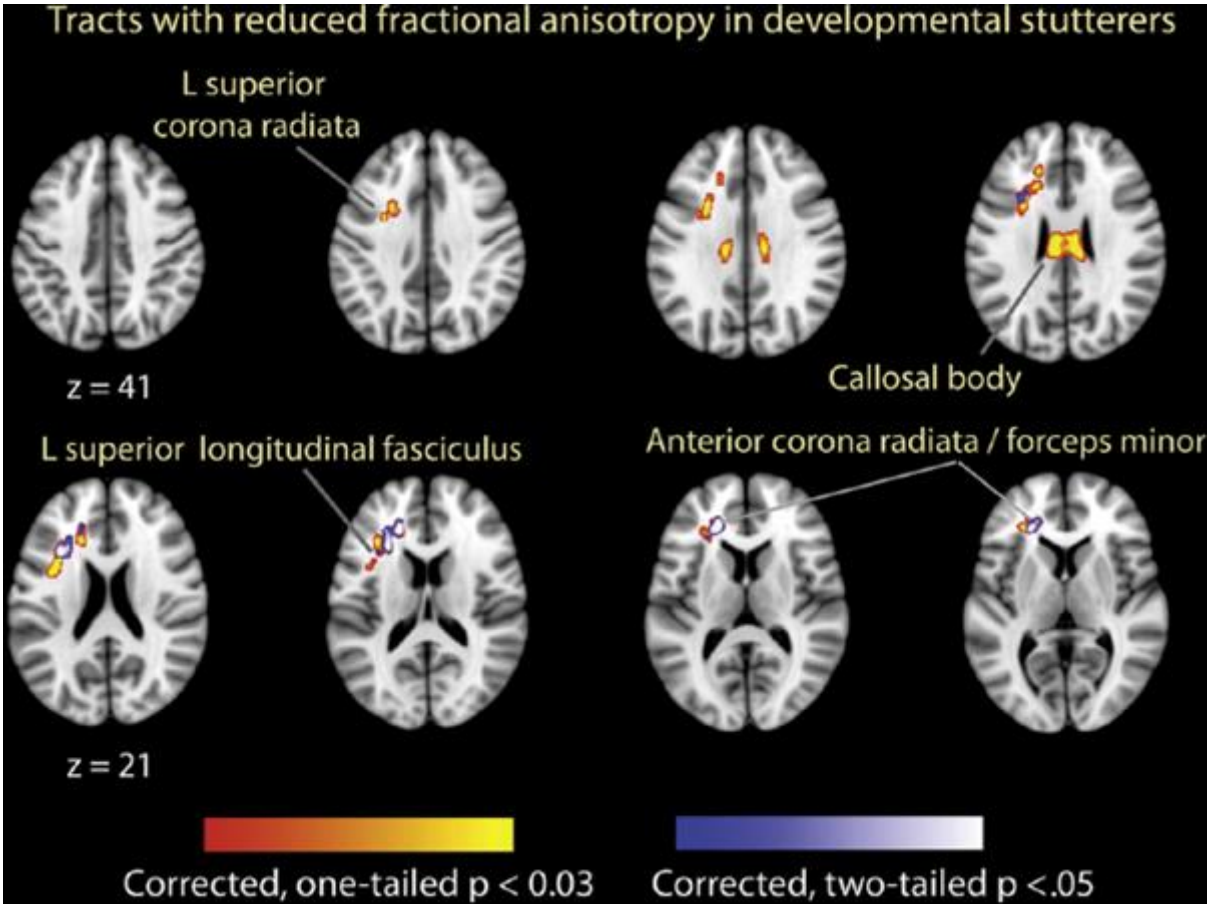

Figure 11. Reduced white matter integrity in PWS. *White matter integrity was decreased in left superior corona radiata, left superior fasciculus, forceps minor, and callosal body. Displayed are axial, coronal and sagittal views of the brain, and affected areas are shown in one-tailed (red to yellow) and two-tailed (blue to white) results (image from Cykowski et al., 2010 [80]).*

Furthermore, increased radial diffusivity was observed in the study of Cykowski *et al.* (2010) [80], suggesting impaired myelination in all these areas. The myelination process is a mechanism which wraps a lipid bilayer around neurons to increase the conductance to ensure fast action potential signalling. It is known that the white matter fibres in these regions continue to myelinate until the second or third year of life [81,82,83], resulting in a proposed hypothesis that this incomplete myelination could be important for the development of DS. This is fundamentally different from multiple sclerosis, where increased degradation of white matter fibres is observed.

Two studies by Chang *et al.* from 2010 [84] and 2011 [85] further examined functional connectivity differences between PWS and non-stutterers. In the 2010-study [84], higher FA was observed in the right RO, including the superior longitudinal fasciculus, which is consistent with studies that found increased WMV in right-hemispheric speech areas [39,44]. Moreover, this increase was positively correlated with the severity of stuttering, as measured through the Stutter Severity Instrument (SSI) (figure 13) [84]. Considering that this white matter increase in the right RO was

not observed in children with DS [48], it is thought that this might be the result of a compensation attempt during adulthood for the decreased white matter integrity observed in the left hemisphere [48,76,79].

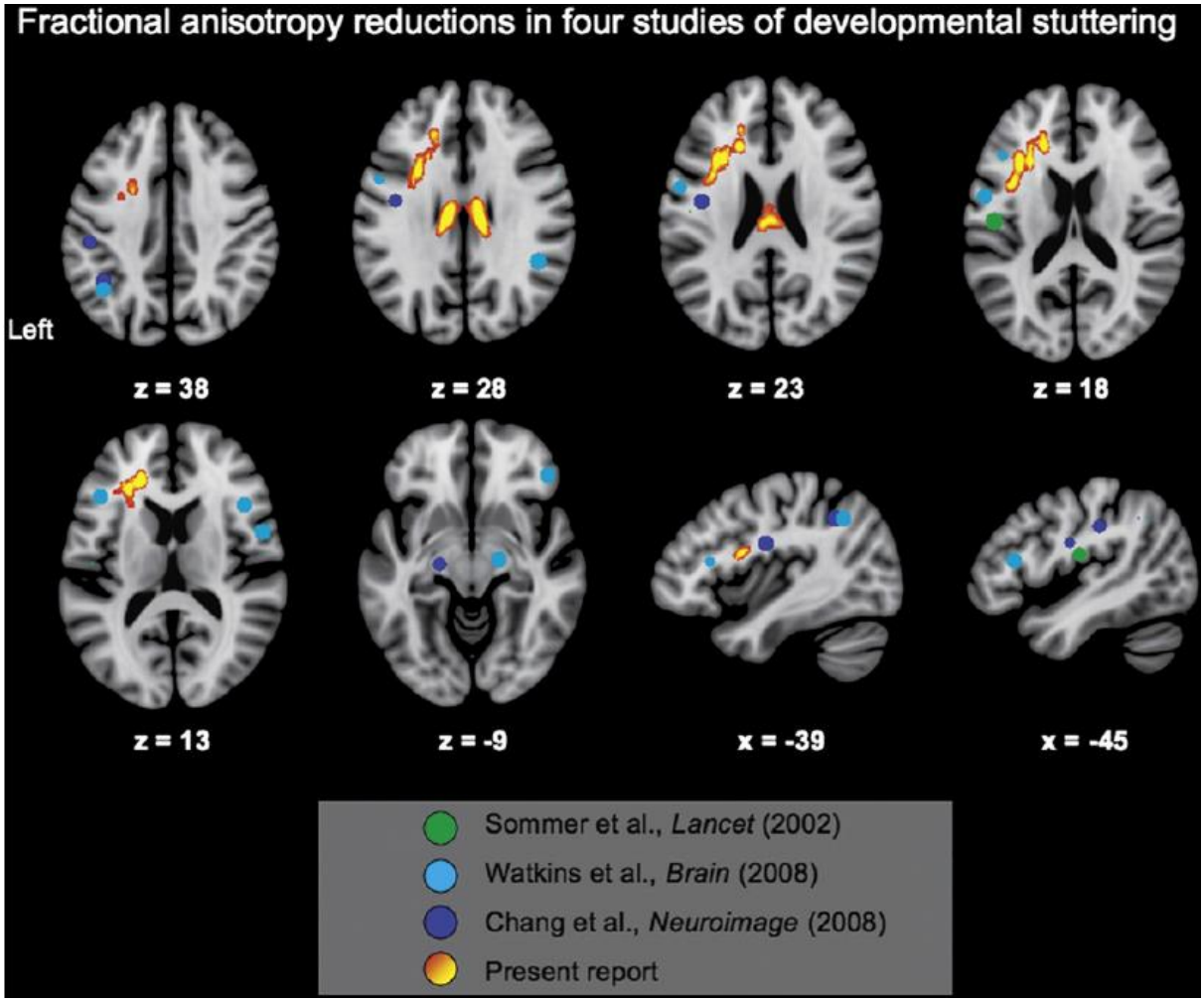

Figure 12. Four studies which showed reduced white matter integrity in PWS. *Displayed are the results of four studies which found reduced FA in adults and children with DS (image from Cykowski et al., 2010 [80]).*

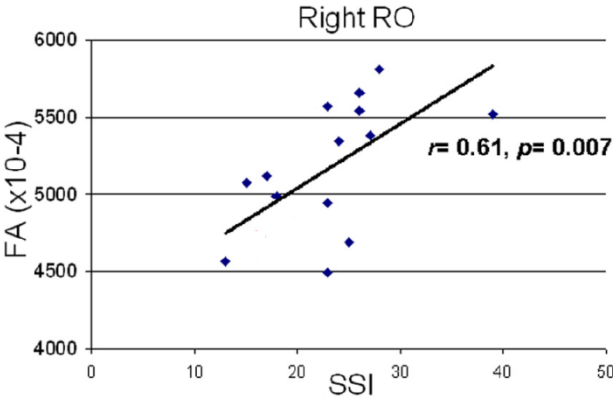

Figure 13. Correlation between FA in the right RO and stutter severity in PWS. *Stutter severity, as measured by the Stutter Severity Instrument (SSI), and mean increased FA in the right Rolandic Operculum (RO) are positively correlated with each other in PWS (image from Chang et al., 2010 [84]).*

In the 2011-study by Chang *et al.* (2011) [85], decreased connectivity was observed in white matter tracts from the left IFG to premotor regions, and increased structural connectivity was observed in the right IFG to premotor connections in PWS [85]. This confirms and underlines previous research which show the same left- and right-sided abnormalities in white matter in PWS [44,45,48,76,79,80,84].

A large resting-state brain activity study in forty-four PWS and sixty-four controls by Xuan *et al.* (2012) [61] found decreased resting-state functional connectivity (FC) between the left IFG and right IPL, as well between the Posterior Cingulate Cortex (PCC) and Default Mode Network (DMN) in PWS. Furthermore, increased resting-state FC was observed between the left IFG and left premotor cortex, and between the PFC and DMN regions [61]. The DMN is a network of brain areas which are active during rest, and include the anterior cingulate cortex (ACC), mPFC, angular gyrus, and bilateral inferior parietal lobes [86,87]. Although the decrease in FC between the left IFG and right IPL has been observed previously [85], Xuan *et al.*, (2012) [61] observed an unprecedented increased resting-state FC between the left IFG and left premotor cortex. A speculative explanation could be that the resting-state FC between the left IFG and left premotor cortex in PWS is relatively at a higher level compared to controls. Therefore, the increase found between rest and speech production in controls [85] can hardly be observed in PWS. Another explanation is that some of these findings could be the result of a compensation attempt in PWS.

In the most recent study of children with DS [88], decreased FC was found in the basal ganglia-thalamocortical (BGTC) loop (including the putamen and SMA). Also, in boys with DS, decreased FC was observed in both hemispheres between STG and ventral primary premotor cortex (pars opercularis) compared with girls. Finally, decreased structural white matter connectivity was observed between the putamen and cortical motor - and auditory regions in the left hemisphere in children with DS compared to controls. These new results, taken together with previous findings in children with DS [43,48,52,68], provide strong evidence that brain abnormalities exist even during childhood and that not all white matter deficiencies observed in adulthood [44,45,49,61,67,76,79,80,84] are the result of compensatory attempts.

The most recent research about white matter differences confirms previous results about reduced white matter integrity in PWS [76,79,80], and found new white matter differences between twenty-nine PWS and thirty-seven controls [89]. Reduced FA was observed in the bilateral arcuate fasciculus (figure 14a) (superior longitudinal fasciculus), all three cerebellar peduncles (figure 14b), and left corticobulbar tract in PWS relative to controls. Furthermore, FA in the left corticospinal tract was reduced compared with its opposites on the right side (figure 14c), and stuttering severity correlated negatively with the white matter integrity in the left angular gyrus in PWS (figure 14d) [89]. The hypothesis that dysmyelination could be important for the development of DS was also suggested by Cykowski *et al.* (2010) [80], making local myelination an important player in the development of DS, and may indicate that these deficiencies are the cause, rather than the consequence of DS.

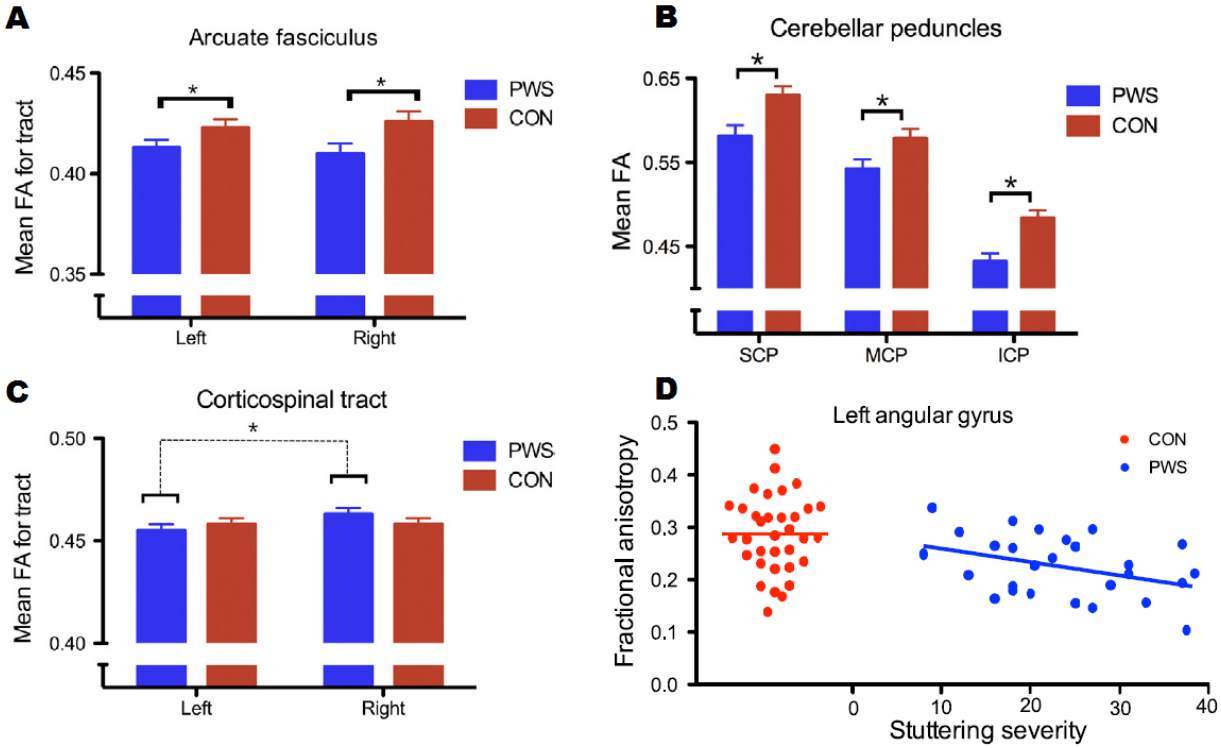

Figure 14. Correlation and FA differences between PWS and controls. *Displayed are FA values in the arcuate fasciculus (A), cerebellar peduncles (B) and corticospinal tract (C) of PWS (blue) and controls (red). Also, FA in left angular gyrus correlates negatively with stuttering severity in PWS (D). SCP = superior cerebellar peduncle, MCP = middle cerebellar peduncle, ICP = inferior cerebellar peduncle. Error bars = SE, * = significant difference (images from Conally et al., 2014 [89]).*

4.3 Summary

Neuroimaging research about white matter connectivity and anatomy differences in people with DS has been abundantly conducted in the last years. Up to now, it has been proven that the IFG, STG, precentral gyrus (primary motor cortex), MFG, insula, MTG, premotor cortex, and CC play important roles in white matter connectivity and anatomy differences between PWS and non-stutterers. Summarizing the white matter brain anatomy abnormalities in PWS, increased WMV was observed in the right-lateralized STG (planum temporale), IFG (pars opercularis), precentral gyrus (primary motor cortex), MFG, insula, and MTG [43,44,45], and rostrum and anterior midbody of the CC [67] in adults with DS. In children with DS, however, some studies found no difference [68] or observed a decrease [52] in the WMV of the brain. The white matter connectivity reductions were primarily observed in the bilateral RO (superior longitudinal fasciculus), bilateral precentral gyrus (primary motor cortex), bilateral IFG, corticospinal tract, corticobulbar tract, CC, and cerebellar peduncles, both in adults [76,79,80,89] and children [48] with DS. Moreover, Chang *et al.* (2013) [88] found even more differences in children with DS. Together with the results of previous studies in children with

DS [43,48,68], this indicates that white matter brain abnormalities exist even during childhood, and are not only the result of compensatory attempts. In adults with DS, however, not all abovementioned white matter connectivity results are supported by all studies. Some only observed differences in specific regions [48,76,84], found opposite results in some brain areas [85], found other results during rest [61], or did not find any difference in FA at all [49]. Unfortunately, for most findings it is still not clear whether these changes in morphology are the result of compensatory attempts, or are the causal underlying factors leading to DS. Thus, it is a complex task to point out the white matter abnormalities accountable for DS. Although, it is very likely that the IFG, STG, precentral gyrus (primary motor cortex), MFG, insula, MTG, premotor cortex, and CC tend to be key players in DS.

5. Conclusion

By the various studies concerning activity and anatomy differences in the grey matter, it can be concluded that the primary motor cortex, IFG, STG, MTG and SMA are important key players in adults and children with DS, both in rest and during speech. For white matter differences in anatomy and (functional) connectivity in adults and children with DS, it seems very likely that –again- the IFG, STG, and premotor cortex are involved in DS, as are the precentral gyrus, MFG, RO and CC. For some brain regions in the speech-related network of the brain, general agreement about differences between PWS and controls has been reached. However, not every study supports all observed results in grey or white matter, or only found differences in specific (lateralized) brain regions. Thus in general, it can be concluded that brain activity, anatomy and connectivity in speech important regions of the brain is altered in persons with DS, and that some differences are not the result of compensatory attempts, but already exist during childhood and thus may be the causal underlying factors which contribute to DS.

Most studies which tried to unravel the neurobiological correlates of DS have been performed on adults with DS. This makes interpretations of results difficult due to the possible compensatory brain differences because of their lifelong disfluent speech. This makes comparisons between adults with and without DS hard, as it remains unclear whether these differences are the cause or the consequence of DS. Beside the fact that handedness (lateralization) and gender have an effect on the results found in all studies [29,30], another cause of apparent inconsistencies between studies is the difference in speech production tasks, imaging techniques, and data analysis. In the studies of Chang *et al.* (2009) [57] and Kell *et al.* (2009) [49] or instance, the brain activity during speech is mainly derived from non-stuttered speech: any disfluencies during speech in PWS were not included in the data analysis [59]. Also, fMRI and rCBF measured using PET are different imaging techniques, which makes these studies difficult to compare. Furthermore, speech production tasks -like oral reading and spontaneous speech- are fundamentally different speaking tasks which may involve different speech-related brain areas, and thus can have an effect on the

results. Finally, speech rate is a factor which has completely been ignored in almost all studies. The speech rate of PWS in adulthood is usually slower compared with control speakers [90]. It is likely that differences in speech production rate have an effect on brain activity. Therefore, these variations have a major effect on the neuroimaging results, and comparisons between studies are significantly influenced.

Although in this chapter no attention was paid to the basal ganglia system, it is clear that this system also tends to play an important role in DS [91,92,93]. Previous studies have shown that PWS have increased dopamine activity in specific brain regions [12], and that dopamine blockers decrease stuttering severity [5,14,16]. However, dopamine blockers are not a useful way to prevent stuttering, because of the large side effects. These studies, taken together with the results discussed in this thesis, provide compelling evidence that neurobiological differences exist between adults with DS and non-stuttering persons.

Although a growing number of studies have investigated the neurobiological differences in PWS, there is a pressing need for longitudinal studies in children with DS. In this way, the functional and structural brain differences between PWS and controls, as well as the underlying mechanisms of recovery from DS can be monitored during the years. These brain areas can be used as markers or indicators for developing DS in children, and could serve, to potential (surgical) intervention possibilities in PWS, like transcranial direct-current stimulation (tCDS) or transcranial magnetic stimulation (TMS). Also, these brain markers or indicators can be used as new potential neuropharmacological targets for the development of new possible medicines. Furthermore, when abnormalities are observed in these brain markers or indicators, possible speech-therapy before the emergence of DS could be started in an attempt to prevent the possible onset of DS. Finally, it is still not clear what the possible long-term effects and differences are between spontaneously and SLP-induced recovery of DS.

Finally, extensive research about the genetic background of DS has been done [9,17,18,19,20,21,22,23,24,25,27] and three genes involved in the lysosome pathway are found being implicated in DS [26]. Further research to unravel the possibly sequential pathway of genetic abnormalities, biochemical alterations affecting the lysosomal pathway, and possibly leading to e.g. WM abnormalities are urgently required. In that sense, it is tempting to suggest that locally diminished activity of one of these genes might result in e.g. diminished myelination within (some of) the specific brain regions as has been discussed above. That would give a hand as to the possible chicken or egg discussion, with respect to the neurological differences found sofar. Indeed, it appears that the gene expression is variably in brain areas throughout the brain [49], although these genes are basically present in all cells.

An increased knowledge about DS could potentially open new ways for treatment of PWS. This could result in a decreased prevalence of DS, and social interaction would tremendously improve due to less anxiety, shame and irritation in PWS. Both in professional as in private conditions, the quality of life would increase in millions of stutterers.

Although the picture is still far from complete, the neuroimaging research conducted in the last years has revealed both functional and structural involvement of different brain regions in DS, and greatly improved our knowledge of DS. It is crucial to get a clear-cut univocal consensus about brain regions which are important in the development of DS. Further studies are needed to extend these findings in order to disentangle the neural correlates of DS.

6. Acknowledgements

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