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Differences in Speech Perception and Production Networks Between Persons who stutter and Controls

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Veileder
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Preface

This paper presents results from the ongoing project "Auditory Perception, Lateralization of language and Stuttering". The project is a multidisciplinary collaboration between the Bergen fMRI Group, the University of Bergen (the Master Program in Logopedics and the Professional Studies of Psychology), and the National Support System for Special Needs Education (StatpedVest). Andresen, Heitmann, and Specht (2012), and Milford (2012), have previously made contributions to the project.

We would like to thank our supervisor, Professor Karsten Specht, for all the assistance, advice and valuable information he has provided throughout the entire process, and for all his patience. He has given us important insight into some of the mysteries of neuroimaging research. Also, we would like to thank him and the University of Bergen for allowing us to participate at the 7th World Congress on Fluency Disorders in Tours, France, this summer, where our knowledge of fluency disorders was multiplied.

In our data collecting process, we worked together with Renate Milford, a master student in Logopedics. We would like to thank her for all her work and effort, and for a great collaboration.

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Abstract

Previous research has demonstrated atypical lateralization and brain asymmetry in persons who stutter (PWS). It has also been demonstrated that PWS show atypical activation patterns when processing language stimuli.

We wanted to investigate differences between PWS and controls in speech perception and production processing tasks. Dichotic listening (DL) and soundmorph fMRI paradigms were applied to obtain functional measures. In addition we investigated structural differences by using diffusion tensor imaging (DTI) and analysing our data with voxel-based morphometry (VBM).

The results indicate that stuttering is related to abnormal activation patterns in both speech perception and production. There were bilateral differences in activation between PWS and controls in both the soundmorph paradigm and the DL production task. However, in the DL paradigm, the results were only significant with an uncorrected p-value. We also found lower fractional anisotropy (FA) (at an uncorrected level) in PWS in left inferior frontal gyrus (IFG), indicating dysfunctional connectivity, but no differences in grey matter. The results lend support towards functional abnormalities in speech lateralization, and to a differential involvement of the dorsal stream of speech processing in PWS. The results also lend support to the notion of a strong involvement of STS in speech perception in both PWS and controls. However, these this study is part of an ongoing project, and the findings may change as more data is collected.

Sammendrag

Forskning har vist atypisk lateralisering og strukturell hjerneasymmetri hos personer som stammer (PSS). I tillegg har man funnet atypiske hjerneaktiveringsmønstre hos stammere under ulike oppgaver som involverer språkprosessering.

Formålet med vår studie var å undersøke forskjeller mellom en gruppe med PSS og en kontrollgruppe under utførelse av talepersepsjons- og taleproduksjonsoppgaver. Funksjonelle avvik ble undersøkt med to fMRI-paradigmer, dikotisk lytting (DL) og soundmorph. Strukturelle avvik ble undersøkt med ”diffusion tensor imaging” (DTI) og voxelbasert morfometri (VBM).

Resultatene indikerer at stamming er knyttet til avvikende hjerneaktiveringsmønstre, både i talepersepsjon og taleproduksjon. Vi fant bilaterale forskjeller i aktivering i PSS og kontrollgruppen i både soundmorph- og DL-paradigmene, selv om funnene i DL bare er signifikante med ukorrigert p-verdi. Strukturundersøkelsene viste lavere grad av fraksjonell anisotropi (FA) (med en ukorrigert p-verdi) i venstre inferior frontale gyrus (IFG) hos PSS - en indikasjon på dysfunksjonell konnektivitet, men ingen forskjeller i grå materie. Resultatene gir støtte til hypoteser om avvikende aktivering i talelateralisering, og ulik involvering av den dorsale taleprosesseringsstrømmen hos PSS. Funnene støtter også oppfatningen om sterk involvering av superior temporal sulcus (STS) i talepersepsjon hos både PSS og kontrollgruppen. Det understrekes imidlertid at våre funn er del av et større pågående prosjekt, og kan bli endret ettersom mer data innhentes.

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Abbreviations

Language can be defined as

> "*a socially shared code or conventional system for representing concepts through the use of arbitrary symbols and rule-governed combinations of those symbols*" (Owens, 2012, p. 6; Owens, Metz, & Haas, 2007, p. 28).

According to Chomsky (2000), the brain has an inborn capacity to acquire any of the spoken languages of the world. Language opens rich and diverse possibilities for human interaction (Wickens, 2005). Language is a unique form of intellectual organization, which has enabled human beings to transfer knowledge about history, and allowed for the evolution of culture (Chomsky, 2000). Human social and intellectual advances have accelerated since the development of language, especially during recent centuries (Bazzett, 2008). According to J. Ward (2006), the driving force behind human language is to communicate ideas to the people around us. Language is a social interactive tool, which is both rule-governed and creative (Owens, 2012). The arrangement of language symbols is governed by underlying rules or patterns that occur repeatedly. Shared rule systems allow users of a language to comprehend and create new messages. Words can refer to more than one thing, they can be combined in a variety of ways, and they often have synonyms, and may be used in metaphors. These are just some examples of the creative nature of language. Most languages can be transmitted by speech. Speech can be defined as a verbal means of communicating (Owens, 2012). Some important qualities of speech are voice quality, intonation, and rate. However, speech is not the only essential feature of language. Language may also be communicated through written symbols, through body language and gestures, through tactile impressions for blind people, and different sign languages are used by the deaf and mute (Penfield &

Roberts, 1959). As the focus of this paper is on the perception and production of speech, further references to language will concern speech.

Components of Language

According to Passer & Smith (2007), human language has a hierarchical structure with five basic steps: phonemes, morphemes, words, phrases, and sentences. The phoneme is at the base of the hierarchy, and can be defined as the smallest linguistic unit of sound that can signal a difference in meaning in a given language (Matlin, 2005; Owens, 2012; J. Ward, 2006). The human speech mechanism can produce approximately 600 possible language sounds, including different ways of pronouncing single letters (Owens, 2012). Phonemes should not be confused with the sound of single letters (J. Ward, 2006). Humans can produce approximately 100 phonemes (J. Ward, 2006). However, no known language uses all of these sounds (Passer & Smith, 2007). Phonemes have no inherent meaning, but alter meaning when they combine with other phonemes or language elements. Phonemes can be combined into morphemes, defined as the smallest units of meaning, and the smallest grammatical units in a language (Matlin; 2005; Owens, 2012; J. Ward, 2006). Morphemes form words, phrases consist of combined words, and phrases finally combine into sentences at the top of the hierarchy (Passer & Smith, 2007; J. Ward, 2006).

Another way to explain language is by breaking it down into its functional components (Owens, 2012). The field of linguistics has provided a language processes taxonomy (Binder, 2006). However, different authors use different definitions of functional language components. Binder (2006) claims that these processes include phonetics, phonology, orthography, semantics, and syntax. According to Binder (2006) Phonetics consists of the processes governing production and perception of speech

sounds. Phonology can be defined as the processes by which speech sounds are represented and manipulated in abstract form. Orthography is composed of processes by which written characters are represented and manipulated in abstract form. Semantics concerns the processing of word meanings, names and other declarative knowledge about the world. Syntax can be defined as the process by which words are combined in a certain order to make sentences, and how sentences are analysed to reveal underlying relationships between words. Binder (2006) further claims that a basic assumption of language mapping is that different activation tasks can be designed to make varying demands on these five processing subsystems. Owens (2012) presents a somewhat different taxonomy, dividing the basic rule systems of language into the following five components: syntax, morphology, phonology, semantics, and pragmatics. The components that are mentioned by both Binder and Owens are explained in quite a similar way. Owens (2012) further claims that morphology governs that appropriate words, word beginnings and endings clarify meaning in sentences; while pragmatics is used to achieve communication ends such as gaining information or responding.

According to Owens (2012), language components may be an artificial analytic devise for linguists to use in discussions of language. Binder (2006) claims that it is methodologically questionable whether it is possible to study single components of language in isolation, as processing subcomponents of language often act in symphony.

Detection of Brain Regions that Influence Human Language

Language functions were among the first human brain functions to be ascribed a specific cortical location (Binder, 2006; Penfield & Roberts, 1959; Wickens, 2005). Several brain regions that influence language have been detected through post-mortem studies of people who suffered from language impairments due to a known brain

damage (Rosenzweig, Breedlove, & Watson, 2005). In the 1860s, Paul Broca presented a post-mortem analysis of the brain of a patient who had been unable to talk for several years (Penfield & Roberts, 1959; Rosenzweig et al., 2005). Broca found a lesion in the left posterior inferior frontal gyrus that today is called Broca's area (e.g. Binder, 2006; Rosenzweig et al., 2005; Toates, 2007; Wickens, 2005). This area is known to be involved in speech production, and has later been tied to the language impairment known as Broca's aphasia (e.g. Wickens, 2005). Carl Wernicke described aphasia after injury to the left posterior superior temporal gyrus (adjacent to the primary auditory cortex), which interferes with language comprehension (e.g. Binder, 2006; Powell et al., 2006; Rosenzweig et al., 2005; Wickens, 2005). This area has since been known as Wernicke's area, and the aphasia Wernicke's aphasia.

|In the early 20th century, Korbinian Brodmann histologically analysed the cellular organization of the cerebral cortex using tissue stains (Gazzaniga, Ivry, & Mangun, 2002; Zilles & Amunts, 2010). Brodmann made an important contribution to the research on functional-structural relationships in the brain (Zilles & Amunts, 2010). Previous research had found that different brain regions possessed different functions, so it seemed plausible that different regions would also look different at the cellular level (Gazzaniga et al., 2002). Brodmann found 52 distinct cerebral regions during comparative studies of the brains of other mammals as well as the human cortex (Zilles & Amunts, 2010). He made different species-relevant cytoarchitectonic maps of the brain (Gazzaniga et al., 2002; Zilles & Amunts, 2010). Over the years, the human map has been modified, and today it comprises 43 areas belonging to 11 regions (Gazzaniga et al., 2002; Zilles & Amunts, 2010). According to Zilles and Amunts (2010), areas with the numbers 12-16 and 48-51 are not shown in Brodmann’s map of the human cortex.

Broca's area has previously been ascribed Brodmann area (BA) 44 and 45 (Gazzaniga et al., 2002; Hagoort, 2005a; Whalen & Lindblom, 2006). Wernicke's area has been ascribed BA 22, 37, 39 and 40 (Catani, Jones, & ffytche, 2005; Whalen & Lindblom, 2006). However, what constitutes Broca's and Wernicke's area is still being discussed today (Toates, 2007). New terminologies, such as Broca's complex (Hagoort, 2005a, 2005b; Xiang, Fonteijn, Norris, & Hagoort, 2009), Broca's territory, and Wernicke's territory (Catani et al., 2005) have been introduced in recent years, which include larger areas of the cerebral cortex.

For over two decades, Penfield, Roberts, and colleagues, performed pioneering research while preparing patients who were undergoing open brain surgery (Gazzaniga et al., 2002; Penfield & Roberts, 1959; Rosenzweig et al., 2005; J. Ward, 2006). Many of the patients were seeking a cure for focal cerebral seizures, a form of epilepsy (Penfield & Roberts, 1959; J. Ward, 2006; Wickens, 2005). Small levels of electrical current were applied directly onto the cortex, in order to examine the functions of different regions of cortex, and to ensure that important regions were not removed by surgery. The patients were fully conscious and talking during the procedures, which made it possible to discover specific parts of the cortex that were devoted to each individual's speech function (Penfield & Roberts, 1959). Penfield and Roberts (1959) provided a map of language-related zones of the left hemisphere. Electrical stimulation in different cortical areas would for example lead to vocalisation, dysarthria and distortion of speech, repetition, slurring, hesitation, or arrest of different speech functions (Penfield & Roberts, 1959; Wickens, 2005). This work also led to *the homunculus,* which is a map of how the human body surface is represented in the cortex (Gazzaniga et al., 2002). Ojemann (1983) and colleagues have done further stimulation

research, and shown that the extent of the cortical language zones varies greatly between individuals in both size and location.

The use of language mapping methods such as the intraoperative cortical stimulation mapping (ICSM) gradually declined as the amytal aphasia test, better known as the Wada test, became a common method for localizing the dominant language hemisphere (Binder, 2006; Penfield & Roberts, 1959). In the Wada technique, the anaesthetic sodium amytal is injected into one of the two carotid arteries, which supplies blood to the hemispheres (Toates, 2007; Wickens; 2005). Sedation of the speech-dominant hemisphere (as well as the contralateral side of the body), results in disruption of speech. The effect only lasts for approximately five to ten minutes.

Since the 1980s, different brain imaging techniques have been used to investigate language related brain areas (J. Ward, 2006). Cognitive neuroscience combines various techniques with the experimental strategies of cognitive psychology to examine how brain function supports mental activities (Raichle, 1998). Advances in brain imaging in recent years have enabled researchers to monitor cerebral blood flow during specific linguistic tasks (Owens, 2012; Raichle, 1998; J. Ward, 2006). This simplifies research that aims to detect brain structures and the functions involved in speech perception and production.

Electroencephalography (EEG) records spontaneous electrical signals generated by the brain, via electrodes placed on different points of the scalp (e.g. Gazzaniga et al., 2002; Huettel, Song, & McCarthy, 2008; Rosenzweig et al., 2005; J. Ward, 2006; Wickens, 2005). Many neurons need to be active at the same time to generate a large enough electrical field to be detected (Rosenzweig et al., 2005; J. Ward, 2006). The EEG results are usually compared to activation in a site that is thought to remain

relatively uninfluenced by the variable under investigation (J. Ward, 2006). EEG is a harmless and non-invasive method (J. Ward, 2006). Event-related potentials, or ERP's, are large cerebral electrical potential changes evoked by sensory, motor, or cognitive events (Gazzaniga et al., 2002; Rosenzweig et al., 2005). The method relies on EEG measurements, and is an especially important method when measuring the relative timing of cognitive events (Gazzaniga et al., 2002; J. Ward, 2006. Usually, many ERP's are averaged in order to obtain a reliable estimate of stimulus-elicited brain activity (Rosenzweig et al., 2005; J. Ward, 2006). Both EEG and ERP have good temporal resolution, but it is difficult to localize where the cerebral activation originated (Gazzaniga et al., 2002; Rosenzweig et al., 2005).

All electrical currents, including those that are brain-generated, have a potentially measurable magnetic field (Gazzaniga et al., 2002; J. Ward, 2006). Magnetoencephalography (MEG), like EEG, measures the fields that are generated by the activity of neurons, but with better spatial resolution than EEG (Gazzaniga et al., 2002; J. Ward, 2006). The MEG signal is recorded with a superconducting quantum inference device (SQUID), which is an apparatus that requires liquid helium for extreme cooling and isolation in a magnetically shielded room (J. Ward, 2006). It is a non-invasive, but also an expensive method (e.g. Gazzaniga et al., 2002).

Positron emission tomography (PET) is an imaging method with the objective to obtain images of brain activity rather than detailed brain structure (Gazzaniga et al., 2002; Rosenzweig et al., 2005). Short-lived radioactive chemicals are injected into the blood stream, which makes this an invasive method, and the emission of radioactive signals from highly active brain regions are used to create a computer-generated image

(Rosenzweig et al., 2005). PET and fMRI (explained later) measure metabolic changes correlated with neural activity, rather than direct neural events (Gazzaniga et al., 2002).

Magnetic resonance imaging (MRI) was first introduced in the late 1970s under the name nuclear magnetic resonance, and has had an enormous development since then (Huettel et al., 2008). MRI is considered one of the most important advances in medicine during the twentieth century, and Paul C. Lauterbur and Sir Peter Mansfield received the Nobel Prize of medicine in 2003 for their contributions to its development (Huettel et al., 2008; J. Ward, 2006). Since our study applies MRI and fMRI measurements, these methods will be explained in more detail than the aforementioned methods. MRI is a non-invasive method with a very high spatial resolution potential, used for obtaining images in any plane through the human body (Huettel et al., 2008; J. Ward, 2006). MRI is used to create images of the body's soft tissue (J. Ward, 2006). The body's single protons found in water molecules have weak magnetic fields that usually are oriented randomly (Gazzaniga et al., 2002; J. Ward, 2006). Any atom with an odd number of electrons, such as hydrogen - which is essential in water, has an inherent rotation, which is called spin in MRI-terminology (Gazzaniga et al., 2002; Wickens, 2005). In order to acquire an MRI scan, a sequence of events needs to happen as follows. A strong magnetic field, measured in units called tesla (T), is applied constantly during the scanning across the part of the body that is to be scanned, for example the brain (Gazzaniga et al., 2002; J. Ward, 2006). This will force some of the protons to align with the applied magnetic field. A brief radio frequency pulse then knocks the aligned protons into a new orientation, 90 degrees away from their previously aligned state. While the protons spin in their new orientation, they produce a detectable change in the magnetic field (Gazzaniga et al., 2002; J. Ward, 2006). This forms

the basis of the MR signal, which is then detected by an antenna, for example the head coil that is used for brain imaging (Huettel et al., 2008). Eventually, the protons return to their original alignment with the magnetic field, emitting a radio wave that can be detected by the antenna. After the protons have returned to their original alignment the process can be repeated (J. Ward, 2006). Importantly, each type of body tissue contains different amounts of water and the respective protons need different times for returning to the original alignment, which leads to different MR signals (J. Ward, 2006). This makes it possible to construct three-dimensional images of the layouts of different body tissues, such as ligaments, grey matter, white matter, tumours, blood vessels, and bones (Huettel et al., 2008; J. Ward, 2006).

Cognitive neuroscience research was utterly revolutionized when functional MRI (fMRI) was introduced in the 1990s (Rosenzweig et al., 2005). The basic technology of fMRI is the same as for MRI-scanning, but fMRI-scanning is used to detect brain function through small changes in brain metabolism, rather than structural information (Huettel et al., 2008; Rosenzweig et al., 2005). This is achieved by high-powered, rapidly oscillating magnetic-field gradients for a rapid acquisition of the MRI image. Thus, fMRI has not only high spatial resolution, but also reasonably high temporal resolution, and is adaptable to many types of experimental paradigms (Huettel et al., 2008; J. Ward, 2006). Functional brain mapping is made possible by using the venous blood oxygenation level-dependent (BOLD) MRI contrast (Gazzaniga et al., 2002; Kim & Bandettini, 2006; Raichle, 1998). Both increased and decreased activation in a cerebral area leads to BOLD-detectable changes in regional blood flow (Raichle, 1998). Because of its content of iron, blood has magnetic properties. Oxygenated haemoglobin (Hb) is diamagnetic, while deoxygenated haemoglobin (dHb) is paramagnetic and

therefore a safe endogenous contrast agent (Huettel et al., 2008; J. Ward, 2006). The BOLD contrast relies on changes in dHb, or the ratio of Hb to dHb, since changes in local cerebral dHb concentration leads to alterations in the signal intensity of MR images (Kim & Bandettini, 2006; J. Ward, 2006).

Cognitive subtraction is an experimental design used in fMRI (J. Ward, 2006). According to the principle of cognitive subtraction, by comparing the activity of the brain in a task that involves a particular cognitive component with the brain activity during a baseline task that does not, it is possible to find out which regions are specialized for this cognitive component (Aguirre, 2006; Hirsch, 2006; J. Ward, 2006). In fMRI studies, a comparison between two or more tasks or conditions is always necessary, as the brain is always physiologically ”active”. However, the principle of cognitive subtraction is associated with several methodological fallacies. For instance, the choice of baseline tasks may have important implications for the results.

According to Specht, Osnes, and Hugdahl (2009), research on functional asymmetry in auditory perception is often methodologically limited. One of the reasons for this is that studies use fixed stimulus categories such as pure tones, synthetic sounds, sounds from musical instruments and speech sounds. The contrasts between the different categories may include several aspects/processes occurring together (Specht et al., 2009). The imaging data may become ambiguous if the baseline task is not right, and it is important that the baseline task or stimuli is as similar as possible to the experimental task (J. Ward, 2006). When choosing the baseline task, having a good cognitive theory of the elements involved in the task therefore becomes important.

A more general problem of cognitive subtraction is the assumption of pure insertion or pure deletion (Aguirre, 2006; Hirsch, 2006; J. Ward, 2006). These assumptions hold

that adding or removing a component will not influence on the operation of earlier components in the sequence.

A factorial or a parametrical task design may reduce the fallacies of cognitive subtraction (Osnes, 2012; J. Ward, 2006). In a parametric design the variable of interest is treated as a continuous dimension rather than a categorical distinction (Price et al., 1997) This involves measuring associations between brain activity and changes in the variable of interest, rather than measuring differences in brain activity between two or more conditions. When choosing an experimental design the researcher also has to decide how the stimuli should be ordered (J. Ward, 2006; Friston et al., 1999). In a block design, stimuli that belong together are grouped together whereas in an event-related design different stimuli or conditions are intermingled with each other. The different conditions are then separated out when analysing the data. Event-related-designs or e-fMRI can only be used within fMRI (not in PET or structural MRI). There are advantages and disadvantages with both designs. While block designs have more statistic power than event-related designs, event-related designs makes a greater variety of experimental designs possible. E-fMRI designs are also more similar to experimental designs within cognitive psychology, and some types of empirical questions can only be addressed using event-related designs (J. Ward, 2006; Friston et al., 1999).

Language Processing

The brain functions holistically. Specific brain areas may be involved in several different processes. According to Owens (2012), it is therefore difficult to identify the exact spot where language and speech reside in the brain. Despite decades of research, the exact location and function of language processing is not fully understood (Hickock & Poeppel, 2007; Owens, 2012). According to Gazzaniga et al. (2002), we are only just

beginning to learn the cerebral cortex's functional organization. Some areas seem to be more important to language processing than others, especially the frontal and temporal lobes (Owens, 2012; Price, 2010). Areas of the frontal lobe that are important for speech production are not speech-specific; they also participate in non-speech tasks (Owens, 2012). , Language systems for comprehension and production overlap partially, but the neural organization of speech seems to be task dependent (Hickock &Poeppel, 2007; Owens, 2012; Price, 2010).

The human brain is said to be plastic, and continuously adapting to new situations. This means that other brain areas may get involved in language functions as a course of normal development or as a result of injury (Owens, 2012; Wickens, 2005). This may explain why there often is significant recovery of functions in the first months after a stroke (Wickens, 2005). It is also the reason why it is important to investigate more than one individual in order to be able to make inferences on a group level. As previously mentioned, the extent of the cortical language zones varies greatly between individuals in both size and location (Ojemann, 1983). In most research contexts, it is also useful to have knowledge of each individual's medical health history, and knowledge of previous treatment that may have changed brain networks.

The brain processes sequences of speech sounds approximately seven times faster than non-speech sounds (Owens, 2012). However, the speed of the linguistic analysis varies with the complexity of the information as well as the speed of the incoming information. To extract information from spoken linguistic stimuli, the brain is influenced by both bottom-up and top-down processing (Owens, 2012). During bottom-up processing, individual elements of stimuli are analysed and then combined to form a unified perception, in a data-driven way (Matlin, 2005; Toates, 2007). Bottom-up

processing is a somewhat shallow analysis of perceptual data, which has to work its way up to more sophisticated cognitive processes (Matlin, 2005; Owens, 2012). Top-down processing on the other hand, is conceptually driven (Matlin, 2005; Owens, 2012; Toates, 2007). During top-down processing, sensory information is interpreted in light of memory, existing knowledge, concepts, ideas and expectations (Matlin, 2005; Owens, 2012; Toates, 2007). Contexts, both linguistic and non-linguistic, enable humans to predict the form and content of incoming linguistic information. According to Owens (2012), it is likely that bottom-up and top-down processing occurs simultaneously, or that they are used for particular tasks. Matlin (2005) claims that the very first part of stimulus processing may be bottom-up, but that top-down processing begins almost simultaneously.

There are many theoretical issues to be ware of when studying language processing. The design and tasks of language studies often involve several additional brain functions, such as motor, sensory, attention, memory and central executive functions (Binder, 2006). When researchers choose a control task to contrast the language task, they also establish which task components they find uninteresting. Researchers may attempt to study the same language process, but their implicit definitions may vary so that they apparently report conflicting results (Binder, 2006; Hickock & Poeppel, 2007). Price (2010) published an article that reviews 100 fMRI studies of speech comprehension and production that exemplifies this. Not only may researchers' definitions of language processes vary, they may also use different anatomical terms for the same cerebral region. A cerebral region might be referred to by its Brodmann name, a cytoarchitectonic name, a gross anatomical name, or a functional name (Gazzaniga et

al., 2002). However, the functional names of brain regions change rapidly as new information is gathered.

Theories and Models of Language Processing

Disconnection theory - the Wernicke-Geschwind model. Wernicke introduced a connectionist perspective that suggests that language deficits can be understood as disruptions in an interconnected network of components, where every component is involved with a particular feature of language analysis or production (Geschwind, 1964; Geschwind, 1970; Rosenzweig et al., 2005; Wickens, 2005). Geschwind developed this perspective further in 1972, suggesting that when a spoken word is heard; the auditory cortex transmits the information to Wernicke's area, which decodes and analyses the meaning of the sounds (as cited in e.g. Rosenzweig et al., 2005; Toates, 2007; Wickens, 2005). In order to articulate an aurally perceived word out loud, Wernicke's area transmits the intended message to Broca's area via the white nerve fibres that constitute the arcuate fasciculus. Broca's area activates a speech plan and transmits the plan to the face area of the adjacent motor cortex. The motor cortex may then activate the relevant articulatory muscles, to enable speech. If a person wants to name a visually perceived object, for example a chair or some written material, the Wernicke-Geschwind model hypothesizes that visual information is sent from the visual cortex to the angular gyrus. The angular gyrus is thought to translate the visual code into an auditory code, which in turn activates the auditory pattern in Wernicke's area. This information then proceeds via the arcuate fasciculus to Broca's area and the motor cortex as previously described for aurally perceived words (Rosenzweig et al., 2005; Toates, 2007; Wickens, 2005). Most of this processing is hypothesized to take place in the left hemisphere, but the information may also cross the corpus callosum to the right hemisphere and back

(Wickens, 2005). The basics of this model are generally accepted today as well, although the sharp functional distinctions between regions as implied by the model are no longer thought to exist (Wickens, 2005; Toates, 2007). In addition, researchers today also credit the role of subcortical regions in language processing (Wickens, 2005).

Motor theory of speech perception. This theory assumes that a heard auditory signal is matched onto motor representations, which humans use to produce speech (J. Ward, 2006). Lieberman and Mattingly (1985) call these motor representations intended (phonetic) gestures, and claim that there are lawful dependencies between gestures, articulatory movements, vocal-tract shapes, and the heard auditory signal. Lieberman and Whalen (2000) have later called them articulatory gestures, and explain them as changes in the cavities of the vocal tract, such as openings and closings. While other theories have assumed that the process of speech perception goes through different cognitive stages before the individual phonemes are categorized and understood, this theory assumes that special neural structures make up special modules that make perception of heard stimuli immediate (Lieberman & Mattingly, 1985; Lieberman & Whalen, 2000). Summed up, the theory claims that humans recognize phonemes by inferring articulatory movements, which would be necessary to produce heard language sounds (J. Ward, 2006). It further suggests that the motor gestures we perceive constitute essential phonetic units, while the sounds we perceive only supply the information for immediate perception of the gestures (Lieberman & Mattingly, 1985; Lieberman & Whalen, 2000) . The motor theory thus implies a tight link between speech perception and production (Lieberman & Mattingly, 1985).

Two-loop timing hypothesis. Another motor control theory of speech production is called the two-loop timing hypothesis (Foundas, Bollich, Corey, Hurley,

& Heilman, 2001; Foundas et al.; 2004). This theory or model assumes that there are two main neural networks or circuits, an outer linguistic and an inner phonatory loop, that cooperate to coordinate speech production (Foundas et al., 2004). According to Foundas et al. (2004), the outer linguistic loop involves perisylvian speech-language areas and interconnecting white matter pathways. To be more specific, the loop includes the involvement of the PT, the inferior parietal lobe (IPL), and the pars triangualis (PTR), and pars opercularis (POP) in the inferior frontal lobe (IFL). The model assumes that the linguistic loop is involved with phonologic, lexical, syntactic, and semantic language functions, as well as the more elemental processing of auditory verbal information, for example selecting and monitoring speech sounds (Foundas et al., 2001; Foundas et al., 2004). The inner phonatory loop is thought to be involved with the motor programs of the vocal apparatus, and may be important for motor control of speech output. The inner loop includes the involvement of cortical-striatal-cortical circuits. Specific brain areas involved in the phonatory loop include the primary and premotor cortex (PMC), especially the motor cortex along the length of the central sulcus (CS) and the supplementary motor area (SMA). In addition, caudate nucleus (CN), globus pallidus (GP), substantia nigra, and the subthalamic nucleus also hold important roles in the inner loop (Foundas et al., 2004).

Memory, unification and control (MUC) model. Hagoort (2005b) proposed that memory, unification and control are the core functional components of language processing, and that the MUC model can be applied to both language production and comprehension. He focused on language comprehension and the component called unification because of the contributions of Broca's area and surrounding areas to the processing of language. Hagoort (2005a) specified that Broca's area must not be

mistaken as a language specific area, as it almost certainly contributes to other cognitive functions as well. He hypothesizes that while producing and comprehending language, our memory retrieves lexical word information and combine this information into larger units in the component called unification (Hagoort, 2005b). Unification consists of several parallel operations that take place at the semantic, syntactic, and phonological levels of processing. The control component relates language to action, for example during turn taking in conversations; and the memory component specifies which types of language information that are stored in long-term memory, and how they are retrieved.

Hagoort (2005b) specifies the contribution of Broca's complex to language processing in terms of unification operations. Broca's complex refers to the left inferior language area, including BA 44, BA 45, BA 46, BA 47, and ventral BA 6 (Hagoort, 2005a, 2005b; Xiang et al., 2009). Hagoort (2005a, 2005b) suggests that BA 44 and parts of BA 6 contribute to phonological processing, while BA 44, BA 45, and BA 46 contribute to syntactic processing, whereas BA 47 and 45 have a role in semantic processing. Thus, the left inferior frontal gyrus (LIFG) has a central role in this model, being involved in all the domains of language processing that Hagoort suggests (and especially in unification), via different sub regions.

Persisylvian language networks of the human brain. Catani et al. (2005) introduced a model of two parallel language pathways, which connects temporal and frontal brain regions, including an indirect pathway not previously described. The model consists of a direct and an indirect pathway. The direct pathway is similar to the classical language pathway, which connects frontal and medial temporal lobes via the arcuate fasciculus, which is a white matter neuronal fibre tract. This pathway is thought

to relate to phonologically based language functions such as automatic repetition. The indirect pathway seems to run parallel and lateral to the arcuate fasciculus, and is further divided in an anterior and a posterior segment. The anterior segment connects Broca's territory with the inferior parietal lobe, while the posterior segment connects the inferior parietal lobe and Wernicke's territory. The indirect pathway appears to relate to semantically based language functions (Catani et al., 2005).

Dual-stream model of speech processing. As far back as in the 1870s, Wernicke proposed a dual stream model of speech processing (Hickock & Poeppel, 2007). Many modern theories have also suggested a dual stream model for auditory language processing (e.g. Hickock & Poeppel, 2007; Kaas & Hackett, 1999; Saur et al., 2008). In Hickok and Poeppel's model (2007) a ventral stream, which involves superior and middle temporal lobe structures, processes speech signals for comprehension (Hickock, 2012; Hickock & Poeppel, 2007; J. Ward, 2006). The model assumes that the ventral stream is largely bilaterally organized, although the two hemisphere systems have important computational differences (Hickock, 2012; Hickock & Poeppel, 2007). This means that the ventral stream itself comprises parallel processing streams. A dorsal stream, involving structures in the posterior frontal lobe and posterior dorsal aspects of the temporal lobe and parietal operculum (area Spt), maps acoustic speech signals to frontal lobe articulatory networks. It captures explicit phoneme segmentation, which is essential for speech development and normal speech production (Hickock, 2012; Hickock & Poeppel, 2007; J. Ward, 2006). The model assumes that the dorsal stream is strongly left-hemisphere dominant. According to Hickock and Poeppel (2007), the majority agrees that the auditory ventral stream supports the perception of speech. There is more disagreement regarding the functional role of the auditory dorsal stream, but it

has been suggested that the auditory dorsal stream supports an interface with the motor system. Hickock and Poeppel (2007) suggest that the crucial portion of the STS, which is involved in phonological-level processes, is bounded anteriorly by the most anterolateral aspect of Heschl's gyrus, and posteriorly by the posterior-most extent of the Sylvian fissure. Their model has been cited in many published works during the recent years.

Language Lateralization and Brain Asymmetry

According to Owens (2012), the two cerebral hemispheres have specialized functions and skills. They perform different but complementary functions (Rosenzweig et al., 2005). For example, the left hemisphere is dominant for control of speech- and non-speech-related oral movements and for language processing (Owens, 2012; Wickens, 2005). The left hemisphere is adept at perceiving rapidly changing sequential information, such as the acoustic characteristics of phonemes in speech (Matlin, 2005; Owens, 2012). However, processing phonemes for meaning, involves both hemispheres (Owens, 2012). The right hemisphere engages in holistic interpretation, while the left hemisphere is better at step-by-step processing (Owens, 2012; J. Ward, 2006). Some of the right hemisphere language-related skills include comprehension and production of speech prosody and affect, metaphorical language and semantics, and comprehension of complex linguistic and ideational material (Matlin, 2005; Owens, 2012; Wickens, 2005). The right temporal lobe processes paralinguistic input such as intonation, stress, rhythm, and rate (Owens, 2012).

Geschwind and Galaburda (1987) claim that the simplest theory of lateralization is that asymmetrical patterns are strongly determined genetically, and that this theory is widely accepted. It may be that the cerebral language centres originated from a

spontaneous gene mutation that mediated the development of cerebral structures used for interpreting auditory information and producing vocalizations (Bazzett, 2008). Penfield and Roberts (1959) reported that regardless of the handedness of an individual, the left hemisphere is usually dominant for speech, except after occurrence of cerebral injuries early in life. According to Owens (2012), approximately 98% of humans are left hemisphere dominant for language. Over 90% of the cases of aphasia due to brain injury are caused by damage to the left cerebral hemisphere (Rosenzweig et al., 2005). Generally, almost all right-handers and approximately 60% of left-handers are left-hemisphere dominant for language (Owens 2012). Very few individuals display bilateral linguistic performance, with no apparent dominant hemisphere. However, women seem to have a slightly more even distribution of language functions between the hemispheres, evidenced by research showing that women who suffer left hemisphere strokes are less likely than men to show severe aphasic symptoms, and show better recovery of language function afterwards (Owens, 2012; Passer & Smith, 2007; Wickens, 2005). Dyslexia and stuttering are both examples of language impairments that are found more often in males than in females (e.g. Wickens, 2005). This may imply the important organising effects of testosterone on the developing brain (Wickens, 2005). Geschwind and Behan (1982) proposed that excessively high levels of foetal male hormone (testosterone) during a critical stage of prenatal brain maturation might slow down the neural development of the left hemisphere. This might lead to a more symmetrical brain or reduced functional asymmetry between the hemispheres (Beaton, 2003; Wickens, 2005; Geschwind & Behan, 1982; Geschwind & Galaburda, 1987). Since the female foetus is exposed to less testosterone than the male foetus, females may have a lower probability of developing disturbances in the left hemisphere

language functions than males (Silverman, 2004). According to Guitar (2006), the testosterone hypothesis has not received empirical support yet, but the proposal of a delay in the development of language functions in the left hemisphere, as a cause for language disorders is still very interesting.

Earlier findings have shown both functional and structural brain differences between the right and left hemisphere in the primary and secondary auditory cortex (Specht et al., 2009). Within the field of auditory laterality there is an area that is structurally different in the left and right hemisphere. The planum temporale (PT) is a small triangular area in the posterior temporal gyrus (Hugdahl, 2003). It is comprised of auditory association cortex important in higher order processing, and the left PT is thought to be part of Wernicke's area (Foundas et al., 2004; Habib & Robichon, 2003; Wickens, 2005). Lesions of the PT often lead to Wernicke's aphasia, especially if the lesions are significant and in the left hemisphere (for right-handed subjects) (Galaburda, 1995). A summary of anatomical studies that investigated structural differences found that the PT was larger in the left hemisphere than in the right, in approximately 73% of right-handed individuals (Habib & Robichon, 2003), while others report a larger left PT in 65% of the population (Wickens, 2005). These structural asymmetries are present before birth (Galaburda, 1995; Owens, 2012; Wickens, 2005). In relation to the abovementioned hormone theory, Geschwind and Behan (1982) mentioned that testosterone would affect the development of the PT negatively in the left hemisphere, leading the right PT to grow larger in order to compensate. The PT was earlier thought to have different roles in left versus right hemisphere because of differences in size and activation patterns. Recent neuroimaging studies have showed that both cerebral hemispheres are involved in phonological processing as a part of auditory speech

perception, contrary to earlier findings (Specht et al., 2009). There are also more differing views of the role of the PT. Some studies are suggesting that the PT has a more general function in analysing complex sound structures, such as rapidly changing cues. Hickock and Poeppel (2007) claim that a human speech recognition system is bilaterally organized, but that the two hemispheres have important computational differences. Empirical evidence from different lesions studies suggests that we may process speech sounds sufficiently well to access our mental lexicon despite unilateral brain damage in either hemisphere (Hickock & Poeppel, 2007).

Dichotic listening (DL) is an important method for the study of auditory laterality (Hugdahl, 2003). In a dichotic listening task, two different stimuli are presented simultaneously, one to the right ear and one to the left (Bryden, 1988). The foundation of the DL situation is to simultaneously present more stimuli than the brain can consciously analyse, and investigate which of the stimuli that is selected (Hugdahl, 1995, 2003). Results from dichotic listening experiments normally show that more items are correctly reported from the right ear, than from the left (Kimura, 1961; Hugdahl, 2003). This is called the right ear advantage (REA). Approximately 85% of right-handed persons and 65% of left-handed persons show the REA (Hugdahl, 1992). Kimura (1967, as cited in Hugdahl, 2003) proposed a neuroanatomical model that suggests several interacting factors as an explanation of the REA effect. These factors are: auditory input to the contralateral hemisphere is more strongly represented in the brain; the left hemisphere is specialized for language processing; the contralateral auditory information suppresses information sent along the ipsilateral pathways; and information that reaches the ipsilateral right hemisphere must be transferred across the corpus callosum to the language processing areas in the left hemisphere (Hugdahl,

2003). Kimura's model of the REA effect has received a great amount of empirical support (Hugdahl, 2003). The REA-effect is modulated when participants are instructed to focus attention on either the left or right ear stimulus (Hugdahl et al., 2009).

A more recent addition to the research of speech lateralization is the fMRI soundmorph paradigm (Specht, Rimol, Reul, & Hugdahl, 2005). Specht et al., (2009) explored possible variations in lateralization of response to verbal and non-verbal auditory stimuli using a soundmorph paradigm. They varied the spectral complexity of speech and music sounds in seven steps. The stimuli were presented in an event-related design, and the evoked brain responses were measured by fMRI. They found that the left temporal lobe was more sensitive to gradual manipulation of the speech sounds, while the right temporal lobe responded to all sounds and manipulations. This effect was especially strong within the middle region of the left superior temporal sulcus (mid-STS). The posterior area of the STS showed a linear response to the manipulation to speech sounds. The anterior adjacent area of the STS showed strongest interaction between the speech and the music sound manipulations. These responses were not found when the sound morphed into a music stimulus. Implications from this study supports the hypothesis that the mid-STS area in the left hemisphere is more sensitive to speech signals compared to the corresponding region of the right hemisphere (Specht et al., 2009).

Speech Perception

Hickock and Poeppel (2007) separate speech perception from speech comprehension, and define speech perception as sublexical tasks, such as syllable discrimination. Speech perception tasks require processes that allow the listener to maintain sublexical representations in an active state during the performance of the task,

as well as the recruitment of task-specific operations. This means that the speech perception tasks involve some degree of executive control and working memory, which might explain the association with frontal lobe lesions and activations. In our study we have applied Hickock and Poeppel's definition of speech perception in the discussion of our results.

Speech perception leads to language comprehension, and involves processing speech stimuli from the ears and sending them to Heschl's area (an area of each auditory cortex) with 60% of the information crossing to the opposite hemisphere and 40% staying on the same side (Penfield & Roberts, 1959; Owens, 2012). According to Owens (2012), initial phonological analysis begins in the bilateral Heschl's gyri. It separates incoming information, dividing linguistic from paralinguistic data, sending the linguistic data to Wernicke's area in the left temporal lobe. Wernicke's area processes the linguistic information with aid from the angular and supramarginal gyri. The angular gyrus is known to be involved in word recall, while the supramarginal gyrus is known to be involved in sequential and syntax processing (Owens, 2012). Rosenzweig et al. (2005) report that injury to the supramarginal gyrus is known to interfere with repetition of heard speech.

Research has also implicated a potential role of the premotor cortex (PMC) in speech perception (Price, 2010). Osnes, Hugdahl, and Specht (2011) used a soundmorph paradigm to investigate the PMC involvement in speech processing through a behavioural task and an fMRI study. The results showed that PMC was only present at step 5, an intermediate step where the speech sounds became identifiable but were still distorted. PMC involvement does not seem to be necessary for speech perception but it may facilitate interpreting a sound as speech when acoustic information is limited

(Price, 2010; Osnes et al., 2011). The fMRI data were modelled with dynamic causal modelling (DCM). Effective connectivity between Heschl's gyrus (HG), PT, STS, and PMC was tested. The resulting dynamic causal model shows interconnections between HG, PT, and STS when processing speech sounds. It shows bidirectional connections between PMC and STS and from PT to PMC. Osnes (2012) therefore hypothesizes that these structures constitute the different parts of a cerebral network of speech perception. Price (2010) concludes that cerebral activation during prelexical speech comprehension is mainly in the bilateral superior temporal gyri. Hickock & Poeppel (2007) also reports that listening to speech activates the superior temporal gyrus (STG) bilaterally, including the dorsal STG and superior temporal sulcus, when contrasted with a resting baseline. Research has found that portions of the STS are important for representing and processing phonological information (Price, 2010, Osnes et al., 2011). Both lesion and functional imaging studies suggest that the PT performs phonologic and lexical analyses or decoding (Foundas et al., 2004).

Speech Production

Several authors have claimed that being able to speak is one of our most complex cognitive and motor skills (e.g. Brown et al., 2005; Levelt, 1994; Matlin, 2005). Over 100 different muscles are involved in producing overt speech (Levelt, 1994; Matlin, 2005), and as previously mentioned, several cognitive processes, such as motor, sensory, attentional, memory and central executive functions are involved at the same time (Binder, 2006). There is less reported research on speech production than speech comprehension (Cutler, Klein, & Levinson, 2005; Eysenck & Keane, 2010; Matlin, 2005; Price, 2010). Speech production produces signal artefacts due to movement of the mouth and head during speech, which makes it more difficult to use neuroimaging

techniques to study speech production (Price, 2010; Whalen & Lindblom, 2006). However, the use of event-related fMRI overcomes this limitation to some extent. Another limitation is that it may be hard to manipulate what a person wants to say or write in a controlled setting (Cutler, Klein, & Levinson, 2005; Eysenck & Keane, 2010; Matlin, 2005).

Price (2010) refers to speech production as a complex multistage process, which links conceptual ideas to articulation. She claims that given all the processes that support speech production, it is unsurprising that several different brain areas are involved.

Posner and Raichle (1994) summarized PET studies that examined brain activation during different levels of word processing. They found that passive exposure to spoken words shifted the focus of maximum brain activation to the temporal lobe, while repeating the words orally activated the motor cortices bilaterally, the supplementary motor cortex, and a portion of the cerebellum and insular cortex. According to Owens (2012), during speech production, the left insula is found to be one of the most active brain areas. Messages are transmitted from Wernicke's area to Broca's area via the arcuate fasciculus (Owens, 2012). Broca's area is responsible for detailing and coordinating the programming for verbalizing the message. It programs the motor strip or motor cortex, which in turn sends nerve impulses to the muscles of speech. Whalen and Lindblom (2006) claim that Broca's area is essential to voluntary speech articulation; and that motor, premotor, and anterior (insula) areas have important roles as well; while the cerebellum is thought to be involved in controlling the timing of speech.

Regions that are involved in speech production overlap partially with regions that are activated in speech perception (Price, 2010). In addition, the following cerebral regions are involved in speech production: left mid-frontal gyrus, left anterior insula, left putamen, bilateral head of caudate, anterior cingulate, preSMA, SMA, motor cortex, and cerebellum (Price, 2010). The left mid-frontal gyrus is associated with word recall during controlled articulation. Price (2010) further reports that articulatory planning activates the left anterior insula, whether a sound is produced or not, while the initiation and execution of audible speech activates left putamen, pre-SMA, SMA, and motor cortex. Research has found that the anterior cingulate and bilateral head of caudate nuclei are activated while suppressing unintended responses (Price, 2010).

Stuttering

"Fluent speech is the consistent ability to move the speech production apparatus in an effortless, smooth, and rapid manner resulting in a continuous, uninterrupted forward flow of speech" (Owens et al., 2007, p. 220).

We all depart from perfect fluency some times (Van Riper, 1982), and levels of fluency differ between individuals (D. Ward, 2006). Stuttering is a disorder that disrupts the individual's ability to produce fluent speech (Owens et al., 2007). Even though disfluency is a part of normal speech, there are factors that appear to distinguish normal and abnormal disfluencies. Abnormal disfluencies tend to be more severe, occur more frequently, involve more effort and tension, and consist of more syllable or part-word repetitions compared to normal disfluencies (Conture, 1990; Guitar, 2006; D. Ward, 2006). Stuttering has been with us throughout recorded history, and occurs in different cultures (Van Riper, 1982). It is found in all parts of the world, and affects both genders, and people of all ages (Guitar, 2006).

Today, there is still no widely accepted definition of stuttering that gives a fully satisfactory description of the disorder (Bloodstein, 1995). Several attempts have been made to capture the most essential features of the stuttering (Alm, 2005; Ward, 2006). Understanding what stuttering comprises of is important when it comes to guiding research and treatment (Yairi & Ambrose, 2005). Different theories of the aetiology of stuttering will lead to different thoughts about treatment, depending on whether they are based on a hypothesis of stuttering caused by psychological, organic, linguistic, or behavioural factors (Yairi & Ambrose, 2005). Even though it probably is the speech language disorder that has been given most attention, the aetiology of stuttering is still far from understood (D. Ward, 2006). Van Riper (1982) describes the complexity of the disorder as "*a complicated, multidimensional jigsaw puzzle, with many pieces still missing"* (p.1).

One of the most frequently cited definitions of stuttering is the one proposed by Wingate (Silverman, 2004; D. Ward, 2006). According to Wingate (1964):

The term "stuttering" means: 1. (a) Disruption in the fluency of verbal expression, which is (b) characterized by involuntary, audible or silent, repetitions or prolongations in the utterance of short speech elements, namely: sounds, syllables, and words of one syllable. These disruptions (c) usually occur frequently or are marked in character and (d) are not readily controllable. 2. Sometimes the disruptions are (e) accompanied by accessory activities involving the speech apparatus, related or unrelated body structures, or stereotyped speech utterances. These activities give the appearance of being speech-related struggle. 3. Also, there are not infrequently (f) indications or report of the presence of an emotional state, ranging from a general condition of "excitement" or "tension" to more specific emotions of a negative nature

such as fear, embarrassment, irritation, or the like. (g) The immediate source of stuttering is some incoordination expressed in the peripheral speech mechanism; the ultimate cause is presently unknown and may be complex or compound. (p. 488).

The Epidemiology of Stuttering

There are two main forms of stuttering: Developmental stuttering and acquired stuttering (D. Ward, 2006). Developmental stuttering is the most common form, and it usually has an onset during the preschool years (Starkweather, 1997; Yairi & Ambrose, 2005). This form of stuttering is also sometimes called idiopathic stuttering (Andrews et al., 1983; D. Ward, 2006). Acquired stuttering is divided into neurogenic stuttering, which often results from a neurological disease or trauma (Owens et al., 2007), and psychogenic stuttering, which may be related to a distressing event (D. Ward, 2006). Developmental stuttering may start at any time during childhood, from around 18 months up until puberty, but it is most likely to occur between the ages of two and five years (Andrews et al., 1983; Guitar, 2006; Silverman, 2004), and studies have shown that about 75% of all who stutter start before the age of six (D. Ward, 2006). Yairi & Ambrose (2005) go even further, and claim that more than 85% of stuttering occurs before the age of 3 ½ years.

Prevalence numbers refers to the percentage of the population that stutters at any point in time, while incidence refers to the number of people who have stuttered at some point in their life (Andrews et al., 1983). Bloodstein (1995) reviewed and summarized results of 37 studies of school-age children in Africa, Europe, the US, Australia and the West Indies. These studies showed a prevalence of stuttering of around 1%. Incidence numbers vary depending on inclusion criteria in the studies that investigate stuttering. The incidence numbers appear to be around 5% when cases of stuttering lasting less

than 6 months are excluded (Andrews et al., 1983). The difference between prevalence and incidence numbers indicates that most people who suffer from stuttering will recover from it (Guitar, 2006). Longitudinal studies of children, who are identified shortly after they begin to stutter, show that approximately 75% of children recover from stuttering without formal treatment (Guitar, 2006). According to Yairi and Ambrose (2005), natural recovery from stuttering is most common within a period of a few months to three years after the onset. Many factors have been related to recovery, but the most consistently identified ones are good phonological skills and being female (Guitar, 2006).

There is a difference in the number of males and females who stutter, with the number of males being consistently higher than the number of females (Bloodstein, 1995; Van Riper, 1982). Bloodstein's review (1995) showed a male to female sex ratio of 3:1 in children in the first grade. Research also indicates that the sex difference increases, as the children get older (Andrews et al., 1983; Bloodstein, 1995; Yairi & Ambrose, 2005). The increasing gender difference has been replicated by longitudinal studies (Kloth, Kraaimaat, Janssen, & Brutten, 1999; Månsson, 2000). As the risk of stuttering is greatly reduced after the preschool age, the considerable gender difference in adults suggests higher prevalence of recovery in girls than in boys (Yairi & Ambrose, 2005).

There is evidence for hereditary factors in stuttering. The proportion of stutterers that report having stuttering relatives is higher than among people who do not stutter (Bloodstein, 1995; Guitar, 2006). First-degree relatives of stutterers are more than three times more likely to develop stuttering than the general population (Andrews et al., 1983; D. Ward, 2006). In addition, the concordance of stuttering in monozygotic twins

is considerably higher than in fraternal twins, and the risk of stuttering for a monozygotic co-twin is approximately 77% (Andrews et al., 1983) Results of research on the heredity in stuttering also show the important influence of environmental factors, e.g. by showing the significant proportion of discordant monozygotic twins (Andrews et al., 1983).

Components of Stuttering

Stuttering can be divided into three components (Guitar, 2006): Core behaviours, secondary behaviours, and feelings and attitudes. Core behaviours is a term used to describe the basic speech behaviours of stuttering: repetitions, prolongations and blocks (Van Riper, 1982). These behaviours are involuntary, in contrast to the secondary behaviours, which a person who stutters obtains as a way to try to control the core behaviours (Guitar, 2006). Repetition is the reiteration of sounds, syllables, or single-syllable words. This is the core behaviour that is seen most often in children who are beginning to stutter (Andrews et al., 1983; Van Riper, 1982).

Prolongations typically appear later than repetitions (Van Riper, 1982.). During prolongations, sound or airflow continues, but movement of articulators is stopped. Blocks are usually the last of the three core behaviours to appear (Guitar, 2006). During a block there is an inappropriate stop in the flow of air or voice, and often the movement of the articulators as well. A block can affect any part of the speech production mechanism: respiratory, laryngeal, or articulatory (Guitar, 2006). The blocks often become longer and tenser as stuttering persists, and tremor in the speech musculature, and in some severe instances even in the arms and legs, can become evident (Van Riper, 1982). The core behaviours correspond to the part-word repetition,

single-syllable word repetition, and disrythmic phonation categories of the Illinois Disfluency Classification System (Yairi & Ambrose, 2005).

Guitar (2006) divides secondary behaviours into two categories: escape and avoidance behaviours. Escape behaviours occur when the person experiences an episode of stuttering and tries to cease the stutter and finish the word. Examples of escape behaviours are eye blinks, head nods, jaw jerks, and verbal interjections (Silverman, 2004). The escape behaviours often help to end the stutter, and they therefore become reinforced (Guitar, 2006). Escape behaviours appear to exert their effect by distracting the stutterers attention away from the uttered speech, but lose their effect once the novelty factor wears off (Bloodstein, 1995). The behaviours often become habituated, and remain even after the effect has diminished (Silverman, 2004). Avoidance behaviours occur when the person anticipates that he or she will stutter, and tries to employ behaviours that previously served as escape behaviours that terminated the stutter (Guitar, 2006). In addition, the person who stutters can change the wording of the planned utterance. For a subgroup of stutterers, avoidance becomes the most significant part of the stutter; this is called “interiorized”, or covert, stuttering (D. Ward, 2006). For these individuals, the negative perceptions of their own stuttering are dominating. The stuttering may be totally concealed to a listener, but extensive avoidance strategies are being used to prevent any episodes of stuttering (D. Ward, 2006).

A range of negative emotions and attitudes may accompany stuttering as the child becomes increasingly aware of his or her disfluency and difficulties of speech (Van Riper, 1982). Among these are: frustration or shame for not being able to express what he wants to say without difficulty; fear and anticipatory anxiety of new episodes of stuttering; and hostility towards listeners (Guitar, 2006).

Several conditions have been shown to have a fluency-inducing effect in individuals who stutter (Andrews et al., 1983; Guitar, 2006; D. Ward, 2006). Based on a review of available theories and research, Andrews et al. (1983) list seven conditions where stuttering has been found to be reduced by as much as 90 to 100%. These are: chorus reading, lipped speech (articulating without phonating), prolonged speech and delayed auditory feedback (DAF), rhythmic speech, (e.g. with a metronome), shadowing, singing, and slowed speech. With delayed auditory feedback a small electronic device plays back speech to the stutterer at a short delay (Silverman, 2004).

The Aetiology of Stuttering

The cause of stuttering is still unknown (Conture, 1990). However, a number of different theories exist about the aetiology of stuttering, and they can broadly be divided into psychological, behavioural, linguistic, and organic theories (Guitar, 2006; Owens et al., 2007).

Psychological theories. Psychological theories claim that stuttering is the result of some form of neurosis, connected to unconscious needs and conflicts (Owens et al., 2007). However, psychotherapy seems to be an ineffective method in the treatment of stuttering, and most psychological theories of stuttering as a neurosis are not supported by research (Andrews et al., 1983; Owens et al., 2007). In addition, controlled studies have not shown that stutterers differ from fluent controls in personality factors related to neuroticism (Andrews et al., 1983).

Behavioural theories. Behavioural theories of stuttering claim that it is a learned response to conditions outside of the individual (Owens et al., 2007). Wendell Johnson's diagnosogenic theory from the 1940s is one of the most well known theories belonging to this category (Alm, 2005; Guitar, 2006; Owens et al., 2007). According to

Johnson, the speech disfluencies of children whose parents believed them to be stuttering did not differ from the disfluencies of children whose parents did not judge them to be stuttering (Andrews & Harris, 1964). The difference lay not with the children's behaviour, but with the parents' reactions to the behaviour. As a response to the parent's reactions, the child is thought to develop anxiety related to speech, which increases the problem (Andrews & Harris, 1964).

Another behavioural theory of stuttering is the anticipatory struggle hypothesis (Bloodstein, 1997). The hypothesis suggests that stuttering develops from early experiences of failure in communication, leading to beliefs about difficulties of speech and anticipation of further speech failures (Bloodstein, 1995). These communication difficulties are not necessarily disfluencies (Guitar, 2006). Stuttering is viewed as tension and fragmentation of speech initiation, as a result of speech pressure from the environment (Bloodstein, 1997).

Starkweather (1987) elaborated the thoughts of the anticipatory struggle hypothesis, in his demands and capacities model (as cited in Alm, 2005; Bloodstein, 1995; D. Ward, 2006). The demand and capacities model claims that stuttering results when demands placed on the child are greater than the child's linguistic, cognitive, motor or emotional capacities for producing fluent speech (Alm, 2005; Bloodstein, 1995; Starkweather & Gottwald, 1990). The demands refer both to those of the child's internal environment, and the demands of the external environment (Guitar, 2006). This theory allows the explanation of the apparently contradictory research finding that stutterers in general are a bit behind in language development, but a minority of stuttering children are linguistically superior (Starkweather, 1997; Starkweather & Gottwald, 1990). The discrepancy between capabilities and demands is the central

factor for both groups. Starkweather (1997) stresses that the demands and capabilities model is not a theory of the cause of stuttering, but may be a tool for understanding and organizing the forces that influence the development of stuttering.

Linguistic theories. The influence of linguistic factors on stuttering has generated interest from researchers (Guitar, 2006). An explanation of stuttering from a language production perspective was presented by the covert repair hypothesis (CRH) (Guitar, 2006; Kolk & Postma, 1997). The CRH assumes that all speakers use an internal monitoring process to control speech while it is being formulated, and detect potential errors of the speech plan (Guitar, 2006; Kolk & Postma, 1997; Owens et al., 2007). Errors can be lexical, syntactic, morphological or phonological, and detected errors must be corrected before speech production can proceed (Guitar, 2006). According to Kolk and Postma (1997) stuttering is not an error, but a result of the need for several corrections of a faulty phonetic speech plan.

Organic theories. Organic theories propose a physical cause for stuttering (Owens et al., 2007). Theories of a physical cause of stuttering date all the way back to Aristotle, who believed stuttering was caused by the tongues inability to follow the commands of the brain (Van Riper, 1982; Watson & Freeman, 1997). During the first half of the 19th century the association between stuttering and dysfunctions of the nervous system was introduced (Alm, 2005).

One early organic theory, which has later been supported by modern research, is based on the hypothesis of stuttering being related to the basal ganglia (Alm, 2005). From 1916 and into the 1920s an epidemic of encephalitis occurred in Europe. It was named Economo's encephalitis after the doctor who first described it. This form of encephalitis was known to affect the striatum; the largest part of the basal ganglia

system, and the symptoms included stutter-like speech disturbances (Freund, 1966, as cited in Alm, 2005). The basal ganglia are involved in a network relating to motor control (Gazzaniga et al., 2002; Toates, 2007; J. Ward, 2006; Wickens, 2005). The regulation of dopamine release is central for a functioning basal ganglia system (Alm, 2004, 2005; Toates, 2007; Wickens, 2005). If too much dopamine is released this leads to disinhibition of motor and other behavioural impulses. If the dopamine release is not sufficient, however, this leads to inhibition of movements and impulses (Alm, 2004). It is suggested that the basal ganglia-thalamocortical motor circuits through the putamen are involved in stuttering (Alm, 2004). Support for this hypothesis comes from the observation that in many cases, the cause of neurogenic stuttering is lesions of the basal ganglia-thalamocortical circuit, usually in the left hemisphere (Alm, 2004). The basal ganglia are thought to provide cues for initiation of the next segment in a learned motor sequence, such as speech (Alm, 2004, 2005). It is proposed that impairment of this basal ganglia function leads to stuttering. The hypothesis of basal ganglia involvement allows explanation of several factors related to stuttering, such as the fluency-inducing effect of for example chorus speech and speaking with a metronome, as these situations provide external timing cues for speech, reducing the need for internal control (Alm, 2004).

One of the most influential modern theories of stuttering is the cerebral dominance theory, by neurologist Samuel Orton, and psychologist and speech pathologist Lee Travis, in the late 1920s and 1930s (Van Riper, 1982). The theory was based on the assumption that a large proportion of the group of stutterers were either left-handed or ambidextrous, that had been forced by their environment to switch to using their right hand (Bloodstein, 1995). The muscles that produce speech are paired structures, and receive impulses directing movement from the contralateral hemisphere

of the brain. These impulses must be accurately synchronized in order to produce smooth movements (Bloodstein, 1995). It was thought that in order for this to occur, one of the hemispheres needed to have a dominating influence over the other one. Orton and Travis believed that this dominance was disturbed in stutterers, as a result of the forced change of hand use, and that this led to a conflict in the control of speech (Guitar, 2006). However, the hypothesis that handedness, ambidexterity or change of handedness was related to stuttering did not receive conclusive empirical support (Andrews & Harris, 1964; Guitar, 2006; Van Riper, 1982). There was a revival of interest in the subject of the cerebral lateralization in the 1960s, partly because of research showing that lateralization of speech and language may differ from that of handedness (Penfield & Roberts, 1959; Silverman, 2004). Research applying the WADA test or dichotic listening procedures have provided mixed results, with some studies giving support to the hypothesis of altered cerebral lateralization of language functions in stutterers, while others report stutterers showing the same patterns as fluent controls (Silverman, 2004; Van Riper, 1982).

Advances in neuroimaging techniques have provided further insight into the hypothesis of atypical cerebral laterality in stutterers (Guitar, 2006). Relevant research findings are reviewed in the following section.

Research on Cerebral Differences in Persons who stutter (PWS)

Structural differences. Foundas et al. (2001) used volumetric MRI to investigate anatomical differences in the cortical speech-language areas between adults with persistent developmental stuttering (PDS) and fluent controls, matched for age, sex, handedness, and education. The major quantitative anatomic finding was that the planum temporale (PT) was significantly larger in the subjects with PDS than in the

controls, and that the typical left-dominant asymmetry was significantly reduced. Based on the results, Foundas et al. (2001) hypothesize that atypical structure in the perisylvian speech-language areas may be sufficient to support language development, but they may also lead to an increased risk of stuttering.

Sommer, Koch, Paulus, Weiller, and Büchel (2002) used diffusion tensor imaging (DTI) and found a reduction of white matter located just below the sensorimotor cortical representation of the tongue and larynx in the left hemisphere, in the left rolandic operculum. This suggests a disconnection of superior temporal and inferior frontal language regions of the left hemisphere, and the results are interpreted as evidence for a hypothesis of persistent developmental stuttering (PDS) as caused by a disturbed timing of activation in speech-relevant brain areas (Sommer et al., 2002). Further, Sommer et al. (2002) view increased activation in the right hemisphere, described in the next section, as a compensatory mechanism for the disturbed signal transmission between left-hemispheric frontal language areas and motor regions, rather than a deficit.

Watkins, Smith, Davis, and Howell (2008) used fMRI and DTI to investigate structural and functional differences in PWS. Analysis of the DTI data showed reduced white matter (WM) integrity in ventral premotor cortex in PWS. This corresponded to an area of decreased activation in PWS compared to controls, found in the fMRI analysis conducted in the same study. In addition, the functional measures revealed areas of over-activity in the midbrain, and under-activation of the cortical motor and premotor areas related to speech production (Watkins et al., 2008).

There is also evidence that PWS have anomalous anatomy in areas outside of the speech and language areas in the perisylvian region (Jäncke, Hänggi, & Steinmetz, 2004). Jäncke et al. (2004) applied augmented voxel-based morphometry (VBM) to

compare white matter (WM) and grey matter (GM) in PWS and controls. They found that the PWS had increased WM compared to the controls in a right hemisphere network, comprised of the right superior temporal gyrus (STG), inferior frontal gyrus (IFG), precentral gyrus, and anterior middle frontal gyrus (aMFG). In addition, the PWS showed symmetric WM volumes in the auditory cortex, in contrast to the leftward WM asymmetry observed in the fluent controls. The authors conclude that it remains an open question whether the structural differences are the cause or consequence of stuttering (Jäncke et al., 2004).

Most of the imaging research on stuttering has examined adults, and the findings from these studies may thus reflect structural differences that have developed as a result of years of stuttering (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008). To investigate whether these differences can be observed in children, Chang et al. (2008) used optimized VBM to measure GM volume, and DTI to measure FA, in persistent stutterers, recovered stutterers, and fluent controls. All three groups consisted of right-handed boys between the age of nine and twelve. Both stuttering groups showed a reduction of GM in speech-relevant areas, more specifically in the left inferior frontal gyrus (IFG) and bilateral temporal regions. The FA analysis revealed reduced FA in WM tracts underlying motor regions for the face and larynx in the persistent stutterers, consistent with previous findings in adults (Sommer et al., 2002). In contrast to findings in adults, no increases were found in right hemisphere speech regions, indicating that this may be a result of years of stuttering, and there were no differences in hemispheric asymmetries. Chang et al. (2008) suggest that differences in left hemisphere GM may be related to the risk of childhood stuttering, and that reduced WM in the left speech system is associated with persistent stuttering.

Cykowski, Fox, Ingham, Ingham, and Robin (2010) did a replication analysis of the studies of Chang et al., (2008), Sommer et al. (2002), and Watkins et al. (2008). They also added other DTI-analysis tools (axial and radial diffusivities and diffusion trace). They found that PWS had the reduced FA in in the third division of the left superior longitudinal fasciculus SLF, extending rostromedially into the left anterior corona radiata and left forceps minor (which is an anterior part of the corpus callosum). There were no regions where FA values were significantly higher in PWS than in controls (Cykowski et al., 2010). Hickock and Poeppel's dorsal stream of language processing includes connections between the inferior parietal lobe and the operculum and frontal cortex via the SLF (Cykowski et al., 2010; Hickock & Poeppel, 2007). Cykowski et al. (2010) hypothesize that reduced FA in the SLF could therefore imply that PWS have a dysfunctional connectivity in the dorsal stream of language processing.

Based on earlier findings of white matter differences, Kronfeld-Duenias, Amir, Ezrati, and Ben-Shachar (2012) used DTI to investigate dorsal and ventral language pathways in PWS and controls. In the dorsal pathway the volume of the left long superior longitudinal fasciculus (SLF) was reduced in PWS compared to controls; there was a difference in the fractional anisotropy (FA) profile along the right long SLF; and the PWS had reduced FA in a compact segment of the right long SLF. Analysis of the ventral pathway showed higher FA in a compact segment in the left uncinate in the PWS. The results thus showed that both pathways differed in the PWS and the controls (Kronfeld-Duenias et al., 2012).

Functional differences. A consistent finding in imaging studies of PWS is an over-activation in the right hemisphere during speech production (Braun et al., 1997; Brown, Ingham, Ingham, Laird, & Fox, 2005; De Nil, Kroll, Kapur, & Houle, 2000;

Fox et al., 1996). Fox et al. (1996) used PET to investigate neural correlates of stuttering. Persons who stutter (PWS) and fluent controls were scanned during solo paragraph reading and reading in a fluency inducing condition (chorus reading). Fox et al. (1996) found reduced activation of the left frontotemporal language areas, and right hemisphere dominant over-activation of the motor system in the PWS during solo reading. These effects were largely reversed during the chorus reading condition (Fox et al., 1996).

Preibisch et al. (2003) sought to investigate the hypothesis of compensation by the right hemisphere, by performing two fMRI experiments. They found activation in the right frontal operculum (RFO) in subjects with persistent developmental stuttering (PDS) during reading, and this activation was negatively correlated with the severity of stuttering, indicating a compensatory mechanism (Preibisch et al., 2003). The activation also occurred when the subjects performed a silent synonym judgment without producing an overt response, indicating that the RFO activation functions as a general compensatory mechanism, rather than one limited to the final stages of speech production (Preibisch et al., 2003).

Another finding that has been replicated in several studies is a deactivation of auditory processing areas during stuttering (Braun et al., 1997; Chang, Kenney, Loucks, & Ludlow, 2009; Fox et al., 1996; Ingham, Fox, Ingham, & Zamarripa, 2000; Wu et al., 1995). This may suggest deficits in self-monitoring during speech (Fox et al., 1996). Chang et al. (2009) used fMRI to measure separate BOLD responses for perception, planning, and production of speech and non-speech vocal tract gestures. PWS had reduced activation in the frontal and temporoparietal regions compared to fluent controls, during both speech and non-speech perception and planning. Further, Chang et

al. (2009) found that the PWS differed from the controls during speech production in that they showed less activation in the left superior temporal gyrus (STG), and the left pre-motor areas, but more activation in the right STG, bilateral Heschl's gyrus (HG), insula, putamen, and precentral motor regions. The results suggest that brain activation abnormalities in PWS may not be speech-specific, but related to a general deficit in motor planning and execution (Chang et al., 2009).

In addition to differences in the level of activation, PWS may also display differences in the sequence of brain activation, compared to fluent controls. Salmelin, Schnitzler, Schmitz, and Freund (2000) used magnetoencephalography (MEG) to explore the timing of cortical activation sequences in PWS and fluent speakers during a word-reading task. In fluent speakers, activation of the left inferior frontal cortex (IFC) occurred prior to activation of the central motor region. This pattern was reversed in the PWS, which may suggest that stutterers initiate motor programmes before preparation of the articulatory code. The results give evidence for a hypothesis of disturbed timing in the auditory feedback in PWS (Salmelin et al., 2000).

Neumann et al. (2005) used fMRI to investigate patterns of activation in PWS before and after going through fluency shaping therapy. The results showed increased activation in the left inferior frontal cortex (IFC), the left insula and anterior cingulate, the left superior and transverse temporal gyrus, and in the right middle frontal and superior temporal gyrus (STG). Interestingly, among the regions with increased activation were the left insula and left rolandic operculum (RO), regions where aforementioned studies have shown WM abnormalities (Sommer et al., 2002). This led Neumann et al. (2005) to suggest that therapy effects may include a reorganization of

neural involvement, with a compensatory increase in activation in regions adjacent to areas with structural abnormalities.

Research findings also suggest that the basal ganglia circuits may play a role in stuttering (e.g. Watkins et al., 2008; Wu et al., 1995; Wu et al., 1997). Giraud et al. (2008) investigated the potential involvement of the basal ganglia in stuttering. They used fMRI to investigate patterns of activation in subjects with PDS, before and after they went through fluency shaping treatment, and the correlation of activation with stuttering severity. Before treatment there was a distinct pattern of activation in regions including the bilateral caudate nuclei and the left medial superior posterior parietal/post central region that correlated with stuttering severity. This pattern was modified after treatment. The results thus suggest an involvement of the basal ganglia in PDS. Giraud et al. (2008) propose a functional model of stuttering based on their findings, and available literature (e.g. Salmelin et al., 2000; Sommer et al., 2002). In the model, they hypothesize that the dysfunction of basal ganglia results from structural abnormalities disturbing the information flow between Broca's area and the motor cortex (Giraud et al., 2008).

Hypotheses

In order to test perception and production in persons who stutter and controls, and thus testing the overactivation hypothesis for stuttering, we applied a modified dichotic listening task that included both a speech perception and a speech production task.

In order to test phonological processing and possible timing issues in the early processing steps of phonological processing in persons who stutter, we applied a soundmorph paradigm. Osnes et al. (2011) showed motor involvement during

perception of degraded speech in healthy controls, using the same soundmorph paradigm. As stuttering is often linked to perceptual as well as motor deficits, it was hypothesized that differences in motor involvement during processing of degraded speech signal will occur between persons who stutter and people who do not stutter.

A further aim of this study was to replicate the results on structural differences between stutterers and controls. Therefore, we used diffusion tensor imaging, measuring levels of fractional anisotropy in stutterers and controls, in order to detect signs of altered structural connectivity in people with stuttering. In addition we used voxel-based morphometry to test possible differences in white and grey matter between persons who stutter and controls.

Methods

Participants

Nine persons with persistent developmental stuttering, or persons who stutter (PWS) and 19 controls were included in the study. The PWS were recruited via the, ”Norwegian organization for stutterers” (NIFS) and “Centre for Adult Education “ in Bergen, Norway. The PWS had all been previously diagnosed with persistent developmental stuttering (PDS).

The PWS were between 20 and 36 years of age. The age mean of the PWS was 28.7 years, with a standard deviation of 5.87. Eight males and one female PWS participated in the study whereas there were seven male and 12 female participants in the control group. The controls were recruited from the student population in Bergen via e-mail. They were also between 20 and 36 years of age, but with a somewhat lower age mean of 24.5 years and a standard deviation of 3.68.

The subjects were compensated for their participation. The PWS received an amount of 300 NOK (Norwegian kroner) whereas the controls received 200 NOK. The amount differed because the PWS had to go through screening tests measuring their stuttering severity (SS), which took approximately one hour. Thus the experiment had a longer duration for PWS than for the controls. The experiment took place at Haukeland University Hospital in Bergen. Travel expenses were refunded for participants living far from Bergen.

Inclusion and exclusion criteria. Participants had to have Norwegian as their first language. They had to be right handed and have normal hearing on both ears. The PWS had to be diagnosed with developmental stuttering, and they could not have comorbid speech- and language disorders, reading- or writing disabilities, dyslexia or ADHD. Because of the strong magnetic field in the MR scanner, people who are being scanned can not have metal objects in their bodies (e.g. braces or implants), they can not have had head surgery or have big tattoos (especially close to the head or neck region). Pregnant women and people who suffer from claustrophobia are not recommended to participate in an MR study. These criteria were communicated to the participants via an informed consent form in accordance with the Declaration of Helsinki and institutional guidelines (see appendix), which they had to sign before participating. The scanner criteria were also communicated via the radiographers' oral checklist before the subjects entered the scanner.

Edinburgh Handedness Questionnaire. In most persons (98%), the left cerebral hemisphere is the dominant hemisphere for language functions (Owens, 2012). Among left-handed persons this picture is a bit different and only about 60% have a left-hemispheric dominance for language. This could be a confounding variable when

comparing PWS and controls in terms of brain lateralization, so the participants in the study therefore had to be right-handed to exclude this variable. To determine handedness the participants filled out the Edinburgh Handedness Questionnaire (Oldfield, 1971), before continuing with the experiment. The questionnaire consists of 15 items, where the participants report whether they use their right or left hand/foot or both of their hands or feet when performing different activities. In order to be included in the study, participants had to report using the right hand/foot on 13 of the 15 items. The Handedness Questionnaire led to the exclusion of one participant who turned out to be ambidextrous (equally adept at using both hands).

Hearing. In order to ensure that the participants had normal hearing on both ears, they had to go through a pre-test using an audiometer (Oscilla USB-330, Inmedico, Denmark). The sounds were presented via headphones, at frequencies of 250, 500, 1000, 2000 and 3000 Hz, and participants were instructed to push a response button each time they perceived a sound. The participants were excluded if their hearing threshold was above 20 dB or if their inter-aural difference was greater than 10 dB on any of the frequencies.

Dichotic Listening Pre-test. Because the participants were given a dichotic listening (DL) task inside the scanner, the participants also went through a DL pre-test. This was done in order to make the participants familiar with the task before going into the scanner, and to make sure they demonstrated a right ear advantage (REA) for auditory stimuli. In the DL pre-test we used a consonant-vowel (CV) syllable paradigm. Syllables are clusters of phonemes, centred on a vowel sound (J. Ward, 2006). Different consonant – vowel pairs were presented simultaneously to the left and right ear of the participants. The syllables were read by a male voice with constant intonation and

intensity. The six stop-consonants /b/, /d/, /g/, /k/, /p/, /t/ and the vowel /a/ were used for the pairwise presentation, and formed syllables like /ta/ and /ka/. The participants were exposed to three different conditions. In the first condition they were instructed to report the sound they perceived without paying attention to a specific ear, a non-forced condition (NF-condition). In the second condition they were instructed to report what they heard on the right ear, a forced right condition (FR-condition) and in the third condition what they heard on the left ear, a forced left condition (FL-condition). The FL and FR conditions were presented to the subjects in a randomised order. They reported the syllable by pressing the consonant key of the syllable on a standard computer keyboard. For instance if they heard /ka/ they pressed K.

Screening of stutterers. The PWS were additionally screened in terms of stutter severity (SS) using external and internal measures. The external measure used was the SSI – 4 (Riley, 2009), which measures overt speech disruptions and concomitant movements or sounds when reading and speaking on videotape. For the internal measures of SS, the PWS completed two self-report measures: Wright and Ayre Stuttering Self-Rating Profile (WASSP) (Wright & Ayre, 2000), and the Perceptions of Stuttering Inventory (PSI) (Woolf, 1967).

Scanner Procedures

All imaging data were acquired on a 3T GE-Signa MR scanner. Subjects were positioned in an eight-channel head coil, wearing a MR compatible headphone (NordicNeuroLab; www.nordicneurolab.no). Additional padding was put left and right to the headphones in order to increase the subjects' comfort and to reduce head movements during the data acquisition. The scanning protocol contained several distinct data acquisitions. After a short localized scan, used for positioning the slices for the

following MR scans, a high-resolution T1-weighted MR images was acquired. This T1-weighted image was later used to perform a voxel-based morphometry (VBM) analysis of the grey matter.

This was followed by two fMRI acquisitions, where both a dichotic listening and a so-called "Soundmorph" paradigm were used. The order of these two paradigms was balanced across the subjects, in a way that subjects with an even subject-ID number started with the dichotic listening task, followed by the soundmorph paradigm, and the other way around for subjects with an odd subject-ID. After these two fMRI paradigms, a MR scan, using the diffusion tensor imaging (DTI) technique, was performed. All data acquisitions and their respective analysis strategies are explained in the following paragraph.

Dichotic Listening

The DL task was presented as a block design. We used a DL paradigm with presentation of pairwise combinations of consonant-vowel (CV) syllables. The stimuli used in the scanner procedure were the same syllables that were used in the DL pre-test procedure. The syllables were presented through MR-compatible headphones (NordicNeuroLab; www.nordicneurolab.no) and controlled by a computer using E-prime software (Version 2.0 Psychology Software Tools, Inc.) installed on a computer outside of the MR chamber. Instructions were given verbally before the procedure started, and during the task via goggles (NordicNeuroLab; www.nordicneurolab.no) mounted to the head coil. Unlike a traditional DL paradigm with NF, FL and FR, we did not have any forced conditions inside the MR scanner. Instead, we had one condition where the subjects were instructed to just listen to the syllables that were presented, and one where they were instructed to repeat verbally the syllable they heard the best. The

subjects' responses were recorded through a microphone attached to the head coil (produced by Bergen fMRI Group), and the syllables they reported were transferred to the research administrators via headphones (Sennheiser, Germany), registered manually and recorded using a digital M-Audio MicroTrack 24/96 MP3 recorder (Avid, USA). There were four blocks of each condition, with 10 stimulus trials in each block. Between each block there was a period without stimulation, where the subjects were instructed to rest. This rest period had the same duration as the two active conditions. The order of the tasks was counterbalanced.

Scanner parameters. In total, 164 whole brain images were acquired with a 64 x 64 image matrix, 24 slices, and a voxel size of 3.44 mm x 3.44 mm x 5.5 mm. The first four images were treated as pre-scans and thus rejected prior the subsequent analysis. The acquisition of each image lasted 1.5 seconds, followed by four seconds silence, during which the stimuli were presented and the response was recorded.

Soundmorph

We used a soundmorph paradigm (Spech et al., 2005) containing experimental stimuli and control stimuli, as described earlier by Osnes et al. (2011) and Specht et al. (2009). The soundmorph paradigm used a parametric, event-related, stochastic design (Friston, 1999; Osnes, 2012; Specht et al., 2009; J.Ward, 2006). As in the dichotic listening task, the experimental stimuli were consonant-vowel syllables, lasting for 420 ms. Consonant-vowel syllables /da/ and /ta/ were chosen as speech stimuli because they are more speech like, since the consonants contain rapidly changing and spectrally complex signals, while a stimulation with vowels only would have resulted in a more tonal presentation. In addition /da/ and /ta/ have different duration in voice onset time (VOT), and therefore they were chosen as speech stimuli to control for the fact that

variations in VOT may have different lateralization effects. Control stimuli were music sounds: piano (C major triad on a C3 root) and guitar chords (A3). The stimuli were matched in duration and mean intensity (Goldwave Software). The stimuli were parametrically varied in a way that gradually changed the sound properties in seven steps from white noise into an undistorted music or speech sound using the Soundhack software (Soundhack; www.soundhack.com). The manipulation procedure gradually revealed the specific spectral and temporal qualities of the CV syllables and the music sounds in a stepwise manner. In order to obtain an analysis of the phonetic structures, the speech analysis program Praat was used (www.praat.org) (see Specht et al., 2009). The type of manipulation was the same for the experimental and the control stimuli, and they were presented to the subjects in a randomized order to avoid expectancy effects. Null events were also included to obtain baseline measures. The stimuli were presented via fMRI-compatible headphones. The stimuli were presented as 280 regular events with 20 trials per step, and 7 steps per stimulus category (music/speech), and 72 null events, with 14 target trials. Again, fMRI was used to measure the corresponding brain responses. One rational for the selection of this paradigm was to separate brain areas that follow the gradual manipulation into speech sounds from those that generally respond to spectrally complex acoustic signals.

Osnes, Hugdahl, Hjelmervik, and Specht (2012) investigated the effect of stimulus expectancy using a soundmorph paradigm, and found that when participants were given a stimulus-related instruction before the listening task, this created a stimulus expectancy effect affecting the activation in areas that are relevant for our study, including superior temporal gyrus (STG), inferior frontal gyrus (IFG) and the premotor (PMC). Therefore, during the fMRI data acquisition, subjects were instructed

to do an unrelated task, pushing grips whenever they heard a sound in one ear only. This was meant to distract the participants from focusing on whether the presented stimuli were speech or non-speech sounds. The unrelated task also helped maintain their arousal level since the paradigm has a long duration.

Scanner parameters. In total, 370 whole brain images were acquired with a 64 x 64 image matrix, 24 slices, and a voxel size of 3.44 x 3.44 x 5.5mm. As previously mentioned, the first four images were treated as pre-scans and thus rejected prior to the subsequent analysis. The acquisition of each image lasted 1.5 seconds, followed by a silent gap of 1.3 seconds, during which the stimuli were presented.

Diffusion Tensor Imaging

In order to perform an analysis of fibre tracts by applying a voxel-based analysis of the fractional anisotropy (FA), a diffusion tensor-imaging scan was performed. FA is a measure of coherence of the diffusion within each voxel (Le Bihan et al., 2001; Sommer et al., 2002). In highly ordered fibre bundles such as the corpus callosum, diffusion is mainly in the direction of, rather than perpendicular to the fibre, resulting in high FA values. Low FA values can indicate decreased fibre coherence or myelination defects (Le Bihan et al., 2001). The selected DTI sequence contained 32 diffusion sensitive gradient directions (b-value 1000) and additional four b0 images. The imaging matrix was 128 x 128 matrix (1.72 x 1.72 x 3mm), and 47 slices were acquired.

Analysis

Dichotic Listening and Soundmorph Data

All functional as well as structural data were processed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). With respect to the fMRI data both experiments, i.e. the DL test and the soundmorphing paradigm, were processed in the same way, but

independently from each other. Prior to the statistical analysis, the images were realigned to the first volume to adjust for head movements during image acquisition, and corrected for movement-induced distortions (unwarping). The results were inspected for residual movement artefacts and in order to ensure that the movement was less than 2 mm. Further, the realigned images were normalised to the stereotaxic Montreal Neurological Institute (MNI) reference space provided by the SPM8 software package and resampled with a voxel size of 2 mm x 2 mm x 2 mm. Finally, the images were smoothed by using a Gaussian kernel of 8 mm.

For the statistical analysis, the data were subjected to a general linear model, specified for the two paradigms separately. Thus, for both paradigms, a design matrix was created, based on the stimulus onsets times, as recorded by the E-Prime software. After model estimation, t-contrasts for the different conditions of interest were specified. The corresponding contrast images were then subjected to a second level analysis. In case of the dichotic listening paradigm, the second level analysis was performed as a 2 x 2 ANOVA, with the factor task (perception/production) and the factor group (controls/PWS). The soundmorph paradigm was analysed with a 2 x 7 x 2 ANOVA, with the factor speech/music, factor step (1st-7th), and the factor group. In order to circumvent the problem of multiple comparisons, since statistic test are performed for each voxel, the results from both paradigms were explored with a family-wise error (FWE) correction threshold that is based on the Gaussian-Random-Field theory. This correction takes into account the number of statistical test performed as well as the spatial dependency of neighboured voxel. In the first place, this correction was applied to the peak voxel, which is the most conservative correction. In case of an

a-priori hypothesis, the correction was applied on the cluster-size instead of the peak voxel, which is a slightly more liberal way of exploring the results.

In addition, the results from the soundmorph paradigm were explored with a region of interest (ROI) analysis, using the middle part of left and right STS as ROI, which follows the strategy as described earlier by Specht et al. (2009).

Diffusion Tensor Imaging

The images, containing the corresponding FA values for each voxel, were estimated out of the DTI data using nICE (NordicNeuroLab; www.nordicneurolab.no). Here, the entire DTI data, containing the 32 diffusion sensitive gradient directions as well as the b0 images, were used for estimating apparent diffusion coefficients (ADC), fibre tracts, as well as FA-images. Only the resulting FA images were processed further. In order to normalise these FA-images into MNI space, the accompanying b0 image was normalised to the standard MNI template, like it was done for the fMRI data, and the resulting normalisation parameter were applied to the FA images, and finally smoothed with a Gaussain kernel of 8 mm. The statistical analysis was performed as an ordinary two-sample t-test, but restricted to those voxels, that were within a white-matter mask and had FA values larger than 200. Again, the data were explored with the corrected thresholds as described above.

Voxel-Based Morphometry

Structural magnetic resonance (MR) images of human brains can differ among subjects in many ways (Ahsburner & Friston, 2001). Voxel-based morphometry (VBM) has been designed to be sensitive to differences in the local composition of different brain tissue types, e.g. grey matter and white matter. At the same time, VBM discounts positional and other large-scale volumetric differences in gross anatomy. In general,

VBM methods combine spatial normalisation with tissue classification and the analysis of the ensuing fields of grey level representing variously MR image intensity or estimated concentration of neural grey matter (Bookstein, 2001). At its simplest, VBM involves a voxel-wise comparison of the local concentration of grey matter between two groups of subjects (Ashburner & Friston, 2000). The technique segregates and measures differences in white matter and grey matter concentration (J. Ward, 2006). The procedure is relatively straightforward and involves spatially normalising high-resolution images from all the subjects included in the study into the same stereotactic space. This is followed by segmenting the grey matter from the spatially normalised images and smoothing the grey-matter segments. Voxel-wise parametric statistical tests then compare the smoothed grey-matter images from the two groups. As previously mentioned, our data were explored with the corrected thresholds as described above.

Results

Dichotic Listening

We did a 2 X 2 analysis of variance (ANOVA) with group (PWS/controls) and task (perception/production) as independent variables, with $p(FWE) < 0.05$ and extent threshold of at least 10 voxels per cluster. The analysis showed no significant main effect of group and no interaction effect of group x task. There was, however, a main effect of task with significant differences between the perception and production conditions (Table 1). A problem in studies of speech production is that mouth movements produces artefacts in the activation, particularly in the orbitofrontal cortex. The results were therefore masked to exclude this artefact.

Post-hoc t-tests showed significantly more activity in the production condition than in the perception condition, for both PWS and controls, with $p(FWE) < 0.05$ and

extent threshold of 10 voxels. The control group showed significantly more activation in bilateral postcentral area (BA 43), left somatosensory cortex (BA 3), left premotor cortex (PMC)/supplementary motor area (SMA) (BA 6), bilateral rolandic operculum (BA 48), bilateral retrosubicular area (BA 48), bilateral caudate nuclei, the right temporal pole, the right thalamus, right superior colliculus, and the left dorsal anterior cingulate cortex, left associative visual cortex (BA 19), as well as the right secondary visual cortex (BA 18) (Table 2).

The t-test comparing activation in the production and perception condition for the PWS showed more activity in the left somatosensory cortex (BA 3), left postcentral area (BA 43), left rolandic operculum (retrosubicular area) (BA 48), right primary motor cortex (postcentral) (BA 4), right retrosubicular area (BA 48), left insula (retrosubicular area) (BA 48), left dorsal anterior cingulate cortex (BA 32) during production (table 3).

Further t-tests comparing activation in between the two groups showed no significant differences between PWS and controls, neither in the perception condition nor the production condition with $p(FWE) < 0.05$ and extent threshold of 10 voxels. However, based on our a-priori hypothesis of over-activation in PWS during speech production, we applied a post-hoc t-test with an uncorrected $P < 0.001$, and an extent threshold of 120 voxels (corresponding to a significant cluster extension of $p<0.05$). The results are listed in Table 4. This showed a significant difference in the production condition, with greater activity in the PWS than in the controls (Figure 1). The PWS showed significantly more activation than the controls group in the left retrosubicular area (BA 48), the right dorsolateral prefrontal cortex (BA 46 and BA 9), bilateral superior temporal gyrus (STG)/secondary auditory cortex (BA 22), left orbitofrontal

cortex (BA 11), left anterior entorhinal cortex (BA 34), and right primary auditory cortex (BA 41). T-tests with the more liberal threshold revealed no areas with more activation in the control group during the production task, and no differences between the groups in the perception task.

Soundmorph

We did a 2x7x2 ANOVA with group (PWS/controls), manipulation (1st -7th) and stimuli (music/speech) as independent variables. Applying a corrected threshold of p(FWE) <0.05 and an extent threshold of 10 voxel, the results showed a significant main effects of group (Table 5), speech/music (Table 6) and step (Table 7). We also found a significant interaction effect of speech/music x step (Table 8) and for control vs. stutter: speech (Table 9). We found no significant interaction effects for group x speech/music or group x step. There were no significant three-way interaction effects for group x speech/music x step, and no significant differences in activation between controls and PWS in response to the music stimuli. These results are further elaborated in the following paragraph.

We found significant group differences (a significant main effect of group) in bilateral superior temporal lobe (secondary auditory cortex) (BA 22), right superior frontal area or frontal eye fields (BA 8) close to the motor cortex. The cluster with significant differences involves superior and middle frontal gyrus. We also found a significant difference in the left supramarginal/planum temporale (BA 42/48), left precentral area or premotor cortex PMC and supplementary motor area SMA (BA 6), right inferior parietal areas/ supramarginal gyrus (BA 40), right medial orbitofrontal area (BA11), in an area close to the superior colliculus, which is considered part of the

auditory pathway, and in the left calcarine sulcus in the primary visual cortex (V1) in (BA 17).

We found significant differences in activation between speech and music stimuli in the left secondary auditory cortex (BA 22) and in the right middle temporal gyrus (BA 21). Significant differences in activation between the different manipulations were found in bilateral secondary auditory cortex and in the right middle temporal gyrus (BA 22 and 21).

We found a significant interaction effect between stimuli and step within the primary motor cortex (left precentral gyrus) (BA 4) and in the premotor cortex (PMC) and the supplementary motor area (SMA) (BA 6). We also found significant differences in activation level between the PWS and the controls in response to the speech stimuli.in temporal superior area of the left hemisphere, which is considered to be the secondary auditory cortex (BA 22).

The F-tests were followed up by post – hoc tests were linearly weighted t-contrasts were applied. This was done in order to test which areas demonstrated a gradual increase of activation, following the gradual "sound morphing" manipulation. These post-hoc tests showed gradually increasing activation in controls (Table 10) and in PWS (Table 11) as the white noise morphed into a speech sound (Figure 2).
In the controls we found increasing activation in the right middle temporal gyrus/temporal superior area /temporal middle area (BA 21) and in bilateral superior temporal area/secondary auditory cortex (BA 22).

In the PWS we found increasing activation in the right middle temporal gyrus (BA 21) and in the left superior temporal lobe/secondary auditory cortex (BA 22).

In addition, a region of interest analysis was performed for the left and right superior temporal sulcus, which were the same regions as reported by Specht et al. (2009). The results confirmed the linear increase in neuronal activity, as the sound became more and more a word, and much less pronounced increase when the sound became a music sound. However, no functional asymmetry as well as no group difference was observed.

Diffusion Tensor Imaging

In order to test for significant differences in structural connectivity, a voxel-wise two-sample t-test on the fractional anisotropy was performed. The results were explored with an uncorrected threshold of $p<0.001$ and an extent threshold of at least 120 voxel (corresponding to significant extent threshold of $p<0.05$), in order to test our a-priori hypothesis of reduced structural connectivity in persons who stutter. The results revealed an area of higher fractional anisotropy in controls than in PWS (table 12) within the left inferior frontal gyrus (ventrolateral prefrontal cortex) (BA 47), not far from the ending point of the arcuate fasciculus and just at the border to BA 45, which is a part of Broca's area.

Voxel-based Morphometry

Similar to the analysis of the DTI data, analysis of the structural data exploring differences within the grey matter between the groups was performed. However, there were no significant difference between the groups, neither when a corrected nor when an uncorrected threshold was applied.

Discussion

Results

Dichotic listening. The behavioural measures of DL that were performed in the pre-test revealed no significant differences. In particular, no significant differences were

observed in the REA effect between the PWS and controls (Andresen, Heitmann, & Specht, submitted).

The fMRI study, using the DL paradigm, revealed no significant differences in activation between the PWS and the control group in the perception condition. This differs from earlier findings, which have shown lower activation in PWS than in controls during speech perception (Chang et al., 2009). Analysis with the corrected threshold showed no group differences in the production condition. However, in order to test our a-priori hypothesis of increased frontal activation in PWS during speech production, we also explored the results with a lower threshold and corrected only for size of the cluster. Thereby, we did find clusters of voxels with significantly more activation in the PWS than in the controls in the production condition. This gives support to the assumption of over-activation in PWS during speech production. Based on results of previous studies, the over-activation was expected to occur primarily in the right hemisphere (e.g. Braun et al., 1997; De Nil et al., 2000; Fox et al., 1996). As mentioned, the observed over-activation in the right hemisphere has lead to hypotheses of right hemispheric activation as compensation for deficits in the left hemispheric language pathways. However, the overall results from the DL paradigm did not show the expected right dominant pattern for PWS, since the clusters of higher activation in the PWS were distributed across both hemispheres.

We did find a difference in the right dorsolateral prefrontal cortex (dlPFC). The prefrontal cortex is involved in higher order motor planning, and more specifically, the dlPFC has been implicated in working memory and a network involved in selective attention (Gazzaniga et al., 2002). Higher activation in the right dlPFC in the stutterers may reflect increased attention as a compensation for deficits in the left hemisphere.

Functional imaging studies have shown that the left auditory cortex is active not only during speech perception, but also during speech production in the general population (Hickok & Poeppel, 2000). Previous research on stuttering, however, has revealed findings showing deactivations of the posterior temporal cortex in PWS during speech production, and this is interpreted as deficits in a frontal-temporal system for verbal fluency (Braun et al., 1997; Chang, et al., 2009; Fox et al., 1996; Ingham et al., 2000; Wu et al., 1995). Our results were inconsistent with these findings. The PWS showed significantly more activation than the controls in bilateral regions of the superior temporal lobe (BA 22), in areas that might correspond to the planum temporale (PT) in Wernicke's area and the right homologue.

On the other hand, and in contrast to other fMRI studies on stuttering, our paradigm was selected in order to avoid stuttering during the data acquisition, as this is typically associated with movement artefacts in the images that are difficult to correct. We did avoid the problem of movement artefacts, as all but one of the PWS showed no overt stuttering during the scanner procedures, but the results may have been different if stuttering had occurred (e.g. Fox et al., 1996). However, the occurrence of overt stuttering may not be necessary to observe the brain activation patterns associated with stuttering (Ingham et al., 2000). This could suggest that the stimuli used in the dichotic listening paradigm may not be challenging enough to elicit the hypothesized compensation mechanisms in the right hemisphere, as seen in other studies (Preibisch et al., 2003). This, in addition, may also explain why there were no differences within the basal ganglia. Since the basal ganglia are part of the motor planning circuit, this structure is also often discussed as an anatomical structure that may show functional

and/or structural deviation (Alm 2004, 2005; Giraud et al., 2008). However, since the PWS were not actually stuttering, functional differences to the controls may not emerge.

Previous studies have shown activation in the right frontal operculum, and this region is thought to have a compensatory role since activation in this region is negatively correlated with observed stuttering severity (Preibisch et al., 2003; Sommer et al., 2002). The fact that our study did not show significant activation in this region may further support the hypothesis that our paradigm does not elicit the previously seen activation patterns.

In addition, the PWS that participated in the study have all gone through therapy for their stuttering, and this might be a factor influencing the results (e.g. Neumann et al., 2005). However, an individual history of the therapy could not be collected for each PWS. Nevertheless, such a therapy effect might in particular explain the involvement of areas for higher-order motor planning and attention in the dlPFC, rather then the right frontal operculum.

Soundmorph. In the soundmorph paradigm, we found a significant main effect of group. Significant differences in levels of activation were found in all of the four lobes of the cerebral cortex.

In the temporal lobe there were significant group differences in bilateral superior areas (secondary auditory cortex) and in the planum temporale in a cluster that extends into the left supramarginal gyrus in the parietal lobe. In the frontal lobe, the significant differences were found in the right superior frontal area (or frontal eye fields close to the motor cortex) in a cluster, which involves the superior and middle frontal gyrus. Differences were also found in left precentral gyrus in premotor cortex (PMC) and supplementary motor area (SMA), and in the right medial orbitofrontal area. In the

parietal lobe, significant group differences were found in right inferior parietal areas or supramarginal gyrus an in the occipital lobe these differences were found in the left calcarine sulcus in the primary visual cortex (V1). In addition significant differences were also found in an area close to the superior colliculus, which is considered part of the auditory pathway. In all of these areas, the PWS had higher levels of activation than controls. Some of these structures are considered to be part of the dorsal stream in the dual stream model of language processing (Hickock & Poeppel, 2007) (Figure 3). As previously mentioned, the dorsal stream involves structures in the posterior frontal lobe, posterior dorsal aspects of the temporal lobe and parietal operculum (area Spt). The fact that the PWS have increased levels of activation in structures in this stream compared to controls may indicate that the processing in the dorsal stream is less efficient in PWS. Therefore they need to use more effort to compensate during processing that requires involvement from this stream.

The dorsal stream is thought to be involved in mapping acoustic speech signals to frontal lobe articulatory network and to be involved in explicit phoneme segmentation (Hickock & Poeppel, 2007; J. Ward, 2006). This stream is as earlier mentioned thought to serve an auditory-motor integration role. It becomes particularly important when speech requires more sensory guidance with novel, low frequency, and more complex words (Cykowski et al., 2010). If this process were dysfunctional in PWS, then one would assume that stuttering behaviour occurs more frequently with increased requirements on speech processing sub served by the dorsal stream. Interestingly, this is an important feature of stuttering behaviour (Bloodstein & Ratner, 2008, cited in Cykowski et al., 2010). The dorsal stream is hypothesized to be left-hemisphere dominant (Cykowski, et al., 2010; Hickock & Poeppel, 2007). However, the

main effect of group demonstrated that PWS also recruited the homologue areas of the dorsal stream in the right hemisphere. Assuming that persons with persistent developmental stuttering (PDS) have a deficit in their dorsal stream of language processing, is in line with the findings that suggest that PDS is connected to a deficit in left – hemispheric language areas (Sommer et al., 2002; Cykowski et al., 2010).

As mentioned, the PWS also had a significantly higher activation than controls in the primary visual cortex. This finding does not have a clear explanation, but hypothetically the PWS might include encoding through other sensory perception modalities when perceiving auditory stimuli. Visualizing the syllables may contribute to a compensation for a deficit in left-hemispheric language networks, and could be an effect of therapy as all of the PWS have received treatment for their stuttering.

In the study by Osnes et al. (2011), the findings were, as previously mentioned, analysed with dynamic causal modelling (DCM), with a focus on the involvement of the premotor cortex as part of the dorsal stream in speech perception. The resulting model showed strong interconnections between HG, PT and STS when processing speech and non-speech sounds. Further, it showed bidirectional connections between PMC and STS and a unilateral connection from PT to PMC, but only when speech sounds are processed. The PMC was not part of the network when non-speech sounds were presented. Interestingly, the same areas that were explored with the DCM analysis by Osnes et al. (2011) showed increased activation in PWS when compared to controls. In our study a similar activation pattern was found for both groups in response to speech sounds, in particular replicating the finding of a strong involvement of STS. However, the PWS had a somewhat deviating activation pattern from the controls, as reflected by the main effect groups. The differences in activation between the PWS and controls

may indicate that the PWS have a different network of speech perception. However, we did not perform a DCM-analysis of our data, but further research may apply a DCM-analysis of the data to investigate the network connectivity in PWS. Still, one may want to speculate that the connectivity pattern between HG, PT, STS, and PMC, as described by Osnes (2012), may look different in PWS than in controls. This would in particular be of interest, if such a DCM analysis would also include the right hemisphere. Such an analysis was not part of the model described by Osnes et al. (2011), but in our study differences were seen in right hemisphere between PWS and controls.

In the post-hoc t-tests, an area including middle and posterior parts of the STS showed gradual linear increase as the white noise turned into speech. Both in PWS and controls this gradual increase was much stronger when the noise morphed into speech than when it morphed into a music sound. This result is in line with the findings of Specht et al. (2009) who investigated cerebral laterality in response to speech sounds in healthy subjects also using a soundmorph paradigm. Specht et al. (2009) found a gradual increase in the left STS as white noise gradually morphed into speech sounds. However a region of interest (ROI) analysis of our results in STS demonstrated that in the present study the linear increase of the STS was equally present in both hemispheres. In PWS we could expect to see a similar activation in both hemispheres as stutterers are hypothesized to show atypical lateralization of language. For the controls however, it was expected that the left STS structure would be significantly more activated than its right homologue. This lack of lateralization effect in the controls may be due to sex ratio differences in the samples. Specht et al. (2009) had a sample including only male participants, whereas the present study had more female than male participants in the group of controls. This may have affected the results in the control

group as women as mentioned have less lateralized cerebral language functions than men (Owens, 2012; Wickens, 2005). As mentioned, our findings are preliminary and a data collection from more PWS and controls is currently taking place. It is expected that the result might change, as more male controls are included into the current data material.

Diffusion Tensor Imaging. The uncorrected results of the analysis of the DTI data indicate a difference between PWS and controls in an area in the inferior frontal gyrus close to the pars triangularis (and pars opercularis) in BA 47. The finding was just at the border to Brodmann area 45, which is considered to be a part of Broca's area (Gazzaniga et al., 2002). BA 47 has, as previously explained, also been included as a part of the Broca's complex (Hagoort, 2005a, 2005b). It is uncertain which role BA 47 plays in language processing but it has been hypothesized to be involved in semantic processing. In the two-loop timing hypothesis of speech production, the pars triangularis and the pars opercularis in the inferior frontal lobe (IFL) are involved in an outer linguistic loop that cooperates with an inner phonatory loop to coordinate speech production (Foundas et al., 2004). Our cluster of significant differences between PWS and controls could be situated close to the ending point of both the arcuate fasciculus as well as uncinate fasciculus. We found that the PWS had a significantly lower fractional anisotropy (FA) than controls in this area. This can either mean that the PWS have fewer fibre tracts in this area or that the fibre tracts have less white matter integration in PWS than in controls. The arcuate fasciculus is considered to be a structure that connects Broca's and Wernicke's area (Catani et al., 2005; Rosenzweig et al., 2005; Toates, 2007; Wickens, 2005), and damages to this structure may lead to conduction aphasia (Catani et al., 2005).

However, the detected difference in FA between PWS and controls may also be situated at the ending point of uncinate fasciculus. The uncinate fasciculus (UF) is a WM nerve bundle that forms a connection between temporal areas and inferior frontal gyrus (Duffau, Gatignol, Moritz-Gasser, and Mandonnet, 2008). It has been hypothesized that the UF is part of a parallel-distributed language network within the ventral stream of language processing as proposed by Hickock and Poeppel (2007) together with the inferior occipito-temporal fasciculus (IOF) (Duffau et al., 2008). However, Duffau et al., (2008) failed to find that any language disturbances were elicited by intraoperative electro stimulation of the UF. Still they suggest that the ventral stream works by parallel – processing were IOF is the direct language pathway, essential for semantics, and the UF works as an indirect pathway which can be functionally compensated.

Low FA could be a sign of dysfunctional connectivity between different regions in the brain (Cykowski et al., 2010; Le Bihan et al., 2001; Sommer et al., 2002). According to our a-priori hypothesis the PWS would demonstrate reduced structural connectivity. FA abnormalities in PWS have been found in several different studies, both in children and adults (Chang et al., 2009; Cykowski et al., 2010; Kronfeld-Duenias et al., 2012; Sommer et al., 2002; Watkins et al., 2008).

As previously mentioned, Cykowski et al. (2010) did a replication analysis of the studies of Chang et al., (2009), Sommer et al., (2002), and Watkins et al., (2008), also adding other DTI measures. Their conclusion in their two-way corrected findings was that PWS had the most reduced FA in in the third division of the left superior longitudinal fasciculus (SLF) extending rostromedially into the left anterior corona radiata and left forceps minor. This cluster is close to the cluster that showed

significantly lower FA in PWS in our study. As previously described, the SLF connects inferior parietal and frontal areas of the dorsal stream of language processing as proposed by Hickock and Poeppel (Cykowski et al., 2010) Reduced FA in the SLF could therefore imply that PWS have a dysfunctional connectivity in the dorsal stream of language processing. Our finding may also reflect dysfunctional connectivity in the dorsal or in the ventral stream in PWS, in accordance with the findings of Kronfeld-Duenias et al. (2012), which showed FA abnormalities within the dorsal and the ventral stream.

Language

In dichotic listening tasks, the participants are often presented CV- syllables that have no inherent meaning in the participant's language; they are "semantically meaningless" (Hugdahl et al., 2009). This however, is not the case for most of the CV-syllables that we presented Norwegian participants with. In Norwegian, /ga/, /ta/, /da/, /ba/ and (in several dialects and as an alternative in Nynorsk, one of the official languages in Norway) /ka/ are common words. This leaves /pa/ as the only semantically meaningless syllable in Norwegian in our study. It is possible that these stimuli lead to more cerebral activation than "regular meaningless syllables", due to recognition and lexical processing that might have been activated in addition to the phonological processing. But, as Jäncke, Specht, Shah, and Hugdahl (2003 report, use of verbal stimuli will inevitably activate language relevant structures in the vicinity of perisylvian brain regions. They have also argued that attention effects in DL are related to short-term memory and response selection prior to perception of the stimulus.

Some might claim that the type of language research that relies on methods such as the DL paradigm is artificial. Hagoort (2005b) claims that many psycholinguists are

dissatisfied by the psycholinguistic quality of most neuroimaging research on language. As previously mentioned, Owens (2012) claims that language components may be an artificial analytic devise for linguists to use in discussions of language. Language sounds and language components usually appear in a more complex setting than in a controlled research setting, where most conflicting environmental sounds apart from the chosen stimuli are absent. In addition, regular speech is more complex than the stimuli delivered by the DL paradigm. Words are rarely produced in isolation in everyday language use, while research on speech production rarely requires more complex responses than a single syllable, concept or word (Bock & Griffin, 2000). Co-articulation is always present in normal speech; different phonemes overlap, and therefore a specific phoneme is affected by both the preceding and the following phoneme (Eysenck & Keane, 2010; Matlin, 2005). While pronouncing a phoneme, we prepare the articulation of the next one. This means that phonemes are articulated differently depending on the context it is pronounced in. Binder (2006) claims that it is methodologically questionable whether it is possible to study single components of language in isolation, as processing subcomponents of language often occur simultaneously. Also, individual speakers who are told to pronounce the same word have significant individual differences in the way that they do this (Eysenck & Keane, 2010; Matlin, 2005).

As previously mentioned, researchers may attempt to study the same language process, but their implicit definitions may vary so that they apparently report conflicting results (Binder, 2006; Hickock & Poeppel, 2007). And not only may researchers' definitions of language processes vary, they may also use different anatomical terms for the same cerebral region. This complicates the possibility of gaining a complete

overview of the field of language research for both researchers and other people with an interest in the field.

Language impairments. S. T. Orton was the first to observe of a positive correlation between stuttering and dyslexia in the 1920s, and he proposed that competition between the hemispheres for the control of speech could be the cause of both disorders (Iaccino, 1993). As previously mentioned, dyslexia and stuttering are both language impairments that are found more often in males than in females (e.g. Wickens, 2005). It is suggested that this may be due to the important organizing effects of testosterone on the developing brain (Wickens, 2005). Geschwind and Behan (1982) proposed that excessively high levels testosterone during a critical stage of prenatal brain maturation, may slow down the neural development of the left hemisphere. Also, men are more prone to birth stressors such as oxygen deprivation that may affect future language disabilities; and finally, women have better language skills due to less speech lateralization, which could lead to women being less vulnerable for left hemisphere deficits (Iaccino, 1993). All in all, there are many possible factors that may influence the fact that there are more male than female stutterers and dyslectics. There seems to be a certain degree of genetic heritability for handedness, stuttering and dyslexia (Beaton, 2003; Geschwind & Behan, 1982; Iaccino, 1993). However, the complete neurobiological basis for both dyslexia and stuttering is still unknown, and there might be a possibility that they represent subtypes of related language disorders (Binder, 2006; Iaccino, 1993).

Future research may use fMRI to study the structural and functional effects of different treatment programs for both developmental stuttering and dyslexia, and to help

diagnose these language disabilities (Binder, 2006). This particular use of fMRI may lead to a selection of more specific and efficient treatment methods.

Methods

Participants. As mentioned above, there was a difference in sex ratio between the PWS group and the controls. It was easier to find male subjects in the PWS group. This was probably due to the fact that there are generally more boys than girls who suffer from persistent developmental stuttering (PDS), and this sex difference seems to increase with age (Bloodstein, 1995; Kloth et al., 1999; Månsson, 2000), making it more difficult to find adult women with PDS. The controls were recruited from the student population in Bergen, where there are generally more women than men, as is the case in most institutions of higher education in Norway (Statistisk Sentralbyrå, 2010). Women seem to have a less left-lateralized distribution of language functions than men (Owens, 2012; Passer & Smith, 2007; Wickens, 2005). The high number of women in the control group may therefore have been a confounding variable in the study when examining differences in lateralization of speech perception and production tasks between PWS and controls.

Because left-handers show a different pattern of language lateralization, we only included right-handed participants in our study to avoid this as a confounding factor. However, in doing so we might not have captured the complete picture of stuttering.

The control sample size of 19 participants was also much bigger than the PWS sample of nine participants, creating more variance in the PWS group than in the control group. Again we emphasize that the findings in this study are preliminary. A further collection of data from additional PWS and controls is currently taking place.

Experimental design. Even in studies with a high degree of experimental control, there is always a possibility that the participants engage in a confounding mental operation in addition to, or instead of, the one of interest in an on-going study (Aguirre, 2006; Binder, 2006). Language processes may occur at any time while the participant is in the MR-scanner; also during resting state image acquisition where the participant is told to relax (Binder, 2006). This may affect results of fMRI studies in general, as fMRI indicates all brain areas that demonstrate activity-related changes during a given task, regardless of whether a given brain area is critical for task performance or not (Pouratian & Bookheimer, 2006). A comparison between two or more tasks or conditions is therefore always needed when conducting an fMRI study (J.Ward, 2006).

As earlier mentioned, the principle of cognitive subtraction for fMRI assumes that by comparing the cerebral activity in a task that involves a particular cognitive component with the brain activity during a baseline task that does not, it is possible to find out which regions are specialized for this cognitive component (Aguirre, 2006; Hirsch, 2006; J. Ward, 2006). However, to avoid the different fallacies associated with this principle, and with the principle of pure insertion and pure deletion, choice of a suited experimental design and baseline task are important. The different ways, in which the stimuli are ordered, may also have implications for the result (Friston, 1999; J. Ward, 2006). In the soundmorph paradigm a parametric experimental design was used (Osnes, 2012; Price et al., 1997; Specht et al., 2009; J. Ward, 2006). This way we could compare activation in response to different levels of the same stimuli for both speech and music sounds.

In the DL paradigm we used a block design, whereas in the soundmorph

paradigm we used an event-related design to order the stimulus representation. As mentioned earlier, both designs have strengths and weaknesses. Like Specht et al. (2009), and Osnes et al. (2011), we chose music stimuli with similar acoustic qualities as the speech stimuli as baseline stimuli in the soundmorph task, The music and speech sounds were subjected to the same manipulations and they had the same duration. Although they may not be as familiar as speech sounds, the guitar and the piano sounds are quite familiar instrumental sounds for most people (Osnes, 2012). The experimental and control stimuli were presented randomly and null-events, in which no stimuli were presented, were also included. When choosing different tasks in the DL paradigm, we used the same syllables in both the perception and production conditions to make the tasks as similar as possible. In addition we only applied a non-forced condition to avoid potential confound from attentional control processes.

Artefacts. Small head movements may distort the measured MR-signal (J. Ward, 2006). For this reason, producing overt speech is often avoided in fMRI procedures. In our study this was especially relevant in the DL speech production task, when people were to repeat the syllable they had perceived. However, the head movements were monitored during the task performance, and if the movements exceeded a given threshold, the participants would be excluded from the study. None of our participants were excluded due to movements inside the scanner that could lead to image distortion. The collected data were pre-processed and corrected for head movements using the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm), as described in the data analysis.

Another important possible artefact during image acquisition is that brain tissue in different cerebral regions has different magnetic properties (J. Ward, 2006). This

makes brain regions that are close to air voids in the head - such as the sinuses, ear canals and the oral cavity - susceptible to signal distortion, which makes cerebral regions such as the orbitofrontal cortex and some temporal lobe regions hard to image (J. Ward, 2006). In our study, this is especially relevant for activation in the temporal regions.

The MRI-scanner produces an intense noise during image acquisition, in the form of quasi-tonal stimulation, that often can become very loud (>95 dB) and of high frequency (1000-4000 Hz) (Hall, 2006; Huettel et al., 2008). It can be particularly bothersome for persons who are averse to noise (Hall, 2006). The noise also reduces the sensitivity for detecting stimulus-evoked activation, which previously made the MRI-scanner less attractive for studying auditory processes than for example PET (Hall, 2006; J. Ward, 2006). To avoid the problem of reduced sensitivity due to scanner noise, the DL and soundmorph tasks were presented as sparse sampling designs. The stimuli were presented to the participants in silent gaps in between image acquisitions, making it easier to infer activation as a response to the stimuli and not the scanner noise. This was also necessary in order to be able to hear the responses in the speech production task of the dichotic listening paradigm.

Summary of Findings

Interestingly, the soundmorph and the DL speech perception tasks, which were supposed to measure the same language components, and both involved syllables as speech stimuli, showed different results. The soundmorph task showed significant group differences between PWS and controls in many different clusters at a corrected level, whereas the DL-task showed no significant difference between the groups. However,

the soundmorph task involves gradual manipulations, while the DL task does not. It can therefore be questioned whether the tasks are directly comparable.

The soundmorph task may have posed more challenges to the participants than the DL task, since it involves both gradual manipulation and more novel stimuli (e.g. sounds mixed with white noise). If this was the case, then perhaps we could hypothesize that involvement from the dorsal language stream would be more prominent within the different manipulation steps in the soundmorph task than in the dichotic listening task, where the stimuli always consist of pure syllable sounds. The dorsal stream becomes particularly important when speech requires more sensory guidance. Higher activation in this stream may indicate that the processing is less efficient in PWS, and that they therefore need to use more effort when processing via this stream is required. The PWS also recruited the homologue areas of the dorsal stream in the right hemisphere.

The differences seen in activation between PWS and controls in response to the DL production task only became evident with an uncorrected p-value, and one must be cautious when interpreting these findings. As previously mentioned, the DL task did not elicit stuttering behaviour in the scanner. If the task had elicited stuttering behaviour, then perhaps the activation differences in the DL production task would have been evident at a corrected level as well.

Despite of the caution with regard to the power of the DL results, our overall findings lend support to the assumption of over-activation in PWS. The PWS showed significantly more activation than the controls in several brain regions in both the DL production and the soundmorph task. The DL and soundmorph findings overlapped in bilateral regions of the superior temporal lobe, in areas that might correspond to the Spt and the planum temporale (PT) in Wernicke's area and the right homologue (Figure 4).

Interestingly, the same areas that were explored with the DCM analysis by Osnes et al., (2011) showed increased activation in PWS when compared to controls. Our study found a similar activation pattern for both groups in response to speech sounds, in particular replicating the finding of a strong involvement of STS. However, the PWS had a somewhat deviating activation pattern than the controls, as reflected by the main effect of groups.

The DTI fractional anisotropy (FA) measures revealed a significantly lower level of FA in PWS compared to controls in BA 47 at the border to BA 45. However, the significant difference was found at an uncorrected level only. If we hypothesize that our finding is at the ending point of the arcuate fasciculus, then it could be associated with our functional findings in dorsal stream areas. The differences in activation between PWS and controls in the dorsal stream (and right homologue) could be reflected in structural differences in white matter (WM), with the PWS having dysfunctional connectivity between some speech relevant areas.

It is important to emphasize that our results show correlations only. It is therefore difficult to draw conclusions about the causality. Are the activation patterns and structural differences causes of stuttering in PWS, or are they consequences of stuttering? As previously discussed, the participants in the PWS group had received treatment for their stuttering, which may have affected the results (e.g. Neumann et al., 2005). Further research will therefore need to include PWS who have not received therapy for their stuttering. In addition, more studies should investigate brain activation patterns in children, to provide answers to the question of causes and consequences of stuttering.

Conclusion

The results of our study indicate that stuttering is related to abnormal cerebral activation patterns in both speech perception and production. There were particular evident bilateral differences in activation between PWS and controls in the soundmorph paradigm. The results lend support towards abnormalities in speech lateralization, and to deficits in the dorsal stream of speech processing in PWS. The results also lend support to the notion of a strong involvement of STS in speech perception in both PWS and controls.

This study is part of the on-going "Auditory Perception, Lateralization of Language and Stuttering" project. The project is a multimodality study, which combines behavioural measurements with fMRI techniques.

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Table 1. Anatomical location of main effect of task, given with cluster size, F-value and MNI coordinates

Cluster size	P(FWE) peak-level	F-value	x	y	z	Localization
6413	0.000	167.13	-52	-10	34	L Primary sensory cortex
	0.000	147.70	-60	-2	24	L Postcentral
	0.000	85.96	-56	2	14	R Rolandic operculum
1311	0.000	149.54	52	-8	28	R Primary motor cortex
	0.000	135.71	60	0	16	R Rolandic operculum
	0.000	100.26	44	-10	32	R Primary motor cortex
1256	0.000	114.37	-10	12	38	L Dorsal anterior cingulate
	0.000	108.79	0	10	52	L SMA
	0.000	102.44	-2	-4	66	L SMA
14	0.001	75.47	-4	-104	12	L Cuneus
78	0.001	58.09	66	-36	14	R Superior temporal gyrus
	0.006	49.11	56	-38	14	R Superior temporal gyrus
91	0.004	46.21	-60	-44	20	L Superior temporal gyrus
83	0.004	43.74	48	-20	-14	R Inferior temporal gyrus
10	0.016	37.16	12	-20	-24	R Perirhinal area

F-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right; SMA = supplementary motor area;

Table 2. Anatomical location of Control: Production – perception given with cluster size, T-value and MNI coordinates

Cluster size	P(FWE) peak-level	T-verdi	x	y	z	Localization
2932	0.000	12.29	-58	-6	26	L Postcentral
	0.000	11.82	-48	-14	38	L Primary sensory cortex
	0.000	8.71	-54	4	20	L medial SMA/lateral PMC
822	0.000	9.64	60	-2	16	R Rolandic operculum
	0.000	8.61	56	-8	26	R Postcentral
	0.000	7.96	42	-12	32	R Retrosubicular area
1198	0.000	7.78	36	8	-6	R Retrosubicular area
	0.000	7.17	56	6	-16	R Middle temporal pole
	0.001	6.55	50	12	-10	R Superior temporal pole
1232	0.000	7.77	-10	12	36	L Dorsal anterior cingulate
	0.000	7.39	-6	12	44	L Dorsal anterior cingulate
	0.000	7.23	0	-2	68	L SMA
340	0.001	6.38	8	-20	4	R Thalamus
	0.002	6.29	20	-12	6	R Thalamus
	0.003	6.08	2	-24	0	R Superior colliculus
32	0.001	6.36	-6	-90	40	R Associative visual cortex
139	0.002	6.28	20	6	18	R Caudate
	0.005	5.94	20	-2	22	R Caudate
80	0.002	6.28	16	-66	-22	R Cerebellum 6
	0.004	6.00	6	-76	-16	R Vermis 6
168	0.002	6.18	-20	-8	28	L Caudate
	0.004	6.00	-20	-14	16	L Caudate
39	0.006	5.85	-28	16	18	L Retrosubicular area
12	0.019	5.49	-48	-8	8	L Rolandic operculum

T-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right; SMA = supplementary motor area; PMC = premotor cortex

Table 3. Anatomical location of Stutter: Production – Perception given with cluster size, T-value and MNI coordinates

Cluster size	P(FWE) peak-level	T-verdi	x	y	z	Localization
634	0.000	8.15	-52	-10	34	L Primary sensory cortex
	0.000	7.25	-60	-2	24	L Postcentral
	0.003	6.07	-54	0	6	L Rolandic operculum
468	0.000	7.8	50	-6	30	R Primary motor cortex
	0.000	6.69	60	2	16	R Retrosubicular area
26	0.005	5.91	-24	-18	30	L Caudate
36	0.009	5.74	-36	12	-2	L Insula
	0.026	5.38	-46	10	-6	L Insula
19	0.018	5.5	36	10	-2	R Retrosubicular area
14	0.020	5.48	-10	12	38	L Dorsal anterior cingulate

T-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right

Table 4. Anatomical location of Production: Stutter – Control given with cluster size, T-value and MNI coordinates

Cluster size	P(unc.) peak-level	T-value	x	y	z	Localization
121	0.000	4,9	-44	-30	28	L Retrosubicular area
257	0.000	4,8	36	32	40	R Dorsolateral prefrontal cortex
	0.000	4,42	32	30	50	R Dorsolateral prefrontal cortex
214	0.000	4,7	-64	-46	18	L Superior temporal gyrus
202	0.000	4,42	-22	20	-14	L Orbitofrontal cortex
	0.000	3,89	-16	4	-20	L Anterior entorhinal cortex
	0.000	3,86	-18	12	-20	L Orbitofrontal cortex
172	0.000	4,11	42	-40	14	R Primary auditory cortex
	0.000	3,92	64	-36	12	R Superior temporal gyrus

T-contrast with an uncorrected $p < 0.001$ and at least 120 voxels per cluster. L = left; R = right;

Table 5. Anatomical location of main effect of group given with cluster size, F-value and MNI coordinates

Cluster size	P(FWE) peak-level	F-verdi	x	y	z	Localization
77	0.000	66,35	52	12	52	R Middle frontal gyrus
122	0.000	54,5	-60	-16	4	L Superior temporal gyrus
131	0.000	41,23	36	10	66	R Superior frontal gyrus
	0.003	27,99	20	12	62	R Superior frontal gyrus
112	0.000	34,99	-64	-38	22	L Superior temporal gyrus
	0.002	29,71	-48	-34	26	L Supramarginal gyrus
21	0.001	31,47	64	-34	10	R Superior temporal gyrus
21	0.002	29,55	-56	2	44	L Medial SMA and lateral PMC
23	0.004	27,95	0	-14	-8	Superior colliculus
24	0.010	25,61	54	-44	50	R Supramarginal gyrus
11	0.014	24,70	12	54	-10	R Medial orbitofrontal area
11	0.017	24,25	-6	-96	10	L Calcarine sulcus

F-contrast with FWE $p < 0.05$ and at least 10 vexels per cluster. L = left; R = right; SMA = supplementary motor area; PMC = premotor cortex

Table 6. Anatomical location of main effect of stimuli given with cluster size, F-value and MNI coordinates

Cluster size	P(FWE) peak-level	F-value	x	y	z	Localization
1356	0.000	76.56	-64	-16	2	L Secondary auditory cortex
	0.000	39.39	-58	-6	-12	L Secondary auditory cortex
	0.000	32.86	-66	-34	10	L Secondary auditory cortex
877	0.000	57.03	60	-22	-8	R Middle temporal gyrus
	0.000	47.18	64	-4	-8	R Superior temporal gyrus

F-contrast with FWE $p < 0.05$ and at least 10 vexels per cluster. L = left; R = right

Tabell 7. Anatomical location of main effect of manipulation given with cluster size, F-value and MNI coordinates

Cluster size	P(FWE) peak-level	F-value	x	y	z	Localization
294	0.000	15.53	-64	-18	6	L Secondary auditory cortex
463	0.000	10.58	62	-12	2	R Secondary auditory cortex
	0.002	7.7	60	-22	-8	R Middle temporal gyrus

F-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right

Table 8. Anatomical location of interaction effect of stimuli x manipulation given with cluster size, F-value and MNI coordinates

Cluster size	P(FWE) peak-level	F-value	x	y	z	Localization
10	0.014	6.8	30	-22	68	R Medial SMA and lateral PMC
32	0.017	6.73	-30	-26	56	L Primary motor cortex

F-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right; SMA = supplementary motor area; PMC = premotor cortex

Table 9. Anatomical location of Control vs Stutter: speech given with cluster size, F-value and MNI coordinates

Cluster size	P(FWE) peak-level	F-value	x	y	z	Localization
19	0.000	7.88	-60	-16	4	L Secondary auditory cortex

F-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left

Table 10. Anatomical location of Control linear speech given with cluster size, T-value and MNI coordinates

Cluster size	P(FWE) peak-level	T-verdi	x	y	z	Localization
508	0.000	7.59	-64	-18	4	L Secondary auditory cortex
	0.000	5.84	-66	-38	12	L Secondary auditory cortex
	0.003	5.17	-62	-8	-6	L Secondary auditory cortex
68	0.004	5.13	58	4	-10	R Superior temporal gyrus
43	0.021	4.71	60	-26	-8	R Middle temporal gyrus
10	0.023	4.68	66	-12	2	R Secondary auditory cortex

T-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right

Table 11. Anatomical location of Stutter linear speech given with cluster size, T-value and MNI coordinates

Cluster size	P(FWE) peak-level	T-value	x	y	z	Localization
138	0.000	6.33	-62	-16	4	L Secondary auditory cortex
193	0.001	5.40	64	-16	-10	R Middle temporal gyrus
24	0.019	4.74	58	-40	-2	R Middle temporal gyrus

T-contrast with FWE $p < 0.05$ and at least 10 voxels per cluster. L = left; R = right

Table12. Anatomical location of Control - Stutter given with cluster size, T-value and MNI coordinates

Cluster size	P(FWE)	T-value	x	y	z	Localization
152	0.000	4.71	-36	34	0	L Inferior frontal gyrus

T-contrast with an uncorrected $p < 0.001$ and at least 120 voxels per cluster. L = left

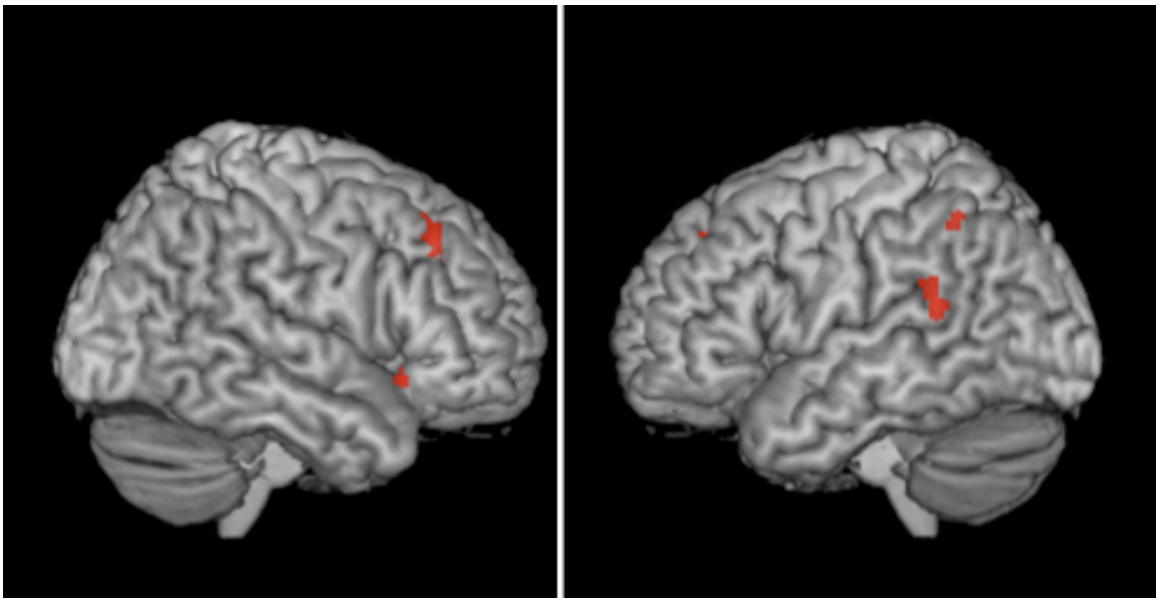


Figure 1. Results of post-hoc t-test, with uncorrected $p < 0.001$ and at least 120 voxels per cluster, of differences between PWS and controls in the DL production condition. Red areas show regions with higher activations in PWS.

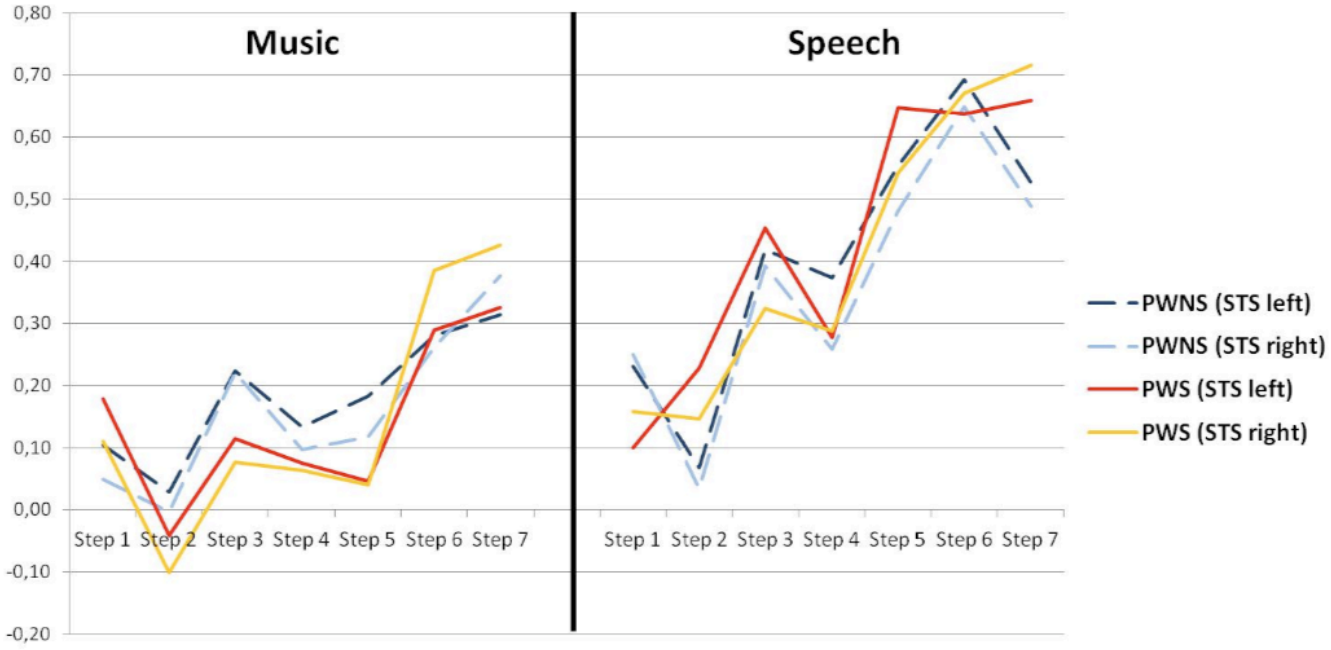


Figure 2. Region of interest (ROI) analysis of activation in bilateral STS in PWS and controls, in different stimulus manipulation steps in soundmorph. STS, superior temporal sulcus.

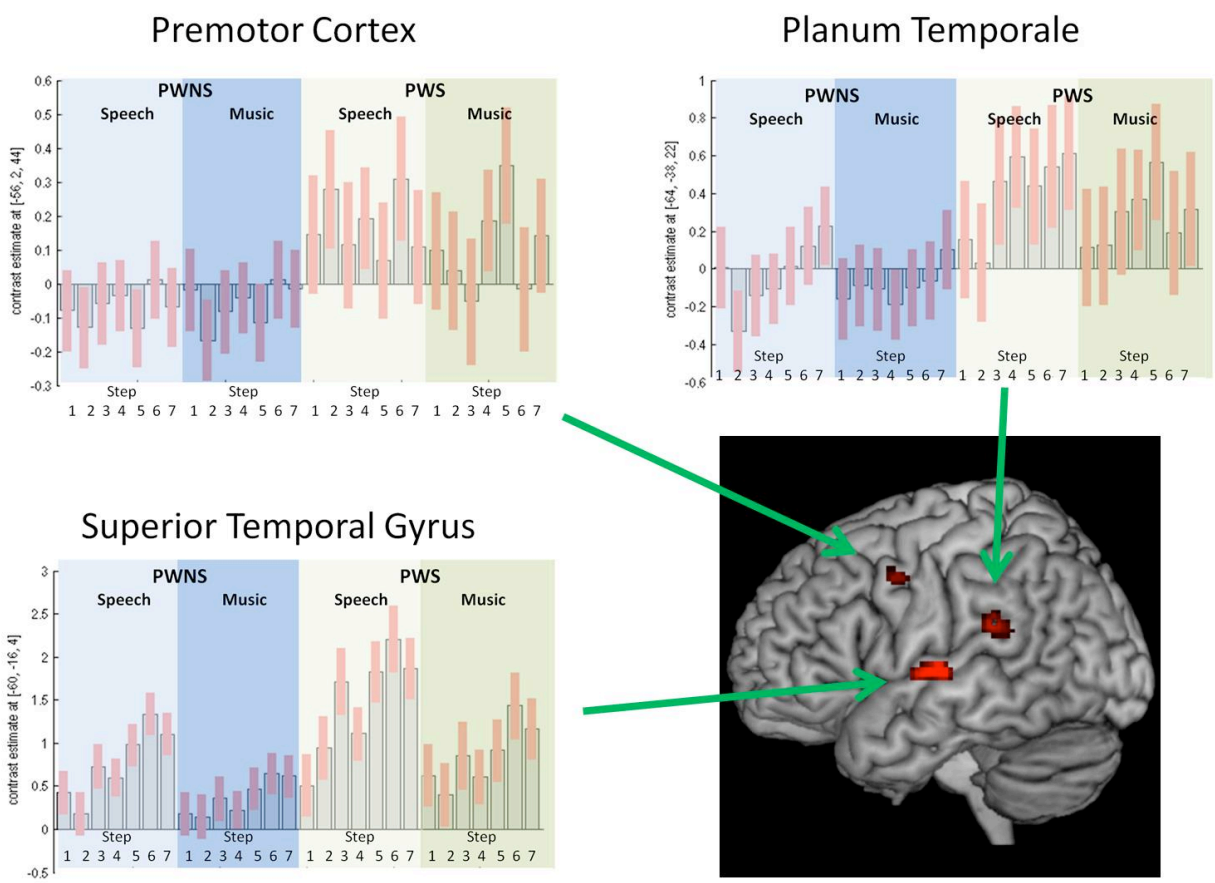
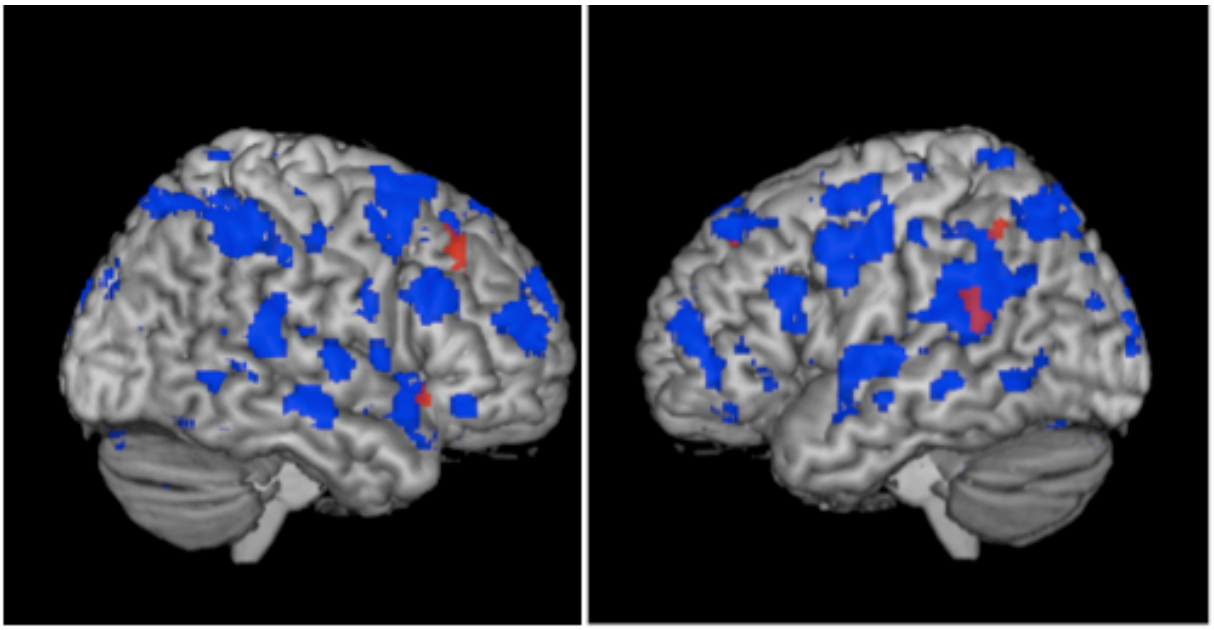


Figure 3. Regions of the dorsal processing stream, which have significantly higher activations in PWS than in controls. The structures include the planum temporale, superior temporal gyrus and premotor cortex.



Figur 4. Blue areas: main effect of group in soundmorph; red areas: post-hoc t-test of group differences in DL.

Abbreviations

ADC -	Apparent diffusion coefficients
ADHD -	Attention deficit hyperactivity disorder
aMFG -	Anterior middle frontal gyrus
BA -	Brodmann's area
BOLD -	Blood oxygenation level-dependent
CN -	Caudate nucleus
CS -	Central sulcus
dB -	Decibel
CRH -	Covert repair hypothesis
CV -	Consonant-vowel
DAF -	Delayed auditory feedback
DCM -	Dynamic causal modeling
dHb -	Deoxygenated hemoglobin
DL -	Dichotic listening
DTI -	Diffusion tensor imaging
dlPFC -	Dorsolateral prefrontal cortex
EEG -	Dlectroencephalography
e-fMRI -	Event-related functional magnetic resonance imaging
ERP -	Event-related potential
FA -	Fractional anisotropy
FL -	Forced left
fMRI -	Functional magnetic resonance imaging
FR -	Forced right
GE -	General Electrics
GM -	Grey matter
GP -	Globus pallidus
Hb -	Hemoglobin
HG -	Heschl's gyrus
Hz -	Herz
ICSM -	Intraoperative cortical stimulation mapping
IFC -	Inferior frontal cortex
IFL -	Inferior frontal lobe
IFG -	Inferior frontal gyrus
IOF-	Occipito-temporal fasciculus
IPL -	Inferior parietal lobe
MEG -	Magnetoencephalography
mid-STS -	Middle region of the left superior temporal sulcus
MR -	Magnetic resonance
MRI-	Magnetic resonance imaging
Ms -	milliseconds
MUC -	Memory, unification and control
NF -	Non-forced
NIFS -	Norsk interesseorganisasjon for stammere
PET -	Positron emission tomography
PDS -	Persistent developmental stuttering
PMC -	Premotor cortex
POP -	Pars opercularis
preSMA -	Presupplementay motor area

PSI - Perceptions of Stuttering Inventory
PT - Planum temporale
PTR - Pars triangularis
PWS - Persons who stutter
REA - Right ear advantage
RFO - Right frontal operculum
RO - Rolandic operculum
ROI - Region of interest
SLF - Superior longitudinal fasciculus
SMA - Supplementary motor area
Spt - Posterior dorsal aspects of the temporal lobe and parietal operculum
SQUID - Superconducting quantum inference device
SS - Stutter severity
SSI - Stutter Severity Inventory
STG - Superior temporal gyrus
STS - Superior temporal sulcus
T - Tesla
UF - Uncinate fasciculus
V1 - Primary visual cortex
WASSP - Wright and Ayre Stuttering Self-Rating Profile
WM - White matter
3T - 3 Tesla