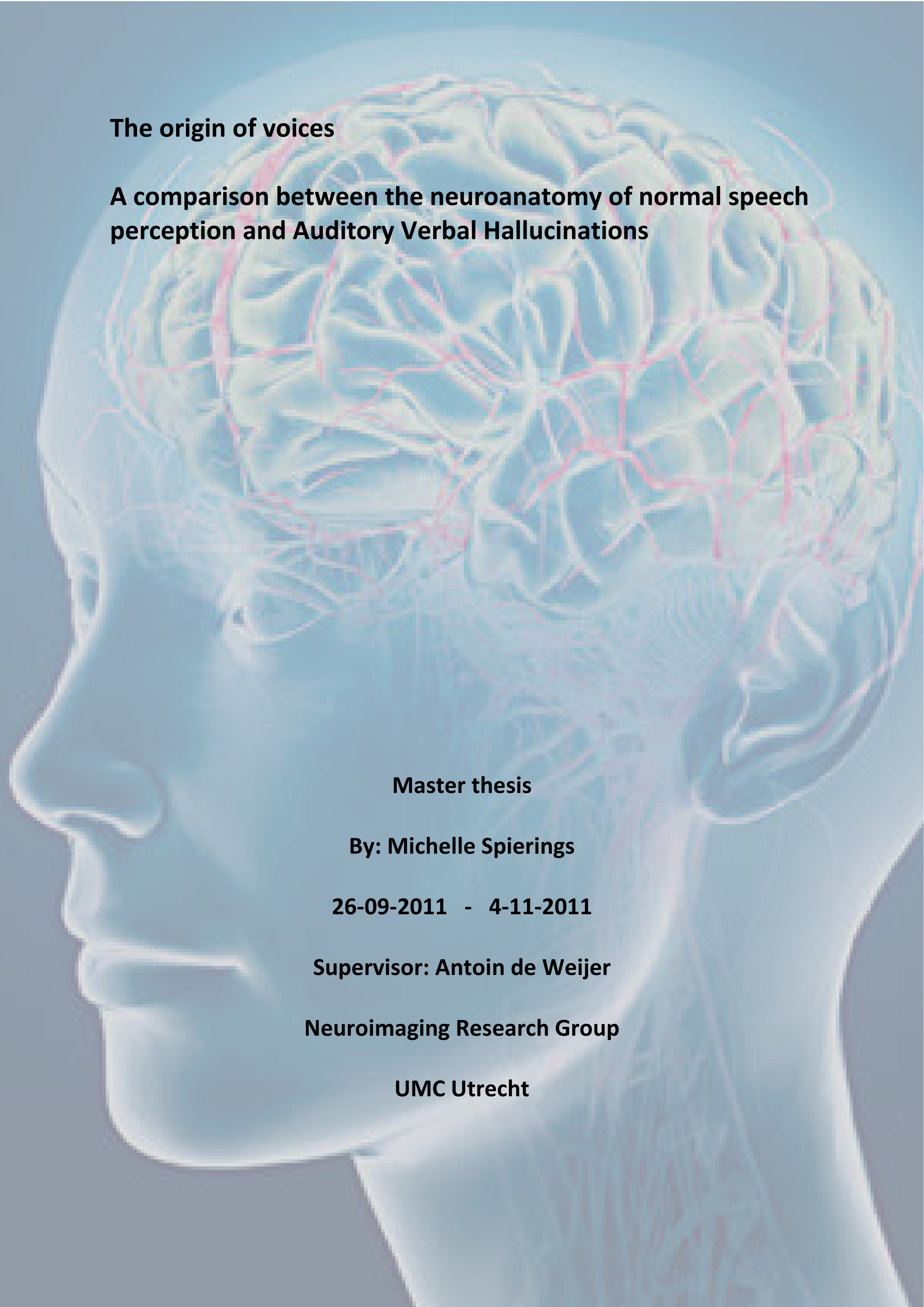

The origin of voices

A comparison between the neuroanatomy of normal speech perception and Auditory Verbal Hallucinations

Master thesis

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26-09-2011 - 4-11-2011

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Abstract

Auditory verbal hallucinations (AVHs) are experienced by the majority of patients with schizophrenia. In a considerable amount of patients this symptom is resistant to medication. Research after these often disturbing and unpleasant voices shed light on several functional brain regions that are activated during AVHs, but a complete model is still missing. This thesis reviews the current knowledge on brain regions that are activated during normal external speech perception and the regions that play a role in AVH perception. The comparison between brain activations during these two forms of speech perception sheds a light on the origin of AVHs. Many active brain regions are similar during external speech perception and AVHs. Furthermore, the emotional content of AVHs could be caused by the activation of the right tempoparietal lobe in schizophrenia patients. This right hemisphere is related to emotions and is less pronounced active during normal speech perception. The activation of Broca’s area during AVHs could implicate that the voices are created by the patients and supports the inner speech mode. Possibly, differences in wiring and connectivity between language related brain areas play a role in the experience of AVH. Research should aim to gain more knowledge on the fiber pathways between functional brain regions in order to establish a more accurate model on AVH perception.

Introduction

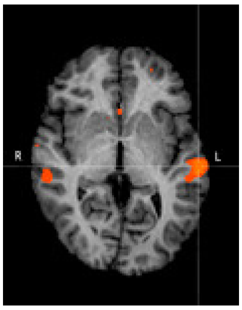
Auditory verbal hallucinations (AVHs) are often disturbing and unpleasant voices and are experienced by 70% of the patients diagnosed with schizophrenia (David 1994; Nayani & David 1996). In 25-30% of schizophrenia patients this symptom is resistant to medication (Shergill 1998). Research on brain regions and connective pathways that play a role in AVH perception increase our knowledge and might open the way to new treatments. This thesis aims to provide a clear overview of the current knowledge on brain regions involved in AVHs and how this correlates to normal speech perception. This will add to the current discussion on the origin of voices.

The leading definition of AVHs is that they are verbal perceptions without corresponding sources in the external world (Jardri et al. 2011) The number of voices, whether they are directed to the hearer or not and how recognizable they are differs between all AVHs. They are similar in several other aspects, such as the use of simple grammar, the concentration around a specific theme and in the negative emotional valence of the content (Nayani & David 1996).

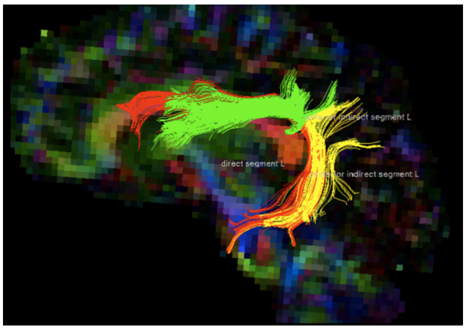
Many studies and reviews aim to find correlating brain regions and pathways that are actively involved in AVHs. In order to accomplish this, models have been established to underpin the structural and cognitive causes of hallucinations. Until now, neuroanatomical research of AVHs has often suggested the role of superior temporal cortical dysfunction amongst other possible models (Dierks et al. 1999; Lennox et al. 2000). However, it has been difficult to establish structural correlates of these functional findings (Weiss & Heckers 1999) and one completely fitting model that is functionally underpinned is yet to be found.

Many studies on the function and involvement of specific brain regions make use of functional Magnetic Resonance Imaging (fMRI). More recently Diffusion Tensor Imaging (DTI) provided new insight in the white matter fiber tracks that connect the brain areas involved in AVHs. Several different methods of meta-analyses have proven useful in the determination of the most likely brain regions involved. Since 2008 a new method was applied to analyse voxel-based morphometry (VBM) and fMRI studies, namely Activation-Likelihood Estimation (ALE). A short explanation of the different methods used in AVH research is given in Box 1.

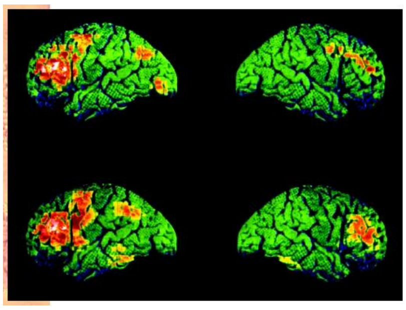
Box 1.
Explanation of the techniques used in studies on AVHs and schizophrenia.



fMRI (functional magnetic resonance imaging) detects changes in blood oxygenation and flow that occur in response to neural activity, the so called BOLD effect (Blood Oxygenation level dependent). Brain areas that are more active consume more oxygen and this oxygen is provided by an increased blood flow. A MRI scanner creates a strong magnetic field that makes the magnetic hydrogen nuclei of atoms in water align with the direction of this field. This alignment creates a signal that is measurable by the scanner. The strength of the signal from the hydrogen nuclei varies depending on their surroundings, making it possible to detect the differences between grey matter, white matter and cerebral spinal fluid. Immediately after the increase of neural activity the blood oxygenation decreases. After this short 'initial dip' the oxygenated blood flow increases and overcompensates the demand.



DTI (diffusion tensor imaging) is a different MRI modality that measures the diffusion of water in tissue. It is based on the principle that a water proton has three dimensions in which it can diffuse. Because brain tissue restricts diffusion, especially in white matter, the water protons propagate along one direction. Diffusion in the direction of the white matter fiber tracts is higher than in the other directions. By calculating this preferred direction of diffusion one can visualize the direction of structures in tissues. This technique allows us to follow bundles of nerve fibers in the white matter of the brain.



PET (Positron Emission Tomograhpy) is a technique based on the detection of positrons by a radioactive tracer isotope that is injected in the blood circulation. When this molecule (usually fluordeoxyglucose) undergoes positron emission decay, it emits positrons. These positrons interact with electrons in the body. This reaction sets free annihilation photons that can be detected by the PET scanner. This shows areas of higher blood flow.

Patients that suffer from schizophrenia perceive AVHs in many different ways. The voices can be familiar or unfamiliar, directed to them or arguing with each other and differ in number and frequency. There are many variables between different AVHs and much is still unknown about the origin of the voices. Comparing the brain regions involved in AVH perception to the perception of normal external speech and inner speech in healthy humans can provide useful insight in the underlying mechanisms of AVHs. A comparison between inner speech and AVHs has been made by several authors (Langdon et al. 2009; McGuire et al. 1996; Shergill et al. 2003; McGuire et al. 1995). They studied the differences in inner speech perception between schizophrenia patients and healthy controls and by modelling how these two voice perceptions can be related on level of brain activation.

Less is known about the difference between normal speech perception and AVHs. Two studies have looked at the different activation patterns when patients and controls were subject to words that were either from or related to their hallucinations or neutral words (Bentaleb et al. 2006; Sanjuan et al. 2007). The fMRI study of Sanjuan et al. (Sanjuan et al. 2007) revealed that when patients where exposed to emotional words, neural activity increased in the frontal lobe, temporal cortex, insula, cingulate and amygdala (right side). This activation was absent in healthy controls and indicated that emotional words (frequently reported to appear in hallucinations) elicit activation in additional brain regions compared to neutral words and healthy controls.

The results from the study of Sanjuan et al. are relevant to the knowledge on AVH perception. In their study they suggest specific brain areas that could be involved in the emotional content of AVHs. Nevertheless, hearing words is not entirely comparable with perceiving AVHs. Therefore, I will review the current knowledge on brain regions related to normal speech perception and perception of AVHs. The comparison between these two forms of voice perception can provide an indication of the overlap of the related brain regions that play a role in hearing normal external voices and hearing internal voices.

In order to make this comparison, the role of specific grey matter areas and white matter fiber tracts that are involved in normal speech perception and the ones that are involved in perception of AVHs are discussed first. Grey matter consists of neural cell bodies and their network of dendrites and myelinated and unmyelinated axons. Grey matter forms the inner part of the spinal cord, the outer layer of the cerebral cortex, several deep brain structures and the cerebellum. White matter is located in the cerebrum, deep parts of the cerebellum and the outer parts of the spinal cord. It consists mostly of myelinated axons and no dendrites. It functions as connecting tracts between the grey matter areas along which nerve impulses can travel between neurons.

In short, the comparison of this review will shed light on the currently less studied difference between the perception of normal external speech and AVHs. With this knowledge we can understand more about the relevance of brain regions that are active during AVHs, how they relate to external speech perception and what makes AVH perception different from normal external speech perception. This provides useful knowledge to design experiments to understand the role of specific brain areas in the occurrence of AVHs.

Speech perception

Introduction

Since the introduction of brain imaging techniques, knowledge on the neuropathology of language perception has improved rapidly. Research with fMRI and DTI has led to current theories that suggest that language is organized in widespread and overlapping networks (Mesulam 1990; Bornkessel & Schlesewsky 2006). These theories are based on specialised brain areas (Wernicke's and Broca's area) and their interconnecting white matter fiber bundles. Furthermore, studies regarding functional specialization in the human brain have proposed that functional language is lateralized to the left hemisphere. This lateralization to the left hemisphere was found in 95% of the right-handers, lateralization to the right hemisphere was found in 15% of the left-handers (Pujol et al. 1999; Lurito & Dzemidzic 2001). Also volumetric studies of language-related areas reported a leftward asymmetry in the volume of the human planum temporale (Geschwind & Levitsky 1968; Foundas et al. 1995; Tzourio 1998) and of Broca's area (Tzourio 1998; Josse 2003; Falzi 1982; Moffat 1998).

The standard reference model that is used by clinicians to predict aphasic syndromes from lesions in speech related areas is based on the work of Wernicke (Wernicke 1874) and Lichtheim (Lichtheim, 1885). Wernicke was able to localize the recognition of the sound images of words to the posterior superior temporal lobe and the representation of the motor images of words to the inferior frontal lobe. He did this by post-mortem dissections and correlating those findings to the symptoms of the patients. Lichtheim used Wernickes' theory to create the three-component model, which consisted of Wernicke's area, Broca's area and the interconnecting "concept centre" to explain how the brain perceives speech (Lichtheim 1885). The functions of these three parts of the auditory system were noted by three forms of aphasia: Wernicke's aphasia (receptive aphasia) with which a patient can speak fluently, but with a lack of logical content; Broca's aphasia (expressive aphasia) that makes a person unable to properly signal the muscles needed to speak; and conduction aphasia, which is a lesion in the "concept centre" (now arcuate fasciculus). Conduction aphasia presents itself in the inability to repeat words or sentences and paraphesic errors.

Neuroanatomy

This chapter will cover the function and subdivisions of Wernicke's and Broca's area and other involved functional brain regions. And will review the recent literature on the connecting fibers that are involved in speech perception.

Broca's area (left inferior frontal gyrus)

The exact role of Broca's area in speech perception is still controversial. Several studies have shown elevated activation in the left inferior frontal gyrus (LIFG) when an explicit semantic judgment task is used (Thompson-Schill et al. 1997; Wagner et al. 2001; Thompson-Schill 2003). Such a task requires semantic information about single words that had to be explicitly retrieved or selected. Currently, it is argued that LIFG regions also play an important role in processing semantic information when understanding natural speech. It is proposed that the frontal region and especially the LIFG are usually not recruited (Crinion et al. 2003) during the processing of unambiguous sentences that are not easily understood. However, this is not the only opinion; some authors have stated that processing syntax and morphology might be under influence of the frontal brain regions, but that this is not the case for the processing of word meanings. It was suggested that this process relies on temporal lobe regions (Ullman 2001).

Additional relevant research has been conducted on the neuroanatomical subdivisions of the LIFG. These differentiations are interesting when proposing language function, because every subdivision might have its own function. This means that these differentiations could be an explanation of the fact that the LIFG is involved in many different language comprehension functions. Initially the differentiation in Broca's area was based on the layering of the isocortex and the presence of particular cell types (Brodman, 1909). Broca's area is differentiated into a posterior part of the inferior frontal gyrus from the more anteriorly located area BA 45 (Amunts et al. 1999). Recently this differentiation between BA44 and BA45 was demonstrated with a connectivity-based DTI study that focussed on these particular areas (Anwander 2007). In this study they found a three-region division into BA44, BA45 and the frontal operculum.

Wernicke’s area (left tempoparietal junction)

Wernicke’s area is involved in the understanding of both written and spoken language; it encompasses both speech recognition systems and representations involved in the output of speech (Wise 2001). The first knowledge on the functions of this particular area came from dissections of patients with auditory language comprehension disorders (Wernicke’s aphasics). The lesions from these patients were located in the superior temporal gyrus and sulcus (STG/STS) and the middle temporal gyrus (MTG).

Like Broca’s area, Wernicke’s area is no longer regarded as a single functional region of the brain, but has been differentiated in several functional subdivisions. A large portion of Wernicke’s area (BA 22) was differentiated from BA 42 (Brodman 1909). Furthermore, the STG and STS were divided into three sub-parts, one located anterior to Heschl’s gyrus, one located posterior to Heschl’s gyrus and one including Heschl’s gyrus (Raettig 2007). This three-part differentiation seems to correspond to the functional subdivisions in this region (Friederici 2003).

Connecting pathways

The first knowledge on a connecting pathway between the functional areas of speech perception was the “concept centre” of Lichtheim (1885) (Fig. 1). When this was proposed, it was not yet anatomically localized. Nevertheless, it was the foundation for more confound research to the connection between the two brain areas. Neurophysiological and anatomical findings in macaque monkeys led the way to the idea of multiple, parallel streams of processing in the primate auditory system (Rauschecker 1998). This primate research gave scientists the possibility to track activated brain regions in more detail. Since the advent of DTI, tracking white matter fibers became possible in the human brain. Ever since, different models on how these connecting fibers run have been proposed. The two most influential models are summarized in this review.

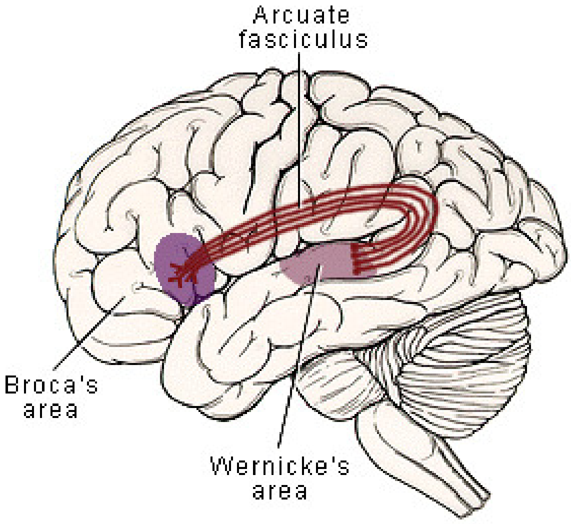


Fig. 1. The location of Broca's area, Wernicke's area and their connecting pathway (Arcuate fasciculus).

Connectivity models

Lexical selection model

One model on speech perception was proposed by Levelt (2001). His model is based on the theoretical framework on how humans produce word content. He states that for a person to produce a sentence he first selects the appropriate item from a mental lexicon. Than the selected item's articulatory shape has to be prepared. These two steps enable a person to correctly answer when they are asked to say what they see. Levelt explains his model by the clear example of a subject that is shown a picture of a horse and asked to name it. The subject can either say horse, stallion or animal. All are correct; it depends on the level of detail that is required. This first step is the selection of words from the mental lexicon and the syntactic description, whether it is singular or plural and has different forms for a different gender. The second step is the syllabification of the word, this is suggested to be an "on the fly" process, when the motor process is formed in order to speak.

This lexical selection model is supported with functional data form the measurement of evoked electrical and magnetic brain responses. The first measures of lateralized readiness potentials (Van Turennout et al. 1997) were able to distinguish between the stages of lexical access. The measurements of this study were based on the electrophysiological brain potential that lead any voluntary hand movements. This means that they could measure the brain activation before a person provided a button-press response to an image and distinguish between different syllables and languages.

Dual-stream model

Hickok and Poeppel (Hickok & Poeppel 2005; 2007) proposed the dual-stream model for auditory language processing (fig.2). This model describes the divergence from the superior temporal gyrus into two processing stream, a dorsal and a ventral stream. The dorsal stream projects dorsoposteriorly towards inferior parietal and posterior frontal lobe regions and is involved in auditory-motor integration. The ventral stream projects ventrolaterally to the middle and inferior temporal cortices. This processing stream serves a sound-to-meaning role.

The dual-stream model was supported by Saur et al (2008) who used fMRI activations and DTI-based tractography to define the cortical network notes and to track the white matter fibers that link these activated nodes. They concluded that the functional dorsal route is mainly restricted to sensory-motor mapping of sound to articulation, whereas linguistic processing of sound to meaning requires temporofrontal interaction transmitted via the ventral route.

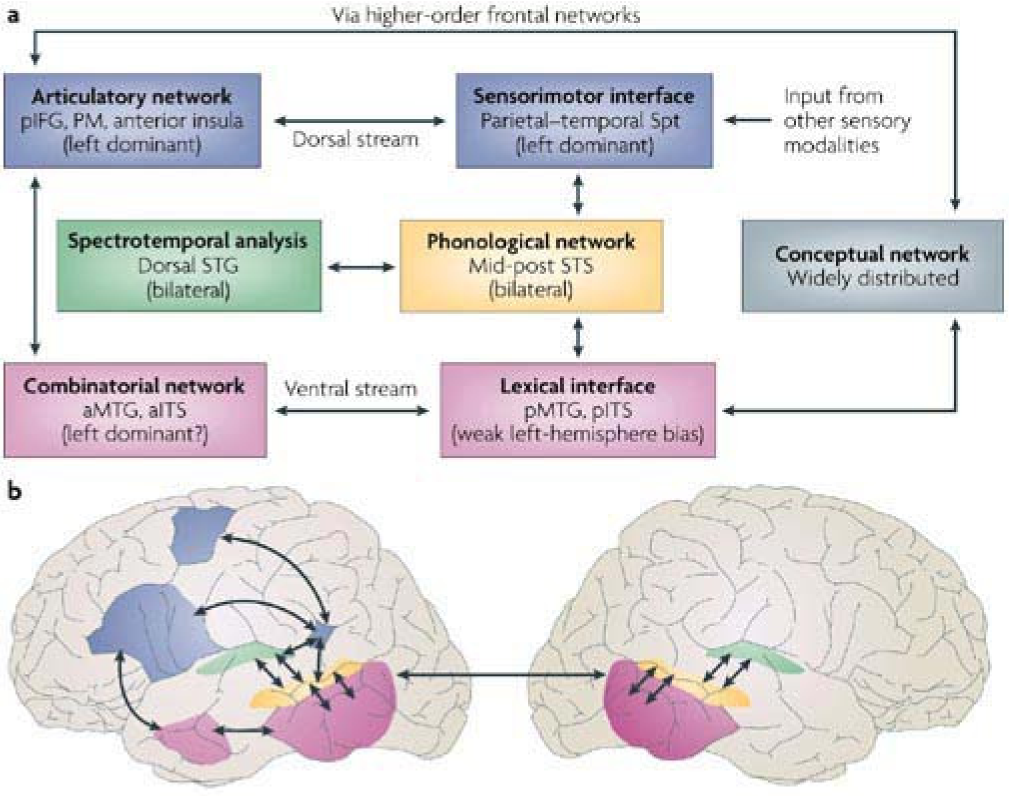


Fig. 2. a. Schematic diagram of the dual-stream model as proposed by Hickok and Poeppel[6]. The blue stream visualizes the dorsal pathway that maps sensory or phonological representations onto articulatory motor representations. The ventral pathway (pink) maps sensory or phonological representations onto lexical conceptual representations. These two stream originate from the phonological network and spectrotemporal analysis in respectively the mid-post STS and the Dorsal STG. Both these computations seemed to differ between the two hemispheres. **b.** Approximate anatomical locations of the dual-stream model components as proposed by Hickok and Poeppel[6]. The green regions indicate the dorsal surface of the STG, involved in spectrotemporal analysis. Yellow regions in the posterior half of the STS are active in honological-level processes. The pink regions are a presentation of the ventral stream, and the blue areas represent the dorsal stream. (From: Hickok and Poeppel, *Nature,* 2007)

The connectivity models show that not only the grey matter is important in speech perception, but that the connecting fibers play an important role as well. It is suggested that the incoming speech signal is processed by the time it reaches the auditory cortex (Eggermont 2001; Frisina 2001). This indicated that the ascending auditory pathways are complex and involved in processing of information. Therefore it is essential to understand their function in order to be able to compare this to the pathways and brain areas involved in AVHs.

Connective pathways

One of the first reports regarding fiber tracts connecting Wernicke's and Broca's area originated from post-mortem dissection studies by Dejerine (Dejerine 1895), after which he defined the arcuate fasciculus. Nowadays, DTI gives us clearer insight in fiber pathways in vivo in the human brain. Studies indicate that the arcuate fasciculus is not the only white matter tract connecting Wernicke's and Broca's area, there are other dorsal and a ventral pathways (Parker 2005). The ventral pathways are labelled as the 'where stream', whereas the dorsal pathways are referred to as the 'how stream' (Buxhoeveden 2001). In this review the ventral pathways are discussed in more detail, because these are the ones processing sounds into meaningful words. The function and location of the dorsal pathways will be discussed in a less elaborate fashion.

Ventral pathways

The ventral pathways have been labelled the 'where' stream', it includes the representation of distinctive features, segments, syllabic structure, phonological word forms, grammatical features and semantic information (Buxhoeveden 2001). Activation was observed lateral to the gyrus of Heschl when stimuli were presented that had the acoustic features of phonetic cues (Binder 2000) and intelligible speech (Scott 2000). This area also became active when the person was stimulated with harmonic tones, frequency-modulated tones (Hall 2002) and sounds with changing spectral structure (Thivard 2000). This indicates that although speech-related activation can be seen here, it cannot spatially be discriminated from responses to non-speech sounds. This could suggest a degree of parallel processing of the speech input.

The ventral pathways have been laid out in four different aspects in order to get a clearer overview of their organisation (Hickok & Poeppel 2007). These aspects included that the pathways were bilaterally organized with computational differences. And that the left hemisphere is not uniquely specialized for processing fast temporal information, but that these mechanisms are predominantly located in the right hemisphere. They suggested that the crucial portion of the STS that 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. This corresponds to the distribution of activation for 'phonological' processing. In short, they provide evidence that the lexical semantic access from auditory input involves the posterior lateral lobe and that the pathways involved in speech perception are bilateral.

Dorsal pathways

The functional role of the dorsal stream has been subject to discussion for quite some time. After it was proposed to serve a spatial hearing role (Rauschecker 1998), it is now widely argued to support an interface with the motor system (Scott & Wise 2004). More specific, the dorsal stream is now assumed to have a sensorimotor integration function (Andersen 1997).

DTI studies have so far located one dorsal pathway that runs from Broca’s area (in particular BA 44) via the superior longitudinal fasciculus (SLF) to posterior temporal lobe with connectivities to BA 40, the lateral STG and MTG (Parker 2005). Another dorsal pathway has been proposed, but with the limitations of the resolutions of DTI, these two pathways are not reliably separable. There is still a debate on the precise number and functions of the dorsal pathways.

Conclusion

In summary, the main areas of the brain involved in speech perception are Broca’s and Wernicke’s area and their interconnecting white matter fibers. Wernicke’s area and the ventral pathways are mostly involved in the processing of sounds into meaning and therefore play an important role in speech perception.

AVH perception

Introduction

Auditory verbal hallucinations (AVHs) are frequent in approximately 70% of patients with schizophrenia and in 4% of the general population (Laroi 2006). Moreover, in 25% -30% of the patients AVHs are resistant to medication (Shergill 1998). Therefore it is important to understand the neurological causes that underline this frequently distressing experience. Unfortunately up to date there is little consensus on the cognitive and neurological mechanisms involved.

First of all, AVHs have many different aspects; the voices are not always heard in the same way. They can be known and unknown, in the first, second or third person, or multiple voices that speak together or separately. In a study by Leuder et al. (1997) a majority of people hearing voices (64%) reported that these voices were clearly the same as a family member or an acquaintance. In 28% of the voice-hearers the voices were incognito. Others heard voices from public figures, these were only people diagnosed with schizophrenia. 96% of the subjects in this study were the subject of the perceived voices (Leuder et al. 1997). It is experienced as if the voices spoke directly to them. Although there is a rather wide diversity in the number of voices, an average was found between 2-3 voices (Leudar 1997; Nayani & David 1996).

Secondly, there are different models that describe the mechanisms of AVHs. The most prominent nowadays are two cognitive models, one is based on AVHs being a form of inner speech, which was first proposed by Feinberg (1987) and Frith (1992) and later received more attention in other reviews (Bick & Kinsbourne 1987; Fernyhough 2004; Leudar & Thomas 2000; Maudsley 1886; Seal et al. 2004; Huang et al. 2001) The other widely used model argues that AVHs are intrusions from memory (Badcock et al. 2005; Waters et al. 2003; Nigg 2000; Berbion 2007). Both models will be shortly reviewed here in order to get an overview of the probable causes of AVHs.

Inner speech & AVHs

Inner speech has been defined as ‘the subjective phenomenon of talking to oneself’, or ‘developing an auditory-articulatory image of speech without uttering a sound’ by Levine, Calvania and Popovics in 1982 (Levine et al. 1982). This definition is still explicitly used in some studies, others have stated ‘the silent articulation of sentences’ as a fitting definition (Shergill et al. 2001). They are both based on the same concept that inner speech is a form of “thinking in words” that makes a person hear voices without there being any external sounds. Healthy humans have inner speech as well. The difference with AVH experiencing patients is that, according tot his model, patients with schizophrenia are unable to recognise the voices as being inner speech. When healthy subjects experience inner speech they are aware that it is inner speech. Patients with AVHs might not be able to do so. This means that they create their own perception via misinterpretation of inner speech.

The assumption that inner speech is involved in AVHs is supported by the evidence that the brain areas involved in inner speech are also activated during AVHs, these are the left inferior frontal gyrus (including Broca’s area) and the right temporal cortex (McGuire et al. 1996; McGuire et al. 1993; Shergill et al. 2004; Shergill et al. 2000; Allen et al. 2007). Inner speech itself was found to recruit activation in the same areas as external speech, being the inferior frontal cortex, the insula and supplementary motor cortex (Huang et al. 2001). Furthermore, AVHs are often related to the ongoing activities of the person, this is similar to inner speech. And AVHs and inner speech both involve a form of internal verbal mentation, like a ‘voice in the head’ (Maudsley 1886).

Memory & AVHs

A different model for the origin of AVHs is that they are result of the ‘‘unintentional activation of memories’’ or ‘‘the failure to inhibit memories of prior events’’ (Badcock et al. 2005). Waters et al. (2003) proposed this model based on the findings that many patients with schizophrenia and AVHs showed a failure of intentional inhibition (Badcock et al. 2005; Waters et al. 2003). This means that these patients are less able to suppress a specific thought when they have decided it is irrelevant (Nigg 2000). This deficit could lead to intrusive thoughts. Nevertheless, this deficit was also found in some patients that did not experienced AVHs. Therefore, Waters and colleagues suggested that the context memory was also involved and that a deficit in this specific ability together with the failure of intentional inhibition would lead to AVHs. Waters et al. and Brebion et al. (2007) suggested that in patients that experience AVHs the content and context memories are separated. This means that they unintentionally activate the *content* of a memory, but do not do this with the *context* of this memory. The representations will therefore be confused with reality, causing AVHs.

Brain regions involved in AVHs

The above described models clarify the probable causes of AVHs. However, this does not tell us which particular brain regions are associated with AVHs. For instance, it is still unclear which areas are involved in the specific types of memory. Therefore, to learn about the neuropathology this review looks at recent fMRI, DTI and ALE studies that suggest grey matter reductions and white matter pathways that could be the cause of AVHs in patients with schizophrenia. In order to compare these brain regions to those involved in normal speech perception, this chapter will also be divided in associated functional regions (including Broca's and Wernicke's area) and the connecting pathways.

Functional brain regions

One of the first fMRI studies that compared activity between a hallucination and the resting state was by Lennox and colleagues (1999). They scanned a patient that experienced a stable pattern of hallucinations: the periods with hallucinations were alternated with 26 sec. periods in which the hallucinations were absent. This study showed an association of the right middle temporal gyrus with the experience of a hallucination. After this study, several different fMRI studies used a comparable set-up with more patients. These studies suggest that the superior temporal lobe is altered in patients with AVHs (McGuire et al. 1993; McGuire et al 1995l Shergill et al. 2000a; Shergill et al. 2000b; Lennox et al. 2000; Halligan & David 2001). These studies also found involvement of the frontal motor and premotor speech areas (Broca's area and supplementary motor area) and tempoparietal speech areas (Wernicke's area). Dierks et al. (1999) was able to monitor the on- and offset of AVHs in paranoid schizophrenic patients within one fMRI session. This study demonstrated an increased signal in Heschl's gyrus during AVHs. It also added the primary and higher-order auditory cortex located in the temporal lobe to the areas involved in AVHs (fig 3).

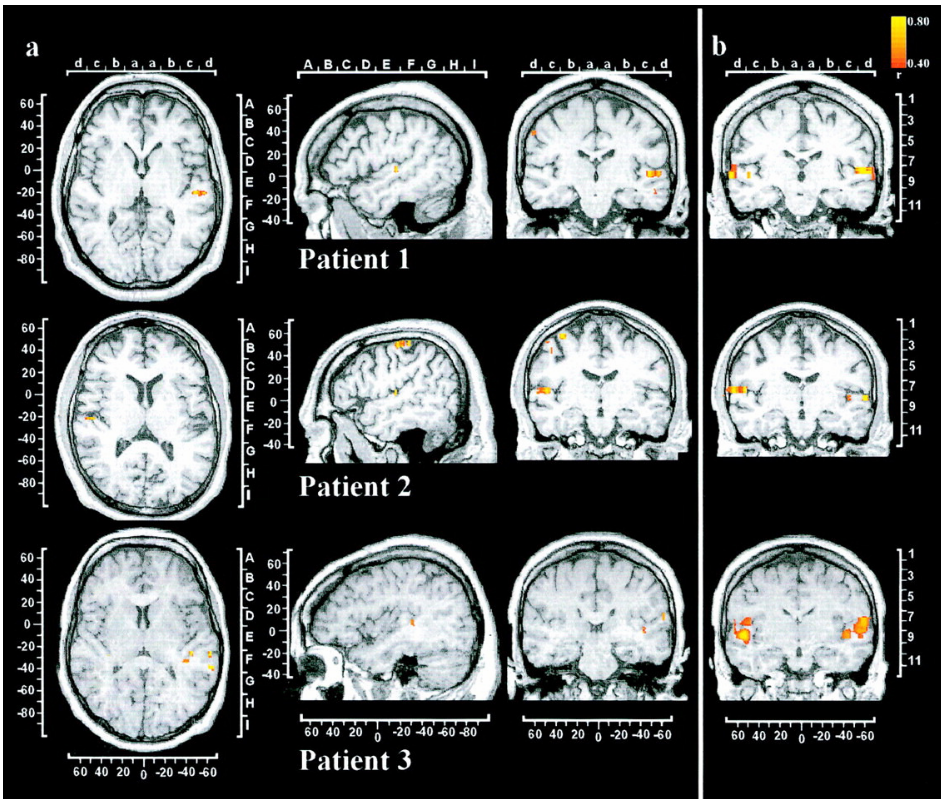


Fig 3. The activation of the auditory cortex in three patients with schizophrenia. Section a shows activation of Herschl's gyrus during AVHs in the hemisphere dominant for handedness. Section b shows bilateral activation during acoustic stimulation. The activation in the right sensorimotor cortex could be due to the button press.

Next to many fMRI studies, PET studies are also used to investigate the role of brain regions in AVH. An interesting PET study by Lahti et al. (2006) on two cohorts of patients with schizophrenia correlated AVHs positively with the regional Cerebral blood flow (rCBF) in the anterior cingulate cortex and negatively with the hippocampus/parahippocampus. This indicates that limbic dysfunctions may cause the production of these positive symptoms of schizophrenia. A comparable set-up has been used earlier by Gur et al. (1995). They found higher metabolism in the superior temporal lobe in schizophrenia patients compared to healthy controls. In order to specify these activations to the perception of AVHs, McGuire et al. (1993) made a precise comparison in single photon emission tomography (SPET) of patients when they were experiencing frequent AVHs and in a period when these hallucinations were absent. They measured hallucination-related activity in Broca's area. In the left anterior cingulate cortex and regions in the left temporal lobe they also found higher blood flow during hallucinations, but these differences did not reached significance.

Meta-analyses are a clear way to find the most consistent findings within the publications of a specific field. Bora et al. (2011) used a coordinate based meta-analysis technique on 79 fMRI studies in order to examine the grey matter and white matter abnormalities in patients with schizophrenia. This study managed to summarize five clusters of grey matter that showed abnormalities in schizophrenia patients. The two largest clusters extended from the insula to inferior frontal cortex and included the superior temporal gyrus (STG), the precentral gyrus and the claustrum. The third cluster extended to the third nucleus in the midbrain and comprised a bilateral reduction in the thalamus. The last two clusters were in the anterior cingulate cortex/medial frontal cortex, one dorsal and one rostral.

These findings were supported by Jardri et al. (2011), in their recent meta-analyses they found comparable brain regions activated during AVHs. These included large clusters that were identified in cortical areas involved in speech generation. For instance, the left pars opercularis (Brodmann's area 44) which is located in the inferior frontal gyrus and extends posterior to the precentral gyrus and in depth to the anterior insula was revealed to play a critical role in verbal imagery (Shergill et al. 2001) and syntactic processing (Fieback et al. 2005). Furthermore, the left middle and superior temporal gyri were shown to have an increased likelihood in Jardri et al.s' analyses. Together these gyri make up the associative auditory cortices. A correlation has furthermore been suggested between the severity of the hallucinations and the amount of grey matter volume reduction within the left superior (Flaum et al. 1995) and middle temporal gyri (Onitsuka et al. 2004).

In short, the superior temporal lobe, anterior cingulate cortex, frontal motor and premotor areas and the temporal speech areas are involved in AVHs. Furthermore, an increased signal in Heschl's gyrus has been related to AVHs, together with the right middle temporal gyrus and the frontal gyrus. Via meta-analyses the involved grey matter regions were concluded to five clusters, including the superior temporal gyrus, precentral gyrus and claustrum in the first two clusters. And the anterior cingulate cortex in the last two clusters.

Connective pathways

According to the model that AVHs are a form of misinterpreted inner speech, Hubl and colleagues (2004) found alterations of the white matter fiber tracts in patients that experienced frequent hallucinations. They recorded higher fractional anisotropy in the lateral parts of the tempoparietal section of the arcuate fasciculus and in parts of the anterior corpus callosum, when they compared patients with AVHs to healthy controls (fig. 4). Differences in the left hemispheric fiber tracts, including the cingulate bundle, were found when they compared patients with AVHs to schizophrenia patients without these hallucinations. They suggested that these higher activations might lead to the inability to distinguish ones own thoughts from external voices.

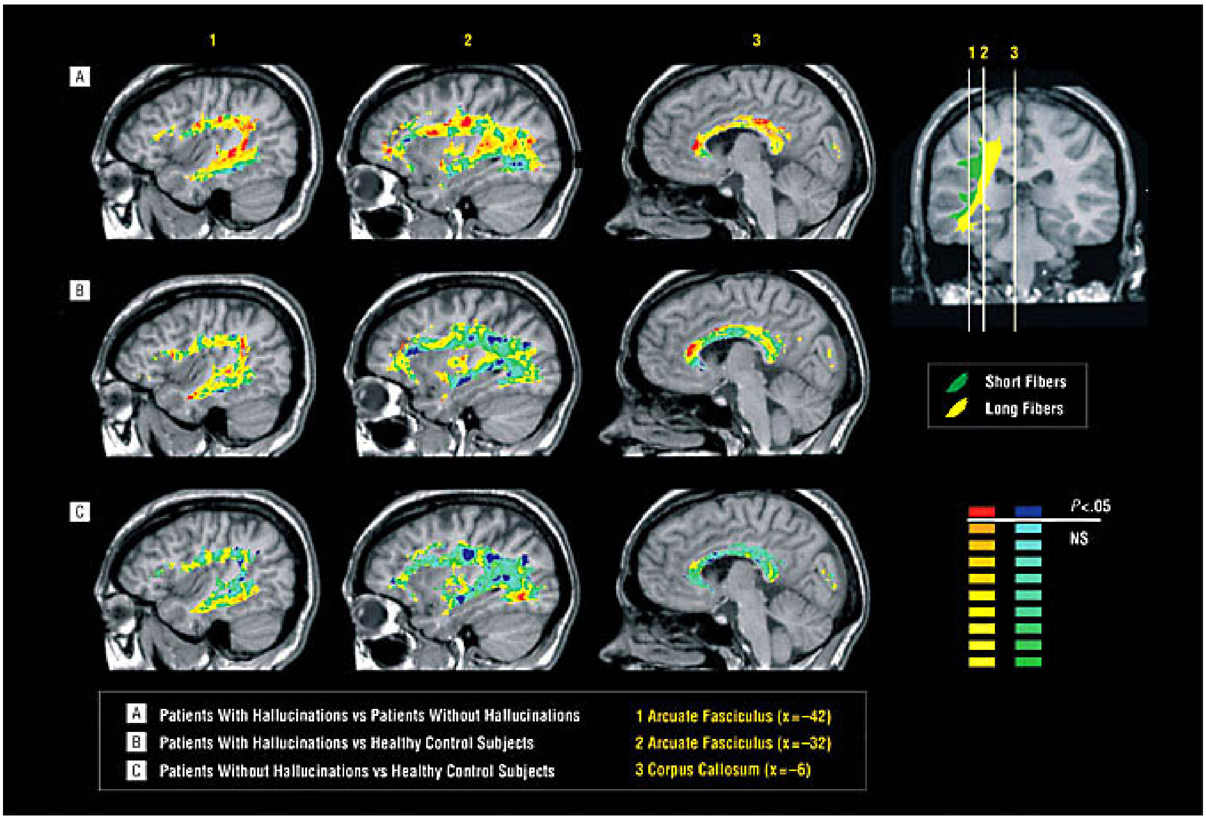


Fig 4. The lateral fibers of the articuare fasciculus (1) and the anterior corpus callosum (3) contained the main difference between patients with hallucinations, and healthy control subjects, as well as patients without hallucinations. The long fibers in the medial part of the arcuate fasciculus connect the frontal with the temporal cortex. The short fibers in the lateral part connect, amongst other, the language related regions in the frontal and parietotemporal lobes. (From: Hubl et al. 2004[77]).

Furthermore, it was suggested that AVHs are caused by disturbed fronto-tempoparietal connectivity (Andreasen 2000). This theory is supported by results from Ford et al. (2002), they reported dysfunctional interactions between frontal, parietal and temporal brain regions in patients with AVHs. The white matter fiber bundles that are connecting these regions and were found to be affected in schizophrenia patients with AVHs include the uncinate fasciculus, cingulum bundle and arcuate fasciculus. In addition, differences in cerebellar penducles were found in a DTI study by Okugawa et al. (2004). The fractional anisotropy (FA) of the right and left middle cerebellar panducles was lower in patients with schizophrenia compared to healthy control subjects.

In the ALE meta-analysis of Bora et al. (2011) they also studied white matter in the cerebellum. They showed two clusters of white matter volume reduction that were detected by fMRI studies. One cluster included white matter bilaterally in the anterior limb of the internal capsule. The second and smaller cluster is located in the right temporal white matter region and includes fibers from the right inferior frontal occipital fasciculi and the inferior longitudinal fasciculus.

When recent DTI studies were analysed, 3 reduced clusters were found to have FA reduction. The largest cluster included the bilateral genu of the corpus callosum, ACC/medial frontal white matter and the right ALIC. The second cluster was found in the left temporal white matter and retrolenticular internal capsule. The last cluster that the analyses revealed included right temporal white matter including fibers from right inferior frontal occipital fascicule.

Summarizing, white fiber tracts connecting the frontal, parietal and temporal brain regions that are involved in AVH perception have been found to be abnormal in schizophrenia patients. These tracts include the uncinate fasciculus, the cingulum bindle and the arcuate fasciculus. Anterior parts of the corpus callosum also show higher activation during AVHs. Lower FA was found in the cerebellar penducles.

Conclusion

To conclude, one complete neuroanatomical model for AVH perception is still missing. Nevertheless, this chapter on involved brain areas and white matter pathways has shown several regions that are interconnected and could therefore all play a role in the perception of AVHs.

To summarize, the functional brain regions activated during AVHs include the superior temporal lobe, anterior cingulate cortex, frontal motor and premotor areas and the temporal speech areas. Heschl's gyrus, the right middle temporal gyrus and the frontal gyrus also showed increased signals during AVHs. These regions are connected via white matter fiber tracts, especially the ones connecting the frontal, parietal and temporal brain regions were found to be abnormal in schizophrenia patients experiencing AVHs. These tracts include the uncinate fasciculus, the cingulum bindle and the arcuate fasciculus.

The secondary somatosensory cortex that was indicated to be active in AVH perception, is essential for perception of objects (Ungerleider & Haxby 1994). The primary perceptual cortex, also related to AVHs, processes the low-level aspects of a percept, for instance the tones of an auditory stimulus (van de Ven 2005). Non-sensory areas are also noted to be involved in AVH perception, for instance, strong activation in the anterior cingulate which is part of the emotional attention centre.

Specific for verbal hallucinations is the involvement of the inferior frontal gyrus that is part of the speech production area and the right inferior frontal gyrus which is its right sided homologue. Furthermore, the anterior cingulate, which is part of the monitoring area, is activated during AVHs. And Wernicke's area is involved, which is known to be the language reception area.

All these regions together form the widespread neuroanatomical basis of AVHs. Each region has its own specific functions in the healthy brain and therefore is likely to influence only an aspect of the hallucination. To understand about these influences, it is key to compare the regions that are involved in normal speech perception to the regions involved in AVHs. In this way we are able to clarify more how they are related to AVHs.

Comparison

The neuroimaging studies reviewed here show that there are several brain regions that are essential for speech perception and also play a role in the perception of AVHs. Nevertheless, there are also specific brain regions shown that do not have this double function and are only activated during AVHs. This comparison will give a clear overview of the resemblances and differences in brain activation between perceiving normal external speech and the perception of AVHs.

Resemblances

The perception of normal external speech and the perception of AVHs are organized in some of the same brain regions. As showed in this review, these two forms of "hearing voices" both involve Broca's and Wernicke's area. When listening to external speech, Wernicke's area acts as a speech recognition system in order to translate sounds into meaningful words. When experiencing AVHs, Wernicke's area also showed higher activation. Especially the STG and MTG were shown to be involved in AVH perception. Lesions in these two subdivisions are often related to auditory language comprehension disorders. MTG was soon associated with the experience of hallucinations (Lennox et al. 1999). A negative correlation was found between the severity of AVHs and the volume of the left anterior portion of the STG (Stephane et al. 2001). Broca's area showed an increased blood flow during AVHs in schizophrenia patients (McGuire et al. 1993) and is actively involved in speech perception and the motor processing of speech.

Another area that is activated during both forms of voice perception is the inferior parietal lobe (Brodmann's area 40). This area was identified as a region of increased activity during AVHs and is also notably involved in speech processing (Binder et al. 1997). The inferior parietal lobe is known to be involved in the interpretation of sensory information and the perception of emotions (Radua et al. 2009).

Furthermore, activation in the right middle temporal gyrus has been shown to be associated with AVHs (Benson et al. 2001). This region is activated in several different tasks. For instance, it is involved in word processing when subjects had to actively listen to words and place them in a specific context (Binder et al. 1996). In addition, the right middle temporal gyrus also showed activation when familiar faces are presented (Phillips et al. 1998). This study suggested that it may have a role in the detection of familiar faces in addition to primary facial processing (Kanwisher et al. 1997)

Differences

Apart from the similar brain regions, there are several regions that are only activated during AVHs and do not respond or respond differently during normal external speech perception. One of these regions is the anterior cingulate cortex. Increased blood flow has been measured when patients with schizophrenia experienced AVHs compared to patients that did not experience AVHs (Cleghorn et al. 1992). In healthy subjects, the anterior cingulate cortex is associated with reward anticipation and empathy (Decety & Jackson, 2004) and in the modulation of emotional responses to the ACC (Bush et al. 2000).

Additionally, reduced white matter integrity has been shown in patients with schizophrenia. An abnormal white matter fractional anisotropy was shown to be present in both hemispheres and widespread, extending from the frontal to the occipital brain regions in patients with schizophrenia (Lim et al. 1999). A later study confirmed a fractional anisotropy reduction in the splenium of the corpus callosum of patients (Agartz et al. 2001).

Not only specific brain regions and pathways show differences in patients with schizophrenia, the lateralization of the involved regions is also changed. In healthy humans, the auditory centre has left hemispherical dominance. Schizophrenia patients show activation in the auditory area's of both hemispheres, the right temporal cortex is more active than its left homologue when patients are experiencing AVHs (Shergill et al. 2000). In addition, the right inferior frontal gyrus is activated during AVHs (Sommer et al. 2008), which is the right hemisphere homologue of Broca's area. Activation in the right inferior frontal gyrus has also been found in a study on language lateralization in schizophrenia patients compared to non-pshychotic subjects with AVHs (Diederen et al 2010). This makes it unclear whether activation in the right hemisphere language areas is related to AVH perception. Nevertheless, the right hemisphere is generally related to the understanding of emotional prosody (George et al. 1996), and is referred to as the “emotional brain”. Therefore, any influence of right hemispherical brain regions on AVHs could be the cause of the emotional content of the voices.

Related to the models

Because the grey matter regions that are active during AVHs are comparable to those active during normal speech perception, it is conceivable that AVHs are perceived similar to external voices. Nevertheless, their origin is harder to determine exactly from the DTI and fMRI studies. The possible cognitive models that have been proposed in this thesis were a relation of inner speech with AVHs and the involvement of memory in AVHs. The inner speech model states that AVHs are a result from “thinking in voices” and that these voices are misinterpreted as external. The memory model describes the origin of AVHs as ‘‘unintentional activation of memories’’ and presses that the inability to inhibit memories could be a plausible cause. The deactivation of the parahippocampal gyrus prior to AVHs (Diederen et al. 2010) supports the theory that memory is involved in AVHs on some level.

The knowledge gained from this thesis makes it plausible that AVHs are a combination of inner speech and memories. This seems logical, because inner speech is usually related to subjects that are part of the memory of the individual. Since an exact neuroanatomical model for memory has yet to be found, no direct neurological combination between memories and AVHs can be found. The involvement of memory is predominantly based on the topics and familiarities of the voices. That inner speech forms the origin of AVHs can be learned from the resemblance in activated brain regions. Plus, it puts it a step further in the sense that the difference between healthy subjects and schizophrenia patients lies probably not in grey matter differences, but in the connectivity between the functional areas. Inner speech is likely to not be processed via the usual routes and is therefore misinterpreted by the divisions of Wernicke’s area as external voices.

Conclusion

In short, to me this comparison supports the inner speech model and gives direction to the cause of AVHs. The most evident underlying neurological mechanism for AVHs is the connectivity between the brain regions involved in inner speech and those in speech perception. The active functional areas are comparable between the perception of normal external speech and that of AVHs. Nevertheless, the connecting white matter pathways are not examined to the fullest. To date their influence in AVHs is rather unclear. This thesis suggests that these pathways that play a role in the misinterpretation of inner speech that causes AVHs. The role of memory is included in this conclusion, not neuroanatomically, but on accordance with the interpretation of the voices. Memories are included in inner speech which could explain why the voices of AVHs are often familiar and their topics often related to ongoing events.

General Conclusion

In many ways, AVHs are related to normal speech perception. Similar brain regions are involved as the left inferior temporal cortex and the left tempoparietal lobe. Nevertheless, the fact that there is no external stimulus during AVHs means that there has to be a deficit that produces voices that are perceived in a similar fashion as external voices. This thesis aimed to provide insight in the brain regions involved in both forms of voices in order to clarify the similarities and differences in active brain regions during normal speech perception and the perception of AVHs.

The voices heard in AVHs are often recognized by the patient, they are frequently family members or other well known voices. In addition, schizophrenia patients with AVHs showed a failure of intentional inhibition and often related to the ongoing activities of the person. This indicates an influence of memory and inner speech, as both of these have the same characteristics.

Whilst most functional brain regions that are activated during AVHs are similar to those active during external speech perception, the connectivity between these areas is altered in schizophrenia patients. These white matter fiber tracts influence how the functional brain regions interact and how signals are transported through the brain. Therefore, exactly these pathways are able to influence the processing of memories and inner speech. When they are malfunctioning, this will lead to the misinterpretation of the voices that are produced in healthy individuals as well, as inner speech and the process of recalling memories.

The emotional content of AVHs could be caused by the activation of the right tempoparietal lobe in schizophrenia patients. The right hemisphere is highly related to emotions and processing of feelings. In healthy individuals the right tempoparietal lobe in less active and has a lower influence on speech perception. This could create the difference between normal inner speech and the emotional voices heard during AVHs. Furthermore, the involvement of the inferior parietal lobe could also influence the emotional tones of AVHs.

Because this region is involved in the perception of emotions in the healthy brain, it could add to the emotional content of AVHs.

Lastly, the higher blood flow in Broca's area during AVHs could indicate they might be creating their own perceptions. This corresponds to the inner speech model, stating that they hear self created speech. Broca's area is actively involved in speech perception and the motor processing of speech. When it is more active, this could indicate that speech is being processed. When this processed speech is misinterpreted by faults in the connections with Broca's area, this might implicate that an AVH is self-generated speech.

Still, much stays unknown about the neuroanatomical causes of schizophrenia. The precise functions of regions involved could clarify their attribution to the hallucinations. Moreover, defining the exact anisotropy of the white matter pathways that connect the functional regions will illuminate differences between the healthy and the hallucinating brain. These neuropathways could be the underlying factor that enhances different activation patterns, influencing perception of memory and inner speech. Therefore, future research should focus on connectivity and search for the differences in white matter pathways between healthy subjects, patients with schizophrenia without AVHs and patients with AVHs. When research is able to track their influence, this will open the way to more confound knowledge on the origin of the perception of AVHs.

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