Brain activation during auditory hallucinations in the schizophrenia-patient.

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Abstract

Introduction: Auditory hallucinations are the most common positive symptoms in schizophrenia. The main goal of this review is exploring the activity of the brain during this phenomenon. **Material and method:** Searching Pubmed for activation studies with auditory hallucinations and schizophrenia yield 53 potential articles. After selecting 10 interesting remained. Using MRIcro the spots of maximal activation are marked. **Results:** All most all articles reported bilateral activation of the STG and MTG in the temporal lobe. Also activation of the inferior frontal lobe was found in both hemispheres, including Broca's area and his right homologue. Moreover activation of the cingulate gyrus and the parahippocampal gyrus was found, bilaterally. Preceding the occurrence of hallucination Diederen *et al.* showed an prominent decrease of activation in the left parahippocampal gyrus. **Dissussion:** these finding suggest activation of a cortical network of language areas involved in auditory hallucinations. There are multiple explanations for the function of this network in hallucinations. One is that auditory hallucinations are internally generated thoughts that are misrecognized as coming from an external source. Because there is a defect in the monitoring of self-generated inner speech. The other explanation is that auditory hallucinations are spontaneously retrieved verbal memories.

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Introduction

Schizophrenia is psychiatric disease hitting 0,5-1,5 percent of the population. It is characterized by a combination of multiple not-pathognomonic symptom that impair occupational and social functioning. These symptoms can be divided into two categories, positive and negative. The positive symptoms are due to a distortion of normal functions, like perception, language and thought processing, attention and self-monitoring. Resulting in hallucinations, disorganized speech and catatonia. Negative symptom arise when normal functions are diminished or lost. This includes deficits in the expression and intensity of emotions, the production of thought and speech and the imitation of goal-directed behaviour leading to affective flattening, alogia and avolition(First *et al.*,2007)

With 70% of the patients experiencing them, hallucinations are characteristic for schizophrenia(Sartorius *et al.*, 1986 from Copolove *et al.*,2003 and Plaze *et al.*,2006). Hallucination can arise from any sensory system, but auditory hallucinations are the most common(First *et al.*,2007). During auditory hallucinations patients perceive external speech in the absence of a stimulus(Sartorius *et al.*, 1986 from Plaze *et al.*,2006). Typical for schizophrenia patients is hearing two or more voices critically conversing the behaviour of the patient(First *et al.*,2007).

The neural substrate for auditory hallucinations is widely studied, but remains unknown. However involvement of the left temporal lobe it suggested. Penfield and Perot (1986) found that in epileptic patients, electrically stimulating the superior temporal gyrus(STG) results in auditory hallucinations (Penfield and Perot,1986 from Suzuki *et al.*,1992 and McGuire *et al.*,1993). The STG contains the primary and secondary auditory cortices, important for hearing and language processing. These are located in Brodmann's area (BA) 41/42 respectively the caudal part of 21/22. Moreover the left hemisphere contains the most important regions for the processing of language, like Wernicke's area and Broca's area. However nowadays the right hemisphere is also thought to be involved in language processing (Kandell *et al.*,2000;bear *et al.*,2007).

This review will discuss articles that explore the activity of the brain during auditory hallucinations in schizophrenia. The main goal is to investigate with brain regions are involved in the occurrence of auditory hallucinations. To achieve this Pubmed was searched down for imaging studies with schizophrenia and auditory hallucinations in the title. Article reporting changes in activation were selected and analyzed, hoping to get a clear picture of the brain areas related to auditory hallucinations.

Material and Method

Articles

To find activation studies with schizophrenia and auditory hallucinations in the title, the following search, developed by Ruud Kortekaas, was entered in Pubmed:

schizophren* [ti] (hallucinat* [ti] OR percepts [ti]) (("(15)O-labeled water" OR "(15)O-labelled water" OR "[(15)O] H(2)O" OR "[(15)O]-H(2)O" OR "[15(O)]H2O" OR " [15O]H2O" OR "[15O]-H2O" OR "[15O]-H2O" OR "[15O]water" OR " [H2(15)O]" OR "15O water" OR "15O-H2O" OR "15O-labeled water" OR "15O-labelled water" OR "15O-water" OR "15-O-water" OR "H(2)(15)O" OR "H2 15O" OR "H2 15O" OR "H2(15)O" OR "H2(15)O15O" OR "H2O" OR "O15 water" OR "O-15-labeled water" OR "O-15-labelled water" OR "oxygen 15-labeled water" OR "oxygen-15 water" OR "[O-15]water") OR "brain activation" OR "brain perfusion" OR "cerebral perfusion" OR "cerebral blood flow" OR rCBF OR fMRI OR "functional MRI" OR "functional magnetic resonance imaging" OR BOLD OR "blood oxygen level dependent"). 4 quoted phrases were not found.

Pubmed came up with 53 hits, these included activation as well as volumetric studies. After selecting, 10 articles were used to base this review on. The first selecting was based on language and availability. Only full articles written in English were used. These articles had to be freely available via Pubmed or ruglinks. Next the titles and abstracts were read. Based on this, potential articles were selected. These articles were scanned and only activation articles were analyzed. Based on the materials and methods only articles with methods reported by two or more articles were used, so that comparisons could be made. Furthermore reviews were excluded.

Coordinates

All reported coordinates were checked with Talairachclient(Lancster *et al.*,1997;2000). ° indicates that the area is located in a different BA in the same lobe. * indicates that it is located in a different lobe. Talairachclient was also used to locate the BA when the Talairach coordinates were given. If MNI coordinates where given, these were first converted to Talairach coordinates, using the MNI to Talairach converter from Yale(Rajeevan and Papademetris).

Visual representation

Different methods to represent the coordinates in a visual manner were explored. The first methods was an meta-analysis developed by Sergi Costafreda. Unfortunately this method required that the studies used a similar design. This was not the case, so this method could not be used.

An alternative was to draw point in the Brodmann's areas atlas. Doing this by hand is inaccurate. So software had to be found that draws a point for you, after entering the coordinates. It turned out that MRIcroN could be used for this purpose. However MRIcroN is not familiar with Talairach coordinates. Since most articles give these coordinates, using MRIcron is not practical. A program where you can enter Talairach coordinates is MRIcro. Hence this program is used to visual represent the coordinates of maximal activation given by the articles. After entering the coordinats MRIcro determents the location in the brain and a spot could be drawn there using the regions of interest tool box. These spots are marked in the sagittal plane of template ch2bet. Not every slice is used, only the ones one between -60 and 60 and ending on 5 and o. So steps of 5 mm are made between the slices.. Differences is radius of the marked are random and therefore do not represent anything. This approach resulted in the visual representation showed in appendix A.

Results

The left hemisphere

Temporal lobe

Before and after dissolving auditory hallucinations

Almost all the studies find an activation somewhere in the temporal lobe. Because the most important areas for language and hearing are located in the superior temporal gyrus, this is the part most studied. Suzuki *et al*. were one of the first to examined regional cerebral blood flow in schizophrenia patient in hallucinating and hallucination free periods. They showed an increase in the blood flow of the left STG during hallucinating periods. They did not report coordinates or brodmann's areas, but according to them this area roughly corresponds with the auditory association area. After treatment with a neurolepticum the auditory hallucinations dissolve and the blood flow normalized. There was an third scan made of patient 5 because he had a psychotic relapse, this scan replicated the increase in blood flow in the left STG(Suzuki *et al*.,1993). McGuire *et al*. used the same design, except the patients remained on stable doses of medication between the scans. Unlike Suzuki *et al*. they found no significant differences in the temporal lobe between the hallucinating and non hallucinating state(McGuire *et al*.,1993).

Indicating onset and offset hallucinations

The button-pressing paradigm is a commonly used way to let the patient report the experience of hallucinations during the scan. The patient has to press a button at the onset of the hallucination and release the button or press a different button at the offset. This way multiple studies reported an increase in activation in the STG. Lennox *et al*. showed an increase in the left STG corresponding with BA 22(-56,-52,28*) in one patient and to BA 42(-34,16,-22°) in patient 2. Patient 2 also showed an increased blood flow in the middle temporal gyrus(MTG), BA 39(-36,-80,26*)(lennox *et al*.,2000). Copolove *et al*. used the same method, but scanned the patients with a PET-scanner. They also found activation in the left STG, in the posterior part, corresponding to BA 22(-54,-42,12)(Copolove *et al*.,2003).

Shergill *et al*. used the button pressing method to validate a new paradigm, the random sampling method. In this new method patients did not have to make any movement, because they report the occurrence of auditory hallucinations afterwards. The fMRI begins to scan at random intervals, the noise generated by the scanner when it starts scanning, served as a auditory cue. After the scan patients have to describe what they were experiencing in the few seconds before the cue. Because there is a time delay of 3 to 5 seconds between the neural activity and the maximum BOLD signal, the fMRI image shows the activity that was occurring a few seconds before the onset of the cue, so when there was no auditory input. Only the button-pressing method found activation in the left STG, corresponding to BA 22(-55,-8,4).In this paradigm they also found an increased activation in the middle temporal gyrus, corresponding to BA 21(-52,-8,-13 and -61,-33,-7). With the random-sampling method, the only change found in the left temporal lobe, was located in the middle temporal gyrus, BA 39(-49,-67,4*)(Shergill *et al*.,2000a).

In a study done by Diederen and her group, patients had to squeeze a balloon to indicate the on- and offset of the hallucinations. To correct for the brain activity related to the balloon squeezing the healthy controls were also instructed to squeeze a balloon 10 times at random intervals. Comparing the brain activity of the two groups revealed an increased activity in the left STG(MNI:-48,0,0 and -56,24,16)(Diederen *et al*.,2003). This study did not mention in which Brodmann's area the activated spot was located, but entering the given Montreal Neurological Institute coordinates in the MNI to Talairach Coordinate Converter gave the corresponding Talairach coordinates(-46,-2,3,and -54,22,16). These were, according to TalairachClient located in the left insula, with BA 13 as nearest gray matter and in the left precentral gyrus, BA 6. Diedren also showed activity in the middle temporal gyrys(MNI:-48,-64,12)(Diederen *et al*.,2003). Conversion gives back the Talairach coordinates: -47,-63,15. This spot is indeed located in the MTG, with BA 19 as nearest gray matter.

This study also explored the activity in the brain preceding auditory hallucinations to investigate which areas are responsible for the initiation. Analyzing the 6 seconds before the onset revealed a

pattern of deactivation in the brain, also in the left STG(MNI:-44,16,-24,Talairach:-43,11,-18)(Diederen *et al*.,2003). TalairachClient located this deactivation this spot in BA 38 of the STG.

External speech

An alternative approach is to investigate the brain activity during language tasks. Originally, the use of cognitive activation paradigm was intended to reduce the variation between the measurements. Nowadays these paradigms are also used to challenge specific neuronal systems and reveal abnormalities related to specific symptoms, like hallucinations(Plaze *et al*.,2006). Woodruff *et al*. investigated the responsiveness to external speech in schizophrenic patients with and without a history of auditory hallucinations, in comparison with healthy volunteers. The combined groups of schizophrenic patients with and without a history of hallucinations showed less activity in the left STG, BA 22(-52,-17,4°), compared with healthy controls(Woodruff *et al*.,1997). They also showed less activation in the auditory association area, BA 42(-61,-17,9). Comparing the response to external speech in patients when they experience hallucinations with hallucination free periods the left STG, BA 22(-58,-6,4) was less activated during hallucinations.(Woodruff *et al*.,1997).

Plaze *et al*. also used speech as an external stimuli, except they used short sentences instead of multi-speech babble. They showed a negative correlation between the severity of the hallucinations and the activity in the posterior part of the left STG, BA 22(-48,-28,12°). The more severe the hallucinations, the lower the activity of the left STG in response to external speech. According to Plaze *et al* this posterior part of the left STG corresponds to Wernicke's area (Plaze *et al*.,2006).

Inner speech and auditory verbal imagery

Another cognitive activation paradigm is Auditory Verbal Imagery (AVI). This studies the generation and monitoring of inner speech. Psychological models propose that auditory hallucinations arise when internally generated verbal thought are misrecognised as coming from an external source(Frith *et al*.,1987 from Mcguire *et al*.,1996). The baseline condition in this paradigm consists of silently repeating a presented word. In the inner speech condition the patient has to put the presented word after a learned sentence and repeat this without saying it . The AVI condition is the same as the inner speech condition except now the subject has to imagine the same sentence being spoken to them in their own or a different voice. This paradigm was used both by shergill *et al*. and Mcguire *et al*., they compared the brain activity of hallucinating patients who were not experiencing hallucinations at the time of the scan and healthy people. Both studies showed that there were no significant changes during the inner speech condition(Shergill *et al*.,2000b;McGuire *et al*.,1996). During AVI McGuire *et al*. showed an reduced activation of the left middle temporal gyrus, BA 21(-60,-34,0 icw controls;-56,-30,0 icw non hallucinators)in the hallucinators in comparision with both the controls and non

hallucinators. This difference was due to an increase relative to baseline in the controls and non hallucinators and an decrease relative to baseline in the hallucinating group(McGuire *et al*.,1996).

Conclusions temporal

Most of the studies reported an increased activation of BA 22 in the left STG during hallucinations. BA 42 is also reported to be involved in the generation of auditory hallucinations. The reported areas involved in hallucinations were auditory association areas, none of the experiment showed involvement of the primary auditory cortex, BA 41.

The activation of the left STG, including Wernicke's area, is related to the understanding and interpretation of the hallucination(Copolove *et al*.,2003;Plaze *et al*.,2006).

To explain the lowered activity of the STG in respons to external speech during hallucinations Woodruff *et al* and Plaze *et al* postulated that there is a competition between external stimuli and auditory hallucinations for processing in the STG. A possibility is that the STG is occupies by the processing of the hallucination, leaving less resources for the processing of external stimuli. Moreover the activity of the STG is negatively correlated with the severity of the hallucinations, this support the competition hypothesis(Woodruff *et al*.,1997;Plaze *et al*.,2006).

McGuire *et al*. come up with another explanation. In non hallucinating people, the MTG is activated during the perception of inner speech. Because there was only a difference in this region during the AVI, hallucinations are likely to emerge from a deficit in a mechanism specific to the monitoring of self-generated inner speech. For inner speech it is necessary to generate and silently articulate word, but it does not require a lot of monitoring. Imagining someone talking to you also involves the generation of inner speech, but also requires monitoring of this speech(McGuire *et al*.,1996 from McGuire *et al*.,1996 and McGuire *et al*., 1995 from Shergill *et al*.,2000). Interpreting a study done by Creutzfeldt *et al*.(1989 from McGuire *et al*.,1996) McGuire *et al*. states that the MTG is activated by the generation of speech and to a lesser extend to external speech. This suggests that the activation of the left MTG is related to the intention to speech, rather that hearing. Other areas involved in to generation of speech, may report to the MTG that the speech is internally generated. The reduced activity of the MTG found during AVI in hallucinating schizophrenia patients can come from less input from other region. So the MTG does not get the information that the speech is self-generated, but still hears it. This defect in communication between areas involved in the generation of speech and areas involved in the perceiving of inner speech could lead to a misrecognition of the internally generated speech, experiencing it as coming from an external source (McGuire *et al*.,1996).

Frontal lobe

Before and after dissolving auditory hallucinations

McGuire *et al*. showed that there was an significant increase in blood flow in the left inferior frontal cortex, corresponding to broca's area, during hallucinations(McGuire *et al*.,1993). However Shergill *et al* found no changes in the left frontal lobe(Shergill *et al*.,2000a).

Indicating onset and offset hallucinations

Comparing the activity in periods with and without hallucinations, Lennox *et al* reported an increased activation of the middle frontal gyrus(-57,15,24)(Lennox *et al*.,2000). In one patient this increased activity was located in the inferior frontal gyrus, corresponding to BA 46(-54,21,21°). In the other patient the activation was also found in BA 46, but in the left middle frontal gyrus(-22,42,36°)(Lennox *et al*.,2000).

The button-pressing method as well as the random-sampling method found an increased activation in the left inferior frontal gyrus, BA 44(-35,8,31° respectively -43,8,9°) (Shergill *et al*.,2000a). They also reported activation in BA 9 in the middle frontal gyrus, using the button pressing method(-35,6,37 and -14,39,31)(Shergill *et al*.,2000a).

Using balloon squeezing to indicate the occurrence of hallucinations Diederen *et al*. reported an increased activation in the left inferior frontal gyrus, including Broca's area(MNI:-48,4,8;Talairach: -46,1,10). TalairachClient revealed that these coordinates correspond to BA 44. They also reported activity in the superior frontal gyrus(MNI: -28,-12,68, Talairach:-28,-8,61), this corresponds to BA 6. In the 6 seconds preceding the occurrence of a hallucination the middle frontal gyrus shows a decreased activity(MNI -36,16,28, Talairach:-35,15,27)(Diederen *et al*.,2010). These coordinates, after converting them into Talairach coordinates, are located in BA 9.

Inner speech and auditory verbal imagery

The auditory verbal imagery paradigm reveals activation in the inferior frontal gyrus in the inner speech condition as well as in the auditory imagery conditions. However in both conditions the activation in hallucinators did not differ from the activation pattern in the control groups(McGuire *et al*.,1996;Shergill *et al*.,2000b) On the contrary hallucinators displayed reduced activity in the left medial prefrontal cortex, corresponding to BA 8(-12,44,36) in the AVI condition. This difference arise from a reduced activity in the hallucinators and a increased activity in the controls only, relative to the baseline condition(McGuire *et al*.,1996).

Conclusions frontal lobe

Increased activation was seen in BA 44, which is part of Broca's area and in BA 9. Because a previous case study done by Lennox *et al* in 1999 shows that the frontal activation comes after the activation of the temporal cortex, they suggest that the activation in the frontal lobe is related to the emotional response to the hallucination or to the recall of verbal memories. According to lennox *et al*. a studies done by Fletcher *et al*. showed an increased activation during verbal recall in the frontal lobe(Fletcher *et al*.,1995;1998 from Lennox *et al*.,2000).

However according to McGuire *et al*. Broca's area is more likely to be involved in the generation of inner speech, independent of the occurrence of hallucinations. Broca's area is found to be activated in normal subject in response to the production of inner speech(Paulesu *et al*.,1993 from McGuire *et al*.,1993 and Wise *et al*.,1991;Paulesu *et al*.,1993;Price *et al*.,1994 and McGuire *et al*.,1996 from McGuire *et al*.,1996). It probably correspond to the silent articulation of inner speech, explaining the activation of the inferior frontal gyrus in all three groups during both the inner speech and the AVI conditions(Smith *et al*., 1992;McGuire *et al*., 1996 from McGuire *et al*.,1996). The decrease in activity reported in hallucinators relative to baseline condition was not seen in non hallucinators, however it did not differ significantly from non hallucinators. Therefore one cannot be sure that this decrease is related to auditory hallucinations or that is a common feature of schizophrenia.

Cingulate cortex

Before and after dissolving auditory hallucinations

Suzuki *et al*. showed an increased blood flow in the anterior cingulate cortex of two patients. When the hallucinations were dissolved, this was only normalize in one patient. In the other patient the increase blood flow persisted and was also showed in the third scan of this patient when this patient had a psychotic relapse (Suzuki *et al*.,1992).However these observed changes were not significant. McGuire *et al*. reported an strong trend, p=0.06 for increased blood flow in the left anterior cingulate cortex during hallucinations(McGuire *et al*.,1993).

Indicating onset and offset hallucinations

In both the button pressing and random sampling method Shergill *et al* reported an significant increase in the activation of the anterior cingulate gyrus. In the random sampling method this corresponded to BA 32(-23,19,26*). The button pressing method showed activation in BA 24(-20,-19,37 and -20,22,20*)(Shergill *et al*.,2000a).

Shergill *et al*. (2000a) also reported an increase in the posterior part of the cingulate gyrus, BA 29(-6,-39,20). This was however, only found in the button pressing paradigm. Using the button pressing

paradigm, Copolove *et al*. also reported an significant increased activation in the left posterior cingulate, BA 29(-2,-54,12)(Copolove *et al.*,2003).

Inner speech and auditory verbal imagery

During the inner speech McGuire *et al*. showed an activation of the anterior cingulate cortex in the schizophrenia patient with and without hallucinations. However in the control group there was a decrease in the posterior anterior cortex during the inner speech conditions. The AVI was associated with an decreased activity in the posterior cingulate gyrus in the controls and an increased activity in the hallucinators. However there were no significant difference between any of the groups in this region in both conditions(McGuire *et al.*,1996).

Conclusions cingulate cortex

A few experiment show a (trend for) activation in the anterior and posterior cingulate cortex during hallucinations. Interpreting other studies, done to investigate the function of the cingulate gyrus, Plaze *et al*. postulate that activation in this region differs for stimuli that are critical to self or non self (Northoff and Bermpohl, 2004 from Plaze *et al* 2006). Therefore they suggesting that activity in the anterior cingulate cortex may be related to whether the speech is addresses to self or non self.

McGuire *et al* relates the activity in the anterior cingulate cortex to the selection and initiation of movement, including speech, instead of an activation specific to language(Petersen *et al*.,1988, Frith *et al*.,1991,Friston *et al*.,1993 from McGuire *et al*.,1993). As activation in this region is related to movement this can also be induced by the movements used to indicate the occurrence of hallucinations, like pressing a button.

Precentral gyrus/supplementary motor area

Indicating onset and offset hallucinations

Using the button pressing method, Shergill *et al*. reported activity in the primary motor cortex in the precentral gyrus, BA 4(-46,-8,31° and -40,-8,48°)(Shergill *et al*.,2000a). Diederen *et al*. also found activity in the precentral gyrus(MNI:-36,-16,64 and -48,0,16)(Diederen *et al*.,2010). Converting these into Talairach coordinates(-36,-12,58 and -46,-1,17)located these spots to the BA 6 respectively BA44.

Inner speech and auditory verbal imagery

In the AVI paradigm activation in the precentral gyrus was found in the hallucinating patients, during both the inner speech and the AVI conditions. This activation however did not differ from that in controls.(Shergill *et al*.,2000b). On the other hand McGuire *et al*. found a reduced activity of the

rostral supplementary motor area, BA 6 in the hallucinating patients compared to both the controls(6,12,64) and the non hallucinators(-8,8,56). When compared to baseline hallucinators showed an decrease in activity, while nonhallucinators and controls showed an increase.

Conclusions Precentral gyrus/suppelmentary motor area

The primary motor cortex and the supplementary motor area are normally activated when voluntary movement are made, including speech(Roa *et al*.,1996 from Shergill *et al*.,2000a and Goldberg,1985 from McGuire *et al*.,1996). So the paradigms used to indicate the occurrence of the hallucinations could explain the activation in this area.

However according to the study of McGuire *et al*. there was a marked difference between the hallucinators and the control groups when they imagined speech. In healthy patients this area is activated when they imagine speech(McGuire *et al*.,1996;McGuire *et al*.,1996 and Shergill *et al*.,*in press* from Shergill *et al*.,2000a). Activation of the SMA may account for the recognition of the inner speech as self generated, even if all the other characteristics of the speech are different from the own voice(McGuire *et al*.,1996). Therefore Shergill *et al* and Mcguire *et al* propose another explanation for the reduced activity in the SMA of the hallucinators. Damage to this area results in the alien limb syndrome. In this syndrome the patient losses awareness that the movements of this limb are self-generated and assign the movement to someone else(Gasquoine, 1993 from Shergill *et al*.,2000a and from McGuire *et al*.,1996). The reduced activity seen in hallucinating patients might be related to a lack of awareness that the generated movement, that is in this case speech, is self generated. Therefore the hallucinators experiencing the speech as coming from an external source (McGuire *et al*.,1995 from Shergill *et al*.,2000a;McGuire *et al*.,1996).

Parietal lobe

Indicating onset and offset hallucinations

3 studies reported an increased activation in the left inferior parietal lobe. Comparing the activity during hallucinations and hallucinations free periods, lennox *et al*.,(2000) found an increase activity in BA 39(-51,-27,30*). Only in the button pressing method, Shergill *et al*.(2000a) showed an increased activity in the inferior parietal gyrus, BA 40(-46,-28,26). Diederen *et al*.(2010) also found activation in the inferior parietal lobule(MNI:-52,-20,44;Talairach:-51,-18,41). TalairachClient located this to BA 3 in the postcentral gyrus of the parietal lobe. They also showed activity in the postcentral gyrus(MNI:–52, –20, 44 and –56, –20, 16). Converting this into Talairach coordinates(-51,-18,41 and -53,-20,17) located these to BA 3 and BA 40 in the postcentral gyrus.

Conclusions parietal lobe

None of the articles discuss an explanation for the increased activity in the parietal lobe or the postcentral gyrus. BA 3 in the postcentral gyrus is involved in somatosensoric cortex, involved in the experiences of touch(Bear *et al*.,2007). However this is unlikely to be related to the hallucinations, since these are auditory experiences. BA 39, mentions by Lennox *et al*., is involved in the processing of language(Bear *et al*.,2007). This could be related to the processing of auditory hallucinations. Nevertheless Lennox *et al*. do not discuss any involvement of this brain area.

The right hemisphere

Temporal lobe

Indicating onset and offset auditory hallucinations

Comparing hallucination and hallucination free periods, Lenox *et al*. reported a significant activation of the right temporal lobe(45,-21,0) in all patients. In three patients this activation was located in the superior temporal lobe, BA 42/22(70,-39,6 and 46,-28,16°) in two and in one patient in BA 22 only(51,15,-3*). The last patient also showed an increase in BA 22, but in the part that is located in the middle temporal gyrus, (27,-63,21°)(Lennox *et al*.,2000).

Shergill *et al* showed an significant activation in the right superior gyrus, in both the random sampling method and the button pressing method. During the button pressing this activation was located in BA 22(49,-25,4°) as well as in BA 42(35,-25,20*). BA 22 was also activated in the random sampling method (61,-22,4). This method showed additional activity in the MTG, corresponding to BA 21(58,-33,-2)(Shergill *et al*.,2000a).

Increase activation of the STG(MNI: 44,-4, -8 and 64,-44,16) and the MTG(MNI:60,-48,0) was also found by Diederen *et al*.(2010). Converting these coordinates gives back the following Talairach coordinates, 41,-6,-2;62,-43,18 and 58,-48,5. Entering these into TalairachClient locates the first spot to BA 13 and the second two, to BA 22, in respectively the superior and middle temporal gyrus.

Copolove *et al* reported as only one, an increased activation in BA 37 in the posterior part of the MTG, (50,-52,-8°) (Copolove *et al*.,2003).

Other studies

In the study of Woodruff *et al* schizophrenia patient showed significantly more activation compared to healthy controls in the MTG, BA 21(61,-8,-2) in response to external speech. When comparing

hallucinating and hallucinating free periods, external speech activated the MTG, BA21(61,-6,4°) significantly less during the hallucinations(Woodruff *et al*.,1997).

Shergill *et al* reported an increased activation of the MTG and STG(43,-10,-11, and 43,-31, 0) in patients during the AVI condition(Shergill *et al*.,2000b). TalairachClient located these areas to BA 21 and BA 41. McGuire *et al*.(1996) found also an trend for increased activation of the STG, BA 24 in hallucinators during AVI, compared to both non hallucinators(54,-32,16°) and controls(46,-28,16°). In hallucinators this area was activated relative to baseline, while the other two control groups showed no change in this region(McGuire *et al*.,1996).

Conclusions temporal lobe

Researchers showed increased activity in the MTG and STG during hallucinations. This was mostly located in BA 22 and 42 in the methods were patients had to indicate the occurrence of an hallucination. This activity is proposed to be relayed to the prosodic and emotional processing of the hallucination. Auditory hallucinations are usually hostile in contest and tone(Coplove *et al*.,2003;Woodruff *et al*.,1997;Shergill *et al*.,2000a). In healthy subjects this emotional processing activates the right temporal lobe(Pell *et al*.,1999 from Copolove *et al*.,2003 and George *et al*.,1996 from Shergill *et al*.,2000a)

Woodruff also postulates that the lower response to external stimuli during hallucinations can be due to a competition for processing between the hallucination and the external stimuli. Paying attention to an unexpected external stimulus leads to a greater response of the right temporal lobe(Woodruff *et al*.,1996; McGuire *et al*.,1996 and Levanen *et al*.,1996 from Woodruff *et al*.,1997). Because auditory hallucinations are mostly unexpected the reduced activity to external speech can be because the right STG is also occupied by the auditory hallucination(Woodruff *et al*.,1997).

According to McGuire *et al*. this increase activation of the STG is related to the production of internal speech. This region is normally activated when subject hear externally generated speech(Wise *et al*.,1991 and Price *et al*.,1996 from McGuire *et al*.,1996). However the hallucinating patients also showed an increased activity in this region during auditory verbal imagery. This may be related to a defect in communication between areas that inform the STG that the speech is self-generated. The STG does not receive input that the verbal stimuli are internally generated, resulting in locating its origin to an external source(McGuire *et al*.,1996).

Frontal lobe

Indicating onset and offset auditory hallucinations

Using the button pressing paradigm, Lennox *et al* revealed activation of the frontal lobe in all four patients. In three patients this activation was located in the inferior frontal gyrus, BA 47 (48,36,-14;18,-42,21° and 45,39,-18°). One patient only showed activity in the middle frontal lobe BA 46(22,42,36°) and in one patient activation in the middle frontal gyrus was additional to the activation in the inferior frontal gyrus, BA 46(56,39,14). Copolove *et al*.(2003) reported activity in Broca's homologue in the inferior frontal gyrus, BA 45/46(48,22,20).

Comparing the activity in the button pressing method and the random sampling method Shergill *et al* indicated activity in the frontal lobe in both paradigms. In the button pressing method auditory hallucinations were correlated with activation in BA 10(12,50,15) and BA9(23 50 26°). The random sampling method showed activation in BA 8(29,19,42) and BA 46/10(38,39,20)(Shergill *et al*.,2000a)

Diedren *et al*.(2010) found activation all over the frontal lobe, in the inferior(MNI:44,16,12;Talairach:42,14,14), middle(MNI:40,-8,60 and 44,20,36; Talairach:41,-4,55 and 43,21,35)), and superior frontal gyrus(MNI:28,48,20) and in the precentral gyrus(MNI:56,8,32). Broca's homologue was one of these region. TalairachClient located the region in the inferior gyrus to BA 13, in the middle frontal gyrus to BA 6 and BA 9 in the precentral gyrus. The activations in the superior(27,47,19) and precentral gyrus(54,8,32) were located in BA 10 respectively BA 9. They also found an decrease of the activity in the inferior frontal gyrus(MNI:52,36,8 and 36,32,4;Talairach: 50,35,10 and 43,29,6) preceding the onset of hallucinations. This decreases were located in the BA 46 and BA 13, according to TalairachClient.

Conclusion frontal lobe

Frontal activation changes were found during and preceding hallucinations. During hallucination an increased activation was found in multiple regions, including the homologue of Broca's area(BA 45/46). Preceding hallucinations the activity in BA 46 and 13 decreased. None of the researches discuss the activation in the right frontal lobe, except Lennox. According to them the right frontal lobe can be activated due to an emotional response to hallucinations or to recalling of verbal memory. Research from Fletcher *et al*(1995,1998 from lennox *et al*.,2000) associates activity in the frontal region to verbal memory recall. This leads to the idea that spontaneously recalling verbal memories is responsible for auditory hallucinations.

Cingulate cortex

Indicating onset and offset auditory hallucinations

Three studies reported an increased activity in the anterior part of the right cingulate cortex. Lennox *et al*.showed activation in this region in one patient, BA 32(8,24,28)(Lennox *et al*.,2000). Using the random sampling method, Shergill *et al* also found an increased activity in BA 32 (6,25,37)(Shergill *et al*.,2000a). Copolove *et al*. also reported activation in the anterior cingulate cortex, but in BA 24.

Conclusions cingulate cortex

Referring to an article from Lee *et al*, Copolove links activity in the right anterior cingulate to an increased attention. Activity in the right anterior cingulate is found in tasks which asks a lot of attention(Lee *et al*.,1998 from Copolove *et al*.,2003). Therefore Copolove *et al*. postulate that the activity in the right anterior cingulate gyrus is related to the attention that the patients give to the experiencing of hallucinations, instead of to the hallucination itself(Copolove *et al*.,2003)

Parahippocampal gyrus

Indicating onset and offset auditory hallucinations

Some studies also reported activation in the left, right or bilateral parahippocampal gyrus. Lennox showed activation in the right parahippocampal gyrus in one patient (9,-39,3). Shergill *et al*. showed in both methods, the random sampling method and the button pressing method, activation of the parahippocampal gyrus. In the random sampling method this activation was located in the left parahippocampal gyrus, BA 35/36(-23,-39,-7). Using the button pressing method activation was found in the left parahippocampal gyrus, BA 35/36(-26,-33,-13), as well as in the parahippocampal gyrus of the right hemisphere BA 30(12,-36,4*)(Shergill *et al*.,2000a). Copolove *et al*.(2003) also showed activation in the left parahippocampal gyrus, using a button pressing paradigm(-22,-32,-4), Diederen *et al*. found the most prominent decrease of activity preceding hallucinations in the left parahippocampal gyrus(MNI:-36,-24,-16 and -24,-28,-12). TalairachClient revealed that this coordinates(-34,-25,-10 and -23,-29,-6) are located in the hippocampus and in BA 27 of the parahippocampal gyrus.

Conclusion Parahippocampal gyrus

There are two explanation for the activation of the parahippocampal gyrus. Shergill *et al*. found an increase of the left parahippocampal gyrus, but when normal volunteers imagine non-self speech this region is not activated. Interpreting other studies Shergill *et al*. state that the left parahippocampal gyrus is activated when people encounter unexpected stimuli(Stern *et al*.,1996 from Shergill *et al*.,2000a). Previous studies suggest that it is part of a network involved in self-monitoring(Liddle *et*

al.,1992 from Shergill *et al*.,2000a). According to Shergill *et al*. this suggests that the activation in the left parahippocampal gyrus is a neural response to the internally generated speech, which the patients are unaware they generated (Shergill *et al*.,2000a).

Copolove *et al* and Diederen *et al*. give another explanation for the activity of the parahippocampal gyrus. They postulated that it is related to the retrieval of verbal memory (Coplove *et al*,2003 and Diederen *et al*.,2010). The parahippocampal gyrus plays a central role in memory retrieval(Cabeza and Nyberg, 2000 from Copolove *et al*.,2003). It receives information from the association cortices and passes this on to the hippocampus where it is recognized. This information is given back to the parahippocampus and redistributed to the association cortices(Van Hoesen,1982, Eichenbaum *et al*,1996,Eichenbaum,2000 and Eichenbaum *et al*.,2007 from Diederen *et al*.,2010). The decreased activation of the parahippocampal gyrus preceding hallucinations, can lead to an activation of the auditory cortex, resulting in a spontaneous retrieval of memories. These memories can be perceived as auditory hallucinations(Diederen at al.,2010).

Discussion

Although there is variation between the reported regions involved in auditory hallucinations, bilateral activity in the temporal and frontal lobes, as well as the cingulate gyrus and the parahippocampal gyrus, has been found in these articles. These variation can be caused by the different paradigms used to investigated the occurrence of hallucinations. A commonly used method is to let patients signal the occurrence of hallucinations. However to do this patients need to make some kind of movement. Multiple studies, like the one from Diederen, instruct the control groups to make the same movement to control for this variation. However not all the studies control for movement. Another variable is the scanner, used to make the images. Both fMRI and SPECT or PET scanners are used. The PET scanner does not generated a lot of noise, however because it uses radioisotopes, the number of scans that can be safely made in each patient is limited(Shergill *et al*.,2000a). On the contrary fMRI allows you to make more images without harming the patient. However it is noisy and can therefore activate the auditory cortex on its own. This has to be taken into account when design the paradigm. Also the fact that the patients are taking anti-psychotic medicines at the time of the scan can induce variation. Because patients take different kind and different doses of drugs.

Despite these variations in research designs most studies find activation in similar regions. Activation is found in the frontal and temporal lobe of both hemispheres as well as in the cingulate gurus and

the parahippocampal gyrus, bilaterally. Moreover an decrease in activity in the left parahippocampal gyrus was observed. According to McGuire *et al*. these regions are anatomically interconnected(Pandya From McGuire *et al*.,1993), suggesting that an increased activation in a network of cortical language areas is involved in the generation of auditory hallucinations(McGuire *et al*.,1993). Indeed looking at the reported activation in these articles suggests that activation is primarily found in language association areas. None of the articles reported activity in the primary auditory cortex, located in BA 41 in the left STG.

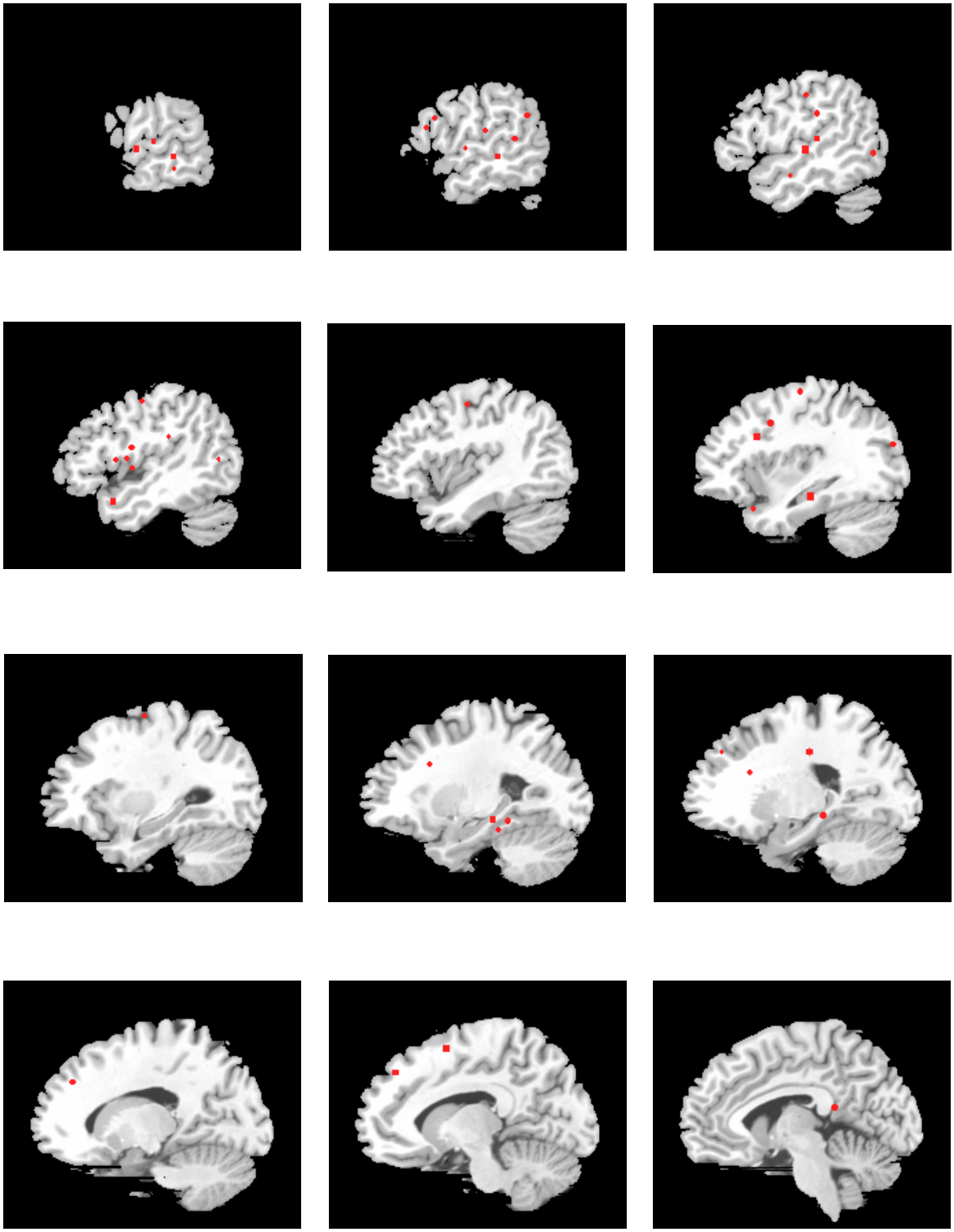
There are multiple explanation for the function of this network. McGuire *et al* and Shergill *et al* postulate a theory about misrecognition of self-generated speech, leading to the perception of internally generated thoughts as coming from an external source. This misrecognition is probably due to a communication defect in the self-monitoring of internal generated speech in hallucinating patients(McGuire *et al*.,1996;Shergill *et al*, 200a;200b).

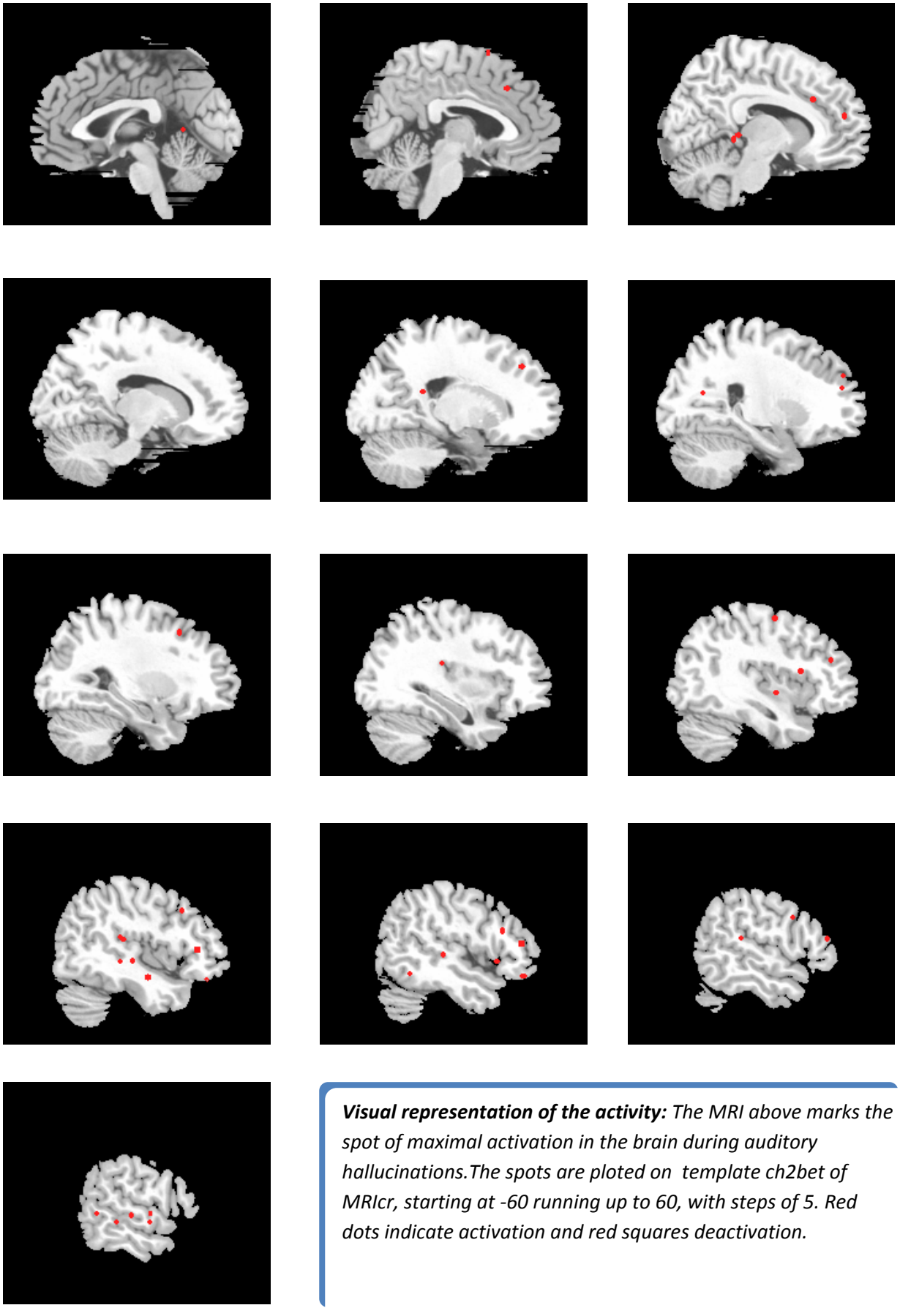
However this network, especially the parahippocampal gyrus, is also suggested to be involved in the retrieval of memory. The other explanation, postulated by diederen *et al*., is that auditory hallucinations occur because of the spontaneous recall of verbal memories. The inactivation of the parahippocampal gyrus is also seen in memory retrieval. In auditory hallucinations this decreased activity of the parahippocampal gyrus can leaded to an activation of the association cortices. Resulting in the spontaneous retrieval of verbal memories, which are interpreted as auditory hallucinations(diederen *et al*.,2010;Copolove *et al*.,2003).

The last hypothesis suggest that the external stimuli compete with the auditory hallucinations for processing, leading to the reduced response to external speech(Lennox *et al*.,2000;Woodruff *et al*.,1997).

So gathering these information it is difficult to answer the question this article was set up for, about which brain areas are related to auditory hallucinations. Involvement of regions within the temporal and frontal lobe of both the left and right hemisphere were found. This suggest the involvement of a language related network. Changes in the parahippocampal gyrus were also reported, implying that deficits in the retrieval of verbal memories may play a role.

Appendix A: visual representation.





Visual representation of the activity: *The MRI above marks the spot of maximal activation in the brain during auditory hallucinations.The spots are ploted on template ch2bet of MRIcr, starting at -60 running up to 60, with steps of 5. Red dots indicate activation and red squares deactivation.*

Appendix B: Overview of discusses articles

Author	Design	Method	Activated areas
Suzuki et al. 1993	5 patients, during AH and when AH resolved due to neuroplectic treatment	SPECT	Left STG ↑
			Anterior cingulate ↑ (in 2 patients)
McGuire et al. 1993	12 male patients, during AH and when AH resolved spontanisly	SPECT	Left broca's area (BA 44/45) ↑
			Left anterior cingulate (BA 32/24) ↑(trend, p=0,06)
Shergill et al. 2000(a)	6 male patients, in two paradigms: 1) random sampling, reporting the occurence afterwards 2) reporting the occurence of AH by pressing a button	fMRI	Left inferior frontal gyrus (BA44) ↑
			Left middle frontal gyrus (BA 9) ↑
			Left parahippocampal gyrus (BA 35/36) ↑
			Right superior temporal gyrus (BA 22) ↑
Copolov et al. 2003	8 male patients, reporing the occurunce of AH by pressing a button	PET	Right medial frontal (BA24) ↑
			Right inferior frontal gyrus (BA 45/46) ↑
			Left posterior STG (BA 22) ↑
			Right posterior MTG (BA 37) ↑
			Left posterior cingulate (BA29/30) ↑
			Left parahippocampal gyrus/hippocampus ↑
Lennox et al. 2000	4 schizophrenia patient, reporing the occurunce of AH by pressing a button	fMRI	Left STG (BA 22/42) ↑
			Right STG (BA 22/42) ↑
			Left inferior parietal cortex (BA 39) ↑
			Left middle frontal gyrus (BA 46) ↑
Diederen et al. 2010	analysis brain activity in 24 patients during and 15 patients preceding AH	fMRI	Bilateral post central gyrus ↑
			Bilateral inferior parietal lobule ↑
			Bilateral inferoir frontal gyrus ↑
			Bilateral superior frontal gyrus ↑
			Bilateral middle frontal gyrus ↑
			Bilateral STG ↑
			Bilateral MTG ↑
		Preceding AH:	Left parahippocampal gyrus ↓
			Left superior temporal gyrus ↓
			Left middle frontal gyrus ↓
			Right inferior frontal gyrus ↓
McGuire et al. 1996	comparing hallucinators, nonhallucinators and controls in inner speech and AVI conditions	PET	Left MTG (BA 21) ↓
			Left SMA (BA 6) ↓
			Left prefrontal cortex (BA 8)↓ only i.c.w. controls
			Right STG (BA 42) ↑
Woodruff et al. 1997	the response to external speech in 7 male patients during hallucination and hallucinating free periods	fMRI	Left STG (BA 22) ↓
			Right MTG (BA 21) ↓
	8 male patients with and 7 patients without history hallucinations compaired to 8 healthy controls	fMRI	Left STG (BA 22) ↓in schizophrenia patients
			Left auditory association cortex (BA 42) ↓in schizophrenia patients
			Right MTG (BA 21) ↑
Plaze et al. 2006	respons to a language perception task in 15 schizophrenia patients	fMRI	Negative correlation between severity and activity in left STG (BA 22)
Shergill et al. 2000(b)	comparing hallucinators and controls in inner speech and AVI conditions	fMRI	Right STG ↑ in the AVI-conditions
			Right MTG ↑in the AVI-conditions

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