Quantitative meta-analysis on state and trait aspects of auditory verbal hallucinations in schizophrenia

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<td>auditory verbal hallucinations, schizophrenia, quantitative meta-analysis, Broca, superior temporal gyrus, fMRI</td>
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Quantitative meta-analysis on state and trait aspects of auditory verbal hallucinations in schizophrenia

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Abstract

Auditory verbal hallucinations (AVHs) have a high prevalence in schizophrenic patients. An array of studies have explored the neural correlates of AVHs by means of functional neuroimaging and have associated AVHs with diverse brain regions some of which have been shown to be involved in speech generation, speech perception and auditory stimulus processing. We divided these studies into state studies comparing periods of presence and absence of AVHs within-subject and trait studies comparing patients experiencing AVHs with patients without AVHs or healthy controls during tasks with verbal material. We set out to test the internal consistency and possible dissociations of the neural correlates of AVHs. We used activation likelihood estimation (ALE) to perform two quantitative meta-analyses on brain regions reported in state and trait studies on AVHs to assess significant concordance across studies. State studies were associated with activation in bilateral inferior frontal gyrus, bilateral postcentral gyrus and left parietal operculum. Trait studies on the other hand showed convergence of decreases in hallucinating subjects in left superior temporal gyrus, left middle temporal gyrus, anterior cingulate cortex and left premotor cortex activity. Based on the clear dissociation of brain regions that show convergence across state in comparison to trait studies we conclude that the state of experiencing AVHs is primarily related brain regions that have been implicated in speech production i.e. Broca’s area whereas the general trait that makes humans prone to AVHs seems to be related to brain areas involved in auditory stimuli processing and speech perception, i.e. auditory cortex.

Keywords: auditory verbal hallucinations, schizophrenia, quantitative meta-analysis, STG, Broca, fMRI, PET
**Introduction**

Hallucinations have been described since antiquity but were only recognized as components of mental illness during the past two centuries (1). In schizophrenia auditory verbal hallucinations (AVHs) occur with a high frequency of up to 60–80% (2). Since AVHs cause high levels of distress and functional disability, understanding the pathophysiological basis of this symptom might lead to more effective treatments to alleviate hallucinations.

A multitude of neuroimaging studies have associated occurrences of AVHs with activation in diverse brain regions including brain regions usually associated with auditory stimuli processing, speech generation and speech perception (e.g. 3-13).

Generally one can distinguish two categories of studies on AVHs. On the one hand there are studies that attempt to capture the precise neural signature of hallucinations by comparing periods of patient-reported presence with periods of reported absence of hallucinations in a within-subject analysis (functional *state* studies, 14). On the other hand there are studies that compare brain activity in hallucinating with that of non-hallucinating schizophrenic patients or healthy control subjects. Oftentimes participants are engaged in tasks involving verbal material such as generating inner speech or listening to pre-recorded speech. In these studies the contrast of interest results from a between-subject analysis and the results reflect rather functional *traits* as opposed to functional *states*.

To our knowledge there has been no systematic assessment of brain regions associated with the functional *state* vs. *trait* of AVHs in schizophrenia. The distinction between brain regions derived from within (*state*) vs. between-subject (*trait*) studies might provide an opportunity to dissociate the involvement of brain regions involved in speech generation and speech perception.
Therefore we performed two quantitative meta-analyses on studies that report functional *state* or *trait* differences associated with AVHs in order to assess the correspondence of neural activations across multiple neuroimaging studies respectively. The activation likelihood estimation (ALE) approach (15,16) allows us to explore statistically significant concordance of activated voxels across numerous studies while controlling for chance clustering. ALE tests for statistically reliable clustering of activations in standardized locations avoiding spatial distinction errors and problematic incongruence of labelling across studies that can befall narrative-based reviews and tabular meta-analytic approaches.

*Methods*

*Study selection*

Studies were selected using a systematic search of peer-reviewed articles published in English until June 2010. We used two separate databases (Pubmed, ISI Web of Knowledge) with the keywords “neuroimaging” <OR> “fMRI” <OR> “PET” <OR> “hallucinations” <OR> “auditory verbal hallucinations” and “schizophrenia”. The reference lists of these selected papers were searched for additional studies that fit these criteria. From the papers found we selected studies for our *state* ALE analysis that reported within-subject contrasts of periods in which AVHs were compared with periods in which no AVHs were experienced. Typically patients reported the presence or absence of AVHs by means of button presses. We excluded studies in which participants received any kind of visual or auditory stimulation at the same time. Our focus was solely on reported increases of brain activity during AVHs, since deactivations were hardly ever mentioned (see Table 1A). For the *trait* ALE analysis we selected studies that reported between-subject contrasts between patients experiencing AVHs and patients not experiencing AVHs or healthy controls usually while listening to verbal stimuli or generating inner speech. Since
increases and decreases of brain activation where reported with a comparable frequency we decided to include all group-differences irrespective of their direction and analyzed them separately (see Table 1B). We included data from fMRI and PET studies in order to provide an all-embracing overview over the attempts to identify the neural correlates of AVHs. Only studies of which we were able to obtain either Talairach (17) or MNI coordinates were included. For studies reporting multiple single cases separately, the coordinates of each single case were included as a separate study (with n= 1; (5)). For the state ALE analysis we included 10 studies (12 studies when taking the three separately entered single case studies of Dierks et al. (4) into account) with 123 foci and altogether 95 participants (Table 1A). For the trait ALE analysis we included altogether 8 studies with 43 foci and altogether 189 participants (Table 1B).

Creation of ALE maps

The ALE method provides a voxel-based meta-analytic technique for functional neuroimaging data (15, 16). Unlike typical within-study general linear model analyses where every voxel within the image is tested against a null hypothesis of no activation, the ALE method assumes that for each study of interest there is a given spatial distribution of activity and an associated set of peak coordinates. The hypothesis tested is then: given that for each neuroimaging study that meets certain criteria and has an associated set of coordinates, to what extent are the spatial locations of the activation foci overlapping across independently conducted studies? If the null hypothesis is true, then each set of coordinates may reasonably be assumed to have come about randomly. However, if there are areas of increased spatial density or clustering whereby the underlying process generating the coordinates is non-random the null hypothesis is rejected. We computed statistically significant concordance in the pattern of brain activity among several independent experiments by means of the software Brainmap GingerALE (http://brainmap.org/ale/). ALE
maps were derived based on foci of interest, which comprise statistically significant peak activation locations from multiple studies. Coordinates reported in MNI were converted to Talairach using Matthew Brett’s transformation script (18; http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m). In the approach taken by ALE, localization probability distributions for the foci are modelled at the center of 3-D Gaussian functions, where the Gaussian distributions are summed across the experiments to generate a map of inter-study consistencies that estimate the likelihood of activation for each voxel as determined by the entire set of studies. The false discovery rate (FDR) method was employed to correct for multiple comparisons at a significance threshold of $p < 0.01$ and a cluster threshold of 100. To test for overlap between the convergence found in the state and the trait ALE analysis we computed a conjunction analysis between both ALE maps on a lowered threshold (FDR $p < 0.05$, no cluster threshold).

Results

The result of the state ALE analysis is shown in Figure 1. All investigations reported activity increase in hallucinating compared to non-hallucinating states. At a conservative threshold we found significant convergence across studies in brain regions in bilateral inferior frontal gyrus (IFG, BA 44) and bilateral postcentral gyrus (BA 3) and in left parietal operculum (PO, BA 43/40) that is part of the left inferior parietal lobule (IPL). Coordinates of concurrence can be found in Table 2A. In order to explore any possible convergence across studies in superior temporal cortex as reported by some studies (4,6,19,20) we lowered the threshold to FDR $p < 0.05$ but still found no significant convergence in temporal cortex.

Regarding trait studies we separately analyzed studies reporting 1) decreases (22 coordinates from 6 studies altogether) and 2) increases (21 coordinates from 6 studies altogether) of brain
activity in hallucinating compared to non-hallucinating participants. When applying a threshold of FDR $p < 0.05$ (with clusters > 100 voxels) we found significant convergence in studies reporting decreased activity (hallucinating < non-hallucinating) in left STG (BA 22), left MTG (BA 21), ACC (BA 24, 32) and left premotor cortex (BA 6) (Figure 2B, Table 2B) but no convergence across brain regions of increased activity in hallucinating compared to non-hallucinating subjects.

In a conjunction analysis on state and trait ALE maps we did not find any overlap between concurrence found within both analyses. To explore the possible confound of visual stimulation present in one trait study (21) we repeated the analysis excluding this study, but the resulting areas of convergence did not change.

**Discussion**

With the present quantitative meta-analysis we assessed the strength of evidence for the presence of a core network of brain regions involved the experience of AVHs in schizophrenic patients. We classified neuroimaging studies exploring AVHs into two categories: First, state studies that compare periods of presence with periods of absence of hallucinations within-subject. Second, trait studies that compare brain activity between-subject in hallucinating with that of non-hallucinating schizophrenics or healthy control subjects.

By means of voxel-wise quantitative meta-analysis methods we determined significant concordance across state studies in bilateral inferior IFG, bilateral postcentral gyrus and left parietal operculum (PO); whereas concordance of decreases in brain activity of hallucinating compared to non-hallucinating patients across trait studies was found in left STG, left MTG, ACC and left premotor cortex.
The direction of the difference between hallucinating and non-hallucinating participants in *trait* studies is difficult to interpret since brain activity is first compared on a within-subject basis and this difference is then contrasted between participants. Therefore hallucinating patients could have tonically high activity (or tonically low activity) in the temporal lobe which would lead to similar small differences in the within-subject contrast between conditions and therewith to seemingly less activation in hallucinating compared to non-hallucinating participants. As a general problem in fMRI studies, one should therefore interpret this finding as hallucinating participants showing less discriminating activity in the brain regions indicated by our meta-analysis compared to non-hallucinating participants.

The overall clear dissociation of brain regions between *state* and *trait* studies in the absence of any overlap between *state* and *trait* studies suggests that the momentary phasic *state* of experiencing AVHs is associated with brain areas that have previously been related to speech production when coinciding with a more permanent alteration in activity of the temporal cortex.

In the following we will discuss the concurrence of brain activation found in *state* and *trait* studies in more detail. Brain activity in left IFG or Broca’s area has classically been found in neuroimaging tasks that involve preparation of overt speech and in the generation of inner speech (22,23). Lesions in left IFG have been associated with the disruption of inner speech (24). Although speech production is usually lateralized to the left IFG, it has been shown that recovery of articulation after stroke in the left IFG relies on the homotopic region on the right (25). In healthy participants right IFG has been shown to be active during word-stem completion (26). Sommer and colleagues (27) on the other hand argue that the occurrence of right rather than left IFG activation during AVHs might be at the core of AVHs. Furthermore it has been shown that left IFG is not only involved in speech production but likewise in speech perception (28). In studies exploring the processing of meaning it has been suggested that temporal brain areas are
involved in the storage of semantic meanings and the frontal areas such as left IFG are involved in executive processes necessary to act on these meanings (29). The postcentral sensory regions found could reflect motoric feedback of subtle face related movements in line with previous studies that reported the presence of heightened electromyographical (EMG) activity during AVHs and subvocal speech (for an overview 30). On the other hand the concurrence in postcentral gyrus could be due to the confound that participants indicated the presence of AVHs by means of button presses. This could be avoided in future studies by instructing participants to press one button during the presence of AVHs and another during the absence of AVHs. The PO has been reported to be activated during tongue sensations, swallowing and intraoral stimulation (31). The fact that PO is part of the inferior parietal lobe could also indicate a higher level function of this observed concordance (see below for further discussion).

The tonic trait-like vulnerability to experience AVHs on the other hand involves alterations of activity in the temporal lobes (STG, MTG) that have classically been associated with auditory processing (32) and speech perception in particular (for an overview 33). Interestingly, some of the state studies do report activation in the temporal lobe during reported experiences of AVHs but statistically this concordance in STG areas is low and their involvement in AVHs states is less reliable across studies. This might reflect more fluctuant levels of activation. A higher topographical diversity is less likely as e.g. the primary auditory cortex - being situated within the STG - exhibits relative small variations compared to other areas found in the current analysis (34). On the other hand the dissociation between state and trait studies might suggest that the momentary presence of AVHs is elicited rather by inner speech production than by momentary alterations in speech perception areas such as the auditory cortex. The deviant sensory perception processes in auditory cortex itself seem to be a more permanent feature that dissociates patients experiencing AVHs from healthy controls and patients not experiencing AVHs. In order to
explore possible abnormalities in brain areas involved in normal inner speech processes further research is needed that focuses more strongly on the comparison of hallucinating and non-hallucinating schizophrenic patients. Based only on the concurrence observed in the state analysis it might well be that patients suffering from AVHs have no pathology of speech generation but the literature is contradictory (e.g. 28 shows no differences, 35 show differences). The question whether the trait-related activity is based on alterations of the structure of the temporal cortex itself (as suggested by a multitude of studies focussing on the anatomy of STG such as 36,37) or alterations of the functional connectivity between brain regions involved in inner speech and speech perception (38,39) cannot be answered based on the present quantitative meta-analysis.

Two other possible confounds of the studies included should be mentioned. First, state studies could be confounded by the fact that AVHs might frequently co-occur with feelings such as anxiety or hallucinations in other modalities. But none of the regions identified in our meta-analysis are situated within the limbic system or sensory cortical areas. Second, in trait studies that compare patients suffering from AVHs with healthy controls the amount of antipsychotic medication is a confounding factor. Since the state studies compared hallucinating vs. non-hallucinating episodes within one scanning session the effect of medication should be similar in both conditions and may be neglected.

But taken together the presented results provide support in favour of theories that explain AVHs as resulting from a defective monitoring of inner speech (40). Moreover they might help to identify the neural correlates of misattribution processes that lead to the conclusion that the “voice” belongs to somebody else. Apart from concurrence observed in brain regions usually associated with speech generation and speech perception areas we found state studies to be consistently associated with activation in left PO that is part of the left IPL and trait studies with ACC. In context of the alien limb syndrome Spence (41) argued that inappropriate activation of
the right IPL leads to misattributions of ownership. In clinical trials TMS at frequencies of around 1 Hz over left temporoparietal regions have been successfully used to reduce the intensity of AVHs (42, 35). These findings are in line with the assumption that hyperactivity of the IPL is associated with distortions in agency ascription.

The ACC on the other hand - that demonstrated significant concurrence in *trait* studies - may be involved in increasing the person’s awareness of the conscious content (43). ACC has been associated with self-monitoring functions and could play a causal role in the perception of inner speech as being alien. Due to a failure of this inner speech monitoring the patient might perceive his own covert speech as AVHs (44, 45, 23). Our results bear resemblance to findings reported in context of passivity phenomena in schizophrenia. Spence et al. (46) observed hyperactivation in IPL and ACC in schizophrenic patients when they felt their actions were controlled by alien forces that remitted when passivity decreased over time. This similarity suggests that distortions of agency ascription processes in schizophrenia might have a common neural substrate that encompasses hallucinations, namely perceiving internally generated speech as if it originated externally as well as passivity phenomena, namely perceiving own actions as if they were being made by an external agent.

To summarize, our results advanced the idea that AVHs are caused by a defective monitoring of inner speech (40) and experienced during momentary phases of internally generated speech that are misidentified by more permanent speech perception distortions in the temporal lobe. We found concordance across a multitude of neuroimaging studies that reveal a neural dissociation between the AVHs *state* that involves activation in brain areas related to inner speech production (bilateral IFG, bilateral postcentral gyrus, left PO) and left IPL that could play a role in the misattribution of the speech as not being self-generated and the AVHs *trait* that involves
activation in areas associated with speech perception (left STG, left MTG), left premotor cortex and ACC that could similarly to left IPL play a role in the distorted self-monitoring of speech.
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   Engagement of brain areas implicated in processing inner speech in people with auditory 

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   substrates of voice recognition in Chinese schizophrenic patients with auditory verbal 
   hallucinations: An event-related functional MRI study. Acta Psychiatrica Scandinavica, 
   2008a; 118: 272-280.

   hallucinations with cerebral asymmetry in patients with schizophrenia: An event-related 
Figure captions

Figure 1: *State* ALE meta-analysis maps for correlates of presence vs. absence of auditory verbal hallucination in schizophrenic patients demonstrating significant concordance across within-subject studies (FDR corrected, p < 0.01, cluster > 100 voxels).

Figure 2: *Trait* ALE meta-analysis maps for brain activity resulting from between-subject contrasts between patients experiencing auditory verbal hallucinations (AVHs) and patients not experiencing AVHs or healthy controls demonstrating significant concordance for the contrast hallucinating < non-hallucinating participants (FDR corrected, p < 0.05, cluster > 100 voxels).
State ALE meta-analysis maps for correlates of presence vs. absence of auditory verbal hallucination in schizophrenic patients demonstrating significant concordance across within-subject studies (FDR corrected, p < 0.01, cluster > 100 voxels).

449x349mm (72 x 72 DPI)
Trait ALE meta-analysis maps for brain activity resulting from between-subject contrasts between patients experiencing auditory verbal hallucinations (AVHs) and patients not experiencing AVHs or healthy controls demonstrating significant concordance for the contrast hallucinating < non-hallucinating participants (FDR corrected, p < 0.05, cluster > 100 voxels).
Table IA: List of included publications on functional state studies exploring auditory verbal hallucinations in schizophrenia

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MODALITY</th>
<th>N</th>
<th>FOCI</th>
<th>COORDINATES</th>
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<tbody>
<tr>
<td>Copolov et al. (2003)</td>
<td>PET</td>
<td>8</td>
<td>6</td>
<td>Talairach</td>
</tr>
<tr>
<td>Dieder et al. (2010)</td>
<td>fMRI</td>
<td>39</td>
<td>26</td>
<td>MNI</td>
</tr>
<tr>
<td>Dierks et al. (1999)</td>
<td>fMRI</td>
<td>1+1+1</td>
<td>14+4+9</td>
<td>Talairach</td>
</tr>
<tr>
<td>Hoffman et al. (2008)</td>
<td>fMRI</td>
<td>6</td>
<td>6</td>
<td>Talairach</td>
</tr>
<tr>
<td>Lennox et al. (2000)</td>
<td>fMRI</td>
<td>4</td>
<td>4</td>
<td>Talairach</td>
</tr>
<tr>
<td>Raij et al. (2009)</td>
<td>fMRI</td>
<td>11</td>
<td>6</td>
<td>Talairach</td>
</tr>
<tr>
<td>Shergill et al. (2000)</td>
<td>fMRI</td>
<td>6</td>
<td>27</td>
<td>Talairach</td>
</tr>
<tr>
<td>Shergill et al. (2001)</td>
<td>fMRI</td>
<td>1</td>
<td>3</td>
<td>Talairach</td>
</tr>
<tr>
<td>Shergill et al. (2004)</td>
<td>fMRI</td>
<td>2</td>
<td>9</td>
<td>Talairach</td>
</tr>
<tr>
<td>Silbersweig et al. (1995)</td>
<td>PET</td>
<td>5</td>
<td>9</td>
<td>Talairach</td>
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</tbody>
</table>
Table 1B: List of included publications on functional trait studies exploring auditory verbal hallucinations in schizophrenia (H = hallucinators, NH = non-hallucinators, C = healthy controls)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MODALITY</th>
<th>N</th>
<th>FOCI</th>
<th>COORDINATES</th>
<th>TASK</th>
<th>DIRECTION OF EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. (2007)</td>
<td>fMRI</td>
<td>10 H, 10 NH, 11 C</td>
<td>4</td>
<td>Talairach</td>
<td>Listening to speech (source: self/ nonself, quality: distorted/ undistorted)</td>
<td>C/NH &gt; H ( + interaction)</td>
</tr>
<tr>
<td>Copolov et al. (2003)</td>
<td>PET</td>
<td>8 H, 8 C</td>
<td>5</td>
<td>Talairach</td>
<td>Listening to speech</td>
<td>H &gt; C</td>
</tr>
<tr>
<td>McGuire et al. (1995)</td>
<td>PET</td>
<td>6 H, 6 C, 6 NH</td>
<td>10</td>
<td>Talairach</td>
<td>Imagining speech of another person</td>
<td>C &gt; H, NH &gt; H</td>
</tr>
<tr>
<td>Shergill et al. (2003)</td>
<td>fMRI</td>
<td>8 H, 8 C</td>
<td>6</td>
<td>Talairach</td>
<td>Inner speech with varied speed</td>
<td>5 x C &gt; H, 1 x H &gt; C</td>
</tr>
<tr>
<td>Simons et al. (2010)</td>
<td>fMRI</td>
<td>15 H, 12 C</td>
<td>5</td>
<td>Talairach</td>
<td>Inner speech vs. listening</td>
<td>H &gt; C ( + interaction)</td>
</tr>
<tr>
<td>Stephane et al. (2006)</td>
<td>fMRI</td>
<td>8 H, 10 NH, 11 C</td>
<td>8</td>
<td>Talairach</td>
<td>Reading nouns vs. looking at nouns without reading</td>
<td>4 x H/NH &gt; C, 4 x C &gt; H/NH (Wernicke area shows difference between H &gt; NH)</td>
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<tr>
<td>Zhang et al. (2008a)</td>
<td>fMRI</td>
<td>13 H, 13 C</td>
<td>1</td>
<td>Talairach</td>
<td>Voice recognition</td>
<td>C &gt; H</td>
</tr>
<tr>
<td>Zhang et al. (2008b)</td>
<td>fMRI</td>
<td>13 H, 13 NH</td>
<td>4</td>
<td>Talairach</td>
<td>Judge whether speech was presented on right or left side</td>
<td>H &gt; NH</td>
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Table 2A: Convergence of regions involved in functional state studies exploring auditory verbal hallucinations in schizophrenia (FDR p < 0.01)

<table>
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<tr>
<th>ANATOMICAL REGION</th>
<th>BRODMANN’S AREA</th>
<th>COORDINATES (TALAIRACH)</th>
<th>VOLUME (MM³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left parietal operculum</td>
<td>43/40</td>
<td>x -55 y -19 z 16</td>
<td>344</td>
</tr>
<tr>
<td>Left postcentral gyrus</td>
<td>3</td>
<td>x -49 y -17 z 41</td>
<td>256</td>
</tr>
<tr>
<td>Right postcentral gyrus</td>
<td>3</td>
<td>x 36 y -32 z 50</td>
<td>216</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td>44</td>
<td>x -48 y 2 z 6</td>
<td>208</td>
</tr>
</tbody>
</table>

Table 2B: Convergence of regions involved in functional trait studies (including only decreases in brain activity comparing hallucinating and non hallucinating subjects) exploring auditory verbal hallucinations in schizophrenia (FDR p < 0.05)

<table>
<thead>
<tr>
<th>ANATOMICAL REGION</th>
<th>BRODMANN’S AREA</th>
<th>COORDINATES (TALAIRACH)</th>
<th>VOLUME (MM³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left middle temporal gyrus</td>
<td>21</td>
<td>x -56 y -30 z 0</td>
<td>424</td>
</tr>
<tr>
<td>Left premotor cortex</td>
<td>6</td>
<td>x -10 y 3 z 56</td>
<td>376</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>32</td>
<td>x -4 y 26 z 31</td>
<td>160</td>
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<tr>
<td>Left superior temporal gyrus</td>
<td>22</td>
<td>x -44 y -22 z 0</td>
<td>152</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>32</td>
<td>x -42 y 2 z 18</td>
<td>152</td>
</tr>
<tr>
<td>Anterior cingulate gyrus</td>
<td>24</td>
<td>x -9 y 4 z 37</td>
<td>112</td>
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</tbody>
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