Auditory processing in the brainstem and audiovisual integration in humans studied with fMRI
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Chapter 2

Issues on the fMRI of the human auditory brainstem

A review

L.M. Slabu and H. Duifhuis
Abstract

fMRI based on BOLD contrast has gained a primary role in the study of the human brain, both for characterization of normal brain activity and for clinical practice. Although there is a considerable amount of research dealing with activation of the auditory cortex, relatively little information exists on functional imaging of subcortical auditory pathway.

Functional imaging of the brainstem is complicated due to heart beat related motion, blood flow, cerebrospinal fluid movement, tissue deformation, the relative small size, and the morphology of the auditory nuclei. The subcortical areas involved in auditory information processing are: the cochlear nucleus, the superior olivary complex, the lateral lemniscus, the inferior colliculus, and the medial geniculate body. These areas have been studied in general auditory neuroscience research. In clinical auditory research, fMRI has been used to investigate among other disease: tinnitus, unilaterally deaf subjects, and patients with tumoral lesions or cysts.

This paper reviews recent fMRI/MRI studies on the human central auditory pathway, focusing on the brainstem, and emphasizing anatomical, methodological and technical issues.

2.1. Introduction

In cognitive neuroscience several techniques are now combined to explore information processing at the brainstem level: neurophysiology (primarily single-unit recordings), mathematics (computational models), and combined psychological and radiological imaging techniques (functional CT, MRI, and PET). The imaging techniques provide improved information of brainstem responses, in addition to the more classical evoked response methods (such as EEG or brainstem auditory evoked response). The techniques are used to measure brain responses that are evoked by sound stimuli, in order to check the ascending auditory pathways of the brainstem. The tests help to diagnose nervous system abnormalities, and hearing losses, and to assess neurological functions. Abnormal findings may indicate a.o., a hearing loss, multiple sclerosis, a cerebrovascular accident, acoustic neuroma, or central pontine myelinolysis.

In the early 1990s the first papers appeared on functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) contrast. The physical basis of the BOLD contrast is oxygenation-dependent magnetic susceptibility of hemoglobin [e.g., Bandettini et al., 2001]. The brain images reflect local changes in cerebral blood oxygenation (BOLD contrast) which is evoked by cognitive processing that follows sensory stimulation. The region of the brain that responds to the stimulus has an increase in metabolism which requires additional blood flow and oxygen supply to the activated local
brain area. Because of its noninvasive character and the spatial, and, although less precise temporal, resolution, off late, fMRI is used for numerous experiments of the central nervous system.

The fMRI evaluation of the auditory cortex and brainstem is demanding because the absence of the auditory task is hardly a resting condition in a common MRI scanner. The sound generated by the switching gradients of the echo planar imaging (EPI) sequence, up to 120 dB and even above, produces a continuous stimulation of the auditory system [cf. e.g., Bernal and Altman, 2001]. This requires proper MRI-sound protection in combination with special stimulus presentation (e.g., sparse sampling, see below). In addition, auditory stimuli must be presented through devices that are insensitive to the magnetic fields as well as to the RF fields.

fMRI studies have already revealed functional distinctions between structures at different levels of the auditory pathway. Future work can further delineate the functional similarities and differences between structures. These lines of investigation should provide information that is needed for proper neurophysiologic interpretation of fMRI findings in subjects performing auditory psychophysical tasks (e.g., speech perception, sound localization). The increasing body of data in normal listeners gives an important baseline for comparison with data from clinical populations (tinnitus, unilateral hearing loss). Already, fMRI studies of such populations have begun to reveal functional abnormalities which have also provided new insights into normal auditory function.

In fMRI imaging of the subcortical auditory pathway, the types of design commonly used are: event related design, block design, and sparse sampling. The sparse sampling technique relies on the temporal course of the BOLD response, and on the forward masking time course of the scanner sound. When a volume is acquired within 2 seconds, the BOLD response due to scanner sound will hardly influence the acquisition of the BOLD response to the stimulus [Talavage et al., 1999, Hall et al., 1999, Langers et al., 2005a]. In block-related design, stimuli are presented during long on- versus off intervals while MR acquisitions are performed continuously. This allows hemodynamic BOLD responses to the stimulus to reach a steady state which can reliably be measured relative to the baseline signal [Jezzard et al., 2001, Buxton et al., 2002, Langers et al., 2003]. Event-related designs associate brain processes with discrete events, which may occur at any point in the scanning session. Often, they are combined with sparse sampling.

In the following subsections we review the fMRI/MRI studies on the ascending human auditory pathway in the brainstem, and discuss a number of partly solved and unsolved anatomical, methodological and technical issues.
2.1. Gross anatomy of the ascending auditory pathway

The brainstem is that part of the central nervous system which connects the spinal cord with the remainder of the brain and it consists of: (a) the medulla oblongata, (b) the pons, and (c) the midbrain [see fig. 2.1]. The brainstem has three major auditory nuclei: cochlear nuclei (CN), the superior olivary complex (SOC) and inferior colliculi (IC).

![Figure 2.1. The major processing centers of the auditory system: CN - cochlear nuclei, SOC - superior olivary complex, IC - inferior colliculi, SC - superior colliculi, MGB - medial geniculate body, AC - auditory complex: (a) medulla oblongata, (b) pons, (c) midbrain](image)

(a) The CN are divided into three regions, based on the morphology of the cells and on the structures with which they connect: the anterior ventral CN (AVCN), the posterior ventral CN (PVCN), and the dorsal CN (DCN). The regions contain specific cell types which react differently to the incoming auditory nerve impulses, thereby specifically modifying the inputs to the brain [e.g., Martin et al., 1996, Ehret & Romand, 1997]. The AVCN and PVCN project to the SOC. The lateral lemniscus (LL) carries axons from the DCN and PVCN to IC.

(b) From the CN, specific pathways continue through the trapezoidal body of the pons. Some fibers terminate primarily in the contralateral trapezoid body, but most fibers begin their ascent to the brain ipsilateral and contralateral, and synapse within the superior olivary complexes (SOC) in the pons. The olives...
are involved in functions such as balance, coordination and modulation of sound impulses from the inner ear. The superior olivary nuclei are the first nuclei to receive the input from the ipsi- and the contralateral sides of the ear and are responsible for the spatial localization of sounds and interaural time differences [e.g., Romand & Avan, 1997]. The LL carries axons from the SOC (medial and lateral nuclei) to IC.

(c) The midbrain or mesencephalon is the smallest region of the brainstem and is superior to the pons. The tectum of the midbrain consists of four nuclei on the dorsal surface, called corpus (body) quadrigemina or colliculus: two superior colliculi (SC) and two inferior colliculi. The SC are involved in visual reflexes and in audio-visual integration [Calvert et al., 2001, Bushara et al., 2003]. All neurons conducting action potentials from the structures of the inner ear to the brain synapse in the IC.

From the IC, the pathway either crosses to the contralateral IC or continues to the ipsilateral medial geniculate body (MGB) of the thalamus and continues to the auditory cortex. The medial geniculate nucleus is composed of several divisions, but only the ventral division is principal auditory relay nucleus.

The three major divisions of the brainstem receive their arterial supplies from the posterior (vertebral-basilar) circulation:
(a) The medulla is nourished by the vertebral and spinal arteries. The vertebral arteries join to form the basilar artery at the pontomedullary junction.
(b) Three sets of branches of the basilar artery supply the pons paramedian, short circumferential and long circumferential arteries.
(c) The midbrain is supplied by the posterior cerebral artery and basilar artery.

The architecture of the blood vessels shows large inter-individual differences, neuroanatomical studies reporting differences in shape, size, orientation and junctions of the blood vessels.

### 2.2. Issues on brainstem fMRI

Even though fMRI studies of the auditory brainstem are rapidly increasing, the accuracy and reliability of the functional maps is still subjected to discussion. Functional localization of the auditory brainstem structures based on fMRI deals with a number of fundamental problems:
- The BOLD signal does not provide an exact localization of the brainstem nuclei, but give only an approximation of the relative location of these structures [Komisaruk et al., 2002]. Sometimes the functional activation is missed (especially for the lower brainstem, CN, SOC), even in case of no effect of motion artefacts (see below).
- fMRI localization of nuclei in the auditory brainstem is complicated due
to the relatively small size of these nuclei. The dorsal nucleus of the CN is \(\sim 3 \times 3 \times 7 \text{ mm}\), the lateral lemniscus (LL) is \(\sim 2 \times 2 \times 5 \text{ mm}\), the SOC is \(\sim 2 \times 2 \times 2 \text{ mm}\), and the IC is \(\sim 6 \times 6 \times 4 \text{ mm}\) [Giraud et al., 2000, Bazwinsky et al., 2003, Hawley et al., 2005].

- The brainstem is subject to heartbeat related motion, blood flow dependent on individual shapes of the artery network - and cerebral spinal fluid motion. The resulting motion artefact can be minimized using cardiac gating, but this limits the number of slices that can be acquired per time. This limitation also implies that several standard tools used in pre- and post-processing of the images cannot be used with sufficient confidence.

2.3. Objective

Until recently, collection of detailed experimental data on information processing within the auditory brainstem required invasive animal studies. Currently fMRI is one of the important bridges between animal neurophysiology and noninvasive studies of the human nervous system. So far, auditory brainstem fMRI studies, both in normal subjects and in patients, have generally supported the validity of the use of animal model results.

fMRI, and related functional techniques, supposedly never will reach the spatial or the temporal resolution attainable at the single neuron level. Even if submillimeter resolution can be reached, the cell grid is an order of magnitude finer. Therefore, on the one hand the results always show integration over space, and on the other hand, significant acquisition time (order of seconds) remains involved in the BOLD response. In other words, the new techniques provide information about processing of clusters of cells, at a \(\text{mm}^3\)-s spatiotemporal grid.

BOLD fMRI is still in an early stage of transition from research laboratories to clinical applications [Matthews et al., 2006], and auditory brainstem fMRI is not (yet) used as a clinical routine.

This review aims at summarizing the current status of auditory brainstem fMRI in order to enable evaluation of the current possibilities and limitations, and to discuss improvements that may be obtained in the near future.

2.4. Summary of fMRI experiments on human auditory subcortical pathway

Presently there are a few published papers about fMRI on brainstem or/and midbrain. In table 2.1, we summarize the technical parameters and the stimuli used in these experiments. However, obtaining BOLD images of the brainstem activation still remains a technical challenge.
The first studies [1, 3, 4] and some of the more recent ones [9, 10, 11, 14] used 1.5 T scanners, paper [8] a 2 T, and most later papers [12, 13] also used a 3 T scanner, as did the other more recent ones [2, 7]. This might have led to more precise estimates of the number of activated neurons in the different auditory nuclei, but no clear trend is obvious [see table 2.2].

As listed, different types of stimulus and different fMRI paradigms were used to explore the activation of auditory brainstem nuclei. Only one study used a repetition time below 2 s ([8], 1200 ms), other choices were 2 (5x), ~5 (1x), ~10 (6x), and one study used ~20 s [9]. This time reflects the choice of sparse sampling, which aims to minimize the interaction between acoustic stimulus and scanner noise. Both broadband (music, bb-noise, clicks) and narrowband (nb-noise, tones), meaningful (music) and meaningless (noise) stimuli were used, at sensation levels up to 55 dB, at SPLs that would reach the protected ear usually at below 80 dB SPL (relevant specification is not always convincing).

Guimaraes et al. [1] were the first to analyze the role of cardiac gating in relation to heartbeat motion. Most studies followed their conclusion and used gating [1, 3-8, 11-13], but some others did not [2, 9, 10, 14]. This point is discussed in section 2.5.2.

Melcher et al. [3] (n = 7) and to a lesser extent (n = 2) Kovacs et al. [2] applied fMRI to examine tinnitus compared with healthy subjects. They used music and bb-noise stimuli, respectively. Kovacs’ larger patient group (n = 5) regarded oncological cases. Langers et al. [14] investigated the connectivity of the high part of the brainstem and auditory cortex on healthy and unilaterally deaf subjects. The subjects participating in the control groups or in the other reported studies, however, were normal volunteers, distributed over age and sexes, and predominantly right-handed.

In so far, laterization was studied explicitly, using both, monaural and binaural stimulation. The IC receives excitatory and inhibitory input from both ears and the response is largest in the IC contralateral to the ear of stimulation. A similar conclusion was also reached for the dominantly contralateral excitatory input at the MGB level [Langers et al., 2005]. Experimentally data show that the binaural response is smaller than the sum of monaural responses and even smaller than the contralateral monaural response alone. This process may be caused by a binaural inhibitory process or by the contributions from monaurally responsive neurons or neurons whose binaural responses are roughly equal to the sum of their monaural responses [Krumbholz et al., 2002].

Schönwiesner et al. [13] reported evidence for a functional hemispheric asymmetry in the left- and right- side subcortical structures in response to stimuli.
Table 2.1. Summary of fMRI experiments on the human subcortical auditory pathway.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Sequence/ no. of slices-thickness</th>
<th>Field/scanner</th>
<th>Paradigm</th>
<th>Stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1]</td>
<td>asymmetric spin echo</td>
<td>1.5T GE;</td>
<td>Block design</td>
<td>orchestral music, Beethoven Symphony No.7 in A Major.</td>
</tr>
<tr>
<td>Guimaraes</td>
<td>TR ~ 2 s, TE = 70 ms, τ offset = 25 ms; one slice slice thickness = 7 mm</td>
<td>Yes</td>
<td>30 s on 30 s off</td>
<td></td>
</tr>
<tr>
<td>et al. (1998)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kovacs et</td>
<td>TR ~ 5 s, TE = 33 ms, FOV = 230 x 230 mm(^3), voxel size = 0.98 x 0.98 x 1.20 mm(^3), SENSE-reduction factor = 2.5; 32 transverse slices slice thickness = 4 mm</td>
<td>INTERA, Best; No</td>
<td>50 s on 50 s off</td>
<td></td>
</tr>
<tr>
<td>al. (2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[3]</td>
<td>asymmetric spin echo</td>
<td>1.5T GE;</td>
<td>Block design</td>
<td>continuous noise 55 dB SL (threshold was defined as the minimum level at which the noise stimulus could be consistently detected in the scanner room), monaural.</td>
</tr>
<tr>
<td>Melcher et</td>
<td>TR ~ 2 s, TE = 70 ms, r offset = -25 ms; slice thickness = 6 or 7 mm</td>
<td>Yes</td>
<td>30 s on 30 s off</td>
<td></td>
</tr>
<tr>
<td>al. (2000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.1. (..continued..)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
<th>Imaging Parameters</th>
<th>Sound Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>[4] Harms et al. (2002)</td>
<td>1.5T: asymmetric spin echo TR ~2 s TE = 70 ms τ offset = -25 ms FA = 90° 3T: TR = 40 ms or 30 ms TE = 30 ms FA = 90° or 60° in-plane resolution = 3.1 x 3.1 mm²; slice thickness = 7 mm</td>
<td>1.5T GE 3T GE; Yes Block design 30 s on 30 s off 2nd experiment: 18 s on 18 s off</td>
<td>50-55 dB SL (measured for each subject in the scanner room in the absence of scanner-generated sounds) binaural broadband continuous noise and bandlimited noise with a center frequency of 1 kHz and bandwidth of the first, second and third octave.</td>
</tr>
<tr>
<td>[5] Hawley et al. (2005)</td>
<td>EP1 TR ~ 2s TE = 30 ms FA = 90° in-plane resolution = 3.13 x 3.13 mm²; one slice slice thickness = 6 mm</td>
<td>3T Siemens Allegra; Yes Block design 30/32 s on 30/32 s off</td>
<td>50-55 dB SL (measured for each subject in the scanner room in the absence of scanner-generated sounds) binaural broadband continuous noise and bandlimited noise with a center frequency of 1 kHz and bandwidth of the first, second and third octave.</td>
</tr>
<tr>
<td>[6] Sigalovsky et al. (2001)</td>
<td>TR ~ 2 s; one plane</td>
<td>Unspecified; Yes Block design 30 s on 30 s off</td>
<td>35-75 dB SL continuous broadband noise and 35-65 dB SL music binaural.</td>
</tr>
<tr>
<td>Study</td>
<td>Sequence</td>
<td>Field Strength</td>
<td>Imaging Parameters</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>[7] Sigalovsky et al. (2006)</td>
<td>EPI</td>
<td>3T Siemens Allegra; Yes</td>
<td>8 s</td>
</tr>
<tr>
<td></td>
<td>TR ~ 8 s</td>
<td></td>
<td>TE = 30 ms</td>
</tr>
<tr>
<td>[8] Griffiths et al. (2001)</td>
<td>EPI</td>
<td>2T Siemens, VISION Erlangen; Yes</td>
<td>1200 ms</td>
</tr>
<tr>
<td></td>
<td>TR = 1200 ms</td>
<td></td>
<td>TE = 35 ms</td>
</tr>
<tr>
<td>Reference</td>
<td>Protocol Details</td>
<td>Imaging Parameters</td>
<td>Sound Parameters and Stimuli</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>[9] Heßelmann et al. (2001)</td>
<td>EPI PRESTO TR = 23.2 ms TE = 35.2 ms FA = 90° FOV = 230 x 160 mm²; 20 axial slices slice thickness = 3 mm</td>
<td>1.5T Gyroscan ACS_NT, Powertrak 6000 gradient-amplifier Philips; No</td>
<td>0.5 ms monophasic positive clicks, spectral band 50-1800 Hz, 85 dB SPL delivered to the right ear; the left ear was masked with white noise (60 dB) only in the non-click phase; the stimulation frequency = 22 Hz.</td>
</tr>
<tr>
<td>[10] Yetkin et al. (2004)</td>
<td>EPI TR = 12 ms TE = 40 ms FOV = 24 cm matrix size = 64 x 64; 14 axial slices slice thickness = 7 mm</td>
<td>1.5T Neuron/LX GE; No</td>
<td>Sparse sampling design (stimulus presentation every 28 s) 4 s pure tones of 1000 Hz with a rise/fall time of 35 ms and at a rate of 2.5 pulses/s, monaurally.</td>
</tr>
<tr>
<td>[11] Backes &amp; van Dijk (2004)</td>
<td>EPI TR = 10 s TE = 50 ms HBs = 6 s FA = 90° matrix dimension = 64 x 64 voxel dimension = 3.5 x 3.5 mm² 3T: TE = 40 ms or 30 ms; one slice, slice thickness = 7 mm</td>
<td>1.5T Philips; Yes</td>
<td>Event-related design trains of 7 white-noise, 70 ms bursts, 35 ms between bursts 85 dB SPL, binaurally.</td>
</tr>
</tbody>
</table>
| [12] Krumbholz et al. (2005) | EPI | TR ~ 10.5 s  
| | TE = 30 ms | FA = 90°  
| | in-plane resolution = 3 x 3 mm²  
| | 28 ascending slices  
| | slice thickness = 3 mm  
| | interslice gap = 1 mm | 3T Brucker Medspec; Yes | Sparse sampling design | monaural or binaural noise bursts; 50 ms with a rate of 10/s for the binaural conditions:  
- diotic condition - the perception of a stationary sound in the center of the head;  
- move condition - the interaural time differences varied to a continuous linear function of time between -1000 and +1000 μs (it took 2 s for the sounds to move from one ear to the other). |
| [13] Schönwiesner et al. (2006) | EPI | TR ~ 10.5 s  
| | TE = 50 ms | FA = 90°  
| | in-plane resolution = 3 x 3 mm²  
| | 28 ascending slices  
| | slice thickness = 3 mm  
| | interslice gap = 1 mm | 3T Brucker Medspec; Yes | Sparse sampling design | see [11] |
| [14] Langers et al. (2005) | EPI TR = 11 s  
TE = 50 ms  
FA = 90°  
Matrix dimension = 192 x 192  
FOV = 192 mm;  
12 contiguous coronal slices  
slice thickness = 2.5 mm | 1.5T Philips;  
No Sparse sampling design | 0, 40–70 dB SPL monaurally or binaurally, 8s band-passed pink noise and pink noise modulated in the temporal and spectral domain, with a spectral modulation density of ½ cycle per octave and a temporal modulation frequency of 4 cycles/s; spectral range = 125-8000 Hz. |

EPI: echo planar imaging, TE: echo time, TR: repetition time, FOV: field of view, FA: flip angle
Table 2.2. Percentage of activated subcortical auditory nuclei reported.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>IC</th>
<th>MGB</th>
<th>SOC</th>
<th>CN</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] Guimaraes et al. (1998)</td>
<td>100</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>[4] Heßelmann et al. (2001)</td>
<td>0</td>
<td>0</td>
<td>85</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>[8] Yetkin et al. (2004)</td>
<td>94</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>17</td>
</tr>
<tr>
<td>[9] Hawley et al. (2005)</td>
<td>100</td>
<td>0</td>
<td>60</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>[10] Krumbholz et al. (2005)</td>
<td>0</td>
<td>0</td>
<td>84</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>[11] Langers et al. (2005)</td>
<td>75</td>
<td>75</td>
<td>12.5 for left SOC 75 for right SOC</td>
<td>0 in the left CN 75 in the right CN</td>
<td>8+5</td>
</tr>
<tr>
<td>[12] Kovacs et al. (2006)</td>
<td>100</td>
<td>0</td>
<td>75</td>
<td>75</td>
<td>7+17</td>
</tr>
<tr>
<td>[14] Sigalovsky et al. (2006)</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>100</td>
<td>5</td>
</tr>
</tbody>
</table>

N: number of subjects

This asymmetry depends on the acoustic context in which the monaural noise burst stimuli are presented [Schönwiesner et al., 2006]. Sigalovsky et al. showed that fMRI activation increases with increasing broadband noise level at brainstem, thalamus and, cortex [Sigalovsky et al., 2001].
Moreover, it has been demonstrated that fMRI activation increases with increasing bandwidth in CN, SOC and IC [Hawley et al., 2005, Sigalovsky et al., 2001, 2006]. Conversion of temporal regularity into an activity code starts in CN but is not completed at this level. In the IC, the response amplitude increases with increasing rate while response wave shape remains unchanged and sustained. In the MGB, increasing rate produces an increase in amplitude and a moderate change in wave shape at higher rates [Harms et al., 2002].

A comparison between fixed and lively pitch sequences was made by Griffiths et al. [Griffiths et al., 2001]. The stimuli containing temporal regularity were sequences of notes played at the rate of four per second. In one condition, the pitch was fixed, and in others, the pitch was varied to produce note sequences. The relationship between the BOLD response and temporal regularity was more significant in the IC than the CN.

Patients with lateralized tinnitus showed signal change on fMRI studies in the contralateral IC and MGB [Melcher et al., 2000, Smits et al., 2007]. The differences of activation observed in groups with different types of tinnitus suggest a correlation with prognosis. The ability to classify tinnitus by anatomic and functional methods allows another way to evaluate therapeutic results [Altman and Bernal, 2001]. Although a promising tool, fMRI has yet to be implemented in clinical settings.

Even though the amount of fMRI studies of the brainstem is rapidly increasing, the overall reliability of the functional maps is still debatable. Sometimes, functional studies fail and the functional activation is missed [Giove et al., 2004], even in case of no apparent degrading effect of motion; furthermore, the repeatability of results in single subject and in intersubjects studies is still not optimal.

2.5. Discussion

2.5.1. Human brainstem motion

So far relatively few studies have investigated the displacement of the brain, and in particular the brainstem motion, during the cardiac cycle. The motion of the brainstem arises from several factors, such as heart beat, vasculature (arteries and veins attached to the brainstem which impart a movement with each arterial pulsation), cerebrospinal fluid movement, and tissue deformation.

The first study on the role of brain displacement in MRI was done by Feinberg et al. in 1987, who examined the motion of the brain in one dimension. His point of view is that the motion of the central lobes is toward the corpus callosum. The driving force of the displacement is due to the heart beat and is transmitted through the cerebral arterial tree. The corpus callosum opposes the
transverse motion of the midline regions of the brain. For the brainstem and hypothalamus, the force is transmitted through the CSF. Feinberg et al. report that the brainstem velocity at the level of the aqueduct shows a parabolic distribution in the ventral direction with maximum caudal velocity (-1.3 ± 0.44 mm/s) during systolic phase [Feinberg et al., 1987].

Poncelet et al. (1992) report that the brainstem moves in the rostro-caudal, lateral and with lower amplitude in the ventro-dorsal directions in the systolic phase. During diastolic phase the brain returns to its initial shape [Poncelet et al., 1992]. Greitz et al. (1992), opposite to Feinberg et al. findings, shows that arterial expansion causes the major part of the brain displacement, including the brainstem and hypothalamus. According with this study, during the systolic phase the cerebral cortex pushes the brainstem through the spinal cord in a ventro-caudal direction in one displacement. The maximum anterior velocities are: 0.3 mm/s in the postero-medial thalamus, 1.5 mm/s in the pons, and 2.3 mm/s in the medulla. In addition, Enzamnnn et al. (1992) shows that there is an earlier ventro-caudal motion of the lower brainstem with a displacement of 0.14 ± 0.03 mm and the velocity 1.5 ± 0.02 mm/s, and then a motion of the upper brainstem with a displacement of 0.16 ± 0.02 mm and the peak velocity 1.5 ± 0.03 mm/s [Enzmann et al., 1992].

Maier et al. in 1994 shows that the velocities are 2-3 mm/sec in the upper brainstem and 5-8 mm/sec in the lower brainstem in the caudal direction. For the lower brainstem a periodic displacement of 1 mm was found. The displacement for the upper brainstem was on the order of 2-3 mm for the rostro-caudal direction when a forced inspiration followed by breath holding (Valsalva maneuver) was performed.

The brainstem physiologic motion caused by arterial and venous pulsation with each cardiac and respiratory cycle it is expected that produces significant variability of the fMRI signal with a periodic displacement [Meier et al., 1994]. Figure 2.2 illustrate the effects of heart beat related motion on MRI signal (intensity vs. time) in the midbrain (IC) in a single subject. The regions of interest were defined on the EPI images at the IC level. Images were collected using a Phillips Intera 3T scanner (TR = 50 ms, TE = 20 ms, flip angle= 170, FOV = 192 mm, scan resolution 96 x 96, 5 mm slice thickness).

In summary, the resultant movement of the brainstem occurred in ventro-caudal direction. The magnitude of the brainstem motion in the literature differs based on the technique used, the group or individual data presented and the periodicity of the heart rate.
2.5.2. Reduction of motion artefacts

The primary MR imaging techniques that have been developed to overcome the artifacts generated from flowing blood, CSF and other physiologic motions commonly rely on the constraint of the subject, breath holding, and cardiac triggering of the scans [Felblinger et al., 1998, Pattany et al., 2002]. In all the auditory fMRI brain studies the subject's head was restrained. Breath holding was not used in the brainstem auditory fMRI experiments maybe because of the negative influence on functional imaging with reduced blood oxygenation. Using the cardiac gating, the image acquisitions are synchronized in the same heart phase of the cardiac cycle [Vlaardingerbroek and den Boer, 1996, Guimaraes et al., 1998]. Cardiac gating requires a good ECG waveform for the MRI system to detect the QRS complex and trigger the scanning sequence. In clinical ECG measurements, the components of the QRS complex are detected in each of the three standard limb leads, spaced as far as apart as possible to maximize the ECG signal. During fMRI, since the magnetic field gradients across the body will induce differential voltages in the leads, the electrodes are placed relatively close together to minimize the gradient-induced voltages.

Peripheral pulse gating using a plethysmograph positioned on a finger it is easier to use, but is less desirable, because of the delay (150-500 ms) between the R-wave of the ECG and the peak of the peripheral pulse at the finger [Enzmann et al., 1992].

The experiment by Guimaraes et al. investigated the differences between cardiac-gated and ungated data on a 1.5T scanner for the IC and auditory cortex (AC). The images were acquired at the same time of the cardiac cycle, postsystole. Standard deviation of the stimuli on and off at the IC level is presented in table 2.3.

Cardiac gating eliminates the effect of the motion that is directly correlated to the heart beat at the IC level but this effect does not appear at the AC level [Guimaraes et al., 1998].

Figure 2.2. A - the imaging plane for the scan session; B - MRI signal intensity plotted in time at the IC level.
There are also auditory brainstem fMRI studies that do not use cardiac gating, e.g. Heßelmann et al. (2001), Yetkin et al. (2004) and Langers et al. (2005). Yetkin et al. and Langers et al. show consistent activation of the MGB and the IC and in a few cases activation of CN, SOC and LL. Heßelmann et al. show activation of the lower part of the brainstem, CN and SOC.

In summary, it has been shown that cardiac gating is an important tool for increasing the time series signal-to-noise ratio (by decreasing the variance) in imaging the IC at the field strength of 1.5 T. Whether the use of cardiac gating for imaging brainstem at high field strengths improves the contrast to noise ratio still remains a question.

### 2.5.3. Discussion re objectives

An important objective of auditory brainstem fMRI studies is to provide data on information processing in the brainstem. Advance in understanding is hampered by (1) limitations on the stimuli that can be used in auditory fMRI, in level, duration, and number of repetitions, (2) by the wide range of different auditory stimuli used.

In the brainstem, fMRI is not suitable to ascertain tonotopy, and response timing, with high accuracy. This has led to the use of a variety of auditory stimuli, both with respect of physical parameters (time and frequency) and subjective attributes (pitch, timbre, and meaning). These choices hamper the systematic comparison, both within the set presented in section 2.2, and with classical psychophysical and electrophysiological studies which often used simple, highly specified, stimuli.

For the time being it also will remain necessary to use rather high stimulus presentation levels, because of the inherent acoustical background levels. When sound protection is used to reduce the scanner noise, it remains uncertain if the claimed sound reduction can be achieved, because a more reliable standardization of sound levels is required. E.g., the peak durations of the sounds generated by EPI sequences are too short to allow proper level measurement with standard dB(A) measuring equipment (even the standard ‘fast’ is not fast enough). The precise specification of the performed measurements is often lacking. Especially for the higher frequencies (> 1 kHz, and thus also for short clicks) the positioning of the devices on or in the ear requires a high precision and monitoring of the result by proper measurement near the eardrum. One of the binaural issues, viz. stimulus

### Table 2.3. Standard deviation between gated and ungated conditions at the IC level [Guimaraes et al., 1998].

<table>
<thead>
<tr>
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<th>Standard deviation, stimuli on</th>
<th>Standard deviation, stimuli off</th>
</tr>
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<tbody>
<tr>
<td>Ungated</td>
<td>20.5 ± 5.7</td>
<td>19.9 ± 5.0</td>
</tr>
<tr>
<td>Gated</td>
<td>13.9 ± 1.5</td>
<td>14.2 ± 1.5</td>
</tr>
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lateralization in relation to left-right presentation and subsequent processing, has been addressed with success, although the general interpretation of the data remains somewhat problematic. The fMRI data are consistent with, and support the available electrophysiological data. To our knowledge, they have not led to new insights, but they have supported the validity of the use of animal model studies. The time course of fMRI measurements makes it difficult, or even impossible, to measure in detail on the syllabic or sub-syllabic scale (< ~ 0.5 s). Therefore, the application of additional BER measurements remains necessary.

The time course does allow for the measurement of slowly varying processing properties, such as attention. Progress in scientific understanding of operation of the auditory system, and in particular the brainstem, will benefit from a more focused topic approach, and a more precise definition of psychoacoustic design and measurement.

2.6. Conclusions

Functional MRI is noninvasive tool, based on changes of the oxy- and deoxy-hemoglobin ratio related to neural activity with increased metabolism. fMRI of the auditory stimuli is particularly challenging due to the interaction between the experimental auditory stimuli and the background scanner noise (110 dB). The correlation between clinical and fMRI findings is still modest in this area. Nevertheless, brainstem fMRI allows us to directly observe those findings on humans and promises to become a valuable clinical and scientific tool for the non-invasive assessment of brainstem function.

2.7. References


