Understanding the auditory-fMRI

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The neuroanatomy of the auditory system is well established (Brodal, 1998). Input to the brainstem comes through VIII cranial nerve. First station is cochlear nucleus. From the cochlear nucleus, auditory information is split in two. Some nerve fibers going to the ventral cochlear nucleus synapse on their target cells with giant, hand-like terminals. This serves as timing of the signal. The ventral cochlear nucleus cells then project to the superior olives. This projection is bilateral [Fig 1]. In the superior olive, the differences in timing and loudness of the sound in each ear are compared, and from this it is determined the direction the sound comes from.

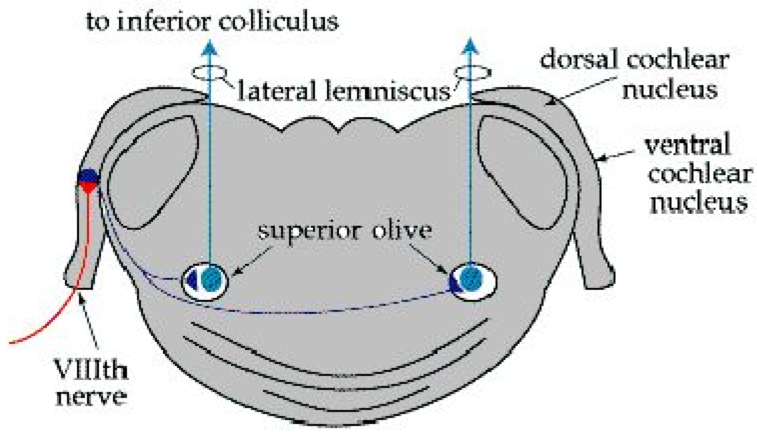


Fig. 1.- Axial schematic cut across superior olives nuclei. Lateral lemniscus originate in this nuclei. (*)

The superior olive then projects up to the inferior colliculus via a fiber tract called the lateral lemniscus. The second stream of information starts in the dorsal cochlear nucleus. This stream analyzes the quality of sound. The dorsal cochlear nucleus picks apart frequency differences which make vowel sounds different. This pathway projects bilateraly to the inferior colliculus, via the lateral lemniscus. From the inferior colliculus, both streams of information proceed to the medial geniculate nucleus. The medial geniculate projects to primary auditory cortex in the horizontal surface of the silvian fissure in temporal lobes [Fig. 2].

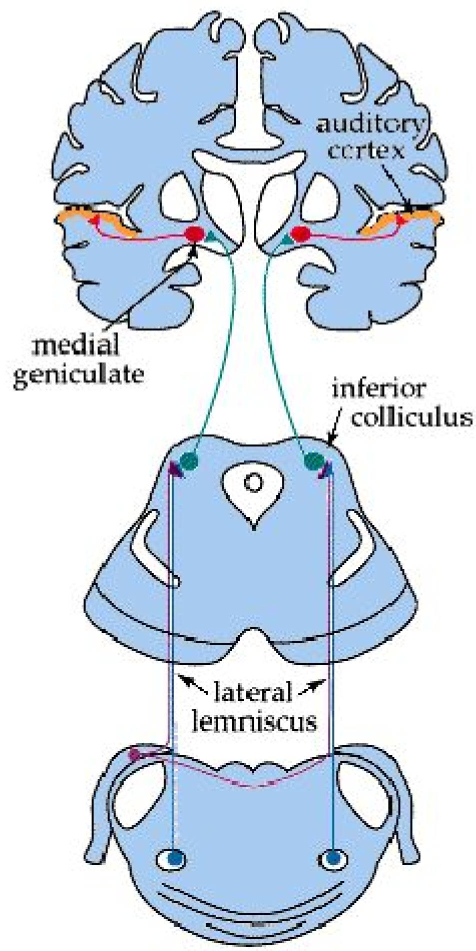


Fig. 2.- Brain stem auditory pathways from cochlear to primary auditory cortex. Fibers cross at many different levels (*).

Anatomic boundaries between auditory processing areas are not precisely known, and may vary among individuals. Nevertheless it is well recognized that the primary auditory cortex is located on the transverse temporal gyrus (TTG) or Heschl's gyrus, which is Brodmann's Area 41, while the secondary auditory cortex is in surrounding regions on the superior temporal gyrus (STG) encompassing Brodmann's Areas 21, 22, 42, y 52 (Celesia, 1976) [Fig 3]. This has been strengthened recentrly by PET studies using baseline noise, tones, words, and speech task that have shown similar bilateral activations within the primary cortices (Lauter et al 1985; Mazziotta et al 1982; Petersen et al 1988; Wise et al 1991). However, speech stimuli produce larger activation posteriorly and superiorly on the left hemisphere than on the right.

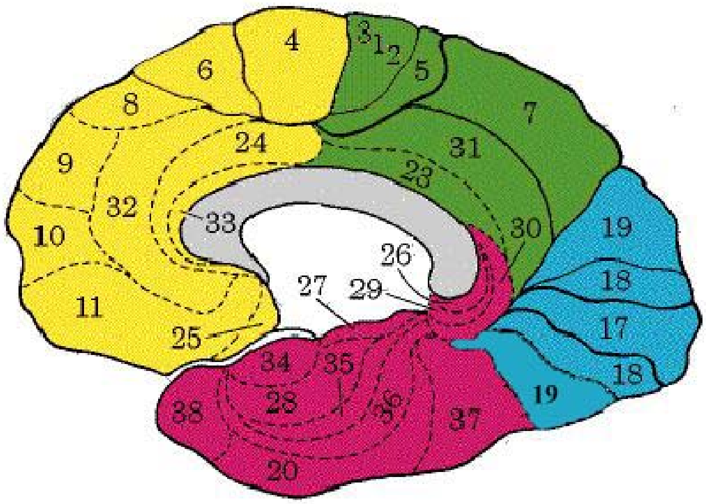


Fig. 3a.- Brodmann's cortical areas. 41.- Heschl's gyrus; 42, 22, 21.- Secondary auditory; 40.- Wernike's; 44.-Broca's area. (**)

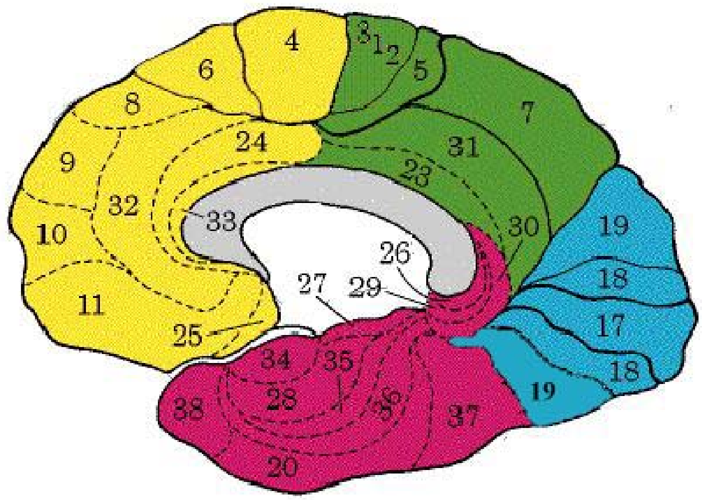


Fig. 3b.- Brodman's cortical areas. Mesial aspect (**)

Left temporal lobe process better language information. Right temporal lobe takes advantage in processing natural sounds without verbal meaning. There is a tonotopic organization in which the higher tones are located medially.

The neuro-physiology of the verbal part is better understood due to capacity to speech out its own function. By means neuropsychological tests now we know that there is first a phonemic analysis of the word, step that is concerned about the contrast between voice and voiceless consonants, e.g.: B vs. P . Such a differentiation is a function of the time the mouth remains close since the sounds start in the larinx. The next step is a semantic analysis done by left parieto-temporal and frontal areas. Finally, syntactic aspects take place in the process, extending the cortex "activation" throughout the junction of the temporal, parietal and occipital lobes, and spreading in frontal areas. Each step takes place in neighbor areas with a centrifugal temporal-spatial arrangement.

Connections or outputs from these areas of processing reach other areas throughout interlobar or inter-hemispheric bundles. For instance: if the limbic lobe is reached, an emotion tint is given to the perception. Areas of cognition, possibly in prefrontal lobes, and areas of episodic memory, could be activated later.

Most of these processes are completely unconscious. Nevertheless, attention to the text is a clear conscious function.

Pathologies of these areas produce important deficits. In adulthood these deficits are clinically well recognized. In contrast, in childhood these syndromes can be difficult to recognize and pitfalls are common when are classified into attencional or dyslexic syndromes.

The acquired language deficit in adults is called aphasia. In childhood, the improper establishment of this specific function is called dysphasia. Aphasia is grouped in two major categories: motor and sensorial. Terms as acoustic-aphasia, agnosic-aphasia, amnesic-aphasia and so on, should have a corresponding representation in the infant. Now a days the term Receptive Developmental Language Disorder it is used to explain this cases.

Functional Magnetic Resonance of Auditory System

Signal production in functional MRI (fMRI) is due to the paramagnetic effect of deoxyhemoglobin. Focal brain activation results in regional increases of CBV, CBF, and oxygen delivery, with a modest increase on oxygen extraction (Belliveau et al, 1991). The ratio between oxyhemoglobin/deoxihemoglobin of venous blood increases and results in less tissue-blood susceptibility difference. Finally, less susceptibility results in less intravoxel dephasing which in turn leads to more signal observable on T2* and T2 images. This is termed the Blood Oxygen Level Dependent (BOLD) effect. Although the direct cause of the increase of the signal is the reduced paramagnetic effect of the deoxyhemoglobin, it could be stated that the more oxyhemoglobin the greater the signal which is also directly related to amount of CBF, CBV, and neural activity.

Functional magnetic resonance imaging (fMRI) of the auditory cortex has unique challenges. The persistent noise produced by the machine does not permit a clean control environment. In addition, several factors as intensity, frequency, rate of presentation, duration of the task, habituation, and cognitive confounds can vary the findings of the procedure.

The auditory evaluation is more demanding than motor because the OFF state of the auditory exam is hardly a resting condition. The noise generated from switching the gradients of the echo plannar imaging (EPI) sequence produces a permanent stimulus of the auditory area.

In fMRI the brain activation is elicited by means a task. A task is repeated several times. Altogether task and settings form a paradigm. In other words, a paradigm consists of an experiment that uses a particular task to depict a brain function. To be reliable it must be simple, clean, reproducible and easy to perform without moving. The defined active task must be compared with a resting or reference task. As an example a motor function will be illustrated. The task is flexion and extension of the right fingers. The reference task is rest, without thinking of the hand task. The active task is sustained for usually 30 seconds and repeated several times alternately with the task of reference. The active task period is named "ON" and the period of reference is called "OFF" (An ON-OFF pair is called a cycle, divided in two epochs). This experiment is performed while the patient lies still in the bore of the magnet and must be performed without the patient moving between the OFF and ON tasks as the images are obtained during this time. Movements beyond 0.5 mm require complicated software correction of the images. The data is then analyzed by a computer utilizing special software to subtract the OFF images from the ON images. For each pixel the computer will find if there was significant variations between the the two tasks. If there is a significant change, the value variation is shown as a color code dot and termed an activated pixel. These results are overlayed on anatomical images. (See apendix 1 to clarify these terms). Contrasted with this clean motor paradigm, the experiments related with auditory stimuli must to deal with some other variables. These will be addressed in the next lines.

Noise at MRI

The sound level of the conventional gradient echo and EPI sequences, the most frequent used in fMRI, is about 100 dB or more. In addition, there are peaks at 500 Hz (Cho ZH, Kim JH, Chung SC et al., 1997). This background noise working in OFF and ON ephocs may scramble the effects of auditory stimulation in auditory cortex fields (Scheich H at al, 1998). The noise level of the 1.5 Tesla General Electric Magneto has been recently reported to be 117 dB SPL, for Ravicz et al, 1997 as referred by Huckins, 1998.

To obtain a good quality of the sound or voice used as stimuli in auditory or verbal assessment, this must be at least 30 dB above these levels. Possible effects of so loud sound noise may include exhaustion or saturation of brain cognitive function, which may reduce the sensitivity of the response during brain activation. By the other hand high levels of intensity may produce sensorial nociceptive responses. Therefore, the reduction of the background noise level is an important goal to reach in order to get easier the assessment of auditory and verbal activation in children's cortex.

The noise outgoing from the MRI may be reduced by isolation of the tubes (which are used to transmit the sound into the magnetic field); headphones o earplugs; noise cancellation devices; or coupling the stimuli with the pulses of the gradient echo changes. The headphones isolation can reduce noise up to 20 dB at 500 Hz (Zang-Hee Cho, Soon-Chul Chun, Dae-Woon L, et al:, 1998). Some techniques has been proposed to be used with the aim of synchronize auditory stimuli and fMRI gradient pulses (Tan CX, Pijker A. and Duifhuis H, 1998: From:Image suppl).

Theoretically, it could be possible to design a device with crystal technology or ceramic components that may work properly into the bore of the magneto. There are some places that are working in that way. With children we need as much as possible a mechanism that does not produce pain, preferable with noise cancellation and high quality. That set must produce a signal between 75 and 90 dB or otherwise 30 dB above the background level (metered in the headphone out-end?). Nevertheless, it pays to mention the experiment of Millen S & Haugton V., 1995, in which they found no differences in the activation of the auditory cortex using pure tones either at 20 dB or 50 dB of sound level pressure (SLP).

Reducing noise levels at different places and steps could be get down noise levels significantly. Scheich et al, 1998, reached 50 dB noise reduction this way: First, they used FLASH sequence that slow down the gradient switching, source of the most aloud noise (TR 176 msec, TE 40 ms and flip angle of 8 degree) reduced the noise level by 30 dB bellow 500 Mhz. Second, using electrodynamic headphones cut down 20 dB more.

Some procedures and devices can reduce the noise:

1. Change the sequence to FLASH
2. Get better acoustic shape to the inner of the exam room.
3. Get better insulation to earplugs and tubes
4. Change transducer to a nonmagnetic speaker as source or a magnetic device placed into a Farady birdcage or a aluminum box, to get higher level of volume.
5. Give output to speaker from an amplifier
6. Feed amplifier with a multimedia computer

The Magnet and Hardware

The 1.5 Tesla magnetic strength of the machine may be not enough reliable in measuring blood flow changes for sub-cortical structures such brainstem nuclei, inferior colliculi and medial geniculate nuclei.

Nevertheless, Melcher, Fullerton & Weisskoff (referred by Huckins S et al, 1998) were successful showing activation of the inferior colliculus in 1.5T FMRI, in 1997.

The head regular coil might be advantageous to depict bilateral functional mapping. However, the use of a smaller 5 inches surface receiver coil has showed improving of the quality of signal to noise ratio, as 30-50%, though exploring only one side at once (Hickins S, 1998). By the other hand it seems the smaller the voxel the better the functional depicting of cortical activation.

Some particular settings of the sequences

The exploration can be done in different planes:

1. Axial, 4mm superior to the bicommissural plane (Berry et al, 1995)

2. Sagital, across Heschl´s gyrus for primary auditory area (The sagital locations of Binder in the experiment of 1994 were not successful in showing verbal asymmetry or different activation from semantic analysis), 8 mm medial to the most lateral point of the temporal lobe.

3. Coronal, up to 8 slices as in the experiment of Huckins S et al, 1998, 10 mm thickness trough temporal superior and angular regions, from anterior commissure to 10 mm posterior to splenium of corpus callosum.

Specific issues of the stimuli

Intensity: 75-90 dB or 20-30 dB over background level, good quality.

Frequency of the stimulus: Tone: 3-5 per second. Speech: 1.5 per second.

Range of tones: 440-2000 Hz

Duration of tones: 100-200 ms

Shape of tone stimulus: Traits, sinus wave or sawtooth.

Duration of each epoch: 8-30 sec

Theoretically given traits of mixed tones as scales, could activate the auditory cortex in a similar manner than tapping thumb-other-fingers do.

Types of ling protocols to be addressed

(Each of them can be done binaural o monoaural, plain or with mask sound named dichotic audition)

No.	On	Off	Subtype	Notes
1	Plain tones	Noise		Primary cortical auditory areas (CAA)
			Non-Discriminatory	Idem
			Discriminatory	CAA activated by attention or reduced by filtering. Eventually can be depicted tonotopic organization
2	Chords	Noise	Non-discriminatory	CAA Primary and secondary
	Chords	Noise	Discriminatory	CAA Primary and secondary. Wider activation.
3	Music	Noise	Non-discriminatory	CAA with greater activation of secondary areas. Better on the right?
	Music	Noise	Discriminatory	CAAs, wider activation. Areas involved in emotion of memories can be activated.
4	Phonemas	Noise	Non-discriminative	CAA (Better at left side ?)
			discriminative	CAA plus discriminatives areas of voice/voiceless letters type.
5	Words	Noise	Non meaning words	CAA (+areas of conscious of words!)
			Meaning words	CAA plus semantic analysis areas (have not been demonstrated)
6	Sentences	Noise	Non-meaning	
			non-attending	CAA (plus…semantic analysis, plus sintactic analysis ….comprehension ?)
			attending	CAA plus discriminative areas plus WM (frontal)
			meaningful	
			Non-attending	CAA plus DA plus unconscious areas of processing
			attending	CAA plus DA plus WM plus areas of semantic process
7	Sentences	words	meaningful	WM+Sintactic meaning area !! (SMA)
8	Sentences	phonemes	meaningful	SMA plus semantic word activated area
9	White words	neutral-words		Positive emotion areas
10	Threatening words	neutral words		Negative emotion triggering areas
11	Music	White noise		CAA (with some laterality)
	Music	non-meaning words		CAA basic laterality ?
12	Music	meaning words		It depends on previous results Which one is the larger area?
13	Regular Music	Backward music		??
14	Natural sounds	Noise		CAA (With laterality)
15	Maternal voice	neutral voice		Memory mother related? Or affective involvement? Both?
16	Audition of text	internal repetition of it		Differences between outside-imputs and inside imputs
17	Audition	Noise	Sedated	Most of them with anesthesia

Some aspects about proceedings with children

1. First of all the main challenge is to find the best sedative drug. This will be that with the least effects in brain metabolism and CBF as well as good safe and easy control.

2. The quality of the sound could be crucial. It needs to be at least 75 dB in intensity besides good definition.

3. It is necessary to get a confident basic paradigm.

4. Possibly the best paradigm to start is that which we would expect producing the widest cortical activation. It seems to me that paradigm could be Verbal-meaningful-sentences with some emotion tint vs. noise, biaural audition. In infants the familiarity with the source voice could be important.

5. It is necessary to obtain excellent definition of the images and state of the art processing software.

Conclusions

FMRI can help us to understand the deficits produced by many disorders in children and make important differences between similar cases, improving the approach for their treatments. Dases as dyslexia, ADHD and autism could be better understood. Schulte-K¨orne G et al (1998) have demonstrated a specific speech processing deficit at the sensory level in dyslexic patients. These findings could be used to identify children at risk at an early age. Anatomic changes have been shown in geniculate nuclei of dyslexic patients (Galaburda AM. et al, 1994). Higher brainstem abnormalities have been found in autistic children (Thivierge J., et al, 1990).

Appendix 1

Glossary of FMRI terms

Exam: A specific type of procedure to perform to a specific patient.

Sequence: One a particular arrangment or setting of TR, TE, Flip Angle, etc.

Run: Group of images with the same sequence for the same porpouse into a exam

Series: Group of specific cycles protocol-related in a specific exam

Cycle: Two or more epochs to be repeated over during a series. Commonly named ON and OFF

Epoch: Each of the parts of a cycle. Each ON, or each OFF.

Block: Number of sets or slices in a epoch

Group: The same as block (Used by Huckins)

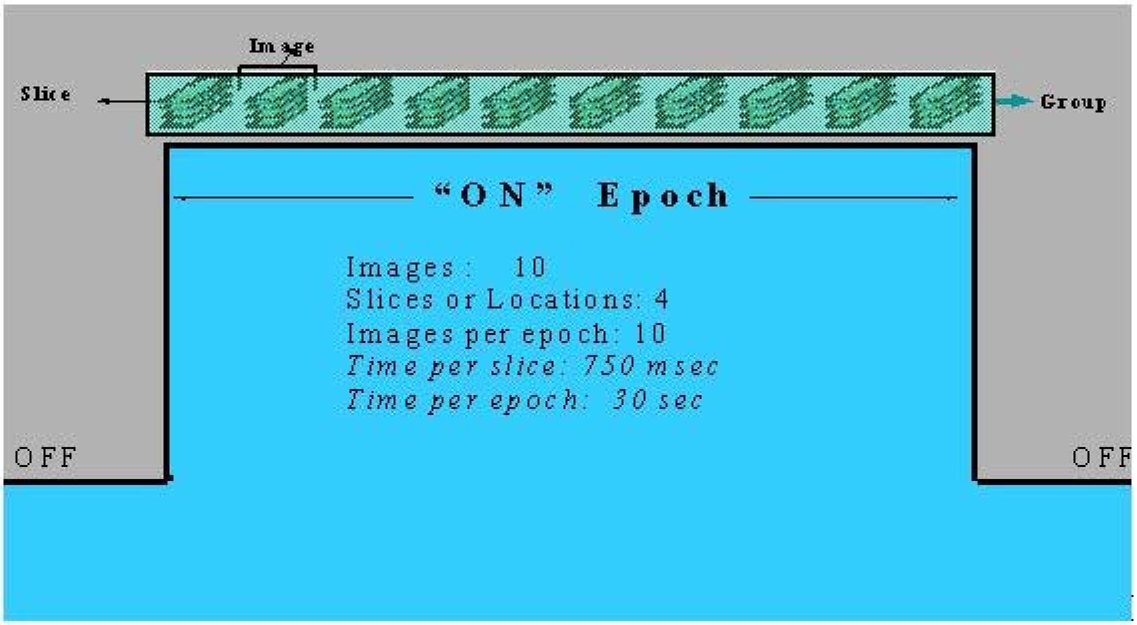
Set: Group or slices in different locations to be scanned in a target area

Scan: The same as set.

Image: Each indivisible part of a study.

Slice: Equal to image

Location: Equal to slice but in keeping with anatomical meaning. Location set is the group of images in the same anatomical location time-course related.



(*) Images 1 and 2 are modified images taken with permission from http://thalamus.wustl.edu/course/audvest.html, a website in which the reader can find more material related with the auditory system.

(*) Images 3a and 3b are images taken with permission from http://www.umich.edu/~cogneuro/Brodmann.html

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