

# Proposed Research on Developmental Language Disorders

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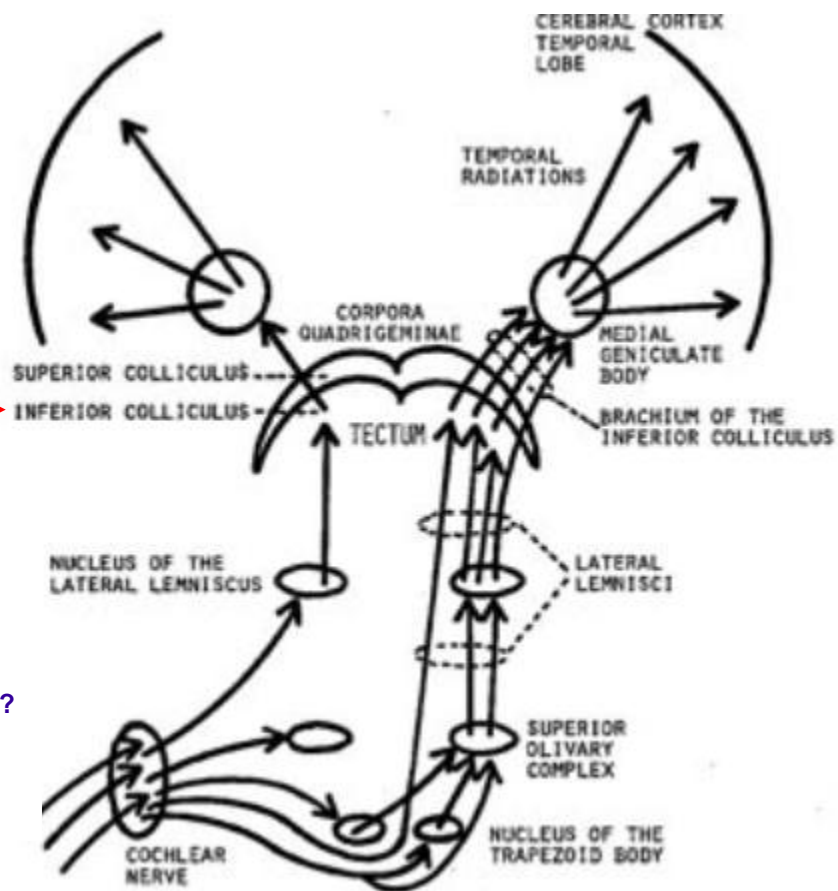
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My interest is in this   
small area of the midbrain

**Question:** Could  
brainstem impairment  
lead to developmental  
language disorders?  
From insults such as:  
Prenatal exposure to alcohol?  
Prenatal infection?  
Asphyxia at birth?  
Toxic exposure in infancy?



**The auditory system of the brain, from cochlear nerve to temporal lobes – essential for language development**

Note: To learn about fMRI, I took a course in Cognitive Neuroscience at the Harvard Extension School with Professor Yoohong Jiang In the spring of 2005. I submitted this proposal as my final course project. Professor Jiang is now at the University of Minnesota, <https://apps.cla.umn.edu/directory/profiles/jiang166>

## Motivation:

### The inferior colliculi appear to be important for speech understanding

- Since 1991, with the advent of magnetic resonance imaging (MRI), eleven cases of deafness and auditory agnosia have been reported, associated with selective (and bilateral) damage of the inferior colliculi.
- Loss of speech understanding ("word deafness") was the primary problem in nine of these cases [1-10].

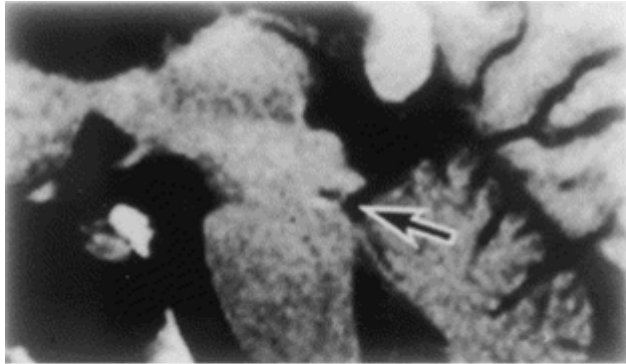
### The inferior colliculi are metabolically the most active site in the brain Blood flow and aerobic metabolism are highest in the inferior colliculi [11-15]

- The inferior colliculi are vulnerable to any catastrophic disruption of aerobic metabolism [16-18, 19-23].
- The inferior colliculi are prominently involved in the brainstem pattern of damage caused by alcohol intoxication, or poisoning by many other toxic substances, which also can often be catastrophic [24-29, 30-37].
- The inferior colliculi are prominently damaged by a brief period of oxygen deprivation before, during or after birth [38-39, 40-49].

### Perinatal compromise can cause damage in the inferior colliculi

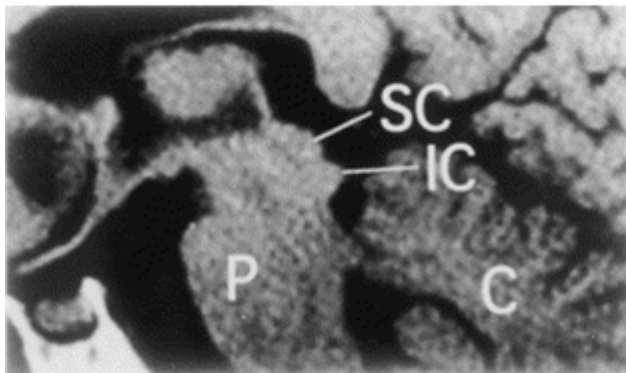
- Impairment of function is likely in infants with prenatal exposure to alcohol and other drugs [50-55].
- Impairment of function is likely in infants who suffer oxygen deprivation during a difficult birth and/or develop neonatal jaundice [56-65].
- Impairment of function should be even more serious for infants than adults who suffer sudden "word deafness" following injury to the inferior colliculi.

## The inferior colliculus may play a special role in analysis of the acoustic features of speech.



Injury in a skiing accident resulted in a "punctate hematoma" affecting the inferior colliculi bilaterally (right). Compare with the normal appearance of the inferior colliculi (bottom picture).

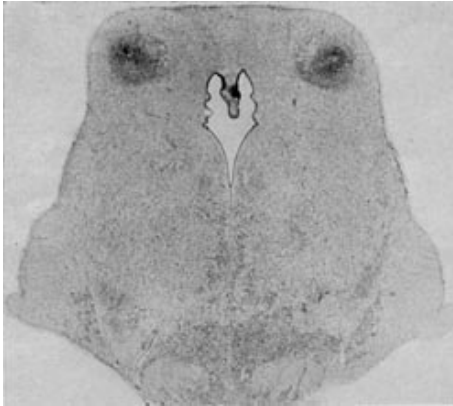
**The skier, whose MRI is shown here, was one of the 9 cases in which comprehension of spoken language was lost following bilateral injury of the inferior colliculi.**



Impact from the free edge of the cerebellar tentorium was thought to have caused this injury.

**How much more serious such an injury would be for an infant, who had not yet begun to speak!**

From Johkura K et al. J Neurol Sci 1998;161:91–96.



From Myers RE (1972) Am J Ob Gyn 112:246

In experiments with newborn monkeys **(an attempt to produce an animal model of cerebral palsy)**, damage to the inferior colliculi was found in animals subjected to asphyxia for 8 to 10 minutes (above) **[38, 39]**.

Damage of the inferior colliculi in human infants has also been observed (bottom right) **[40-49]**.



From Leech & Alvord (1977) Archives of Neurology 34:109

## **Monkeys subjected to asphyxia did not develop cerebral palsy.**

The brainstem damage found was dismissed as minimal, thus perhaps the perception that infants can tolerate asphyxia at birth without serious harm.

## **Brainstem aphasia?**

Gilles (1963), citing the experiments with monkeys on asphyxia at birth, and his own observations suggested:

“...certain congenital brain stem nuclear ‘aphasias,’ for example, Moebius syndrome, may be related to temporary prenatal or perinatal cardiac failure” [40, p318]

**Note: This comment appeared in an abstract of a presentation given at the 38th Annual Meeting of the American Association of Neuropathologists, June 16, 1962.**



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**The purpose of the research proposed here is to use functional MRI (fMRI) to investigate:**

- I. The hypothesis put forward by Gilles (1963) that impairment of function in the inferior colliculi might underlie some developmental language disorders, or
- II. Whether some developmental language disorders occur in the absence of any measurable impairment of auditory function.

**Functional MRI (fMRI) may provide a way to investigate auditory system function in people with acquired or developmental language disorders.**

I wrote a letter in response to the article by CL Pan et al.<sup>1</sup> on auditory agnosia caused by a cancerous growth that invaded the inferior colliculi in a 14-year-old child. This was one of several attempts I have made to point out the long-forgotten papers on damage of the inferior colliculi caused by asphyxia at birth.<sup>2,3</sup>

My letter, with a response from the authors was published in July 2005 [Neurology, 2005 Jul 26;65(2):339], and both are also online at:

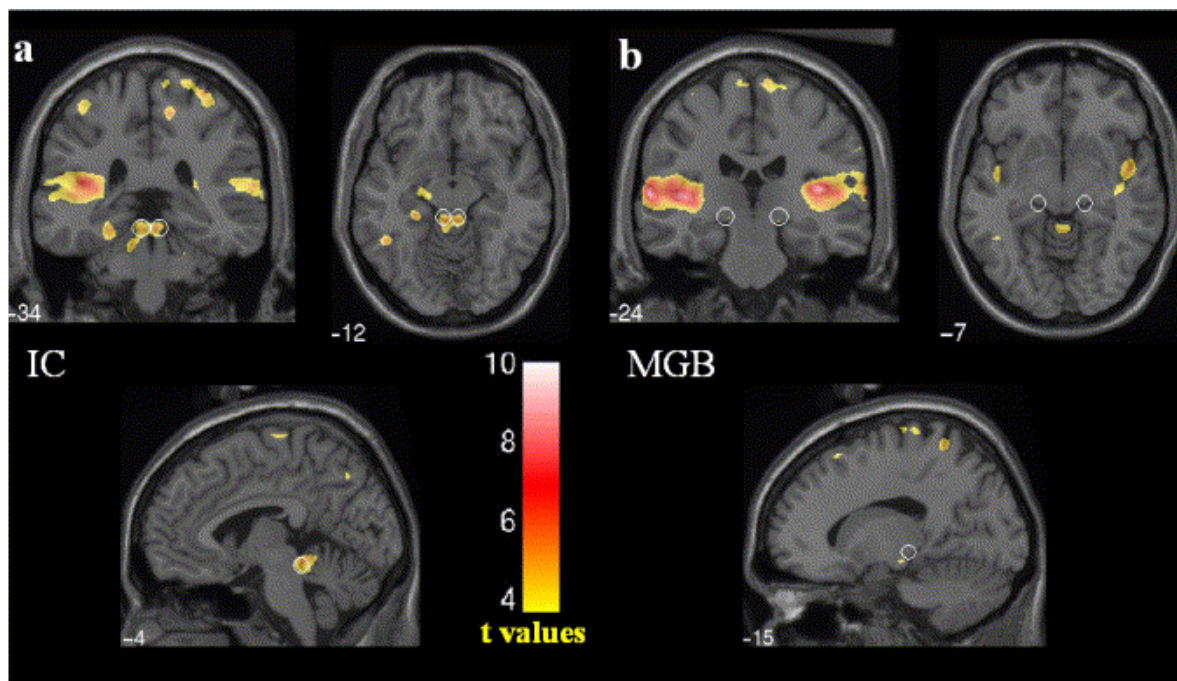
<http://www.neurology.org/cgi/eletters/63/12/2387>

**Note: In their response, authors Hsieh and Pan point out that frequency components of complex sound spectra are resolved in the inferior colliculi, which may be important for language development. They further point out that inadequate anatomical resolution has up to this time prevented investigation of the inferior colliculi in the language disturbance of children with pervasive developmental disorders, but that now, with magnetic resonance imaging, these hypotheses are ready to be tested!**

<sup>1</sup>Pan CL, Kuo MF, Hsieh ST. Auditory agnosia caused by a tectal germinoma. Neurology. 2004 Dec 28;63(12):2387-9.

<sup>2</sup>Windle WF. Brain damage by asphyxia at birth. Sci Am 1969; 221: 76-84.

<sup>3</sup>Myers RE. Two patterns of brain damage and their conditions of occurrence. Am J Obstet Gynecol 1972; 112:246-76.

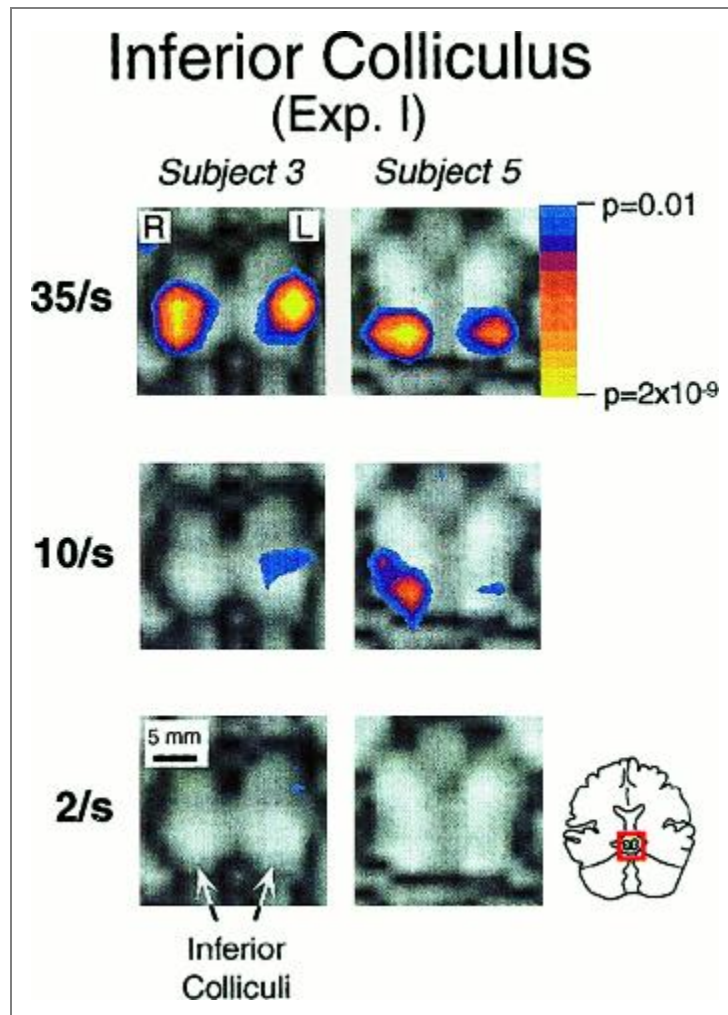


From: Budd TW et al. Neuroimage 2003; 20:1783

- (a) Three orthogonal slices, coronal, horizontal, sagittal – centered on the anatomically defined inferior colliculi (IC), white circles superimposed,
- (b) Slices centered on the anatomical center of medial geniculate bodies (MGB)

## The inferior colliculi on fMRI scans

The special brightness of the inferior colliculi may be because they have the highest blood flow in the brain even in the absence of stimulation.



### The inferior colliculi on fMRI scans

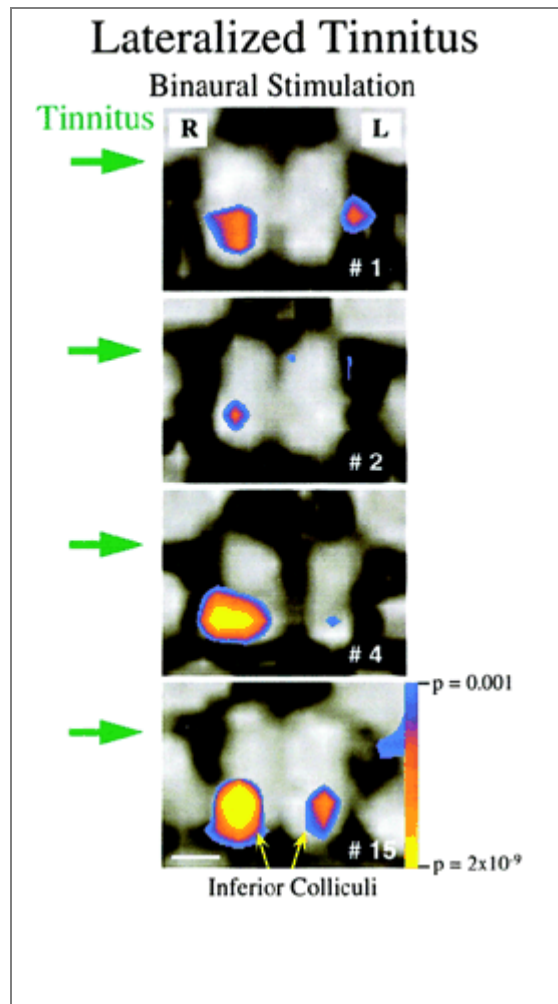
Responses to increasing rates of auditory stimulation

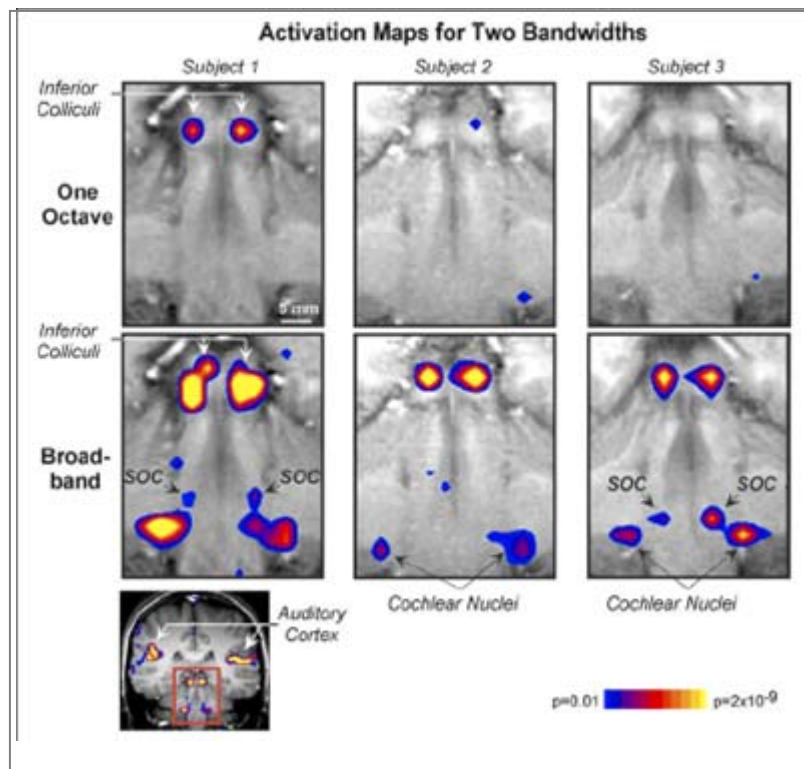
From Harms & Melcher  
J Neurophysiol 2002;88:1433

## The inferior colliculi on fMRI scans

Responses in people with Lateralized tinnitus (ringing in the ears).

From Melcher JR et al.  
J Neurophysiol 2000; 83:1058





## The inferior colliculi on fMRI scans

Recruitment of greater activity with increasing sound bandwidth.

From: Hawley et al.  
Hear Res. 2005  
Jun;204(1-2):101-10.

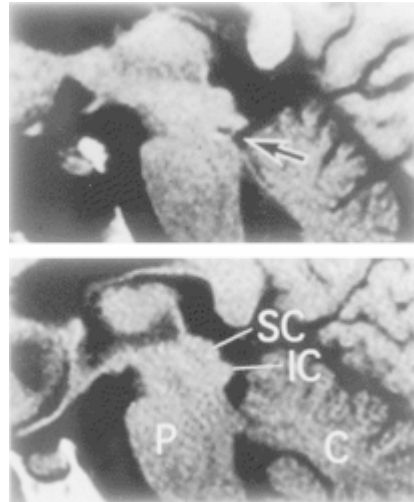
**Subjects for the research proposed here will include children and adults with acquired and developmental language disorders:**

**1. language difficulties following traumatic head injury**

**Note: Loss of speech understanding in instances of closed head injury was attributed to trauma caused by impact from the cerebellar tentorium in 3 cases.**

**Most head injuries result in traumatic injury of wide areas of the brain, but tentorial impact may also occur in many of these cases.**

**If traumatic injury of the inferior colliculi is seen with MRI (as in the case of the ski accident), decreased activity with fMRI would also be anticipated, and could be compared with activity levels determined in individuals with developmental language disorders.**



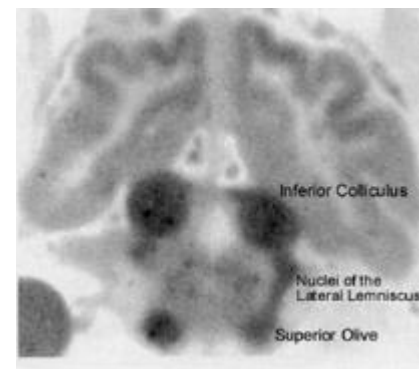
From: Johkura K. Midbrain deafness with normal brainstem auditory evoked potentials. Neurology. 2002 Oct 22;59(8):1293.

- 2. Adults with language problems persisting from childhood, such as autism, Asperger syndrome, dyslexia, stuttering, or hearing impairment.**
- 3. Children with developmental delay learning to speak associated with autism, Asperger syndrome, and/or hearing impairment.**
- 4. Children with cochlear implants (note, MRI is being used following implantation [74-76].**
- 5. Children with problems like stuttering or difficulty learning to read.**
- 6. Adults with presbycusis, which may result from loss of function in the inferior colliculi [77-81].**
- 7. Adults and children (for whom permission can be obtained) with no childhood or current language disorder.**

## Testing strategies:

1. For subjects who are mute or with severe verbal disabilities, investigation with:
  - a) clicks and pure tones presented with increasing repetition rate, from 2/second to 35/second, as in experiments on normal subjects by Harms Melcher(2002)
  - b) pure tones delivered out of phase at each ear, and
  - c) presentation of selected multi-syllabic words.
2. Recognition of multi-syllabic words in quiet (WRIQ) and with increasing levels of background noise (WRIN) would be tested in higher-functioning subjects following some of the methods of Church et al. (1997) [82-83].

**Note: Cardiac gating by the method of Guimaraes et al. (1998) will be used; the high rate of blood flow in the brainstem causes pulsations that mask most auditory stimuli. Quiet MRI as described by Yetkin et al. (2004) will also be employed. The highest rate of blood flow is to the inferior colliculi, as was revealed in the experiments on cerebral circulation by Landau et al. (1955) in radiographic pictures as shown to the right.**



From: Kety SS. Regional neurochemistry and its application to brain function. In French, JD, ed, *Frontiers in Brain Research*. New York: Columbia University Press, 1962. pp 97-120.

- Harms MP, Melcher JR. Sound repetition rate in the human auditory pathway: representations in the waveshape and amplitude of fMRI activation. *J Neurophysiol*. 2002 Sep;88(3):1433-50.
- Church MW et al. Hearing, language, speech, vestibular, and dentofacial disorders in fetal alcohol syndrome. *Alcoholism, Clinical and Experimental Research* 1997; 21:227-237.
- Guimaraes AR et al. Imaging subcortical auditory activity in humans. *Hum Brain Mapp*. 1998;6(1):33-41.
- Yetkin FZ et al. Functional magnetic resonance imaging of activation in subcortical auditory pathway. *Laryngoscope*. 2004 Jan;114(1):96-101.

## Anticipated results:

1. Observing activity changes with different stimuli in victims of head trauma may suggest auditory stimuli most useful in detecting altered activity in fMRI scans of the inferior colliculi in individuals with known damage of the inferior colliculi.
2. It is anticipated that alteration of activity in the inferior colliculi will be found in adults and children with fetal alcohol syndrome, especially with “word recognition in noise.”
3. It is anticipated that alteration in activity in the inferior colliculi will be found in adults with presbycusis (hearing impairment with aging), especially on tests of word recognition in noise (WRIN).
4. It is anticipated that alteration in activity in the inferior colliculi will be found in adults with life-long autism, childhood language delay, or persisting language disorders.
5. Experimentation is planned, to find auditory stimuli that would show a clear difference from normal subjects, and to look for paradoxical high or low activity.

**Children and adults with autism often appear to suffer from hyperacusis, which might be due to loss of inhibitory neurons, but perhaps also increased activity of excitatory neurons [84-86].**

6. It is expected that (as in other investigations) decreased cortical activity with language tests will be found in the studies proposed here for individuals with autism and other life-long language disorders.

## Working Hypotheses & Rationale:

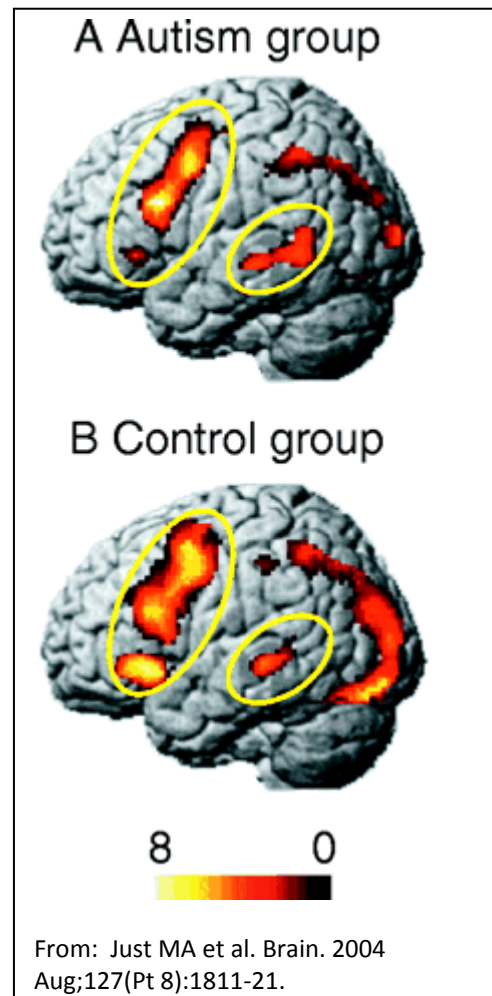
Recent fMRI investigations of language disorder in autism implicate “underconnectivity” and differences from normal in brain symmetry [87-89]

Brain activation of autistic (A) and control (B) groups (Sentence versus Fixation contrast):

Autistic participants show less activation in the left inferior frontal gyrus (LIFG) than the control group, but more activation in the left posterior superior temporal gyrus (LSTG) than the control group.

**Differences from normal are evident in the language areas of the cortex!**

**But what impairs development of the cortical language areas?**



## **Monkeys subjected to asphyxia at birth displayed transient delay in development of motor control.**



**Monkey with  
developmental delay**



**Normal  
monkey**

**They did eventually appear to “catch up.”**

**But examination of the brain many months or years later revealed that brain growth had not progressed normally [90].**

**Neurons were sparser in: The oculomotor nuclei, reticular formation, mammillary bodies, hippocampus, amygdala, corpus callosum, cerebellum (Purkinje cells) and cerebral cortex (parietal and frontal) than in normal monkeys.**

**These sites correspond to where changes are found in the brains of people with life-long autism [91-92].**

## The possible importance of the inferior colliculi for language development is based on four major considerations:

1. Maturation of the cerebral cortex continues after birth guided by trophic neurotransmitters produced in neurons of brainstem nuclei [96-98].



Myelin in the human brainstem auditory pathway at 25 gestational weeks (sagittal view)

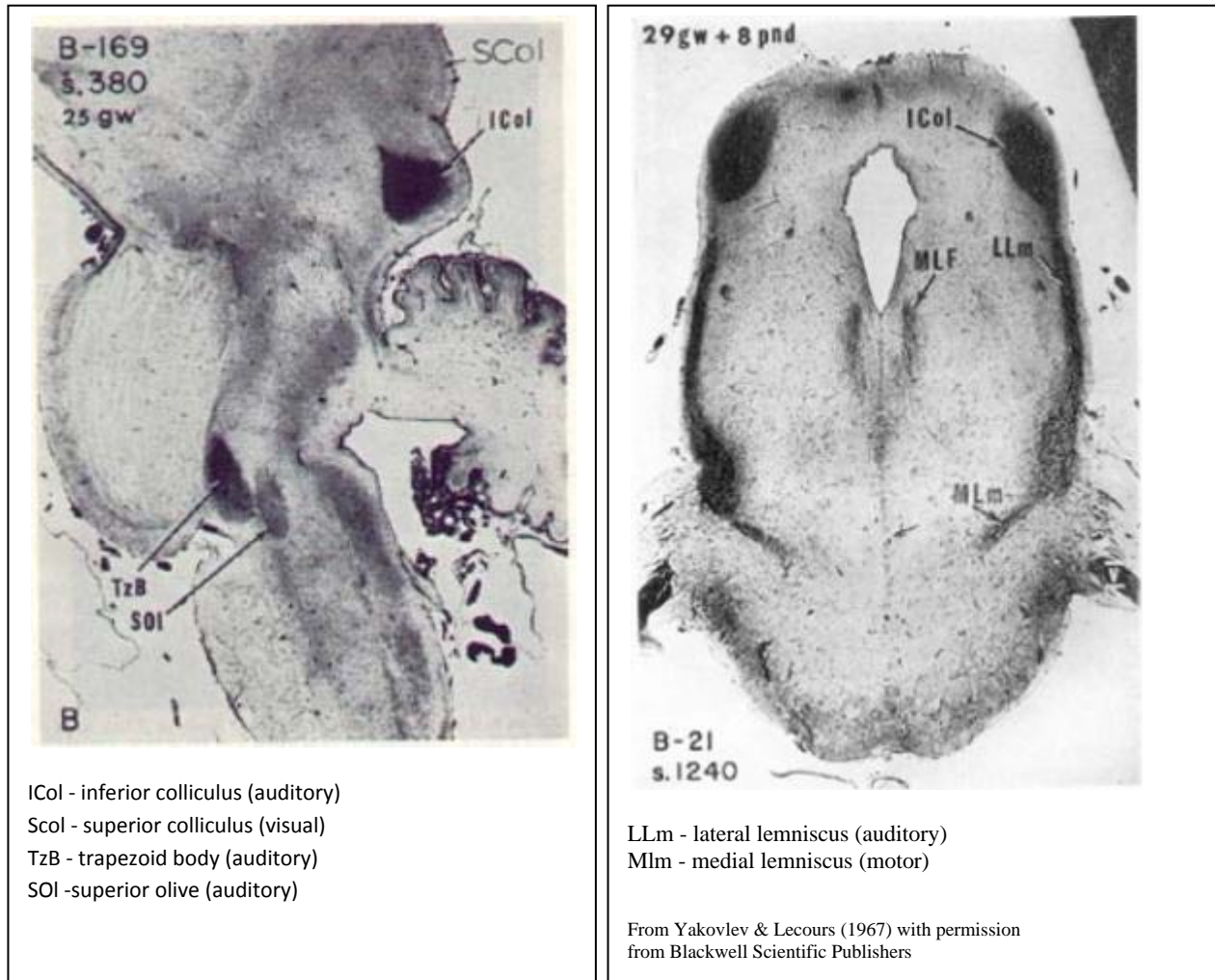
2. The brainstem auditory pathway is fully myelinated and functional in the human fetus by 29 gestational weeks [97, 98].

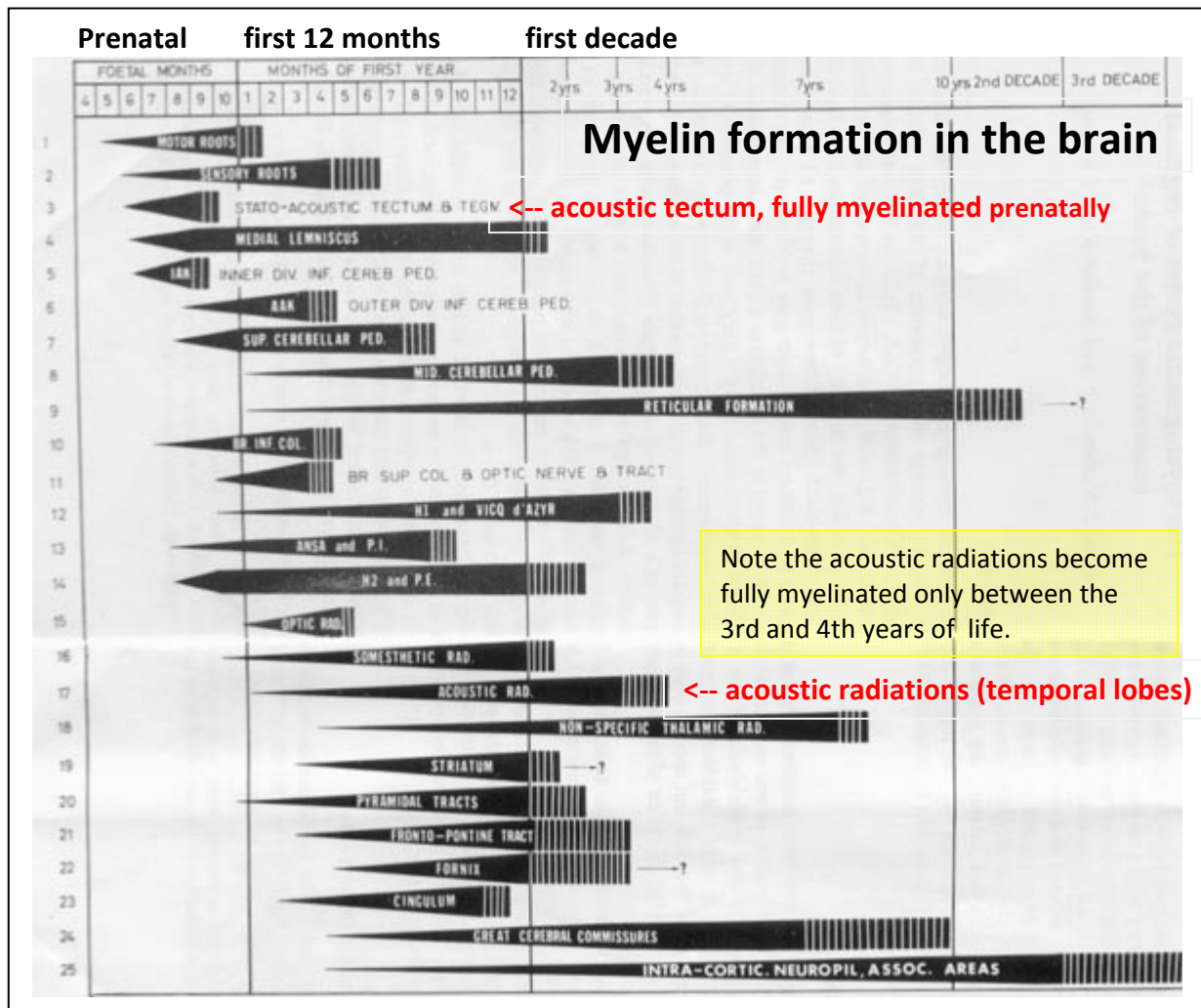


Myelin in the human brainstem auditory pathway at 29 gestational weeks (horizontal view).

3. Myelination of the later maturing target areas for the brainstem auditory pathway (the temporal and frontal language areas of the cortex) continues over the first four years of post-natal life.
4. Thus children normally learn to speak “by ear” before the language areas of the cortex are fully developed.

The brainstem auditory pathway is one of the earliest systems to become myelinated and functional.





## Children learn to speak “by ear”

- Before the language areas of the cerebral cortex are fully developed.
- Children appear to hear and use stressed syllables first, and employ these smallest units of meaning (morphemic units) in the "telegraphic speech" characteristic of baby-talk [[99-102](#)].

Roger Brown and his student Ursula Bellugi came to this conclusion after extensive analysis of copious recordings of the early utterances of three children.

- Children begin to use syntax as maturation of the cortical language areas takes place - but still via the auditory route [[103-106](#)].
- Rapin (1997) suggested that some children with autism exhibit a "verbal auditory agnosia" (VAA), and appear not to recognize syllable and word boundaries in rapid streams of speech [[107](#)].
- Early auditory system impairments in children who are late learning to speak appear to lead to persisting learning problems [[108-113](#)].



Roger Brown 1925-1997

Recognition of the importance of auditory function for normal language development appears to be increasing [[86](#), [114-121](#)].

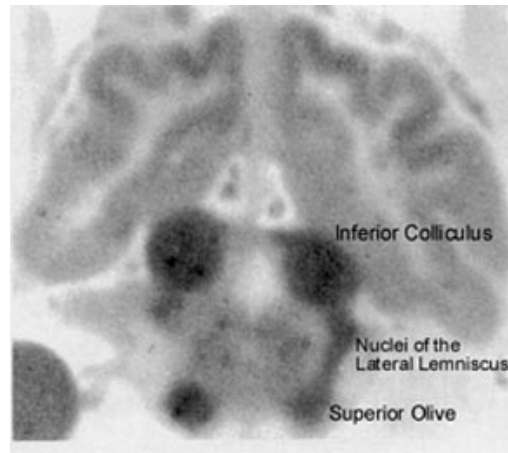
## Blood flow and metabolism are greatest in the auditory system

Experiments on cerebral circulation (in cats) showed greatest perfusion of a radioactive tracer after 60 seconds, thus greatest blood flow, in nuclei of the brainstem auditory pathway<sup>1</sup>.

**Auditory nuclei should therefore be vulnerable to circulatory arrest or asphyxia, or to any factor that disrupts aerobic metabolism.**

### Why is this not always the case?

Protective mechanisms go into action that work to preserve metabolic functions during hypoxia or circulatory insufficiency.



From: Kety SS (1962) Regional neurochemistry and its application to brain function. In French, JD, ed, *Frontiers in Brain Research*. New York: Columbia University Press, pp 97-120.

<sup>1</sup>Landau et al. (1955) The local circulation of the living brain; values in the unanesthetized and anesthetized cat. *Trans Am Neurol Assoc* 80:125

## Protective mechanisms

Increase blood flow and delivery of oxygen to the most active areas of the brain during periods of hypoxia or circulatory insufficiency:

- Vasodilation<sup>1</sup>
- Release of oxygen by hemoglobin in response to the metabolic end-product carbon dioxide (**the Bohr effect**)<sup>2</sup>

The cerebral cortex is most predictably susceptible to damage from circulatory insufficiency or hypoxia. The brainstem pattern of damage has long been reported and discussed as an unusual finding in cases of complete circulatory arrest (Janzer & Friede 1980). The difference is not a matter of degree, but whether oxygen is totally lacking or only in short supply. The Bohr effect is among the most elegant mechanisms that evolved to maintain homeostasis in multi-cellular organisms dependent upon aerobic metabolism.



**Christian Bohr (1855-1911)**

<sup>1</sup>Kelly PA et al. (1995) Enhanced cerebrovascular responsiveness to hypercapnia following depletion of central serotonergic terminals. *Journal of Cerebral Blood Flow and Metabolism* 15:706-713

<sup>2</sup>Jensen FB (2004) Red blood cell pH, the Bohr effect, and other oxygenation-linked phenomena in blood O<sub>2</sub> and CO<sub>2</sub> transport. *Acta Physiol Scand.*182:215

## **Catastrophic factors prevent protective mechanisms from going into action.**

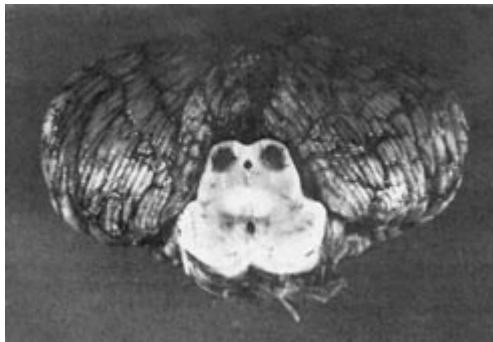
**Suffocation, circulatory arrest, or any factor that disrupts aerobic metabolism can cause damage or impair function in the auditory system, especially the inferior colliculi.**

**The picture to the right shows damage of the inferior colliculi in a human patient maintained on prolonged parenteral feeding that lacked vitamin B1.**

**Vitamin B1 is an essential coenzyme for aerobic enzymes.**

**Any toxic substance that crosses the blood-brain barrier can disrupt aerobic enzymes and cause the same kind of damage.**

**Alcohol intoxication has long been known to cause a brainstem pattern of damage that often involves the inferior colliculi.**



From Vortmeyer AO et al. (1992)  
Haemorrhagic thiamine deficient encephalopathy following prolonged parenteral nutrition. *Journal of Neurology, Neurosurgery and Psychiatry* 55:826-829.

## **Cardiac Arrest Encephalopathy:**

Damage restricted to the brainstem is only seen after total interference with aerobic metabolism occurs; Janzer and Friede (1980) referred to brainstem pathology as "cardiac arrest encephalopathy;" this was the case in monkeys subjected to several minutes of total asphyxia at birth.

**Myers (1972) found that prolonged partial hypoxia late in gestation caused damage to wide areas of the cerebral cortex, which was thought far more important than the brainstem pattern. This was cerebral palsy!**

**Miller and Myers (1970, 1972) found also that adult monkeys sustained brainstem damage with complete circulatory arrest, and widespread cortical damage with partial circulatory insufficiency.**

Janzer RC, Friede RL. Hypotensive brain stem necrosis or cardiac arrest encephalopathy? *Acta Neuropathol (Berl)*. 1980;50(1):53-6.

Myers RE (1972) Two patterns of perinatal brain damage and their conditions of occurrence. *American Journal of Obstetrics and Gynecology* 112:246-276

Miller JR, Myers RE (1970) Neurological effects of systemic circulatory arrest in the monkey. *Neurology* 20:715-724.

Miller JR, Myers RE (1972) Neuropathology of systemic circulatory arrest in adult monkeys. *Neurology* 22:888-904.

## References

**1-10, 11-15, 16-18, 19-23, 24-29, 30-37, 38-39, 40-49, 50-55, 56-65**

<b>Auditory</b>	<b>Highest</b>	<b>Cardiac</b>	<b>Thiamine</b>	<b>Alcohol</b>	<b>Toxic sub-</b>	<b><u>Asphyxia at birth</u></b>		<b><u>Auditory impairments</u></b>	
<b>Agnosia</b>	<b>metabolism</b>	<b>arrest</b>	<b>deficiency</b>		<b>stances</b>	<b>animal</b>	<b>human</b>	<b>prenatal</b>	<b>perinatal</b>

### Deafness and/or auditory agnosia following injury of the inferior colliculi:

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2. Meyer B, Kral T, Zentner J. Pure word deafness after resection of a tectal plate glioma with preservation of wave V of brain stem auditory evoked potentials. *J Neurol Neurosurg Psychiatry* 1996;61:423-424.
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### Sites of highest blood flow and aerobic metabolism in the brain

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## **Catastrophic disruption of aerobic metabolism**

### **I.**

#### **Cardiac arrest encephalopathy**

16. Janzer RC, Friede RL. Hypotensive brain stem necrosis or cardiac arrest encephalopathy? *Acta Neuropathol (Berl)*. 1980;50(1):53-6.
17. Miller JR, Myers RE (1970) Neurological effects of systemic circulatory arrest in the monkey. *Neurology* 20:715-724.
18. Miller JR, Myers RE (1972) Neuropathology of systemic circulatory arrest in adult monkeys. *Neurology* 22:888-904.

### **II.**

#### **Deficiency of thiamine (vitamin B1) - essential for aerobic metabolism**

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### **III.**

#### **Damage caused by alcohol -**

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#### IV.

##### Damage caused by other toxic substances

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**Methyl bromide was formerly used as a fire extinguisher, it is still used as an herbicide.**

**Mercury is oto-toxic, and the neuropathological study of Oyanagi et al. revealed its damaging effects in the brain.**

**Alpha-chlorohydrin was developed for possible use as a male contraceptive.**

**Carboplatin is used in chemotherapy for cancer patients.**

**Troncoso et al. described the symmetric bilateral lesions of the brainstem caused by pyridoxamine, a poison that displaces thiamine at its enzyme attachment points.**

### **Damage of the inferior colliculi caused by asphyxia at birth**

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### **Damage of the inferior colliculi observed in human infants**

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### **Prenatal factors associated with auditory system impairments**

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**Prenatal exposure to alcohol and cocaine are not good, and consideration should be given to the possible deleterious effects of over-the-counter drugs, artificial sweeteners, and other nutritional substances generally assumed to be safe.**

#### **Perinatal or postnatal factors associated with auditory system impairments**

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