

## The non-classical auditory pathways are involved in hearing in children but not in adults

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### Abstract

Auditory information ascends through the brainstem to the cerebral cortices in two parallel pathways, known as the classical and the non-classical ascending auditory pathways. The importance of the non-classical auditory pathway for hearing in humans is unknown but its subcortical connection to limbic structures may be important in tinnitus. In this study we show evidence that non-classical pathways are involved in loudness perception in young individuals but not in adults. We used the fact that some neurons in the non-classical auditory pathways receive somatosensory input and we determined the effect on loudness perception of monaural sounds from electrical stimulation of the median nerve at the wrist. Stimulation of the somatosensory system had the greatest effect on loudness perception in the youngest children that we studied (7–8 years) and the effect was minimal for individuals above 20 years of age. The effect was an increase in loudness in 20 of the 40 individuals we studied and a decrease in 4 individuals; 16 experienced no noticeable change in loudness during somatosensory stimulation. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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The anatomy of the non-classical pathways is different from that of the classical pathways, mainly regarding the thalamic relay nuclei. The classical pathways are interrupted in nuclei in the ventral portion of the medial geniculate body (MGB) [1,14,19] while the non-classical pathways are interrupted in nuclei located in the medial and dorsal MGB [1,6]. It is generally assumed that the non-classical auditory pathways branches off from the classical pathways at the midbrain through connections from the central nucleus (ICC) of the inferior colliculus (IC) [1], where all auditory information is interrupted. Both the external nucleus of the IC (ICX) and the dorsal cortex of the IC (DCIC) belong to the non-classical auditory system, and these nuclei receive their input from neurons of the ICC. Morphologic (retrograde tracers) studies in cats reveal a dual representation of somatosensory and auditory systems in some neurons in the external inferior colliculus (ICX) [1], and there are also connections from the dorsal column of the somatosensory system and from the trigeminal sensory system [7,15] to neurons in the ICX and DCIC. Neurons in the cochlear nucleus (especially the dorsal cochlear

nucleus) also receive input from the somatosensory system (dorsal column nuclei and the trigeminal sensory nucleus [7,15]).

The thalamic nuclei of the non-classical pathways (dorsal and medial parts of the MGB) project to secondary and association cortices and to regions of the brain that are not reached directly by the classical auditory pathways such as structures of the limbic system (the basolateral nucleus of the amygdala [9] and probably the cerebellum [9]). The non-classical auditory pathway provides a subcortical route to the basolateral amygdala nuclei, known as the ‘low route’ [9]. Limbic structures can also be reached through the classical sensory pathways via primary, and association cortices (the cortical or ‘high route’ [9]).

While the neurons of the classical ascending auditory pathways respond distinctly to sound stimuli and are sharply tuned to the frequency of sounds neurons in the non-classical pathways are somewhat less sharply tuned and respond less distinctly to sounds [1,3,16]. While neurons of the classical auditory pathways respond only to sound stimuli some neurons of the non-classical auditory pathways also respond to somatosensory stimuli [1] and their response to sound can be modulated by stimulation of the somatosensory system as shown in the cat [2] and the rat [17]. Our previous studies on the involvement of the non-classical auditory system in

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tinnitus [13] made use of the fact that the non-classical auditory system receives input from the somatosensory system and that the transmission of auditory information in the non-classical pathways can be modulated by somatosensory input.

In the current study, we made use of the same method and presented sounds with no apparent spectral information to individuals between the age of 7 and 45 years, one ear at a time and determined if the loudness of the sound changed during somatosensory stimulation (electrical stimulation of the median nerve). A change in loudness as a result of median nerve stimulation was taken as an indication that the non-classical pathways were involved in loudness estimation of these sounds.

We tested 30 children between 7 and 18 years and 10 individuals between the age of 20 and 45 years using the same technique as described earlier [13]. Individuals listened to trains of impulses (clicks) and compared the loudness of these sounds when presented with and without electrical stimulation of the median nerve. The study was approved by the Institutional Review Board of the University of Texas at Dallas. Parents to children younger than 18 years signed consent forms. Individuals above 18 years of age signed the same consent forms.

Sounds were presented to one ear at a time using conventional earphones with circumaural cushions. The test sounds were generated by applying rectangular impulses, 20  $\mu$ S duration, at a rate of 40 pps (pulses per second) to the earphone and the sounds were presented at a level of approximately 65 dB above normal hearing (HL).

The left median nerve at the wrist was stimulated with rectangular impulses, 100  $\mu$ S duration presented at a rate of 4 pps and applied through adhesive surface electrodes. The reference electrode was placed on muscles of the thenar eminence. The intensity of the stimulation was slowly increased until the subjects felt a strong tingling that radiated out in the fingers that are innervated by the median nerve, but without any sensation of pain. With the electrical stimulation off, the sound was presented to the left ear and the subjects were asked to notice the intensity of the sound. After approximately 10 s, the electrical stimulation was switched on for approximately 5 s and the subject was asked if the loudness of the sound changed during the electrical stimulation. If the person noticed a change in the loudness of the sound the same sound was presented without any electrical stimulation and its intensity was varied until it matched the perception of the sound during electrical stimulation of the median nerve. This procedure was repeated at least twice, after which the sound was applied to the right ear and the entire procedure was then repeated for that (contralateral) ear.

Electrical stimulation of the median nerve caused a change in loudness that was largest in the 7–8 year group. In this group of 10 only one did not experience a noticeable change, 7 experienced an increase and 2 experienced a decrease in loudness during electrical stimulation of the

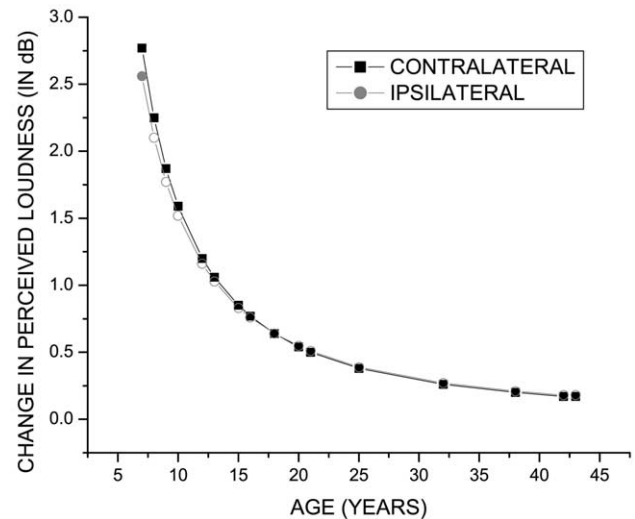


Fig. 1. Average change in perceived loudness during median nerve stimulation, as a function of age.

median nerve. In the age group 9–12 years 2 of 10 subjects experienced no noticeable change and one individual experienced a decrease in loudness. In the age group of 13–19 years 3 of 10 did not experience any noticeable change in loudness, 2 experienced a decrease and 5 experienced an increase in loudness. In the age group of 20–45, only 1 of 10 experienced a noticeable change (increase) in loudness. The effect of median nerve stimulation was similar in the contralateral and ipsilateral ears with mean differences of less than 0.1 dB.

Each individual's change in loudness scores was regressed on age for both the ipsilateral and the contralateral conditions. We found a main effect of age for both the ipsilateral ( $F(1, 38) = 36.3$ ,  $P < 0.001$ ) and contralateral ( $F(1, 38) = 47.9$ ,  $P < 0.001$ ) conditions<sup>1</sup>. Age accounted for similar amounts of variation in the ipsilateral ( $R^2 = 0.49$ ,  $P < 0.001$ ) and contralateral ( $R^2 = 0.56$ ,  $P < 0.001$ ) conditions. The model predicts (see Fig. 1) that, on average, when individuals are young, relatively small differences in age (i.e. from 7 to 9 years) are associated with relatively large decreases in detectable changes in loudness when the median nerve is stimulated (i.e. from 2.56 to 1.77 dB). Conversely, on average, when individuals are older relative large increments in age (i.e. from 25 to 43 years) are associated with relatively small decreases in detectable change in loudness of the sound when the median nerve was stimulated electrically (i.e. from 0.38 to 0.18 dB). Thus, on average, the studied effect decreased at a progressively slower rate with individuals detecting no appreciable difference in loudness levels by 20 years. We therefore concluded that the involvement of the non-classical auditory

<sup>1</sup> The natural log of age and change in loudness for both the ipsilateral and contralateral condition was used in the regression analyses in order not to violate the linearity assumption underlying regression.

pathways was consistent in young individuals but rare in adults.

We interpreted our results as signs of involvement of the non-classical pathways that diminished with age, thus probably a sign of normal maturation. The fact that some of the individuals that we studied experienced an increase in loudness when their median nerve was stimulated while a few individuals experienced a decrease in loudness is in agreement with the reported findings that cells in the ICX can respond to both auditory and somatosensory stimulation and can either enhance or suppress the response to sound [1,2].

There are also other possibilities of interaction between somatosensory and the auditory stimuli. Thus the fact that some cells in the dorsal cochlear nucleus receive somatosensory input provides the neural substrate for such interaction. These pathways may also be regarded as part of the non-classical auditory pathways that make use of the dorsal thalamus. The dorsal cochlear nucleus has been implicated in tinnitus [8].

The change in function of the auditory system that we observed may be an example of specialization where auditory processing is shifted from the phylogenetically older non-classical system, towards the phylogenetically newer classical auditory system that perform finer analysis of sounds. Patrick Wall presented the hypothesis of unmasking of ineffective synapses as a cause of certain forms of neuropathic pain [18] and the results of the present study have led us to hypothesize that the efficacy of synapses that connect auditory input to the non-classical auditory pathways decreases during ontogeny and that these synapses become ineffective at the time of adulthood.

The synapses that connect auditory information to the non-classical auditory system and make the non-classical auditory pathways become involved in loudness perception may become unmasked later in life as an expression of neural plasticity. Examples of that have been shown in connection with severe tinnitus. Thus we showed earlier that 10 of 26 tinnitus patients experienced distinct changes in their tinnitus upon electrical stimulation of the median nerve [13] indicating an involvement of the non-classical auditory pathways in generating the tinnitus in these 10 individuals. Opening of the subcortical route from the dorsal thalamus ('low route' [9]) to the amygdala by activation of the non-classical auditory pathways in patients with tinnitus is further supported by functional imaging studies that showed that structures that belong to the limbic system are activated in some patients with tinnitus [10]. Other studies have also indicated that the non-classical pathways are involved in some forms of severe tinnitus [4].

This subcortical route ('low route') to the basolateral amygdala may be the basis for the emotional reactions to auditory stimuli that are experienced by some patients with severe tinnitus. Normally, highly processed information that is carried by the classical auditory system reaches limbic structures via a long chain of neurons in the cerebral cortex

('high route'). Abnormal routing of auditory information to limbic structures is suggested by the fact that individuals with severe tinnitus often have an abnormal perception of loudness (hyperacusis) and some individuals experience phonophobia [11]. The fact that some individuals with tinnitus perceive sounds from skin stimulation may be a sign of re-routing of tactile information in a similar way as occurs in individuals with neuropathic pain who experience pain from normally innocuous cutaneous stimulation (allodynia) [5,11]. These phenomena may all be explained by unmasking of ineffective synapses [12,18].

The non-classical pathways provide a direct subcortical route to the amygdala [9] that mediates less processed information than the cortical route. Therefore failure in this maturation process that reduces the involvement of the non-classical auditory pathways may cause some of the symptoms in children with some childhood developmental problems. The finding that the non-classical auditory pathways and subsequently the subcortical route to the amygdala are active in children but not in adults may suggest that some of the symptoms in individuals with childhood developmental disorders could be caused by delays of the maturation process that decreases the involvement of the non-classical sensory pathways.

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