

Are the non-classical auditory pathways involved in autism and PDD?

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Objective: To test the hypothesis that some of the abnormal sensory perceptions that characterize autism may be explained by an abnormal activation of non-classical (extralemniscal) sensory pathways.

Methods: Twenty-one individuals, 18–45 years of age who were diagnosed with autism participated in the study. Sounds (clicks presented at a rate of 40 per second and 65 dB above the normal threshold) were applied through earphones. Electrical stimulation (100 μ S rectangular impulses at a rate of 4 per second) was applied through electrodes placed on the skin over the median nerve at the wrist. The participants were asked to match the loudness of the sound with and without the electrical stimulation applied to the median nerve.

Results: Electrical stimulation of the median nerve at the wrist in individuals with autism could change the perception of loudness of sounds presented to one ear through an earphone showing a statistically significant abnormal sensory cross-modal interaction.

Discussion: We interpreted our results to support the hypothesis that some individuals with autism have an abnormal cross-modal interaction between the auditory and the somatosensory systems. Cross-modal interaction between senses such as hearing and the somatosensory system does not occur normally in adults. As only the non-classical (extralemniscal) ascending auditory pathways receive somatosensory input, the presence of cross-modal interaction in autistic individuals is a sign that autism is associated with abnormal involvement of the non-classical auditory pathways, implying that sensory information is processed by different populations of neurons than in non-autistic individuals. [Neuro Res 2005; 27: 625–629]

Keywords: Autism; auditory pathways; PDD

INTRODUCTION

There is considerable evidence that sensory information is processed differently in individuals with various forms of autism. Autistic individuals often find sounds and bright light unpleasant^{1–3} and many individuals with autism perceive sounds abnormally loud (hyperacusis), experience auditory defensiveness, or discomfort or pain from noise exposure. Sometimes certain types of noise such as that from vacuum cleaners or the sound of a school bus engine are perceived as being particularly unpleasant^{3,5}.

Some of the abnormalities in function that are associated with autism have been explained by morphological or functional abnormalities in the amygdala⁶. Some of the symptoms that are ascribed to abnormalities of the amygdala including lack of social contact may be caused by sensory information that reaches the amygdala through a subcortical route from nuclei in the dorsal thalamus. This could occur because of the redirection of sensory information bypassing neurons that normally process sensory information and

targeting neurons that normally do not process auditory information. This may occur because of an abnormal involvement of the non-classical auditory pathways (also known as the extralemniscal⁷, or diffuse or polysensory or non-specific pathways^{8,9}).

Auditory, somatosensory, and visual information can ascend toward higher cerebral cortical centers in two separate pathways, known as the classical and the non-classical pathways¹⁰. These two pathways are different in several ways. The classical pathways are specific to each sense and neurons only respond to one sensory modality, while the non-classical pathways receive input from more than one sensory modality and many neurons respond to more than one sensory modality.

Information that travels in the classical pathways is processed in the ventral thalamic nuclei and projects to primary auditory cortices, while information that ascends in the non-classical sensory pathways is processed in the dorsal and medial thalamus. The targets of the classical pathways are the primary sensory cortices that are specific for the different senses.

Non-classical sensory pathways use the dorsal and the medial nuclei of the thalamus^{9,11–13} and these nuclei connect directly to secondary and association cortices, bypassing the primary sensory cortices.

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The non-classical ascending sensory pathways involve the dorsal and medial thalamus, which connect directly to many structures such as the amygdala (for details see¹⁰) and mostly bypass the primary sensory cortices and target secondary or association cortices instead. This means that an important step in sensory processing (the primary sensory cortex) is bypassed¹⁰. The non-classical pathways provide a direct subcortical route from the dorsal thalamus to the amygdala (known as the "low route"¹³) whereas information normally reaches the amygdala through a long pathway (the "high route")^{10,13}. The high route carries highly processed information that can be controlled by intrinsic brain activity, whereas the low route from the dorsal and medial thalamus of the non-classical pathways, carries information that is little processed and which is under little influence from other centers in the brain.

The non-classical somatosensory system (anteriolateral system) mediates pain and deep body sensation¹⁴, but little is known about the functional importance of the auditory and visual non-classical pathways. Some autistic children enjoy deep body stimulation and may have less discomfort from normally painful stimuli than non-autistic children, indicating an abnormal function of the non-classical parts¹⁰ of the somatosensory system (the anteriolateral system).

Animal studies have shown that the classical pathways perform detailed analysis of sensory information, whereas the processing in the non-classical pathways, which are phylogenetically older than the classical pathways, is much less specific. Neurons in the classical auditory pathway are sharply tuned, whereas neurons in the non-classical pathway are broadly tuned¹⁵.

Yet another important difference between these two types of auditory ascending pathways is that the non-classical sensory systems receive input from more than one sensory system while the classical pathways only receive input from one sensory system¹⁰, and it has been shown that some neurons of the non-classical auditory system respond to stimulation of the somatosensory system^{16,10,17-20} and visual systems²¹. The non-classical pathways thus provide a substrate for cross-modality interaction in the non-classical ascending sensory pathways that the classical sensory system lacks because its neurons only receive input from one specific sensory modality¹⁰.

The fact that the non-classical auditory pathways receive input from the somatosensory pathways has been used in studies of the involvement of the non-classical pathways in humans^{22,23}, in which it was shown that the perception of loudness of sounds was affected by electrical stimulation of the median nerve at the wrist in young children but the effect decreased gradually with age²³. Above the age of 20 years, signs of such involvement of the non-classical auditory system were rare^{22,23}.

The decrease in the cross-modal interaction with age was taken to indicate that the involvement of the non-classical auditory pathways decreases as a part of normal childhood development²³. Other studies of

cross-modal interaction have shown indications that the non-classical auditory system is involved in generating the perception of tinnitus in some individuals²². Abnormal cross-modal interaction between the auditory and the somatosensory system has been shown to occur in patients with tinnitus by other investigators²⁴⁻²⁶.

The signs of involvement of the non-classical pathways in some patients with tinnitus has been taken as an explanation for the hyperacusis and phonophobia that often occur together with severe tinnitus, because re-routing of auditory information to the non-classical auditory system would allow unprocessed auditory information to reach the amygdala through a direct (subcortical) route from the thalamus. It has been hypothesized that these functional changes were caused by expression of neural plasticity^{14,22} and that there is a similarity between some forms of tinnitus and some forms of central neuropathic pain^{10,14,27,28}, which is also often associated with signs of cross-modality interaction (e.g. allodynia) and abnormal involvement of the amygdala^{10,14,29}.

In this paper, we show indications that auditory information in some individuals with autistic disorders ascends in the non-classical pathways to a greater extent than what occurs in non-autistic individuals. Such re-routing of information may explain the abnormal perception of sounds that autistic individuals often have.

METHODS

Participants

Twenty-one participants 18–45 years of age were recruited for this study. Fifteen of the participants (18–38 years of age) (Group I) were recruited from the Autism Treatment Center in Dallas. Individuals who are admitted to the Autism Center undergo rigorous testing to ensure a diagnosis of autism. These tests include the Autism Diagnostic Observation Schedule (ADOS^{30,31}). These participants were relatively severely affected individuals. Six participants (16–45 years of age) were recruited from the autism societies in the area. Each of these participants (Group II) had previously been diagnosed with autism or Asperger's syndrome. The diagnosis was confirmed by one of the authors (J.K.K.) using the criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994). These individuals were relatively less severely affected. We did not specifically test the hearing of the participants, but none of the participants had any known hearing loss.

The study was approved by the Institutional Review Boards of the University of Texas at Dallas and the University of Texas Southwestern Medical Center. For the participants who were under 21 years of age their parents or legal guardians signed consent forms at the Autism Treatment Center. Consent forms for the participants from the autism societies who were over the age of 21 were signed by the participant if the participant was his/her own legal representative, but

signed by the participants' parent or legal guardian if the participant was not his/her own legal representative.

Experimental methods

The experimental methods were identical to those used in a previous study of the involvement of the non-classical auditory pathways in individuals with tinnitus²² and in children of different ages²³. Sounds were presented through headphones, and consisted of repetitive clicks generated by applying short electrical impulses (duration of 20 μ S) at a rate of 40 pulses per second to standard headphones. The sound was presented to one ear at a time, at a sound level of approximately 65 dB hearing level (intensity above normal threshold). The electrical stimulation consisted of electrical impulses (100 μ S rectangular impulses presented at a rate of 4 per second) applied through surface electrodes, one (the negative) placed over the median nerve at the wrist, and the other at the thenar muscle of the thumb on the same side.

Electrical stimulation was always presented to the left hand and its strength was adjusted to give a strong feeling of tingling but no pain. The strength of the electrical stimulation was slowly increased until the participants felt a strong tingling that radiated out in the middle fingers, but without any sensation of pain. With the electrical stimulation off, the sound was presented to the left ear so that the participants could familiarize themselves with the sound. The participants were asked to remember how strong the sound was. The electrical stimulation was then switched on for ~5 seconds and the participant asked if the strength of the sound changed during the electrical stimulation. If the participant noticed a change in strength of the sound the same sound was presented without any electrical stimulation, its intensity was varied continuously, and the participants were asked to report when the sound had the same strength as it had during the electrical stimulation. The difference (in dB) between the strength of that sound and the sound that had been presented during the electrical stimulation was taken as a measure of the effect of electrical stimulation on the perception of the loudness of the test sound. This procedure was repeated at least three times, after which the sound was applied to the right ear and the entire procedure was then repeated for that (contralateral) ear.

RESULTS

The results obtained in studies of 15 patients from the Autism Treatment Center (Group I) showed great variations. Of these 15 individuals, only seven were able to perform the test with reproducible results. Three of these seven patients reported that median nerve stimulation gave no change in loudness. In four of these seven patients, the perceived strength of the test sounds (average for ipsilateral and contralateral sound stimulation) increased during median nerve stimulation with values between 2.7 and 9.9 dB (see *Figure 1*, open circles). Three of the eight individuals who could not perform the test in a satisfactory way reported that the

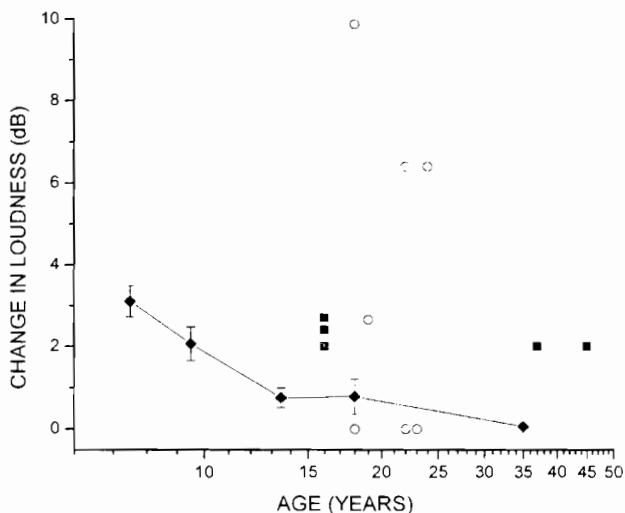


Figure 1: Change in loudness (in dB) experienced during electrical stimulation of the median nerve at the wrist. (Open circles) Results from individual participants of Group I of the present study. (Filled squares) Similar results from Group II. The solid line shows average values from a previous study²¹ of normal individuals (with standard error of the mean)

strength of the test sound increased when the median nerve was stimulated, but they were unable to match their perception of the sound when the median nerve was stimulated to that without stimulation. Two of these, a 37- and a 38-year-old, both female, had reported large changes in their perception of the loudness of the test sounds. All of the seven individuals, who reported that the strength of the test sound changed during stimulation of the median nerve, reported an increase in loudness during median nerve stimulation. Two of the eight individuals who could not perform the test satisfactorily did not understand the task, and three could not be tested at all because of their inability to follow the instructions. Several of the participants expressed emotional reactions to the electrical stimulation of the median nerve, mostly pleasure and one showed an exaggerated response of pleasure.

The results from those participants who could make a confident matching of the loudness of the sounds with and without median nerve stimulation are shown in *Figure 1* superimposed on data from normal individuals from an earlier study²³.

The results from Group II are also shown in *Figure 1*. Of the six participants in this group, five could carry out the required task and one reported large changes in the sound when the median nerve was stimulated but could not make a satisfactory matching. The change in perceived strength of the test sound during median nerve stimulation varied from 2.0 to 2.7 dB (see *Figure 1*, squares) in the five participants who could perform the test satisfactorily. Four of these individuals reported an increase in loudness during median nerve stimulation, and one reported a decrease. This male also reported hypersensitivity to sounds and he felt the electrical stimulation of the median nerve to be very pleasant.

Statistical analysis

The data from the 12 participants with autism who were able to perform the test adequately were compared with the data from the 23 normal controls from a previous study²³. The group with autism ranged from 16 to 45 years of age, with an average age of 23.0 years. The age of the controls ranged from 16 to 43 years, with an average age of 24.7 years. Both groups were relatively evenly distributed in age.

The data were analyzed to determine if perceived loudness met normality distributional assumptions required for parametric tests. As these assumptions were not met, and the distribution of the data appeared to be dichotomous, with 18 of the 35 values of change in loudness being 0, the data were transformed to a binary outcome measure.

Scores of 0 were classified as 0, and scores >1 were classified as 1. The data were then analyzed using a chi-squared test to test for a difference between the autism group and the normal control group (see *Table 1*). A significant difference was found [chi-squared (1)=5.1, $p<0.03$]. As one of the cells had a frequency count of <5, a Fisher's two-tailed exact test was conducted ($p<0.04$). The autism group was more likely to have a perceived change in loudness than controls indicating a greater than the normal involvement of the non-classical auditory system in persons with autism.

DISCUSSION

The results from the present study of autistic individuals showed a statistically significant greater effect of stimulation of the median nerve on loudness perception than that occurring in non-autistic individuals using the same technique²³. This previous study showed a strong cross-modal interaction between auditory and somatosensory stimulation in young children and that was taken as a sign of involvement of the non-classical auditory system, at least regarding loudness perception²³. This cross-modal interaction decreased with age and was very small for individuals 15 years and older²³. The results of the present study showed a similar cross-modal interaction in autistic individuals extending to individuals of older age groups, and the signs of interaction between the two sensory systems was significantly larger in autistic individuals than in non-autistic persons.

It seems reasonable to suggest that the observed cross-modal interaction in autistic individuals is a result of abnormal childhood development during which signs of involvement of the non-classical auditory pathways normally decrease²³. The abnormal

cross-modal interaction observed in autistic individuals may therefore be regarded as a sign of insufficient development of the central nervous system during childhood. Other studies in autistic individuals¹² have shown indications of redirection of visual information, and investigators have shown abnormalities in face recognition³³⁻³⁵, which may be explained by similar redirection of sensory information.

In addition to the effect on loudness perception, electrical stimulation of the median nerve caused the sensation of pleasure that does not occur in normal individuals, and sounds evoked abnormal reactions in many autistic individuals, thus supporting the hypothesis of abnormal sensory processing in autistic individuals.

The neurophysiologic mechanisms for cross-modal sensory interaction, such as observed in this study and in previous studies^{22-24,36}, are insufficiently understood. The fact that neurons in the classical auditory pathways only respond to one sensory modality, while many neurons in non-classical auditory pathways respond to both somatosensory and visual stimulations, has led to the assumption that cross-modally interaction between sensory systems must involve non-classical pathways. Studies of neuropathic pain^{37,38} and severe tinnitus^{22,24,36} have suggested that cross-modal interaction is indicative of abnormal involvement of non-classical sensory pathways.

It has been hypothesized that cross-modal sensory interaction may be caused by the expression of neural plasticity^{10,14,22,38-40}, which may cause the opening of connections that are normally not functional (re-organization of the central nervous system). The masking or unmasking of dormant synapses^{37,38} or severing or establishment of morphological connections may cause such re-direction of information in the CNS. Severance of dorsal spinal roots can cause re-direction of the information in the somatosensory system³⁷ through expression of neural plasticity redirecting information in the spinal cord and that may be one of the causes of central neuropathic pain³⁷⁻¹⁴. Some individuals with central neuropathic pain perceive normally innocuous stimulation of the skin as painful (allodynia)³⁸, and that has been taken as an indication of redirection of sensory information to pain circuits, thus the non-classical somatosensory system^{14,23}.

That expression of neural plasticity can cause symptoms and signs from the nervous system¹⁴ is also supported by the findings that some symptoms of redirection of information can be reversed by appropriate sensory stimulation [for example, transderm electric nerve stimulation (TENS) for pain^{41,42}; tinnitus retraining therapy (TRT) for tinnitus^{43,14}]. This means that the abnormal involvement of non-classical auditory pathways in autistic individuals may also be correctable by inducing neural plasticity, such as can be done by appropriate sensory stimulation. Some of the beneficial effects of therapy in autism⁴⁴ may be achieved by the expression of neural plasticity that correct the abnormal development that cause the signs of autism.

Table 1: Data on change in perceived loudness used for the statistical analysis

Change in loudness	Autism	Normal	Total
0	3	15	18
>0	9	8	17
Total	12	23	35

The present study has limitations because we studied a heterogeneous population with the cognitive limitations of the participants. Most of the individuals we tested were on a variety of medications, many of which are known to have strong psychoactive actions. The possible effects of these drugs on the functions we studied are unknown and that hampers the interpretation of the results of the present study. Medication may also have been responsible for the failure of some of our participants to perform the tests of the present study.

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