Temporal processing 2

Mechanisms responsible for developmental changes in temporal processing
What needs explaining?

- Immature performance in some temporal processing tasks as late as 11 years.
- More certainly, immature temporal processing in infants younger than 6 months old.

We know that by some measures of temporal processing--gap detection, duration discrimination, perhaps backward masking--humans do not achieve adultlike performance until they are 6 or 7 or even 11 years old. Although the TMTF, which is the gold standard for measures of temporal resolution, is mature by 4 years of age, there remains the possibility that temporal resolution is immature before 4 years.

In addition, young infants--3-month-olds are immature by at least one measure--forward masking--when 6 month olds are (nearly) adultlike.

The question is “Can we identify anything about the development of the structures and function of the auditory nervous system that could account for age related changes in performance on temporal tasks?”:
These graphs are period histograms of an auditory nerve fiber responding to each of two tones (two top graphs) and to combinations of the same two tones added with different relative phases. When you change the relative starting phases of the two tones, the time waveform of the sound changes. What these period histograms show is that the auditory nerve fibers still follow the positive parts of the waveform. They do this because they are phase locked to the stimulus.

So these are examples of temporal properties of sound. They are represented in the auditory system by a phase locked response. One thing we can ask (again) is how phase locking develops.
Development of phase locking

- Phase locking takes longer to develop than frequency tuning.
- Phase locking develops in the central nervous system later than at the periphery.
I talked about the data on the left when I talked about phase locking and the representation of frequency (the fine structure of low frequency sounds). They represent the evoked response to an amplitude modulated tone in 1 month olds and adults, measured by Levi et al. The graph shows that the coherence of the response that occurs at the modulation frequency--akin to the synchronization index that we use to quantify the quality of phase locking is better for adults than for 1 month olds and that the difference between the age groups gets greater at high modulation rates. (The top panel is for a 500 Hz tonal carrier and the bottom panel is for a 2000 Hz tonal carrier). These are really the only data we have that more or less directly measure phase locking in infants. People measure this sort of response--now it is called the auditory steady state response--in infants and children, but they are most concerned with using the response to measure the audiogram (absolute thresholds). They have not been concerned about what these response tell us about the development of temporal processing.


Other sorts of evoked potentials provide a somewhat more indirect measure of the development of phase locking. To record an evoked potential, you need to have a lot of neurons firing at the same time. And all of the neurons need to have similar response conduction times, so that the action potentials at the next nucleus in the pathway all occur at the same time, and so on. So the response has to start out phase locked, and then stay synchronous as it travels through the system. Disorders of phase locking (neural synchrony) or disorders that disrupt synchronous transmission (multiple sclerosis) can disrupt the evoked potential and also disrupt temporal processing. So one way of looking at the development of phase locking is to look at the quality of the evoked potential waveform.
These are examples of ABR waveforms measured from infants as young as 31 weeks gestational age, up through infancy, childhood and adulthood. The thing we are looking at here is how distinct the waves that we see in the adult response appear in the infant response. Distinct responses are generated by synchronous action potentials. So we see the usual 5 waves in adults, the 6 year old looks pretty good, the 23 month old looks pretty good, but as the infants get younger we see fewer distinct responses. In the youngest infants it’s hard to see anything but Wave V, which has the largest amplitude of the 5 waves in all listeners.

So these changes in response waveform could reflect maturation of neural synchrony.
These are cortical responses published by Ponton et al. Each set of waves is recorded from a different location on the scalp, and represents the developmental sequence between 5-6 years and young adulthood. Pick any scalp location, and you tend to see changes in the waveform over age— even in childhood. The exact pattern changes with location, suggesting that maturation in different parts of cortex progresses at different rates. This could suggest that you can have nice synchronous action potentials down in the brainstem, but still have more dysynchronous activity up in the cortex.

To the extent that synchronous response is necessary for temporal processing, then, it might not be unreasonable to expect that these sorts of temporal processing would take awhile to develop.
Evoked potential latency development as a measure of temporal processing

Another temporal aspect of evoked responses that is known to undergo considerable development is the latency of the response. This is that same picture of ABR waveforms I showed you a minute ago. The labeled lines indicate the latency of waves I, II, and III in adults, and you can see that at least Wave III has a longer latency in younger listeners. It may not be intuitively obvious to you that faster latencies would be associated with better temporal processing, but if we look at the development of response latencies and figure out why the latency is changing, it gets us to a clearer understanding of why that might be true.
ABR latency development

These are data from Gorga et al. (1988), ABR Wave I latency as a function of conceptional age, obviously from premature infants. Wave I is known to be generated by the auditory nerve. You can see that its latency does get shorter over these weeks of what would normally be prenatal development.

This is a summary slide from Gorga et al. with Wave V latency data from several studies looking at premature infants, for clicks at two different levels, 60 dB nHL left, 80 dB nHL right. The improvement in Wave V latency is certainly more dramatic than that in Wave I latency. So the speed with which the message gets to the brain is improving somewhat in the last weeks of gestation, but the transmission through the brainstem seems to be improving more.
These are data from Gorga et al (1989), showing latencies of Waves I and V during the postnatal period. ABR latencies continue to improve postnatally, at least for Waves III, IV and V. Wave I as you can see, is pretty darn close to adultlike at term birth, Wave V latency, on the other hand continues to improve, out to maybe 24 months of age.

This figure from Gorga et al (1989) shows the Wave I-V latency difference-- also called the interpeak latency. This reflects the time it takes the message from the ear to be transmitted through the brainstem. Clearly, it takes longer for the central latency to reach adult levels.
And if we look at latencies of cortical responses, we get the impression that the longer the latency (i.e., the “more central”, the greater the developmental improvement in latency. These are data from Barnet et al. (1975). Latencies are still improving for some responses beyond 40 months of age.

Possible anatomical correlates

- Myelination
- Other aspects of neural transmission
  - Axonal, dendritic maturation
  - Synaptic development

Let’s consider now why evoked potential latencies might change during development.

The most frequently cited cause of decreases in evoked potential latency with age is increased myelination around the axons of auditory neurons. Myelin as you probably know provides a sort of electrical insulation for the nerve fiber, and myelination increases the conduction time of nerve fibers.

However, myelination is not the only thing that could be happening here. Response latency could decrease because the axons of neurons are still maturing and still growing into the appropriate nuclei. The dendrite of the neurons in those nuclei may still be developing. And perhaps most important, the synapse between those elements may still be developing. If a synapse doesn’t work so well, it will take a longer time for the response to “cross over” to the next neuron in the circuit. If different synapses are a little different while they are still developing (as we might expect), then the message on the other side will not be synchronized as well. In addition, some action potentials may be completely ineffective in “getting through” the synapse, so information is basically lost.
Jean Moore has done quite a lot of research on the anatomical development of the auditory system, particularly in humans. She has summarized many of her observations in this figure, which compares the timing of different events in auditory structural development of the auditory brainstem in rats and humans. She observes a long period during which the main developmental event is the growth of axons to their respective targets, labeled as “expansion and collateralization” in this schematic. In humans that ends in the brainstem at around 26 weeks of gestation. This is followed by a period during which the axons branch to contact their targets, and then jumping down to the bottom line-- it is at the end of this :terminal branching: period when myelination gets underway, around 28-29 weeks gestational age in humans-- probably not coincidentally the first age at which we can record an ABR from infants. So myelination does seem to kick in pretty late in the process.

Moore JK
Maturation of human auditory cortex: Implications for speech perception
ANNALS OF OTOLGY RHINOLOGY AND LARYNGOLOGY 111 (5): 7-10 Part 2 Suppl. 189 MAY 2002
Development of myelination

- Appears in auditory nerve and brainstem around 29 weeks gestational age
- Auditory nerve and brainstem indistinguishable form adult by 1 year postnatal age
- Begins prenatally in projection to thalamus, but colliculus-thalamus and thalamus-cortex take longer to reach adult stage.

A rough time table is described here. Myelination begins in the auditory nerve and brainstem around the same time, 29 weeks of gestation.

In the auditory nerve and brainstem, myelination is pretty much adultlike by 1 year postnatal age, but although you can see a few myelinated nerve fibers projecting out of the brainstem to the thalamus prenatally, those projections and the projection from the thalamus to the cortex only complete myelination later in childhood.

So far, then, myelination looks like a pretty strong candidate in explaining age-related latency changes in evoked potentials.

However, these other aspects of neural development also occur during this time. For example, these micrographs show neurons in the central nucleus of the inferior colliculus in humans at 3 ages—29 weeks gestational age, 1 month postnatal age, and 6 months postnatal age. The neurons are stained for a substance that is found is dendrites. At 29 weeks of gestation, you see some staining; at 1 month postal you can see the dendrites extending away from the cell bodies. But look at all the dendrites in the nucleus at 6 postnatal months. This is a huge difference. There is a lot of development of the dendritic structures in the brainstem and beyond during postnatal development.

Moore JK, Guan YL, Shi SR
MAP2 expression in developing dendrites of human brainstem auditory neurons
Organization of auditory cortex

Moore also studied the development of auditory cortex in humans. This is a Ramon y Cajal drawing of cortex, just to give you some idea of what is in there. There are layers of cortex, each layer has different neurons in it-- these lines coming up to the neurons and running under layer 6 are all projections from the thalamus,
Axonal development in auditory cortex

These are micrographs of cortex at 40 wk gestation age, 4.5 mo, 2 years, and 11 years postnatal age. At term birth, there just isn’t much going on in cortex, There are some neurons, but the aren’t getting much input from anywhere. Cortex has expanded some by 4.5 months, but you still don’t see much ingrowth of axons from thalamic neurons. At 2 years, you start to see more axons growing in and by 11 years, there are many axons there. So at the level of the cortex, it takes a long time to get a mature set of axons projecting from lower levels of the brain. And of course, you can’t have synapses if there aren’t any axons or dendrites.

Moore JK, Guan YL
Cytoarchitectural and axonal maturation in human auditory cortex
JARO 2 (4): 297-311 DEC 2001
Myelination and synaptic transmission contribute to development of ABR latency

Ponton et al published an analysis of ABR data in 1996 that attempted to separate out the contributions of increased myelination and improved synaptic efficiency to age-related changes in ABR latency. The two sets of ABR waveforms here are the same, but the latencies of Waves III, IV, and V are indicated in the left panel, while the latencies of Waves I, II, and II are indicated in the right panel. Waves I and II don’t change much in latency over this age range. The other latencies do decrease with age. The interpeak latencies, II-Iv, IV-V and II-V also decrease with age.

Ponton CW, Moore JK, Eggermont JJ
Auditory brain stem response generation by parallel pathways: Differential maturation of axonal conduction time and synaptic transmission
EAR AND HEARING 17 (5): 402-410 OCT 1996
Based on many studies, Ponton et al assumed that Wave II is generated by axons leaving the cochlear nucleus and that Waves IV and V are generated by axons higher in the system, but that Wave IV is coming from the same neurons as wave III, but as they head up the lateral lemniscus to the inferior colliculus. Wave V is thought to be generated in IC, but by neurons that project from the medial olive. So the neurons that generate Wave II project to the contralateral lateral lemniscuses and IC, uninterrupted, while other neurons that generate Wave III get to the IC on both sides of the brain, through a synapse in the medial olive. So the difference in latency between Waves III and IV just depends on how long it takes the action potential to "travel" along the uninterrupted pathway from the cochlear nucleus to the IC through the lateral lemniscuses. The latency difference between Waves II and V represents the condition time, plus the time it takes to cross that synapse in MSO. So the difference between IV and V latencies tells us how long it takes to cross the synapse.

Of course the difference between Waves II (auditory nerve) and III (cochlear nucleus) also involves crossing a synapse.
Myelination and synaptic transmission contribute to development of ABR latency

So this figure plots the 3 interpeak latencies (relative to adults) for II-IV, IV V and II-III as a function of conceptional age. Notice that the earliest developing interpeak latency is III-IV, the latency that is supposed to only reflect condition time, or myelination. IV-V and II-III take much longer— and both of those would involve crossing a synapse. It is really interesting that the II-II interval actually takes longer to mature— but also notice that the IV-V and II-II rate of development is the same— the lines are parallel. This would suggest that a common mechanism contributes to the development of both.

This analysis, then supports the idea that synaptic transmission immaturity is a big player in the development of central conduction times, which could lead to a lot of "jitter" in the timing of action potentials as they are conducted up the pathway as well as a potential loss of information about sound.
Conclusions: development of phase locking

- Phase locking and neural synchrony develop over a long time course.
- The auditory nerve and brainstem appear to be mature in this regard earlier than other parts of the auditory nervous system.
- Maturation of phase locking could be related to the development of some sorts of temporal processing.
The second part of the lecture deals specifically with the development of adaptation. Adaptation refers to decrements in a neuron's response over the course of stimulation. This figure illustrates that adaptation can distort the auditory nerve fiber's response to a change in a sound over time. On the left an increase in a sound's intensity is the stimulus, on the right a decrease in the sound's intensity is the stimulus. Ideally, the number of action potentials should follow the stimulus, increasing when the level of the stimulus increases and decreasing when the level of the stimulus decreases. However, even in these mature neurons, that's not what you see. The firing rate decreases when the sound level hasn't changed and sometimes increases when the sound level hasn't changed.
Immature neurons seem to be very susceptible to adaptation. These are recording taken from kittens at two postnatal ages, 3 and 8 days. Remember that at 3 days, the auditory nerve only responds at all to intense stimuli. For both of these PST histograms, the sound was presented for 800 ms. By 14 days, we see a PST histogram more or less like what we would expect in an adult. At 3 days, it looks like the neuron can’t maintain its response. It keeps taking little rests from responding. This is an extreme form of adaptation that really distorts the representation of the temporal properties of sound. As the graph on the right shows, something like 80% of auditory nerve fibers show this sort of response during the first week of postnatal life in cats. Similar responses have also been observed in the brain and in other species. So this suggests that susceptibility to adaptation might be a developmental “trend”.

There are two ways that people have looked at susceptibility to adaptation using evoked potentials in humans. The first is by looking at rate effects. Even in adults, the latency gets longer and amplitude gets lower when a higher stimulation rate is used to elicit an evoked response like the ABR. If infants or children are more susceptible to adaptation, then they might sow more pronounced effects of increasing the stimulation rate.

It is also possible to obtain forward masked evoked responses, a more direct comparison to some of the psychophysical studies we’ve already talked about.
Lasky (1991) did a study of premature infants in which he examined both rate effects and forward masking using the ABR. This graph shows the effect of stimulation rate on Wave I latency for three groups of premies and for adults. The lines are best fits to the data for each age group. The lines for the 32 and 36 week conceptional age infants are steeper than those of the 40 wk infants and the adults. The 40 wk infants, though, appear to parallel the adults. So prenatally, humans are susceptible to adaptation, even in the inner ear.

Rate effects in human infants: Wave V

These are the results of Lasky’s study for Wave V. You still see a steeper line for the younger ages, but the 40 wk conceptional age kids still show a somewhat steeper effect than the adults.

Although there aren’t published studies that have really followed this effect into infancy, there is one report that by 3 months of age, the rate effect on Wave V is about the same as what you see in adults.
This slide compares the rate effect for Waves I, III, and V for different ages, where you see some change for Waves I and II, and a bigger effect for Wave V.
Jiang et al examined the effect of rate on the I-V interpeak interval in infants and children. The y-axis is the change in latency you see if you go from 10 to 50/s (blue symbols) or from 10 to 90/s (green symbols). For both rates, you see a decreasing effect up to about 1 year, then it levels off. So this suggests that the neural component of the change in Wave V latency takes a bit longer to mature.

JIANG ZD, WU YY, ZHENG WS, et al.
THE EFFECT OF CLICK RATE ON LATENCY AND INTERPEAK INTERVAL OF THE BRAIN-STEM AUDITORY EVOKED-POTENTIALS IN CHILDREN FROM BIRTH TO 6 YEARS
ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY 80 (1): 60-64 JAN-FEB 1991
Forward masking with ABR

This represents the stimulus situation used by Lasky to measure forward masking with ABR.
These are the unmasked and forward masked thresholds that Lasky found for adults and for newborns. Unmasked is shown in blue; masked is shown in green. Error bars are standard deviations. The difference between masked and unmasked threshold is higher for the newborns than for the adults-- in other words, the infants show more masking. This is consistent with what we see in 3 month olds' psychophysical forward masking and suggests that in these young infants, we may be looking at an immaturity at a fairly low level.
Conclusions: development of adaptation

- Before perhaps 3 months of age, infants appear to be particularly susceptible to adaptation at the level of the brainstem.
- This could explain infants’ susceptibility to forward masking at this age.
Conclusions: Mechanisms underlying development of temporal processing

- Both phase locking and adaptation mature during infancy, at least at the level of the brainstem.
- Low level neural immaturity may contribute to some immaturity in temporal processing.
- Low level neural immaturity cannot explain infants’ poor gap detection performance, however.

Although I haven’t presented these data, there are a couple of studies, one using the ABR and the other using a cortical potential that have measured gap detection thresholds in infants. Bottom line: physiologically, they look like adults. This it is hard to figure out what’s going on with the development of gap detection.

Trainor LJ, Samuel SS, Desjardins RN, et al.
Measuring temporal resolution in infants using mismatch negativity
NEUROREPORT 12 (11): 2443-2448 AUG 8 2001

Human auditory brainstem response to temporal gaps in noise
JOURNAL OF SPEECH LANGUAGE AND HEARING RESEARCH 44 (4): 737-750 AUG 2001