

# Modeling Disordered Perception

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## 1. Background

As duck hunters know, even a bird brain can tell good models from the real thing. Acoustic precision in birds is hardwired, either specified genetically or acquired and fixed during development. In the order *passerines* there is evidence of 'song bird circuitry' specialized for learning and producing species-specific, even sub-species-specific whistles, and for distinguishing a bird's own song.<sup>1 2</sup> Zebra finches have anatomic connections between auditory and vocal systems with parallel projections from auditory thalamus to at least two distinct areas of forebrain.<sup>3 4</sup> Isolation, deafness, or focal lesioning can selectively disrupt song acquisition during a 'sensitive period'.<sup>5 6</sup>

A simple polysynaptic nervous system can reliably distinguish among brief acoustic transients. Hardwiring confers 'behavioral specificity'. Organisms with more complex nervous systems sample their environment in detail and defer processing to more 'plastic' central locations. In mammals sounds induce motion along the basilar membrane of a cochlear apparatus. The location of motions varies with frequency: higher frequency sounds displace the basilar end; lower frequencies displace the apical end. Each ear projects to cortex bilaterally; however, for some movements, input from contralateral ear is represented more richly. The "tonotopic" arrangement of movements for fine-grained analysis of changes in sounds is maintained through laminar thalamic nuclei to cortex and among cortical areas in the geniculate-cortical system.<sup>7</sup> A different 'diffuse' arrangement allowing disparities of movements, and used for locating and orienting to sounds in space is maintained in the collicular-tegmental system. Such 'encephalization' allows a bat to echolocate while growing, to fly over a river in the rain, and to hunt while other bats hunt.

Bats use acoustic transients with constant frequency (CF) and frequency modulated (FM) components and silence for echolocation. The insectivorous horseshoe bat alters the pitch of its chirps on the fly. With echo frequencies relatively constant, subtle changes in echoes from CF components distinguish rate of insect wing beat and wing size; changes in FM components characterize target velocity (e.g., an insect's velocity in flight, or the bat's velocity on landing). The 'acoustic fovea' of bats includes a proportionately larger representation on basilar membrane tuned to the 20-80 kHz frequencies used in echolocation. This fovea is preserved in auditory pathways and auditory cortex; frequency processing in cortex is sharpened by active inhibition.<sup>8 9</sup> In flight, bats listen for insect wing beats; localization involves the collicular-tegmental system.

Humans use brief acoustic transients to communicate; these, too, consist of combinations of CF and FM components and silence. Several lines of evidence suggest that the types of sounds used in languages include a universal 'core' with specifiable dependent classes of sounds. Whether these types reflect anatomic constraints, physiological constraints, or are an artifact of explanation, it is clear that we can synthesize sounds that have some acoustic features like speech sounds<sup>10</sup> and use these to test auditory processing independently of language spoken.

Simplistically, a sound like the vowel **e** can be assembled using three steady state formants ( $F_1$ - $F_2$ - $F_3$ ). Adding FM transients with formant frequency rise produces a sound like **be**; allowing the same

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transient frequencies to rise over a longer time produces a sound like **we**. Adding FM transients with  $F_2$  frequency fall instead of rise produces a sound like **ge**; allowing the same transient frequencies to change over a longer time produces a sound like **ye**. Varying direction and duration of formant change and onset is sufficient to generate the matrix of sounds shown in Figure 1.

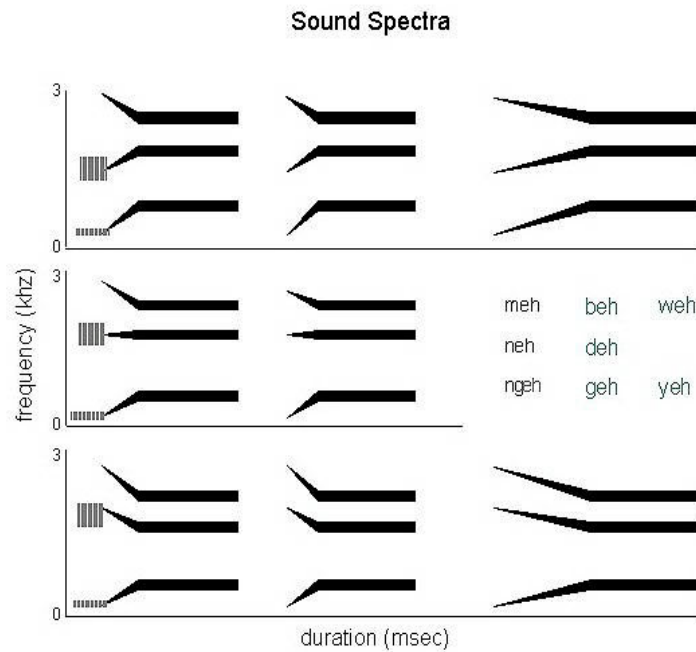


Figure 1. Diagrammatic acoustic spectra of three-formant sounds ( $F_1$ ,  $F_2$ ,  $F_3$ ). Left column: nasals (narrow band noise precedes onset of resonant frequency changes). Center column: stops (brief, rapidly changing formant frequencies/amplitudes). Right column: continuants (slowly changing formant frequencies/amplitudes). Top row: labials (rising  $F_2$ ). Middle Row: dentals (modestly rising or falling  $F_2$ ). Bottom row: velars (falling  $F_2$ ).

With systematic variation of 'transient duration', perception can change abruptly.<sup>11</sup> The schematic acoustic spectra in the upper portion of Figure 2 show sounds of a **GY** set. Transient duration is increased from 20 msec. at *stimulus value 1* to 130 msec. at *stimulus value 12* in 10-msec steps. Patients listen through headphones to sets of randomized sounds and indicate classification of each sound with a motor act, e.g., pointing. Responses can then be arranged in multi-dimensional contingency tables and analyzed.

The lower portion of Figure 2 shows composite classifications for this set of sounds. For each stimulus value, the left ordinate shows percentage of stimuli identified as **ge**. The green curve combines responses from right and left ears for eight **normal** subjects ( $n > 300/\text{value}$ ). The red and blue curves combine responses from eight patients with complex partial seizures (CPS). Each was free of seizure related complaint during testing; four had undergone excisional surgery. The **right ear** results appear in red; the **left ear** results in blue. Patients and controls consistently classified the sounds of *values 1* through *4* as **ge**, and those of *values 8* through *12* as **ye**. At the transition, they classified sounds at *values 5* and *6* less consistently.

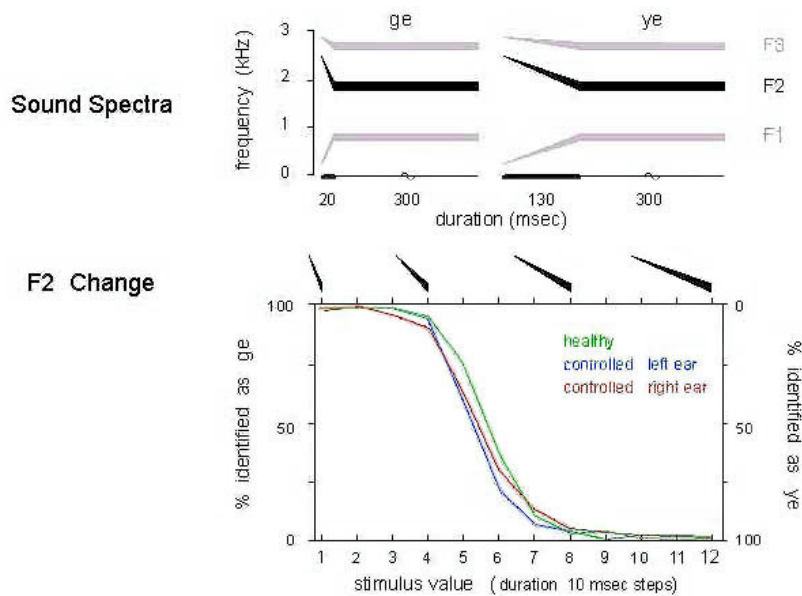


Figure 2. Top: Diagrammatic acoustic spectra of sparse acoustic stimuli (SAS). Ordinate: frequencies in kHz of first three formants (F1, F2, and F3). Abscissa: time in msec. Bottom: cumulative responses to sets of GY stimuli illustrated in upper section Left Ordinate: percent of stimuli identified as **ge**. Right Ordinate: percent of SAS identified as **ye**. Abscissa: stimulus value, representing duration of formant change from value 1 (20 msec) to value 12 (130 msec). Red and blue tracings: cumulative responses for **right** and **left** ear presentations (respectively) from eight women with medically controlled complex partial seizures; four had undergone excisional surgery. Each was free of ictal and medication induced complaint during testing. **Green** tracing: cumulative responses from eight age-matched females free from neurologic complaint. Diagonal lines at top of graph indicate duration of F2 change for corresponding stimulus value. For stimulus values less than 5, subjects classified SAS as **ge**, and for values greater than 5, as **ye**. For values 6 and 7, subjects classified less consistently.

One can also assemble a **BDG** set. With transient duration fixed, rapid F<sub>2</sub> frequency rise produces a sound like **be**, minimal F<sub>2</sub> rise or fall produces a sound like **de**, and rapid F<sub>2</sub> fall again produces **ge**. Stimulus values might reflect 100 Hz changes in F<sub>2</sub> starting frequency. Results would show transitions between **be** and **de**, and between **de** and **ge**.

With tonotopic organization, stimuli of **GY** cover similar extents of auditory cortex but at differing rates; likewise, stimuli of **BW** cover similar extents of auditory cortex (different from **GY**) but at differing rates. Stimuli of **BDG** cover differing extents of auditory cortex. With appropriate sets, **BWs** can provide unlateralized measures of cortical temporal processing, **GYs** reflect processing in cortex contralateral to ear stimulated, and **BDGs** are sensitive to disruptions of cortical connectivity.

## 2. Auditory anomalies and language acquisition

Speakers presume that listeners hear what was said. If the presumption holds for those in the central portion of a Gaussian distribution of listeners, those at the extremes hear more or less than was spoken. A small group of audiometrically normal subjects reports variations occur with **BW** or **GY**. At the shortest durations they detect no change and report hearing **e**; their stop-continuant boundaries are appropriate. We have tested two individuals who can consistently distinguish at least five classes of sounds.<sup>12</sup>

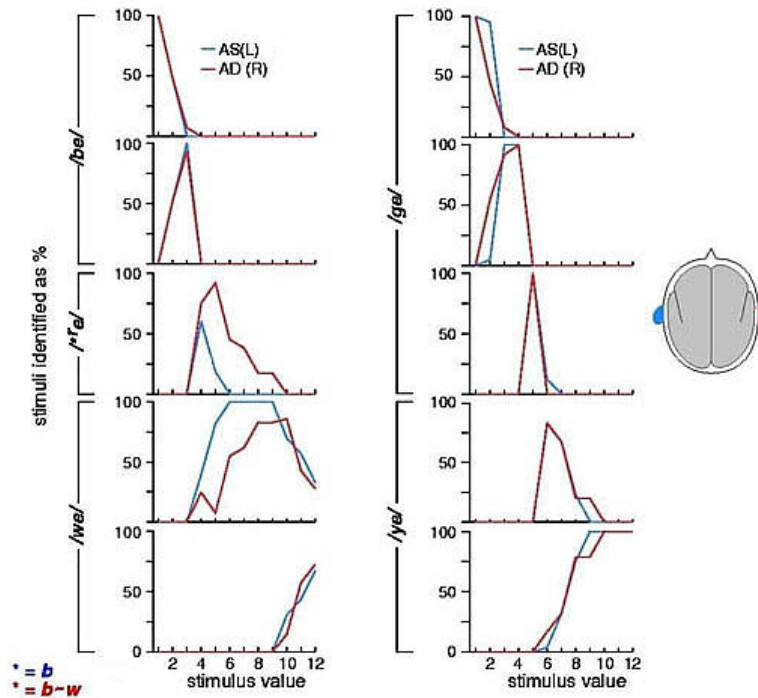


Figure 3. Results from a 33-yr old man who could consistently resolved five classes of sounds in BW and GY sets (cf. Figure 2). Left column: BW. Right column: GY. AS: left ear presentation. AD: right ear presentation. L: left hand responses. R: right hand responses. Blue traces: left ear/left hand. Red traces: right ear/right hand. Left ordinates: stimuli identified as indicated. Right ordinates: now represent stimuli identified as any other sound.  $G^2$  value compares corresponding contingency table with chance performance. In each condition,  $p(X^2 > G^2) < 0.00001$

One, a 33-yr. old woman with normal hearing thresholds bilaterally, could consistently classify **GY** at the right ear as one of three sounds (**g**-colored, an intermediate sound, and **y**-colored). She classified these same sounds to left ear as one of six sounds (four **g**-colored, two **y**-colored). The other, a 33-yr old man with mild high-frequency loss bilaterally, could consistently classify **GY** as one of five sounds (**e**, two **g**-colored, and two **y**-colored) regardless of ear. He could classify **BW** as one of five sounds (**e**, two **b**-colored, a **w**-colored, and an **ue**-colored). As shown in the left panel of Figure 3, he reported predominantly **br**-coloring with the left ear, but **r**-coloring with the right ear.

Both individuals could appropriately distinguish **BW** and **GY** sounds using only two classes. Analogous abilities may appear in other sensory systems. Craig<sup>13</sup> in evaluating vibrotactile readers for the blind encountered individuals with unusual abilities to distinguish rapidly changing stimuli on skin. For the auditory system, these results require that subtle, brief deformations of basilar membrane be preserved, or at least recoverable, centrally. Given such representation, modest differences in cochlea or cochlear functioning might account for differences between ears in either subject.

Hearing too little or otherwise processing aberrantly can impede language use in some modalities; it can also disrupt language acquisition.<sup>14</sup> In some cases, these problems are familial. A 6-yr. old boy was referred with a diagnosis of 'functional dysarthria'.



## Apraxia and Aberrant Perception

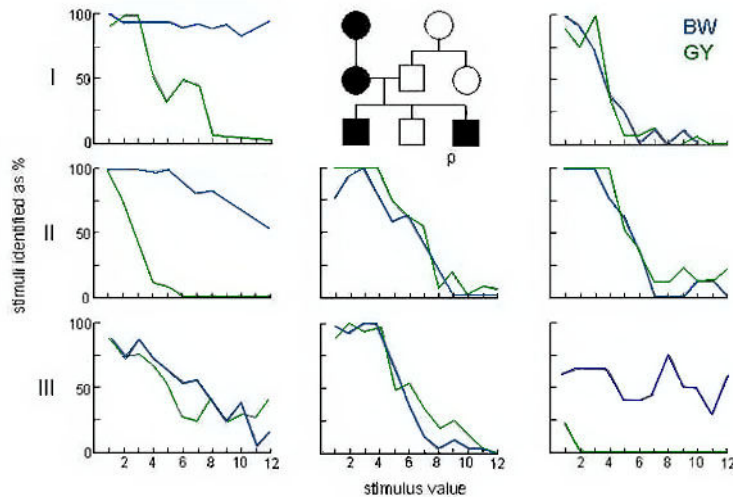


Figure 5. Cumulative results for individuals from three generations of kinship in Figure 4. I, II, III: generational index of lineage in top center. Left to right rank of graphs corresponds to position in lineage. Left ordinates percent of stimuli identified as ge for GY (dark green trace); be for BW (dark blue trace). BW is sum of left, right and binaural BW presentations; GY is sum of left, right, and binaural GY presentations. Note that maternal grandmother (I, left) and mother (II, left) reported GY sound as e or ye. p: propositus (III right) reported all but some of the shortest GY stimuli as ye.

Unaffected members performed without difficulty; they understand unaffected family members and people outside this family without difficulty. The affected family members are another matter. The maternal grandmother and mother had brief **GY** and were unable to distinguish **BW**. They understand each other, but both have some difficulty understanding eldest and youngest boys, greatest difficulty understanding the middle boy. For any of the boys to understand his siblings requires effort. The eldest and middle boys disagreed sharply about classifications of sounds when tested concurrently. The youngest hears “yet me a yar of yape yelly” for “get me a jar of grape jelly”. The source and nature of this family’s complaints are complex; a parsimonious account entails central nervous system involvement.

### 3. Transient anomalous perception

Human primary auditory cortex fills a small six-layered volume in each temporal lobe. It is largely inaccessible from the surface; size and orientation make imaging difficult. Secondary and association areas extend anteriorly in the temporal lobes and posteriorly into the parietal lobes. The cortical auditory system exploits physiologic and anatomic processes common to other sensory systems.<sup>15</sup> Excitatory thalamocortical afferents terminate predominantly in layer 4 on both excitatory and inhibitory neurons; excitatory callosal fibers from homologous areas terminate on these same inhibitory interneurons. Corticothalamic efferents from layers 5 and 6 project to dorsal thalamic nuclei. Corticocortical and local interlaminar fibers arise from layers 3 and 2.

The inhibitory elements<sup>16</sup>, smooth or sparsely spined short axon cells, include axo-axonal chandelier cells<sup>17</sup>, basket cells (a primary source of inhibition for iso-frequency organization<sup>18</sup> and motion/direction selectivity<sup>19</sup>), two local fast-response interneurons (the vertically oriented bitufted

cells<sup>20</sup>, and horizontally oriented multipolar cells<sup>21</sup>), as well as bipolar, neurogliaform, and giant cells of the deeper layers. These are demonstrably GABA-ergic; bipolar cells may also be peptide-ergic.

The inhibitory transmitter GABA acts in cortex through receptors distinguished pharmacologically as GABA<sub>A</sub> and GABA<sub>B</sub>. GABA<sub>A</sub> activity is enhanced with muscimol, blocked with the convulsant bicuculline (BIC). The receptor complex, distributed over post-synaptic dendrite, soma and axon initial segment, increases membrane chloride conductance and is pregnane steroid sensitive. GABA<sub>B</sub> activity is enhanced with Baclofen blocked with flaclophen (but not BIC). On presynaptic terminals, the GABA<sub>B</sub> receptor decreases monoamine and excitatory amino acid release; on postsynaptic membranes it increases potassium conductance. In slices of human temporal cortex, GABA<sub>A</sub> modulates early IPSP components; GABA<sub>B</sub> modulates late IPSP components.<sup>22</sup>

GABA-ergic inhibition shapes receptive field properties of cortical neurons.<sup>23 24 25</sup> In the visual system disinhibition with BIC decreases orientation and direction sensitivity so that cells respond readily to stimuli which had been ineffective.<sup>26 27 28</sup> With complete disinhibition, excitatory receptive fields become large and round; orientation and direction selectivity are virtually abolished.<sup>29</sup> GABA<sub>A</sub> disinhibition can also transiently alter developmentally abnormal stereopsis. In monocularly deprived kittens, BIC temporarily restores binocular receptive fields with normal orientation and direction sensitivity for the deprived eye, but with concomitant loss of specificity for the other eye. Cells again respond monocularly when BIC effects dissipate.<sup>30</sup> In monkeys, monocular deprivation markedly diminishes immuno-staining for GABA<sub>A</sub> receptor proteins in lattices of layer 4 cortex enervated by that eye. The effect appeared within 5 days of deprivation and persisted over 30 days of deprivation.<sup>31</sup>

Studies with GABA or GABA-agonists are more intricate. Ionophoretic GABA depresses spontaneous firing and elevates thresholds of cutaneous cells of cat somatosensory cortex. Receptive field thresholds increase more at the periphery than at the center, effectively reducing field size and narrowing field tuning<sup>32</sup>. GABA<sub>A</sub> agonists can also reversibly alter behavior of awake animals. Ionophoretic muscimol in monkey multimodal finger regions disrupts coordinated finger movements.<sup>33</sup> In bats, muscimol applied to the CF areas impairs ability to resolve frequency differences less than 100 Hz; applied to the FM areas it impairs ability to resolve time sensitive differences less than 20-30 msec. In each case larger frequency or time differences are unaffected.<sup>34</sup>

On the modular level of columns or slabs, diminished inhibition decreases stimulus specificity; enhanced inhibition increases specificity. At either extreme, otherwise appropriate stimuli are not differentiable.

In aggregates of slabs inhibition modulates the extent of excitation<sup>35</sup> and appears to synchronize synaptic level activity. Small decreases in inhibition—less than 20%—can double the extent of horizontally propagated field potentials. With even small decreases, direction of propagation becomes unpredictable in slices of rat sensory cortex.<sup>36</sup> Schwartzkroin and Haglund<sup>37</sup>, using thick slices of human temporal lobe, examined synaptic events that involve repetitive discharge of GABA-ergic inhibitory 'interneurons'. They found activity of fast inhibitory 'interneurons' preceded post-synaptic 'pyramidal' activity, and that both orthodromic and antidromic stimulation elicited IPSPs. They also reported "... repetitive stimuli did not evoke after-discharge from human cortex or mesial temporal lobe" but "... appeared to 'clamp' the cell at a relatively hyperpolarized potential". Interestingly, such synchronized activity can give rise to long lasting inhibition in projected neurons even in the absence of excitatory amino acids.<sup>38</sup>

Active inhibition shapes receptive field properties of auditory neurons and the frequency-intensity sensitivities of the several cochlear representations in cortex.<sup>39</sup> In secondary areas persistence or decay of inhibition shapes direction of frequency change and inherently rate-of-change, since this involves 'adjacent' extents of cochlear representations.

Sir Charles Symonds<sup>40</sup> in describing the "epileptic disorder of function" observed that

"...(Seizures)... may be regarded as occasional expressions of a fundamental and continuous disorder of neuronal function. The essence of this disorder is loss of the normal balance between excitation and inhibition at synaptic junctions. ... (This)... disorder of function may be assumed to be present continuously... "

Patients with focal seizures in auditory cortex have reported that sounds they had heard as stops (such as **deh**) become nasals (**neh**), then laterals or bleats (**leh** or **dleh**), and finally undifferentiated buzzes.<sup>41</sup> Misperceptions affect the transient portions of sounds and abate with control of seizures. Such changes are consistent with diminished inhibition.<sup>42</sup> We have noted other perceptual changes that are consistent with increased inhibition.<sup>43</sup> One surgical and four non-surgical patients illustrate these effects.

### Disinhibition

At age 3-1/2 yrs. this patient developed unilateral subacute hemispheric encephalitis. She suffered recurring partial motor seizures that began in either left hand or foot. By age 4 yrs. she had suffered recurring bouts of partial *status epilepticus* and had developed left spastic hemiparesis. CT scan revealed extensive atrophy of right cerebral hemisphere. She underwent two-stage removal of the right hemisphere sparing 2 cm at the occipital pole. Post-operatively she had left homonymous hemianopsia and a cortical sensory deficit; her spastic hemiparesis persisted.

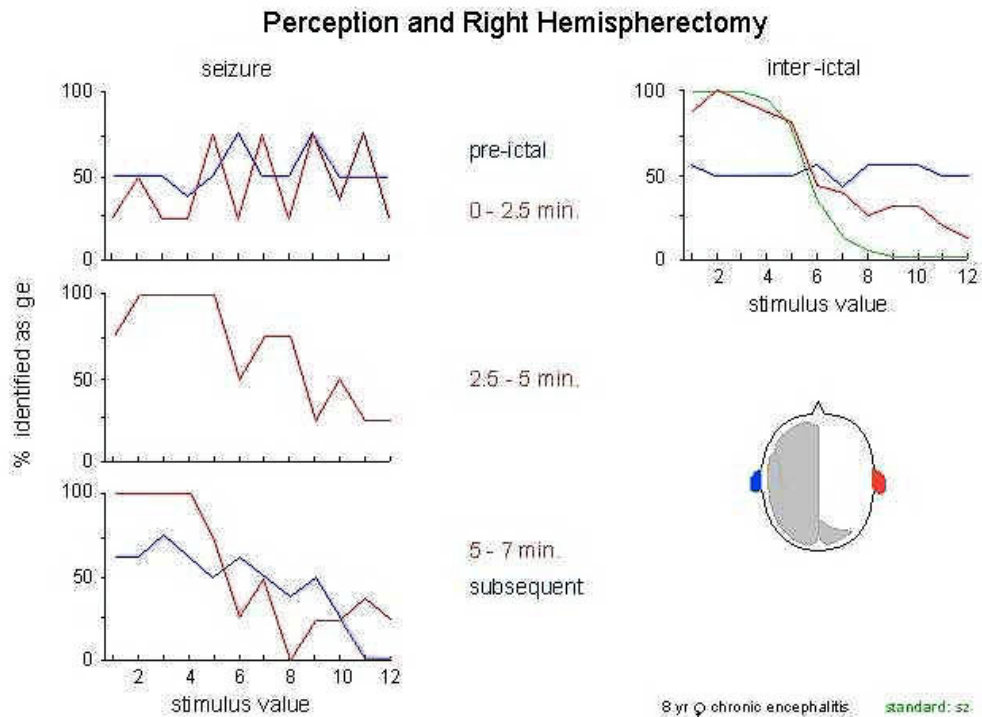


Figure 6. Perception in case with right hemispherectomy and seizures involving remaining hemisphere.

Right panel cumulative interictal performance on GY. Left ear (blue trace) presentations. Right ear (red trace) presentations Normal controls (green trace). Left panel: right ear (red traces) immediately following arrest and continuing approximately 7 minutes in 2.5 min epochs. Left ear (blue traces) before and following right ear testing. Head illustrates extent of resection.

In 15% of such patients seizures eventually develop in the remaining hemisphere. This patient reports two types occur now. In one, all objects lose color, and in a few moments, “everything becomes black”. She feels she will fall but does not. Throughout, voices do not change character. A second type occurs without warning; her mother reports that the child’s eyes open, neck extends, and left shoulder elevates.

With right hand she may reach over to restrain left arm (and abort the seizure); failing this she fumbles with right hand, becomes unresponsive, then may be briefly confused. Spontaneous seizures of this type have occurred during testing.

We tested her at age 8 yrs. The right panel of Figure 6 combines interictal performance over a year. Although she reports hearing clearly, performance with the right ear (contralateral to remaining hemisphere) is neither random, nor equivalent to standard; the left ear (ipsilateral to remaining hemisphere) is at chance levels. The three left panels show performance immediately before and following a spontaneous seizure. In the top panel before seizure, performance with left ear is random. Testing with right ear had just begun when she had difficulty understanding, stared, fumbled, and was briefly unresponsive. As she began responding, she pointed slowly and with small hand movements.

Immediately following the seizure performance with right ear is random, as if auditory cortex in the remaining hemisphere had been ablated. This resolved rapidly. By panel 3, right ear performance is remarkably like the standard. In panel 2, the shift of curve towards larger stimulus values reflects a 30-sec period when longer duration sounds she had identified as **ye** she now reported as **ge**. A similar two-minute episode, again with right ear, followed an unaborted seizure on another occasion. During these episodes, she included some but not all of the longest values, precluding appeal to perseveration. These shifts are consistent with augmented inhibition.

### Augmented inhibition

Similar prolonged lateralized episodes have occurred in non-surgical patients. The patients shown in the upper and middle portions of Figure 7 experienced unilateral shifts lasting over 10 min.

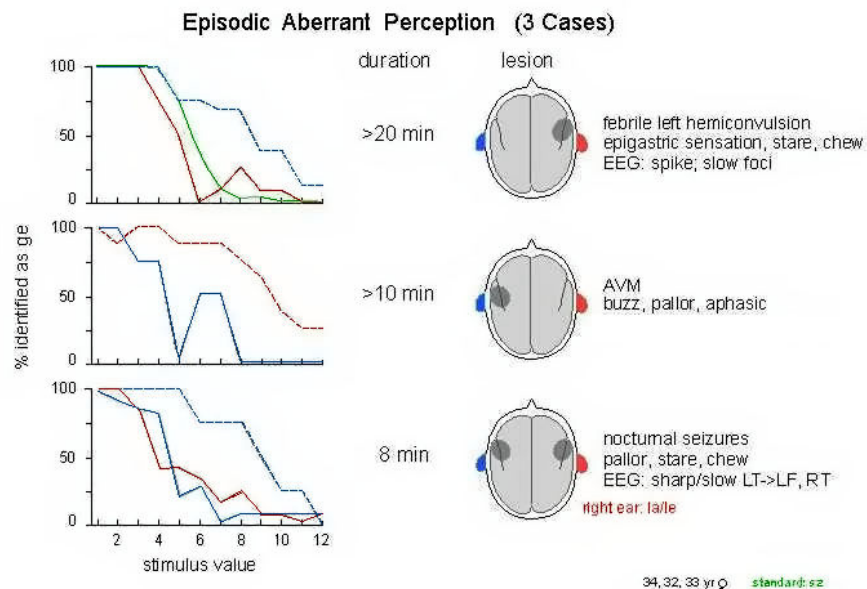


Figure 7. Episodes of aberrant perception in three cases. In each head dark gray area illustrates location of electrographic abnormality. See text for details.

For each patient the shift, shown with a dashed line, appeared at ear contralateral to primary focus. The patient shown in the bottom portion reported misperceptions consistent with disinhibition for the ear contralateral to presumed primary focus; she was unaware of the shift with the other ear.

The upper results are from a 34-yr. old woman who had suffered repeated left hemiconvulsions associated with fever at 11 mo. Her spells began with a rising epigastric sensation, followed by stare, oral automatism, and fumbling. EEG revealed foci of slow waves and of spikes in the right anterior temporal area. During testing she had intervals marked with pallor, lip smacking, and facial twitches, but reported no seizure. Her shift appears with left ear/right hemisphere.

The middle results are from a 32-yr. old woman with left temporal arteriovenous malformation. Her spells begin with buzzing in right ear, followed by pallor and brief stare; she might then become aphasic. Post-ictally she may be amnesic for the interval. Prolonged electrographic monitoring revealed sharp and slow transients recorded over left temporal region. During testing, she had intervals marked by pallor, dilated pupils, and small chewing motions; these might end with a brief smile or transient apraxia. She became aware that the proportions of sounds differed between ears during testing, but denied experiencing aura or seizure. Her shift appears with right ear/left hemisphere.

The bottom results are from a 33-yr. old woman who since childhood has had nocturnal seizures. These begin with forceful expiration and cry, then rigidity, and oral automatism. She has had brief daytime seizures with dizziness or cephalic sensation. In these, sounds become distant and her speech becomes garbled. Post-ictally she is amnesic for the interval. EEG showed sleep sensitive sharp waves over left anterior temporal region, and isolated sharp transients in right homologous area. During testing, the left ear boundary extended 50 msec (dashed line). Following a brief arrest when she failed to respond, she made small chewing motions, her pupils alternately dilated and constricted over 10 sec., then a series of fast blinks followed. When asked to speak responses, boundaries with left ear continued extended. With right ear, she now reported as **la** or **le** sounds she previously had called **ge**. Twice during this, she was again briefly unresponsive. The episode ended abruptly; performance before and following this is shown with solid lines.

Active inhibition for a specifiable time confers asymmetry of "preference" in current accounts of motion-direction sensitivity.<sup>44 45 46</sup> Accepting that movement of these stimuli across cortex elicits some rate dependent level of inhibition, then maintaining that level with increased inhibition would require slower movement. With greatly increased levels, rapid movements might pass undetected.

The results shown in Figure 8 are from a 32-yr. old woman who since age 12 yr. has had complex partial seizures. Her spells begin with a visual hallucination of a small tree at consistent location in the right visual field; followed by difficulty understanding speech and inability to speak, unresponsiveness, and an automatism. Post-ictally she may be amnesic for part of the interval. She has also experienced episodes with visual distortion too brief to characterize and often associated with rotational vertigo; she reports the visual environment seems to "freeze". Telemetered intensive monitoring confirmed episodes with visual distortion were without apparent ictal or electrographic concomitant. She has had episodes in which she has a recurring thought which she is later unable to recall ("forced thinking"). Interictal deficits on language tests parallel frequency and severity of seizures. She has right inferior quadrantanopsia. EEG studies including telemetry reveal focus of slow wave activity in left posterior temporal region.

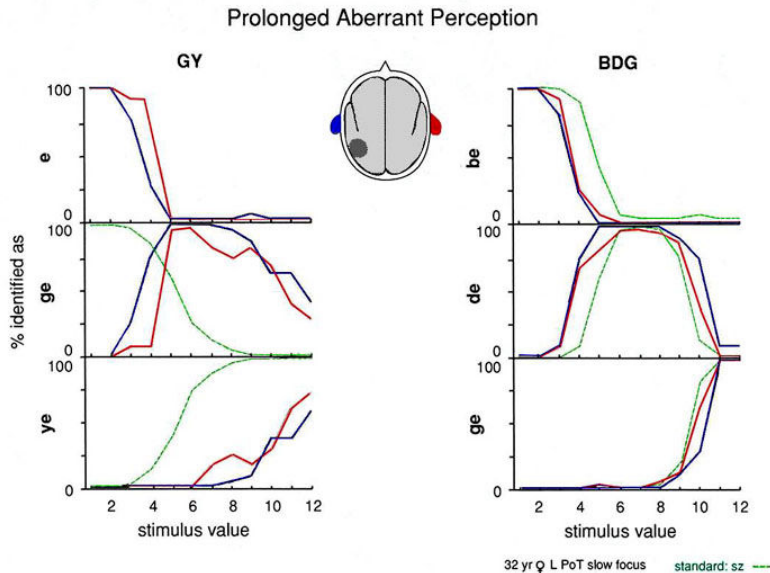


Figure 8. Aberrant perception in a patient with episodes of "forced thinking". Left panel: BDG Right panel: GY. Left ear (blue trace) presentations. Right ear (red trace) presentations. Seizure-free controls (green trace). In head, dark gray area illustrates location of electrographic abnormality.

The panels include results during recurring episodes of "forced thinking". In the left panel (GY) where controls typically detect change longer than 20 msec, she rarely detected any less than 35 ms, reporting these as **e**. Where controls report fewer **ge** sounds, she *began* to report **ge** sounds. **e-ge** boundaries are consistently well-defined. **ge-ye** boundaries varied; she was often unaware of these changes unless she found only one sound in a set. In the right panel (BDG) with sounds of set duration, the **be-de** and **de-ge** boundaries increased approximately 200 Hz beyond controls. She reported the sounds had been clear and identical in any group, "like a stuck record"; she was unaware that boundaries were markedly shifted.

The perceptual shifts in these patients are consistent with enhanced inhibition. The laterality of episodes is consistent with "surround inhibition", the volume of enhanced GABA-mediated inhibition which arises around acute or chronic foci in penicillin, iron, cobalt, and alumina models of experimental seizures. Auditory anomalies in brain remaining after hemispherectomy reflect disease in the remaining hemisphere as well as connectivity altered through loss of callosal fibers. Such alterations can persist even with young, 'plastic' brain. In both surgical and non-surgical patients, the underlying disease gives rise to perceptual aberrations that fluctuate in intensity and that need not correlate with self-reported seizure frequency. The aberrations reflect change in the balance of excitation and inhibition. One class of aberrations reflects insufficient inhibition<sup>47</sup>, even disinhibition; another reflects enhanced, excessive inhibition. In the course of treatment, diminished hippocampal involvement may improve the accuracy of self-reported seizure counts. As the standards in Figure 2 confirm, such aberrations ameliorate and even clear with effective treatment.

#### 4. Systemic changes with vigilance

In mammals, 'states' such as 'wake' and 'sleep' involve several distinct systems. 'Vigilance' -- capacity to remain alert while awake -- involves 'diffusely' projecting collections of neurons in areas

such as the ascending reticular system, the diffuse thalamic systems, and basal forebrain regions; it may involve the tonic action of cells within areas such as the locus coeruleus<sup>48 49</sup>. 'Sleep' involves other populations of neurons, e.g., in midline-raphé nuclei, in caudal areas of raphe. Neither 'sleep' nor 'wakefulness' is a unitary state<sup>50</sup>: persons who have studied all night for exams know that one can be awake without being alert. Whatever the account of states, it is clear that interactions of such systems<sup>51 52</sup> affect the stability of processing in cortical sensory systems.<sup>53 54 55 56</sup>

Familial hypersomnia typically involves excessively and persistently impaired vigilance<sup>57 58</sup>, and possibly episodic cataplexy (muscle weakness provoked by emotion), sleep paralysis (brief bouts of inability to move in the transition between sleep and wakefulness), or hypnagogic hallucinations (vivid visual or auditory sensations which can accompany sleep paralysis).<sup>59</sup> A 29-yr. old woman was unable to remaining alert while reading, driving, or attending church. Her husband confirmed her accounts, and denied experiencing such difficulty himself. Their 12-yr. old son was unable to remain alert while reading, watching TV, or, by teachers' accounts, in the classroom.

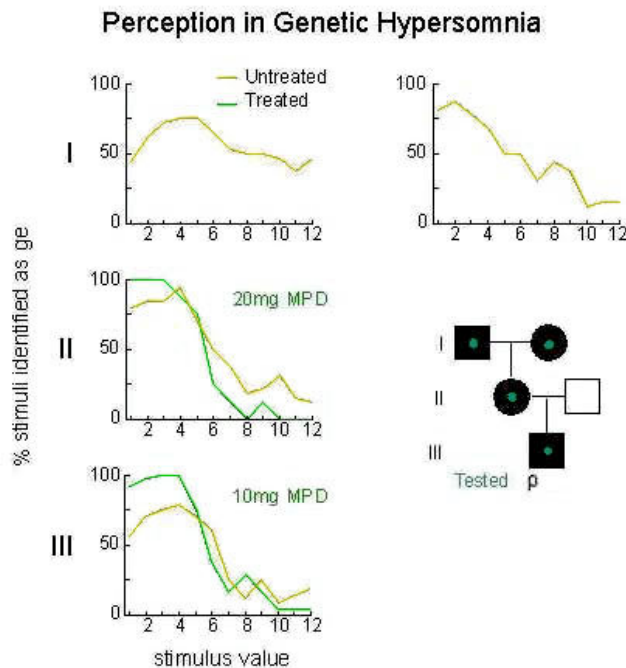


Figure 9. Three-generation kinship with familial hypersomnia  
 p: propositus. teal center: tested individual. Gold traces: untreated. Green traces: 20 min following sublingual dose of methylphenidate (MPD) indicated.

On questioning, the woman's father and mother reported similar difficulties: he had stopped for coffee four times on the 90-mile drive for testing. Figure 9 shows cumulative results from approximately 20 min. of testing.

Each affected family member performed aberrantly when untreated. Untreated performances fluctuated markedly within the test interval; cumulative tracings mask the fluctuations. The trends in untreated performance for both women and the boy preclude appeal to 'inattention' or 'micro-sleep'.<sup>60</sup> The woman and her son had been independently diagnosed; both had been treated with methylphenidate. The treated portion of the tracings (GII and GIII) show results of testing approximately 20 min. after sublingual medication (Mo 20 mg; So 10 mg; untreated vs. treated  $p(\chi^2 > G^2) < 0.001$ ). Changes in performances were dose dependent up to levels which sustained vigilance, and consistent with absorption and elimination kinetics for the compound.

Vigilance sensitive perceptual changes are independent of static auditory anomalies and transient aberrations. Impaired vigilance can co-occur with either static or transient anomalies, confounding diagnosis. Again, as comparison with the control standard in Figure 2 confirms, vigilance sensitive perceptual changes abate and even clear with effective treatment.

## 5. Modeling techniques

We have considered three classes of auditory anomalies:

1. Static anomalies in which a person distinguishes changes in sounds that speakers of his native language typically cannot distinguish, or fails to distinguish changes in sounds that speakers of his native language typically do distinguish. The conditions under which these anomalies become clinical problems depend in part on the conventions of a speaker's linguistic community.
2. Dynamic anomalies in which perception changes as the balance of excitation and inhibition in auditory cortex changes. The sources of these anomalies are manifold. They arise with focal changes in auditory cortex, or with changes in other connected areas.
3. Anomalies in which stability of perception fluctuates. These can arise with 'systemic' changes that alter cortical processing.

The aspects of auditory processing presented here constrain the types of models that can be applied to auditory processing and to the auditory system: auditory processing occurs in time-sensitive, non-linear, dynamic systems.

Artificial neural networks are computational models described by types of nodes, types of connections between nodes, and learning/training and recall/generalization algorithms. *Nodes* have or compute values; they can be arranged as a sheet (where values put out are computed directly from values put in) or as layers of sheets (where values put out of one sheet are the values put into an adjacent sheet). *Connections* between nodes may flow in one direction only (feedforward) or may include values put out with new values put in (feedback). *Learning/training algorithms* converge on stable values put out for specific values put in. *Recall algorithms* describe how new values 'similar' to those put in during training become 'similar' to values put out with training.

A *multi-layer neural network* with at least one intermediate layer (**MultiLayer Perceptron**) can model any continuous function to a specifiable degree of accuracy.<sup>61</sup> Given a set of features which unambiguously represents all patterns of a set, MLP can acquire conditional probabilities that distinguish the patterns. MLP, like multivariate nonlinear regression models, can represent interactions among variables<sup>62</sup>. MLP, however, are time-insensitive. To the extent that change over time can be determined from a sequence of values, sequences of 'previous' values can be summed and put in, creating a *time delay neural network*. Alternately, values from a layer might be held then fed back to the preceding layer, leaving time-sensitive traces. If such *recurrent neural networks* are formally equivalent to finite automata, the input languages they accept must be equivalent to regular sets and to Type 3 grammars. Both time delay and recurrent neural nets<sup>63</sup> have been used in speech recognition engines.

Other lines of research offer time sensitive alternatives. Oscillatory 'objects' can be assembled from 'excitatory' and 'inhibitory' nodes. States of these objects are specified with triples of amplitude, frequency, and phase. The richer representation need not be mapped onto a traditional neural network; for example, it can be *annealed* to avoid the local minima problem<sup>64</sup>.

In some cases apparently random processes can be described and modeled as deterministic chaos. Simplistically, the path of a chaotic process is traced in a phase space of appropriate dimensions. The accumulated path is in fact a trajectory, since each visit to some area of the

phase space comes from different preceding conditions. A chaotic process is inherently 'temporal' but aperiodic. Aihara et al<sup>65</sup> have reported *chaotic nodes* with exponentially decaying refractoriness and graded outputs. Dingle et al<sup>66</sup> have designed chaotic nodes where output values range from linear to periodic to chaotic depending on magnitudes put in. Neither chaotic nodes nor oscillatory objects offer time-sensitivity as a computational 'free-ride'.

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