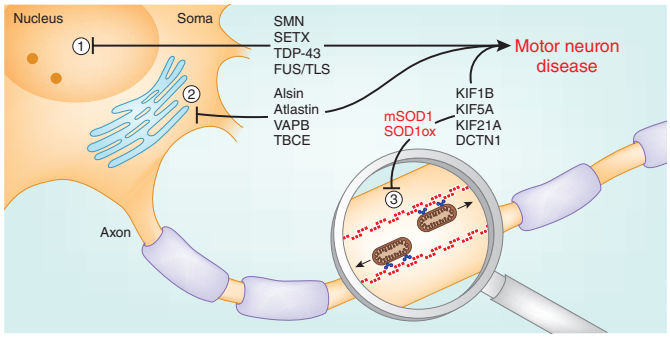

Figure 1 Mechanisms of motor neuron degeneration. A motor neuron and an enlarged portion of the axon are pictured to highlight three separate mechanisms that lead to motor neuron disease. (1) Mutations affecting proteins involved in essential nuclear processes, including DNA translation, RNA processing, microRNA biogenesis, and mRNA splicing and transport, often result in the selective degeneration of motor neurons. (2) Endosomal trafficking and the stabilization of microtubule networks are critical for maintaining motor neuron health. Interference with any of these activities is sufficient to induce motor neuron toxicity *in vivo* and *in vitro*. (3) Motor neurons are exquisitely dependent on functional axonal transport for growth signals, synaptic transmission and membrane turnover. Mutations affecting anterograde and retrograde motor proteins alike cause motor neuron dysfunction and eventually death. Both mSOD1 and oxidized SOD1 (SOD1ox) cause motor neuron toxicity by inhibition of anterograde axonal transport. DCTN1, dynactin 1; FUS/TLS, fused in sarcoma/translated in liposarcoma; KIF1B, kinesin family member 1B; KIF5A, kinesin family member 5A; KIF21A, kinesin family member 21A; SMN, survival motor neuron; SETX, senataxin; TBCE, tubulin-specific chaperone E; TDP-43, TAR (transactive response element) DNA binding protein of 43 kDa; VAPB, vesicle-associated protein B.

ALS may represent a collection of separate diseases that are characterized pathologically by motor neuron loss and clinically by weakness. Nevertheless, the results of Bosco *et al.*[3] suggest that the pathogenesis of fALS linked to *SOD1* mutations is, in fact, closely linked to that of sALS. This is reassuring evidence in support of the relevance of genetic ALS models to sporadic disease. Inhibition of axon transport may be the final common pathway in motor neuron disease, one that is susceptible to genetic and environmental insults (such as oxidation), perhaps representing a pathogenic mechanism that is common to both the familial and sporadic forms of ALS (**Fig. 1**).

Bosco *et al.*[3] also raise intriguing questions about the importance of protein misfolding in neurodegenerative disorders. Misfolded proteins with toxic properties have been implicated in the development of ALS and other neurodegenerative conditions[14,15], but their contribution to disease pathogenesis is still unclear. In part, this is because we lack the appropriate tools with which to examine the role of protein misfolding in neurodegeneration. Although misfolded proteins can be recreated and studied *in vitro*, their prevalence and potential effects *in situ* are largely unknown. Conformation-specific antibodies such as C4F6 represent extremely powerful reagents that may help to illuminate the effects of protein misfolding on neuronal health. Does protein misfolding occur to appreciable degrees *in situ*? The detection of C4F6-reactive species in the motor neurons of individuals with sALS shows that, at least to some extent, it does. How is the toxicity of misfolded SOD1 related to the C4F6 epitope? The misfolded conformer detectable by C4F6 also inhibited axonal transport, suggesting that the C4F6 epitope is important for the acquisition of toxic gain-of-function properties. Is the C4F6 epitope directly responsible for the toxicity of misfolded SOD1? If so, then the C4F6 antibody, or other molecules that mask or alter the C4F6 epitope, may prove to be useful as therapeutics. The utility of such treatments could be maximized by first identifying individuals with detectable accumulations of misfolded proteins with conformation-specific antibodies, such as C4F6. Thus, in the future, these antibodies may be used to prevent or treat neurodegenerative disease and to identify the subset of individuals who stand to benefit most from the treatment itself.

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Categorizing speech

Sophie K Scott & Samuel Evans

Using direct electrode recordings in patients undergoing preoperative surgery, a new study demonstrates that neural responses in the secondary auditory cortex mirror perception, showing categorical responses to continuous stimuli.

Categorical perception relates to the way that a continuous sequence of equal physical changes in a stimulus is instead perceived and grouped as two different categories of stimuli[1]. In speech, we can create a range of synthesized speech sounds moving in equal steps from one sound to another; for example, from a /ba/ to a /da/ (a change in the phonetic feature called 'place of articulation' of the consonants, referring to where in the mouth constrictions occur for a particular speech sound). However, this manipulation doesn't lead to us to hear a set of intermediate, blended sounds; instead, we hear the sounds as either a /ba/ or /da/[1]. This phenomenon suggests that our perceptual experience of the speech is driven by higher order, phonetic aspects of the stimuli, rather than by their lower level physical properties. A new study by Chang *et al.*[2] finds that responses in secondary auditory cortex mirror this perception.

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There have been several functional imaging studies of the categorical perception of speech, which have delineated a network of regions, including the superior temporal gyrus and superior temporal sulcus[3,4]. However, it can be hard with techniques such as functional magnetic resonance imaging to explore very fine-grained perceptual distinctions, especially those that may evolve over very short timescales (such as when discriminating between two sounds). Chang *et al.*[2] used preoperative recordings (from patients who were undergoing surgery for brain tumors or epilepsy) from intracranial high-density cortical surface arrays in the left posterior superior temporal gyrus (STG), which is part of the secondary auditory cortex. In the study, four individuals, whose categorical perception of a synthesized continuum varying in the place of articulation (/ba/ to /da/ to /ga/) was established, listened passively to speech sounds while their neural responses were recorded. The authors found a correlation between neural responses in the STG and the identification and discrimination functions collected before the surgery. Even though the neural responses were measured while the patients passively listened to the stimuli, this correlation held (although the amount by which the neurometric functions fit the behavioral data varied across the different speech sounds). This work demonstrates that the neural responses in posterior STG show some of the hallmarks of categorical perception and that these responses are not driven by purely acoustic factors. Across the cortical surface arrays, there was evidence for a spatially distinct pattern of responses to the different speech sounds, suggesting that there might be phonetic maps for place of articulation in the left posterior temporal lobe.

The precise role of categorical perception in speech comprehension, however, remains unknown. For example, not all speech sounds are perceived in ways that would meet the specific criteria for categorical perception[5]. Vowel sounds are perceived more continuously than consonants and, among consonants, a further hierarchy exists with liquids (for example, 'l'), semi-vowels (for example, the sound at the start of 'young') and fricatives (for example, 'sh') being less categorically perceived than stops (for example, 'd' or 'p')[5]. It has been suggested that, as 'true' categorical perception is not always observed, we should perhaps talk of degrees of rather than absolute categorical perception[6]. It has also been argued that experimental demonstrations of categorical perception are strongly influenced by the way a task is presented[7]. Thus, discrimination tasks using a two-alternative forced choice procedure lead to apparent categorical perception of speech stimuli because they let the subjects use a phonetic strategy. These effects disappear if the task is changed; for example, by using a four-alternative forced choice, which encourages more acoustic strategies. If not all of the phonetic elements of speech are perceived categorically and the evidence in favor of categorical perception can be influenced by task demands, then what is the role of categorical perception in how we hear speech in everyday life?

It is also important to remember that categorical perception is not the *sina qua non* of speech perception that it is sometimes assumed to be in the neuroscience literature. When first studied, categorical perception was identified as a speech-specific phenomenon and was considered to be evidence for a speech mode of perception, but categorical perception is not restricted to speech sounds; other kinds of nonverbal perceptual objects, both auditory and visual, can also be perceived categorically, such as facial identity[8] and some nonspeech acoustic stimuli[9]. Although these stimuli are not linguistic, an important role for verbal labels has been demonstrated; people show categorical perception for morphs between photos of famous faces, but not for morphs between two unknown faces. However, if given verbal labels, people will very quickly learn how these map onto the face continuum and start to show categorical perception[8]. This suggests that verbal labels modulate the outcome of a categorical perception experiment. Furthermore, humans are not the only creatures that can demonstrate categorical perception of speech; following training, chinchillas and Japanese quail have been shown to perceive speech sounds categorically[10,11].

Another issue with the existing studies is that experiments of categorical perception, and particularly neuroscience studies, have often used synthesized speech that differs along just a single acoustic dimension. In Chang *et al.*'s study, the starting frequency of the second formant (F2) was varied to create a continuum of speech sounds. In natural speech, however, there is a high level of redundancy in the signal and no single acoustic dimension underlies intelligibility. For example, in phonetic terms, the difference between 'aba' and 'apa' (such as the difference between the words rabid and rapid) is the voicing (either present or absent) of the medial /b/ or /p/ consonants. Acoustically, however, our perception of this voicing contrast depends on more than 16 separate acoustic properties[12]. More recent experimental work in the field of speech science has tried to tackle this complexity, for example, by using more complex combinations of co-varying acoustic dimensions and multidimensional scaling of responses to speech[13].

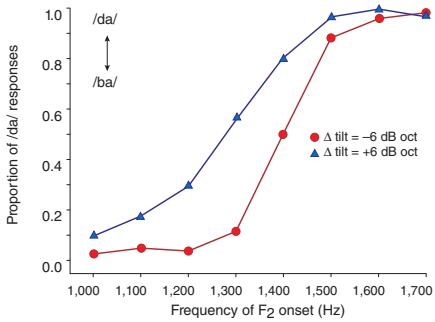

Figure 1 The boundary between the perception of /ba/ and /da/ can shift when the spectral tilt of the speech sounds is modified (figure adapted from reference 14).

Moreover, it has been argued that it is exactly this multidimensional nature of the speech signal that permits us to start to abstract over the surface nature of the acoustic signal and to perceive higher order information[14], and that categorical perception in naturalistic listening represents the manner in which multiple acoustic attributes are combined, similar to perceptual constancy in vision[14]. Restricting the investigation of neural responses to unidimensional manipulations of synthesized speech does not permit these aspects of speech perception to be explored and may lead us to conclude that the neural processing of speech depends on similar one-dimensional mechanisms, such as simple phonetic feature detectors. For example, Chang *et al.* varied the starting frequency of the F2 transition to create a continuum of speech sounds varying in the perceived place of articulation. However, it has been shown that the perceptual consequences of this acoustic manipulation can be altered by other acoustic properties; thus, the category boundary between a /ba/ and a /da/ speech sound can be shifted by manipulating spectral tilt[14] (**Fig. 1**). This indicates that the F2 phonetic feature is perceived in the context of the other information in the speech signal and that covariation of acoustic features has a role in phonetic perception[14].

One of the strengths of the current study is that it clearly demonstrates with preoperative recordings in humans and multivariate analyses that perceptual measures can correlate with neural responses in secondary auditory cortex. Whether one views categorical perception as being specific to speech or not, this is a considerable achievement and this work will clearly have important implications for starting to model exactly how

acoustic-phonetic information is processed in the superior temporal gyrus. For example, a hierarchy of processing has been proposed in which neural responses running lateral and anterior from primary auditory cortex become more selective to linguistic information in the speech signal and are therefore less driven by acoustic properties[15]. With these more sensitive techniques, will we start to refine this into a more comprehensive perspective on the (presumably massively parallel) processes that underlie the mapping of sound to meaning[14]?

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"Yes! We're all individuals!": redundancy in neuronal circuits

Timothy E Holy

In the mouse olfactory bulb, cells with common input respond to odors with similar firing rates but with different timing. This suggests that such 'sister' cells make independent and unique connections with local interneurons.

In small organisms such as *Caenorhabditis elegans*, each neuron in a circuit often serves a distinct functional role; in mammals, with far more neurons, it is sometimes presumed that individual cells are more or less redundant, acting as members of a sizable pool of functionally equivalent neurons. However, the true extent of cellular redundancy in neuronal circuits is generally unknown; only in rare circumstances has it been possible to compare neurons that share common excitatory input. In this issue, Dhawale and colleagues[1] describe experiments examining this issue in the mouse olfactory bulb. Using the light-activated channel channelrhodopsin-2 to identify downstream pairs of neurons ('sister' mitral or tufted cells) excited by the same pool of sensory inputs, they compared the responses of these pairs to a large collection of odorants. In average firing rate, sister cells showed high redundancy, mostly consistent with a view of coding by large pools of interchangeable cells. But the results also contained a twist: substantial differences between sister cells were revealed by examining how their firing was timed relative to the inhalation–exhalation cycle of sniffing. The outcome is consistent with a model in which sister cells make nearly independent connections with local interneurons, and it provides new evidence for parallel streams of representation in olfaction.

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Electronic computers are good examples of processing systems that are largely non-redundant. For example, a single bit in physical memory is most commonly implemented as a single transistor/capacitor pair; failure in a single bit is grounds for replacing an entire memory chip containing billions of transistors. Memory chips intended for more demanding environments frequently implement error-correcting codes, which require a certain amount of redundancy: to detect and correct an error, there has to be some way to check whether a value is unexpected, and this check requires that some extra bits be stored. Such chips can continue to function accurately even if a single bit is damaged. Nevertheless, to pack the most storage into the least space, the degree of redundancy and therefore the capacity to correct errors is typically modest; even in high-end systems, memory corruption is one of the most common modes of failure[2].

In some organisms, of which the nematode *C. elegans* is a prime example, killing individual neurons—or pairs of neurons, because of bilateral symmetry—often results in obvious behavioral deficits. Like computers, such nervous systems would be considered to have relatively little redundancy. In contrast, mammalian nervous systems are frequently suspected of having high redundancy, containing pools of neurons that are essentially 'doing the same thing', and coding is thought to involve averaging the activity of such pools. Even a system such as the retina, which is thought to engage in efficient coding[3], shows significant redundancy in its information transmission[4]. However, estimates of the degree of redundancy more broadly throughout the brain are fraught with large uncertainties[5]. One reason is that, in most brain regions, defining the distinct cell types—each of which could, in principle, encode different information—is still a work in progress; another is our uncertainty over whether two neighboring neurons of the same type make essentially the same connections with other neurons.

A good opportunity to examine this question of redundancy in the nervous system can be found in the olfactory system. Sensory neurons express individual odorant receptor types, and cells expressing the same receptor type project their axons to a common region of neuropil, called a glomerulus. In addition to pooling the outputs of many sensory neurons, a single glomerulus is also the principal source of excitatory input for downstream neurons called projection neurons (in insects) or mitral and tufted cells (in vertebrates, including mice). Although the number of mitral cells receiving input from the same glomerulus varies (with differences between species and even developmental stages[6]), in the mouse there is a pool of several tens of 'sister' mitral cells receiving input from a single glomerulus (**Fig. 1**). Are these sister cells interchangeable? Or might they differ substantially—for example,