Tone deafness: a model complex cortical phenotype

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ABSTRACT – We all know people with tone deafness: these are the people who get thrown out of the choir at school. Although tone deafness is recognised as an output disorder, recent studies have characterised it as one of music perception in the absence of deafness or any associated cognitive disorder. The disorder can therefore be characterised as a form of auditory agnosia. This article considers how the phenotype might be deconstructed to the level of a causal deficit in the perception of pitch pattern. Based on our evolving understanding of the normal brain bases for this process a cortical deficit beyond primary cortex would be predicted. In tone deafness, structural cortical variations have been demonstrated by recent studies that detect subtle changes in the cortical mantle and underlying white matter: these changes are within a right hemisphere network for pitch pattern analysis and working memory for pitch. Studies of multiply affected families are underway to see if the disruption of this network can be caused by single genes. This disorder therefore offers the opportunity to study how a complex phenotype can be characterised as a cortical perceptual disorder potentially explained by a single gene or molecule. Although tone deafness is not pernicious, the underlying abnormality may prove to be a disorder of cortical connectivity that provides a model for disorders that are more so, such as schizophrenia.

KEY WORDS: auditory agnosia, cerebral cortex, genetics, phenotype, tone deafness

Characterising a complex phenotype

Case reports of subjects with lifelong poor singing go back 100 years but it has only been within the last 10 that the disorder has been characterised robustly. Subjects with tone deafness cannot sing in tune but studies using the Montreal Battery of Evaluation of Amusia (MBEA) have demonstrated a deficit in the perception of music.[1] The battery has been important in allowing the characterisation of a deficit that is difficult to assess with rigour. Specifically, it is very difficult to produce a musical equivalent of batteries like the Western Aphasia Battery because in music, much less than in speech, a similar level of exposure, training and interest cannot be assumed. The battery is based on same-different forced choice testing using novel melodies and is motivated by musicological work such as that of Dowling that suggests a serial analysis of melody in which contour ('global structure': the pattern of 'ups' and 'downs' in a piece) precedes the analysis of absolute pitch values (local structure) and tonality or key structure.[2] The battery contains three subtests based on tonal melody pairs with a change in the pitch of one note that might produce a contour violation, a within-key pitch change without contour violation or a key violation. For screening purposes the key violation test at the top of the listening hierarchy is useful and the interested reader can do this online: we have screened more than 130,000 subjects in this way.[3] The MBEA also contains tests of rhythm analysis and melodic memory.

Subjects with tone deafness are not deaf in any conventional sense with no increase in hearing level on the pure tone audiogram compared to controls. Cognitive testing is also unremarkable and some highly educated and intelligent people have had the condition including Ernesto 'Che' Guevara (a physician but not, to my knowledge, a member of this college) and Milton Friedman (founding father of the economic theory of monetarism and Nobel Laureate). The condition is therefore a sensory agnosia; a specific deficit in recognition in the presence of normal function of the sense organ. Converging lines of evidence suggest the presence of a primary deficit in musical perception within the pitch and melody domain, while deficits in rhythm analysis are less consistently reported. Research has been performed on subjects defined using the MBEA that characterises a deficit at the level of the analysis of simple pairs of notes.[4] Subjects with tone deafness have particular problems with the analysis of the direction of pitch excursions (some subjects require more than six semitones to tell the difference between 'up' and 'down'). This test assesses what might be thought of as a 'building block' for the perception of contour in melody (defined as sequences of 'ups' and 'downs') and the work suggests the possibility of a causal low-level deficit. But some subjects with tone deafness have normal pitch direction analysis tested in this way. Moreover, we have used melodies with 'stretched' intervals that are above the threshold for detection of direction in pairs of notes, and subjects with tone deafness still perform badly

with these. It may be that the detection of fixed intervals does not characterise the deficit adequately. When I listen to a particular sufferer singing they can sometimes hit a correct note if this is sustained, but they have major problems with complex pitch trajectories like glorias. This suggests that the deficit might be more accurately characterised by measures of dynamic pitch tracking that require working memory for pitch.

The deficit can be characterised as an apperceptive form of auditory agnosia caused by a deficit in the perception of pitch pattern.[5] Deficits in rhythm analysis can occur, but only if these are in the context of a melody.[6] Pitch pattern analysis is relevant to other domains too and underlies the 'melody of language' as one aspect of prosody.[7] A question that arises immediately is whether subjects with tone deafness might have deficits in prosody perception. When required to make statement-question judgements about phrases, tone-deaf subjects were found to perform as well as controls. However, when the phrases were replaced by sequences of discrete notes that matched the mean pitch of each syllable or a continuous pitch 'track' matched to the speech, tone-deaf subjects showed a deficit.[8,9] Peretz and Hyde originally suggested that the preservation of prosody recognition in whole speech was due to the larger pitch changes in the contour of speech compared to western music.[10] For example, the upward pitch excursion at the end of a phrase that allows us to recognise a question can be more than five semitones. However, the data based on 'extracted' pitch contour do not allow such a straightforward interpretation. The dissociation between deficits in the analysis of speech prosody and the extracted pitch contour might also be based in part on other components of prosody in speech such as the intensity pattern (stress contour) and rhythm: these might provide extra cues to allow the pitch deficit to be overcome.

One other aspect of the phenotype merits comment. Despite their inability to perceive music normally some subjects with tone deafness can still experience pleasure from listening to it. This is interesting in view of the existence of distinct mechanisms for musical emotional analysis suggested by normal functional imaging work and cognitive neuropsychology of subjects with acquired forms of musical agnosia: in terms of the latter a double dissociation has been described in which subjects with strokes might be unable to recognise music but still perceive the accompanying emotion or be unable to experience an emotional effect of music that is normally recognised.[11] Some tone-deaf subjects, however, describe music as unpleasant and try to avoid it: similar behaviour has been observed in patients with stroke who developed deficits in the analysis of pitch-sequences and timbre ('dystimbria').[12] It will be of considerable interest to assess timbre analysis in congenital forms of musical agnosia.

Basis for the phenotype 1: indirect inference from musically normal subjects

Tone deafness can be characterised as a form of auditory agnosia, but that definition cannot be interpreted straightforwardly in terms of the anatomy of any responsible deficit. For example, a form of word deafness (auditory verbal agnosia) can be seen in neuropathy affecting the auditory nerve or in lesions of auditory cortex.[5] Functional imaging of normal subjects, however, suggests that the pitch-pattern deficit in tone deafness is likely to have a cortical basis. The argument is developed in detail by Stewart *et al.*[11] Essentially, there are mechanisms for the representation of the pitch of individual notes in secondary auditory cortex within the Sylvian fissure on both sides, while pitch-pattern perception involves right lateralised mechanisms in the anterior and posterior parts of the superior temporal lobe.[13] The 'active' analysis of pitch patterns when working memory for pitch is required uses right lateralised mechanisms in the posterolateral inferior frontal lobe while tonal analysis involves analysis in deep mesiofrontal areas.[14] The picture that emerges is of increasingly distributed analysis mechanisms for melody as you move to higher levels of the cognitive hierarchy. These studies based on normal functional imaging suggest that the deficit in pitch analysis in the tone deaf might be cortical, within the network for pitch-pattern analysis and working memory for pitch that includes right lateralised mechanisms in the superior temporal lobes and inferior frontal lobe. Studies of patients with temporal lobectomy suggest a critical role for secondary auditory cortex in the right superior temporal lobe in the analysis of pitch direction, argued here to be critical to tone deafness.[15]

Basis for the phenotype 2: direct evidence for a cortical disorder in the tone deaf

At the level of single subjects it is not possible to discern any deficit in brain structure in tone deafness based on magnetic resonance imaging. Studies based on group-level inference do show cortical deficits in areas that are likely to be relevant to the behavioural deficit. Voxel-based morphometry (VBM) seeks changes in grey and white matter density across groups of subjects. The technique does not allow the analysis of data from more than one scanner but using a conjunction analysis a common deficit in white matter density was demonstrated in the posterior inferior lateral frontal lobe in subjects with tone deafness from Montreal and Newcastle.[16] The data can be interpreted in terms of a deficit in connectivity within the right frontotemporal network for perception of pitch pattern and working memory for pitch. In a subsequent study abnormal cortical thickness was demonstrated in the right superior temporal lobe and the right frontal operculum (Fig 1).[17]

Possible underlying genotypes

From first principles, a deficit within the right hemisphere network for pitch-pattern analysis and working memory for pitch in the right superior temporal lobe and right inferior frontal lobe could be produced by a single gene. Disorders of corticocortical connectivity could be produced by a deficit in a molecular mechanism for axonal guidance, while local deficits in cortical structure due to single genes controlling cortical migration are well described.[18] The latter are often associated with epilepsy and mental retardation but an increasingly wide spectrum of phenotypes is recognised. In general, a single-gene pattern of

inheritance is rare but a linkage study in a UK family in which this pattern is strongly suggested is currently being performed.

Concluding comments

Tone deafness represents a complex phenotype that can be deconstructed to some extent to the level of a fundamental deficit in the analysis of a type of sensory pattern. Although the deficit is fundamental, evidence from basic science in normal subjects and studies of abnormalities within the tone-deaf group suggest the deficit is at a high level that involves cortex. Recent work suggests that a single gene basis is possible, but I wonder whether the disorder might be similar to early-onset Alzheimer's disease, in which a presenilin mutation is sometimes identify, but where most subjects have a polygenic basis that is much harder to measure. Apart from occasional breaches of the peace, subjects with tone deafness are generally upstanding contributors to society. However, the disorder illustrates how a complex phenotype can potentially develop into a single gene that determines the function of a network, as a model for more disabling disorders that disrupt cortical networks such as schizophrenia.[19]

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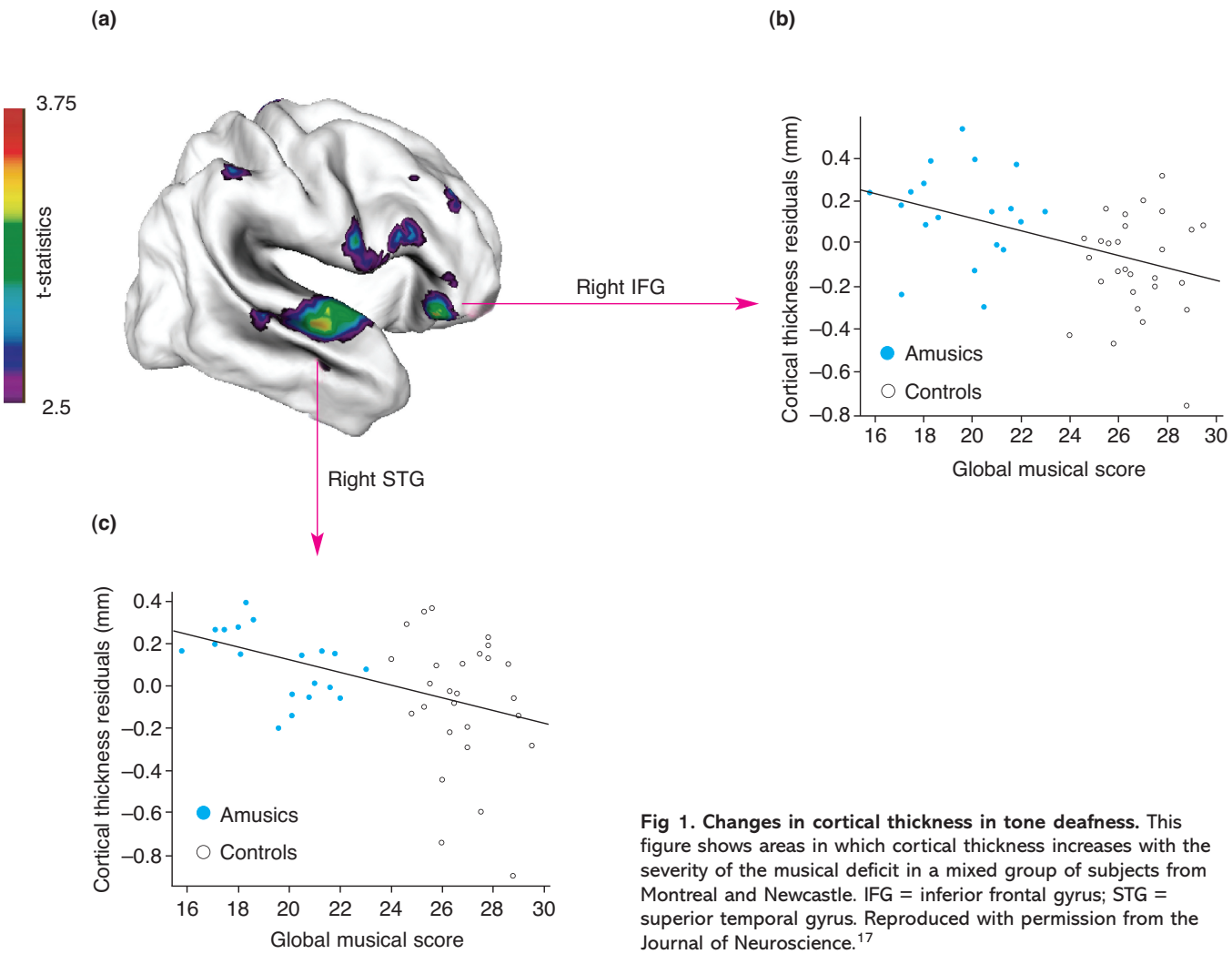

Fig 1. Changes in cortical thickness in tone deafness. This figure shows areas in which cortical thickness increases with the severity of the musical deficit in a mixed group of subjects from Montreal and Newcastle. IFG = inferior frontal gyrus; STG = superior temporal gyrus. Reproduced with permission from the Journal of Neuroscience.[17]

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