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Human complex sound analysis*

T. D. GRIFFITHS
Department of Clinical Neuroscience, Newcastle University Medical School, Framlington Place, Newcastle-upon-Tyne NE2 4HH, U.K., and Wellcome Department of Cognitive Neurology, Institute of Neurology, London WC1N 3BG, U.K.

ABSTRACT

The analysis of complex sound features is important for the perception of environmental sounds, speech and music, and may be abnormal in disorders such as specific language impairment in children, and in common adult lesions including stroke and multiple sclerosis. This work addresses the problem of how the human auditory system detects features in complex sound, and uses those features to perceive the auditory world. The work has been carried out using two independent means of testing the same hypotheses; detailed psychophysical studies of neurological patients with central lesions, and functional imaging using positron emission tomography and functional magnetic resonance imaging of normal subjects. The psychophysical and imaging studies have both examined which brain areas are concerned with the analysis of auditory space, and which are concerned with the analysis of timing information in the auditory system. This differs from many previous human auditory studies, which have concentrated on the analysis of sound frequency. The combined lesion and functional imaging approach has demonstrated analysis of the spatial property of sound movement within the right parietal lobe. The timing work has confirmed that the primary auditory cortex is active as a function of the time structure of sound, and therefore not only concerned with frequency representation of sounds.

INTRODUCTION

Complex sound analysis refers to neither the analysis of simple tones, nor to higher level cognitive analysis of sounds such as speech. Here, I use the term to describe analysis of sounds that change over time, in position. Examples of the first case are amplitude- or frequency-modulated sounds that are perceived as varying loudness or pitch respectively. Examples of the second case are narrow-band sounds producing varying amplitude or phase between the ears, which are perceived as movement of the sound from one side of the head to the other. Mechanisms by which the brain may analyse the cues within these sounds have in the past been investigated by psychophysical techniques on normal humans [1–3] and by neurophysiological studies on mammals [4–6]. Such analysis might be regarded as the extraction of sound ‘building blocks’, features upon which higher level cognitive analysis is dependent.

There has been much recent interest in the way in which certain speech and language disorders may affect the temporal processing of acoustic stimuli [7–11]. Also, the analysis of auditory space involves a complex higher level representation of stimuli arriving at the receptor organ [12], and may be deranged in common clinical disorders such as neglect [13]. The mechanism by which

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Correspondence: Dr T. D. Griffiths, Department of Clinical Neuroscience, Newcastle University Medical School, Framlington Place, Newcastle-upon-Tyne NE2 4HH, U.K.
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the human auditory system extracts temporal and spatial features from sound is therefore of fundamental clinical importance.

PSYCHOPHYSICAL AND IMAGING TECHNIQUES

This work uses complex sounds with carefully controlled spatial and temporal features to investigate how the brain extracts those features. First, psychophysical tests are carried out on subjects with neurological lesions affecting the central auditory pathway and its projections, to establish which features of auditory processing are deficient. This allows a form of cognitive neuropsychology [14] to be carried out, whereby dissociated deficits, in particular auditory functions, are sought. Complete deficits in all auditory functions are not informative, but relating specific lesions to specific deficits allows mechanisms of complex sound analysis to be established. Secondly, functional imaging allows the same stimuli to be used on normal subjects, to show which parts of the brain are active during tasks involving those stimuli. Thus, the use of two independent techniques allows hypotheses about auditory processing to be tested in parallel.

Both the psychophysical studies on neurological patients and the imaging techniques are at an early and challenging stage. Most auditory psychophysics in the past has been carried out on motivated undergraduates or paid volunteers; detailed assessment of, for example, stroke patients is a more difficult proposition. A major focus of current work is to develop a battery of tests which can be realistically used in neurological patients. The application of imaging techniques to auditory work is technically challenging. Studies of actual auditory space are difficult in the scanner environment, although 'virtual acoustic space' techniques allow simulation of sounds in space when they are played over headphones or insert earphones. The marked noise produced by magnetic resonance imaging (MRI) systems when carrying out functional MRI (fMRI) studies is a major problem. New sound delivery systems may make this less of a problem in the future [15].

SPATIAL STUDIES

Much of the work has addressed the question of how the human nervous system analyses auditory space, and in particular what parts of the brain may subserve the perception of sound movement. Work in auditory functional imaging, as in the rest of auditory neuroscience, has tended to focus on the representation of frequency in the nervous system, following the original positron emission tomography (PET) description of tonotopicity in the primary auditory cortex [16]. Recent fMRI studies have extended and qualified the initial PET description [17,18]. However, comparatively little work has been carried out on the analysis of spatial sound properties. Such properties require more extensive computation using the incoming sound signal than frequency representation, which only requires a duplication of the frequency representation that exists at the cochlea.

For some sounds, cues for the detection of position and movement within auditory space exist at either ear alone, but the comparison of the amplitude and time of arrival of sound between the two ears is an important positional cue for many sounds. This comparison first occurs at the level of the superior olive via the trapezoid body. Animal work suggests a mechanism for comparison between the ears dependent on the lateral superior olive for amplitude, and the medial superior olive for phase (time of arrival), although amplitude comparison may also be subserved by higher level convergence in the auditory pathway (described in detail elsewhere [19,20]). In humans the lateral superior olive is a tiny structure of uncertain functional significance, so direct extrapolation of this model may not be appropriate. However, human psychophysical studies confirm the importance of convergence at the superior olive for the detection of certain interaural cues [19,20]. In one study [20] a complete deficit in the detection of interaural phase was demonstrated in a subject with multiple sclerosis, with preserved detection of interaural amplitude. The psychophysical deficit is of interest in its own right, as it proves the existence of distinct mechanisms for the detection of interaural phase and amplitude. Detailed structural imaging of this subject with early disease showed an isolated plaque adjacent to the medial right superior olive, consistent with a need for early convergence at this structure for the detection of interaural phase. Another study [19], of a subject with a vascular lesion at a similar site, demonstrated a more subtle deficit in the detection of dynamic interaural phase and amplitude cues for sound movement perception.

Further detailed lesion studies looked at the detection of similar interaural cues for the analysis of sound movement, due to a cortical lesion in a subject with a right hemisphere stroke [21,22]. A deficit in the detection of interaural phase and amplitude modulation was demonstrated, i.e. the detection of varying timing or amplitude between the ears. The deficit was shown to be dissociated from static sound lateralization tasks, and also from other psychophysical tasks such as frequency modulation detection. This dissociation is important; the psychophysical evaluation of subjects with strokes is a technique which has been little used in the past, especially for auditory work, and the validity of deficits described depends on demonstrating other preserved functions using the same two alternative forced-choice techniques.

These demonstrations of deficits in the detection of interaural cues for the perception of sound movement beg the question as to why this deficit occurs, in both brainstem lesions, and in cortical lesions beyond the primary auditory cortex. I have developed the hypothesis that a cortical area beyond the primary auditory cortex may be necessary for the perception of sound movement, whereas the ascending pathway up to and including the primary auditory cortex is necessary for detection of the interaural component and other cues. This hypothesis has been directly tested in a recent study using both PET and fMRI [23]. The study used a new stimulus which contains both changes in the phase between the ears and changes in amplitude, either of which when acting alone can produce a perception of sound movement (see [20] for a detailed description). The perception of movement due to the two cues can be combined in such a way as to add up, in which case a strong resultant movement is perceived, or to cancel out, so that no resultant movement is perceived. In either case the component sound modulations are the same, so that by comparing the brain activity between the two conditions the effect of the perceptual difference may be assessed. Subjects were required to concentrate on any changes in the position of the sound they could perceive during the scans, without making any motor response or eye movement (there was a visual fixation task). The paradigm was specifically designed to include minimal motor and oculomotor output in an effort to isolate the perceptual difference between the two conditions. Both the PET and the fMRI experiments demonstrated a specific increase in activation during the movement scans compared with the control scans in the right parietal cortex. This is likely to correlate to perceptual analysis in this region, and converges with the lesion evidence demonstrating a deficit in the perception of sound movement due to a right posterior hemisphere lesion outside the auditory cortex [21,22]. However, although motor output was closely controlled, a role for this area in motor or oculomotor preparation cannot be discounted, or an attentional role. The possible contribution of these non-perceptual mechanisms to the activation seen in the right parietal cortex is the major focus of ongoing experiments.

The fMRI data also demonstrated bilateral frontal activation, suggesting the existence of a fronto-parietal network for the perception of sound movement, and attention to it. The fMRI data have been replicated in a recent large study based on 2880 scans (T. D. Griffiths, G. G. R. Green and G. Rees, unpublished work). These data have qualified the initial observation of bilateral prefrontal activation, and suggest that there are two discrete areas of prefrontal activation on each side: a dorsal area in the vicinity of the frontal eye fields and a ventral area concerned with the representation of motor space which is likely to correspond to the ventral premotor area in primates. The dorsal and ventral premotor activations may correspond to oculomotor and somatic motor preparation respectively, in response to the moving acoustic stimulus.

The imaging data therefore suggest a network of areas in the bilateral prefrontal and right parietal cortex involved in the perception of auditory movement in space, attention to it, and preparation for movement in response to it. These studies are the first to demonstrate such a network, and support the hypothesis that analysis at a perceptual level occurs beyond the auditory cortex. What remains to be clarified is the relative contribution of perceptual, attentional and motor preparatory analysis in the different components of the network. A prediction of the hypothesis that this network is for perceptual and higher level analysis, is that similar activation should be produced when the perception of movement is produced by different low-level cues. All of the above work is based on narrow-band interaural cues; in a recent PET study [24], broad-band sound has been used to produce a virtual acoustic stimulus which, when played over insert earphones, is perceived as a sound rotating around the head. A similar bifrontal and right parietal network of activation was demonstrated to that in the earlier experiments.

TEMPORAL STUDIES

Like spatial analysis, temporal analysis of sound has been comparatively less investigated compared with frequency analysis. Since the time of Helmholtz [25], the idea that the pitch of a sound corresponds to a point of excitation within the cochlea has been widely aired. This idea in its original form is no longer tenable, as it cannot explain the pitch of certain stimuli such as the 'missing fundamental'. However, pitch theories based on the spectral 'template' of sound are prevalent to this day [26]. The pitch of some sounds, however, is difficult to explain even with template theories. Such sounds include amplitude-modulated white noise and iterated rippled noise. I have used the latter stimulus in a recent PET experiment carried out in collaboration with R. D. Patterson [27]. This stimulus has not been used previously in functional imaging. The fine time structure, or regularity, of the stimulus can be varied in a systematic way while the auditory spectrum is kept constant. Using such an approach, we have shown that the activity of the primary auditory cortex varies with the temporal regularity of the sound, whereas the auditory spectrum is unchanged. This suggests a coding of temporal regularity at the level of the primary auditory cortex. Moreover, a further analysis to look for variation in activity at a long-term temporal level (in the range of seconds rather than milliseconds) showed such variation in areas of the temporal lobes distinct from the primary and association auditory cortices. This work would thus be consistent with hierarchical analysis in the human auditory system based on timing. The areas where activity was determined by long-term temporal pattern included right temporal areas likely to be involved in tone sequencing, on the basis of studies in patients with acquired 'musical deafness' and musical hallucinations [21,28].

CONCLUSIONS AND FUTURE DIRECTIONS

Both the spatial and timing studies have established brain mechanisms of complex sound analysis in humans, distinct from the better-established processing of sound frequency. The work has suggested mechanisms of complex sound analysis that were not predicted by previous animal work and are relevant to human perceptual disorders.

Current work on the battery of psychophysical tasks will, in the future, allow a portable version of this to be used in psychophysical studies at a population level, as already done in work on dyslexia [29]. Such work will extend the detailed single-case approach that has been used so far. Future functional imaging experiments will include detailed analysis of brainstem processing of complex sound using fMRI, and further investigation of activation due to virtual acoustic space stimuli.

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REFERENCES

1 Green, G. G. R., Heffer, J. S. and Ross, D. A. (1976) The detectability of apparent source movement effected by interaural phase modulation. J. Physiol. **260**, 49P
2 Kay, R. H. (1982) Hearing of modulation in sounds. Physiol. Rev. **62**, 894–975
3 Moore, B. C. J., Glasberg, B. R. and Gaunt, T. (1991) A cross channel masking of changes in modulation depth for amplitude- and frequency-modulated signals. Q. J. Exp. Psychol. **43A**, 327–347
4 Langner, G. and Schreiner, C. E. (1988) Periodicity coding in the inferior colliculus of the cat. I. Neuronal mechanisms. J. Neurophysiol. **60**, 1799–1822
5 Rees, A. and Moller, A. R. (1983) Responses of neurons in the inferior colliculus of the rat to AM and FM tones. Hear. Res. **10**, 301–330
6 Spitzer, M. W. and Semple, M. N. (1993) Responses of inferior colliculus neurons to time-varying interaural phase disparity: effects of shifting the locus of virtual motion. J. Neurophysiol. **69**, 1245–1263
7 McAnally, K. I. and Stein, J. F. (1996) Auditory temporal coding in dyslexia. Proc. R. Soc. Lond. B **263**, 961–965
8 Merzenich, M. M., Jenkins, W. M., Johnston, P., Schreiner, C., Miller, S. L. and Tallal, P. (1996) Temporal processing deficits of language-learning impaired children ameliorated by training. Science (Washington DC) **271**, 77–81
9 Phillips, D. P. and Farmer, M. E. (1990) Acquired word deafness, and the temporal grain of sound representation in the primary auditory cortex. Behav. Brain Res. **40**, 85–94
10 Stefanatos, G. A., Green, G. G. R. and Ratcliff, G. G. (1989) Neurophysiological evidence of auditory channel anomalies in developmental dysphasia. Arch. Neurol. **46**, 871–875
11 Tallal, P., Miller, S. and Fitch, R. H. (1993) Neurobiological basis of speech: a case for the pre-eminence of temporal processing. Ann. N. Y. Acad. Sci. **682**, 27–47
12 Middlebrooks, J. C. and Green, D. M. (1991) Sound localisation by human listeners. Annu. Rev. Psychol. **42**, 135–159
13 Bisiach, E., Cornacchia, L., Sterzi, R. and Vallar, G. (1984) Disorders of perceived auditory lateralisation after lesions of the right hemisphere. Brain **107**, 37–52
14 Ellis, A. and Young, A. W. (1988) Human Cognitive Neuropsychology, Lawrence Erlbaum Associates, Hove
15 Palmer, A. R., Bullock, D. C. and Chambers, J. D. (1998) A high-output, high-quality sound system for use in auditory fMRI (Abstract). Neuroimage **7**, S359
16 Lauter, J. L., Herscovitch, P., Formby, C. and Raichle, M. E. (1985) Tonotopic organisation in the human auditory cortex revealed by positron emission tomography. Hear. Res. **20**, 199–205
17 Talavage, T. M., Ledden, P. J., Sereno, M. I., Rosen, B. R. and Dale, A. M. (1997) Multiple phase-encoded tonotopic maps in human auditory cortex. Neuroimage **5**, S8
18 Wessinger, C. M., Buonocore, M. H., Kussmaul, C. L. and Mangun, G. R. (1997) Tonotopy in human auditory cortex examined with functional magnetic resonance imaging. Hum. Brain Map. **5**, 18–25
19 Griffiths, T. D., Bates, D., Rees, A., Witton, C., Gholkar, A. and Green, G. G. R. (1997) Sound movement detection deficit due to a brainstem lesion. J. Neurol. Neurosurg. Psychiatry **62**, 522–526
20 Griffiths, T. D., Elliott, C., Coulthard, A., Cartlidge, N. E. F. and Green, G. G. R. (1998) A distinct low-level mechanism for interaural timing analysis in human hearing. Neuroreport **9**, 3383–3386
21 Griffiths, T. D., Rees, A., Witton, C., Cross, P. M., Shakir, R. A. and Green, G. G. R. (1997) Spatial and temporal auditory processing deficits following right hemisphere infarction. A psychophysical study. Brain **120**, 785–794
22 Griffiths, T. D., Rees, A., Witton, C., Shakir, R. A., Henning, G. B. and Green, G. G. R. (1996) Evidence for a sound movement area in the human cerebral cortex. Nature (London) **383**, 425–427
23 Griffiths, T. D., Rees, G., Rees, A. et al. (1998) Right parietal cortex is involved in the perception of sound movement in humans. Nature Neurosci. **1**, 74–78
24 Griffiths, T. D. and Green, G. G. R. (1999) Cortical activation during perception of a rotating acoustic stimulus [Abstract, Association for Research in Otolaryngology (U.S.A.), Midwinter meeting] (http://www.aro.org/archives/1990/970.html)
25 von Helmholtz, H. L. F. (1885, English translation 1912) On the Sensations of Tone, Longmans, London
26 Cohen, M. A., Grossberg, S. and Wyse, L. (1995) A spectral network model of pitch perception. J. Acoust. Soc. Am. **98**, 862–879
27 Griffiths, T. D., Buechel, C., Frackowiak, R. S. J. and Patterson, R. D. (1998) Analysis of temporal structure by the human brain. Nature Neurosci. **1**, 421–427
28 Griffiths, T. D., Jackson, M. C., Spillane, J. A., Friston, K. J. and Frackowiak, R. S. J. (1997) A neural substrate for musical hallucinosis. Neurocase **3**, 167–172
29 Witton, C., Talcott, J. B., Hansen, P. C. et al. (1998) Sensitivity to dynamic auditory and visual stimuli predicts nonword reading ability in both dyslexics and normal readers. Curr. Biol. **8**, 791–797