

Experimental approaches to temporal processing in humans

TD Griffiths

1) Auditory Group, Newcastle University 2) Wellcome Department of Cognitive Neurology, UCL 3) Centre for the Neural Basis of Hearing, Cambridge University, UK

At the meeting I consider work that addresses the bases for human temporal processing using two approaches; functional imaging using PET and fMRI and psychophysical studies of neurological patients with central lesions. The discussion below is primarily concerned with recent fMRI data addressing mechanisms of temporal processing in the brainstem and cortex. The intention is to highlight areas of common interest to modelers and animal neurophysiologists.

There are two important problems with the use of PET and fMRI to investigate temporal processing. The first is the fundamental limitation imposed by measuring responses related to slow changes in local blood flow, typically 10s in auditory cortex [1]. This is a particular problem for the investigation of the encoding of fine temporal structure at the level of milliseconds, but is also a problem for the encoding of higher order structure (eg sound sequences) at the level of hundreds of milliseconds or seconds. The second problem is difficulty in imaging the brainstem structures where much temporal processing occurs.

Both PET and fMRI techniques indirectly measure the activity of the brain using measures dependent on the blood flow response to stimuli over seconds. This limits the ability of the techniques to investigate temporal processing in the auditory system; fMRI and PET experiments to investigate temporal processing are critically dependent on the model that is used to interpret the blood-flow data in terms of the underlying neural activity. The blood flow response in such experiments depends on local mean synaptic activity, and with respect to temporal processing there are two important mechanisms related to local mean activity. First, mean local activity can increase when there is an increase in firing rate in a local subpopulation of neurons that might be involved in a particular aspect of temporal processing. Second, modeling studies [2] show that when there is increased *synchronisation* in a population of neurons this can lead to an increased overall activity level. The models were developed for cortex but are based on networks of inhibitory and excitatory neurons that could plausibly exist in auditory brainstem centers too.

Imaging of the brainstem is difficult using PET because of limited spatial resolution. fMRI can achieve greater spatial resolution but fMRI imaging of the brainstem is difficult because of the effect of the pulsation of the basilar artery on the BOLD signal from the brainstem auditory centers. This can be overcome by the use of cardiac triggering. The technique involves acquisition of brain images that is triggered by the R wave of the electrocardiogram so that it always occurs at the same point in the cardiac cycle. The technique was originally developed by the Boston group [3] for a limited number of image slices using a slice angle that passes through important auditory brainstem structures. We have extended this approach to the whole brain by using axial sections of the whole brain that are acquired in an ascending order so that the benefit of the cardiac gating is maximal for the brainstem structures for which it is most important. We have also used sparse imaging as developed by a number of groups (eg [1]) to overcome the effect of the noise of the scanner. Essentially, sparse imaging involves the infrequent acquisition of brain images after long periods of stimulus presentation in the absence of scanner noise. Because the blood flow changes in response to stimulus are slow, images acquired immediately after a long period of stimulus presentation will show a maximal difference between the effect of the stimulus and the effect of the scanner noise. Figure 1 shows that using this technique, we are able to demonstrate activation simultaneously in the whole auditory system.

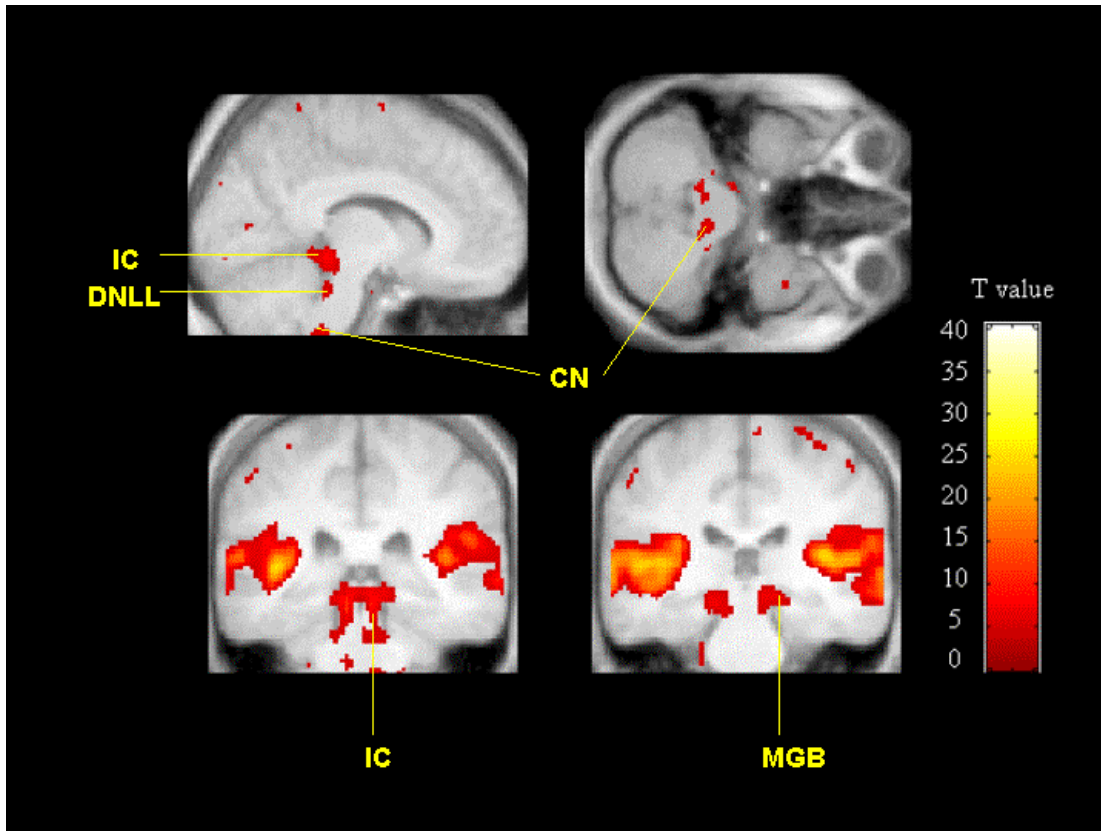


Figure1. Demonstration of brain activity in the ascending auditory system using fMRI with cardiac triggering and sparse acquisition. Data from work carried out in collaboration with S. Uppenkamp, R. Patterson, and I. Johnsrude using an fMRI sequence developed by O. Josephs. Group data for eight subjects for a sound minus rest contrast after conventional pre-processing using statistical parametric mapping. The functional data are rendered onto the mean structural MRI for the group and the colour map refers to the t value for the contrast. **CN** Cochlear Nucleus **DNLL** Dorsal Nucleus of the Lateral Lemniscus **IC** Inferior Colliculus **MGB** Medial Geniculate Body. The data are smoothed using a spatial filter with a full width at half maximum of 5mm and it is not possible to distinguish the DCN and VCN with the (conventional) smoothing imposed.

In figure 1 sound was presented in the form of broadband noise with different degrees of temporal regularity. Regularity of the sound was produced by using an iterative delay-and-add manipulation algorithm to produce regular-interval noise [4]. This has allowed examination of the effect of regularity on the local regional neural activity as measured by the BOLD response within the structures of the ascending auditory pathway. Mean volumes of interest for the CN, IC and MGB for group were defined both anatomically by inspection of the individual subjects' structural scans, and also by the group sound-minus-rest functional data. Table1 shows good correspondence between the functionally and structurally defined coordinates (defined in terms of Talairach [5] coordinates in mm). Within spherical volumes of radius 5mm centered on the coordinates given a contrast was carried out between regular-interval sound and rest. This showed a significant effect of temporal regularity on the regional activity (measured by BOLD response) as early as the CN, and a more significant effect at the level of the IC. Specific analysis for a difference in the effect of regularity on BOLD response in the CN and IC using eigenvariates to estimate the effect in the two centers demonstrated a significant difference (effectively an interaction across areas).

Structure	CN-l	CN-r	IC-l	IC-r	MGB-l	MGB-r
Mean structural co-ordinates [SD]	-8 -41 -47 [1.3 1.1 1.8]	9 -41 -48 [1.1 1.1 1.6]	-5 -35 -10 [0.5 0.9 1.3]	5 -35 -10 [0.7 0.9 1.3]	-16 -26 -8 [1.4 1.8 1.9]	16 -26 -6 [1.1 2.3 2.2]
Functional co-ordinates (group, sound-minus-silence contrast)	-12 -40 -46	8 -34 -48	-6 -34 -12	6 -36 -10	-16 -28 -10	10 -32 -8
Group contrast significance (regular-interval-sound minus noise)	<0.05	<0.05	<0.005	<0.005	<0.05	<0.005

Table 1 Agreement between structurally defined coordinates for brainstem structures and functionally defined coordinates for data set represented in figure 1. The significance levels are for the contrast between regular interval sound and noise to assess the effect of regularity on the mean local activity in each area as assessed by the BOLD response.

What does this mean? There are two possible interpretations of the data in CN; there may be a subpopulation of cells that become more active when they detect a particular temporal interval (perhaps onset chopper cells [6]) or there may be an increase in the mean activity level of a broader population of cells in the CN due to the synchronising effect of the regularity. At the level of the IC, if conversion of regularity into an activity code occurs in a subpopulation of cells in CN, then the data suggest that such conversion is not completed in CN. This would be consistent with a two stage mechanism as suggested for animals by Langner involving *measurement* of time intervals (regularity detection) early in the system and *representation* of those time intervals at a higher level. Our data do not address the question of whether the representation of regularity in the IC is in the form of a map. Alternatively, if the effect of regularity on BOLD response in the CN is due to an effect of synchronisation, this suggests that both measurement and detection of regularity must occur in IC. In either case, a two-stage mechanism for converting regularity into a more robust code is suggested.

In these experiments the higher-level temporal structure of the sounds was also manipulated by producing patterns of sounds with different pitches corresponding to different periodicities in the noise. In contrast to the effect of temporal regularity, there was no effect of such manipulation on the activity in the brainstem structures or the primary auditory cortex in medial Heschl's gyrus. Such an effect only emerged in lateral Heschl's and anterior temporal lobe areas, consistent with a hierarchal processing of temporal structure in the system. Consistent with the imaging data, a recent psychophysical study [7] suggests the pathway up to and including primary cortex being sufficient for the perception of complex pitch in the form of IRN, but not higher order patterns such as melodies.

1. Hall, D.A., et al. Hum Brain Mapping, 1999. **7**: 213-223.
2. Chawla, D., E.D. Lumer, and K.J. Friston. Neural Computation, 1999. **11**: 1389-411.
3. Guimares, A.R., et al. Hum Brain Map, 1998. **6**: 33-41.
4. Yost, W.A., R. Patterson, and S. Sheft. J Acoust Soc Am, 1996. **99**: 1066-1078.
5. Talairach, P. and J. Tournoux, *A stereotactic coplanar atlas of the human brain*. 1988, Stuttgart: Thieme.
6. Wiegand, L. and I.M. Winter. J. Neurophysiol., 2001. **85**: 1206 -1219.
7. Griffiths, T.D., et al. NeuroReport, 2000. **11**: 919-922.