

The neural basis of temporal auditory discrimination

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When two identical stimuli, such as a pair of clicks, are presented with a sufficiently long time-interval between them they are readily perceived as two separate events. However, as they are presented progressively closer together, there comes a point when the two separate stimuli are perceived as one. This phenomenon applies not only to hearing but also to other sensory modalities. Damage to the basal ganglia disturbs this type of temporal discrimination irrespective of sensory modality, suggesting a multimodal process is involved.

Our aim was to study the neural substrate of auditory temporal discrimination in healthy subjects and to compare it with structures previously associated with analogous tactile temporal discrimination. During fMRI scanning, paired-clicks separated by variable inter-stimulus intervals (1–50 ms) were delivered binaurally, with different intensities delivered to each ear, yielding a lateralised auditory percept. Subjects were required (a) to report whether they heard one or two stimuli (TD: temporal discrimination); or (b) to report whether the stimuli were located on the right or left side of the head mid-line (SD: spatial discrimination); or (c) simply to detect the presence of an auditory stimulus (control task).

Our results showed that both types of auditory discrimination (TD and SD) compared to simple detection activated a network of brain areas including regions of prefrontal cortex and basal ganglia. Critically, two clusters in pre-SMA and the anterior cingulate cortex were specifically activated by TD. Furthermore, these clusters overlap with regions activated for similar judgments in the tactile modality suggesting that they fulfill a multimodal function in the temporal processing of sensory events.

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Introduction

The ability to discriminate successive signals separated by time intervals in the milliseconds-range is an important element in the analysis of temporal characteristics of sensory input. Recently, we developed a new methodology to study this aspect of time perception for the tactile sensory modality (Pastor et al., 2004). This consisted of presenting pairs of tactile stimuli at variable inter-stimulus intervals (ISI) during fMRI. The task of the subject was to report the perception of either a single stimulus (for short ISIs) or two stimuli separated in time (for longer ISIs), thus performing a simultaneity-succession judgement. Patients with Parkinson's disease show a deficit in this temporal discrimination (TD) task that is independent of the modality of sensory input. The ISI at which the perceptual transition from one to two events occurs was found to be elevated, irrespective of whether the stimuli were delivered in the tactile, visual or auditory domains (Artieda et al., 1992). These TD thresholds were related to the severity of disease and were improved by dopaminergic treatment (Artieda et al., 1992). Several other studies have demonstrated impaired temporal discrimination thresholds in patients with basal ganglia disorders using both unimodal and multimodal (visual and tactile) stimuli, showing additional impairment in cross-modal presentations (Agloti et al., 2003; Fiorio et al., 2003; Tinazzi et al., 2004). Specifically, in studies using pharmacological manipulation, the dopaminergic system has been demonstrated to be involved in auditory duration discrimination of time intervals in the range of milliseconds and in the visual Critical Flicker Fusion Frequency (Rammesayer and Lima, 1991; Rammesayer, 1999). These observations beg the question whether this aspect of time perception is subserved by a single network that operates multimodally (i.e., a common system for different sensory modalities). To address this question, we have modified the paradigm that we developed for studying tactile temporal processing (Pastor et al., 2004) to investigate TD in the auditory domain. A common processing network for audition and touch might be revealed if a multimodal system performs discrimination of time intervals in the milliseconds-range.

Our paradigm allows us to dissect the temporal aspect of discrimination from general discriminatory and attentional processes. For this, we compare the TD of pairs of stimuli in which subjects report perception of one or two stimuli, with an equally demanding spatial discrimination (SD) task in which subjects have to judge the location of the stimuli. Furthermore, we used a baseline condition in which subjects simply detected the presence of stimuli, using identical stimuli and motor responses. This provided us with a baseline to reveal activation common for both TD and SD discriminations, while still controlling for activity related to the processing of primary sensory information and that associated with the preparation and execution of the motor response.

A major advantage of the ‘one-or-two-stimuli’ temporal discrimination task over other temporal discrimination tasks (e.g., estimation of duration), is that it does not explicitly rely on memory processes that in other tasks are needed to compare test stimuli with previously presented reference stimuli. In our procedure, inter-stimuli intervals never exceeded 50 ms, thus voluntary allocation of attention to one or another element of the stimuli pair appears unlikely. Such voluntary, strategic behavior can occur in temporal discrimination tasks that use longer intervals (e.g., 500 ms to 10-s range) and thus need codification of stimulus duration. Our type of TD, discrimination between successive signals, might be important for the detection of onset/offset limits of long time intervals, and thus for estimating duration of a presented time interval.

Using the ‘one-or-two-stimuli’ task (i.e., simultaneously-succession judgement) in the tactile domain we showed that the brain areas specifically involved in TD were the anterior cingulate cortex and the medial aspect of the superior frontal gyrus in the region of pre-supplementary motor area (pre-SMA), with maximal activity located in the right hemisphere (Pastor et al., 2004). In the present study, we use an analogous experimental design to investigate whether similar brain regions are activated during TD of auditory stimuli.

Experimental procedures

Subjects

Fourteen right-handed healthy volunteers, 7 male and 7 female, (mean age = 32.7; SD = 5.7) participated in the present auditory experiment. None of them took part in the previous study on tactile temporal discrimination (Pastor et al., 2004; see also below). The study was approved by the Joint Ethics Committee of The Institute of Neurology (UCL) and The National Hospital for Neurology and Neurosurgery (UCL Hospitals NHS Trust). Subjects gave informed written consent after explanation of the experimental procedure. Prior to fMRI, subjects were tested psychophysically to obtain individual discrimination thresholds.

Stimuli

Stimuli were pairs of clicks delivered binaurally through headphones. The auditory stimuli were generated by Cogent 2000 software (Cogent-2000, Wellcome Department of Imaging Neuroscience, London). Stimulation comprised a pair of clicks of 0.5 ms duration separated by variable inter-stimulus intervals (ISI). Furthermore, in different trials there was an intensity difference

between click-pairs presented to the left and right ear (interaural intensity difference, IID), yielding a lateralised auditory percept. Importantly, it should be noted that the interaural time difference for each click of the pair was set to the constant value of 0 ms, irrespective of current ISI and IID. Thus, sounds to the two ears were presented simultaneously. On each trial the subject perceived one or two clicks (depending on the ISI) originating from a single position, as determined by the current IID. Throughout the experiment, the IIDs of the clicks-pairs were set so that 50% of the trials had higher clicks intensity in the right ear, and 50% of the trials had higher intensity in the left ear. The IID between ears was varied in steps of 10 dB with the maximum intensity set to 90 dB SPL (sound pressure level). The stimuli series were the same for the temporal and spatial discrimination tasks, and also for the control condition (detection), but in a different randomised order.

Psychophysical study

Prior to the fMRI experiment we conducted psychophysical measurements to select suitable ISI and IID for the main study. Psychophysical testing was conducted inside the scanner during acquisition of Echo-Planar Images (producing acoustic background noise), in order to avoid differences between the psychophysics results and the experimental fMRI scanning sessions. Behavioral data obtained during the experimental fMRI sessions confirmed that the ISIs and IIDs selected during psychophysics produced appropriate effects on the consistency indices (see below).

Discrimination tasks

Temporal discrimination (TD)

A random series of paired clicks with ISIs between 1 and 50 ms in steps of 1 ms (from 1 to 10) and 5 ms (from 10 to 50) were presented binaurally with a ITD of zero (but with different interaural intensities in the left and right ear, that were ignored during this task; see above and below). On each trial, subjects reported whether they were able to hear one or two sounds. The response was a button-press with index or middle finger of the right hand, corresponding to the upper or lower keys of a button-box. Subjects were required to respond as fast as possible but maintain maximal accuracy. The stimulus–response association (one/two stimuli and upper/lower key) was counterbalanced across subjects.

Spatial discrimination (SD)

Pairs of stimuli with varying interaural intensity differences (IID) were presented binaurally with a maximum intensity of 90 dB SPL. The IID was changed in steps of 10 dB SPL, yielding the following possible intensities for the two ears: 90/30, 80/40, 70/50, 50/70, 40/80, 30/90 (dB SPL, in left/right ear respectively). All sounds were presented simultaneously to the two ears (ITD = 0), and therefore stimulus position was determined solely by the difference in intensity levels (IID). On each trial, subjects discriminated the stimulus position as perceived in a location to the left or to the right of an imaginary longitudinal midline through the head. Subjects reported the perceived position with a button-press using the index or middle finger of the right hand, corresponding to the upper or the lower keys of a button-box. The stimulus–response association (left/right stimulus and upper/lower key) was counterbalanced across subjects. To minimise stimulus–response compatibility effects, the two response buttons

were placed in an “upper versus lower” configuration (i.e., orthogonal to the “left versus right” sensory judgment).

Control task (C)

A control (C) task involved simple detection of stimuli. Subjects were required to press a button as soon as a sound was detected irrespective of its location or number. Alternate buttons were pressed on successive presentations. Thus, the control task used the same sensory stimuli as the two experimental discrimination tasks and the motor responses were also well matched. In each trial, the response selection and the time between stimulus presentation and button press (reaction time) were recorded. We should note that the overall difficulty, attentional demands and motor planning of the control task were lower than for the two active discrimination tasks. However, the use of this “lower-level” baseline condition allowed us to highlight common activations for the two discrimination tasks, in addition to the highly-specific direct comparison between the two active tasks.

Consistency index

To index the influence of task difficulty associated with the presentation of auditory stimuli at any given interval (TD) or at any given location (SD), we used a measure of response consistency (consistency index; see also Pastor et al., 2004), based on the variability of the responses for each ISI (TD) or interaural intensity difference between left and right stimulus pairs (SD). The formula used was:

Consistency = absolute $(r1 - r2)/(r1 + r2)$, with $r1$ and $r2$ corresponding to the two types of responses (“one” and “two” for temporal discrimination, and “left” and “right” for spatial discrimination). The consistency index equals unity if the subject always produces the same response for a given stimulus-type. The index equals zero if the subject responds completely by chance (50% for each response type).

fMRI study

Experimental design

We used a factorial design that manipulated orthogonally the type of auditory discrimination (TD versus SD) and the stimulus-type (ISIs/IIDs), so to obtain different levels of response-consistency during discrimination (high versus low consistency). It should be noted that because we use only interaural intensity differences (IID) and not interaural time differences (ITD) to produce lateralised percept of sounds, the spatial and temporal manipulations were orthogonal and did not interact with each other.

Stimuli and tasks

To reduce the total number of possible stimulus-types during fMRI we used the same procedure as for the psychophysical study but selected only four ISIs and four IID. We choose two stimulus-types associated with high response-consistency and two associated with low response-consistency, for each subject. The factorial combination of the 4 positions by 4 time-intervals gave a total of 16 possible stimulus-types. Because only one stimulus attribute (either temporal or spatial) was judged at any time these 16 stimulus-types were collapsed to obtain 8 experimental conditions: 4 conditions of temporal discrimination (2 ISIs associated with high response-consistency and 2 with low response-consistency); and 4 conditions of spatial discrimination (2 IIDs

associated with high response-consistency and 2 with low response-consistency). The same 16 stimulus-types were used for TD, SD and C tasks.

Scanning procedure

Each subject underwent 3 fMRI scanning runs. During each run, discrimination tasks were presented in blocks of 40 s. Each block consisted of 8 trials with the four stimulus-types (2 associated with high response-consistency and 2 with low response-consistency) repeated twice and intermingled in a non-predictable, pseudo-random sequence. The inter-trial-interval was 4 s. Control blocks lasting 20 s (4 trials) were placed between each discrimination block, leading to an alternating sequence: 4C–8TD–4C–8SD–4C–8TD–4C–8SD–... Over the three runs, each subject was presented with 144 trials for each discrimination condition (72 associated with high response-consistency and 72 with low response-consistency) and 144 trials for the simple detection control condition.

Throughout scanning subjects fixated a central fixation-cross. The color of the fixation-cross specified the current task. The associations between color (red, green or blue) and auditory task (TD, SD or C) was arbitrary and counterbalanced across subjects. For every change of task an interval of 4 s preceded delivery of the first trial allowing for task switching.

Data acquisition

Imaging was performed using a 1.5-T scanner (Siemens Sonata, Erlangen, Germany) equipped with a head volume coil. The functional images sensitive to blood oxygenation level dependent (BOLD) contrast were acquired by T2*-weighted echo planar imaging. Each functional image comprised 38 transverse slices (2 mm thickness, 1 mm gap, $64 \times 64, 3 \times 3$ mm pixels, TE = 40 ms) covering the whole brain volume. A total of 193 sequential volumes were acquired per run with an effective repetition time (TR) of 3.42 s. There were three scanning runs of 11 min. To avoid systematic correlation between slice acquisition and stimulus presentation and to guarantee good sampling of the haemodynamic responses, stimulus-onset was randomly jittered with respect to the beginning of each acquired volume.

fMRI analysis

We used SPM2 software for image processing and analysis (<http://www.fil.ion.ucl.ac.uk/SPM>). For each subject and run the first four volumes were discarded to allow for T1 equilibration. The remaining 567 volumes were realigned to the first image, sinc-interpolated over time to correct for phase advance during volume acquisition and normalised to the Montreal Neurological Institute reference brain. The data were spatially smoothed with a Gaussian kernel (8 mm full-width at half-maximum).

We used a two-level analysis procedure for statistical inference at a random effect level. At the first level of analysis (fixed effects) the scans of each subject were analysed separately. For each subject, the 8 event-types were defined by crossing the 3 factors High/Low response-consistency (H/L); Short/Long ISIs (1/2); and Left/Right position (L/R). The eight event-types were modeled using the appropriate stimulus function convolved with a canonical haemodynamic response function (HRF). For each subject we estimated contrasts of interest that were then assessed at the second level of analysis (random effects) with a one-sample t test across all 14 subjects (d.f. = 13). Our study aimed to describe effects that are consistent across subjects and generalisable.

We performed three statistical comparisons. First, we tested for any common effect of the two auditory discrimination tasks (TD and SD) versus control (simple detection). This was tested using conjunction analyses, dividing randomly the control trials into two groups (A, B) and then testing for common activation of TD versus control (A) and SD versus control (B).

The second comparison tested for brain activity specific for one or the other auditory discrimination task (TD, SD). For this critical effect of interest we directly compared TD versus SD, and vice versa. To assign corrected P value we selected the maximally activated voxels for discrimination vs. control (see above) and we defined a centroid for small volume correction. The size of the volume was 8 mm, compatible with the smoothing Gaussian Kernel (8 mm full-width at half-maximum). Note that the overall effect of auditory discrimination and the differential effect of TD minus SD (and vice versa) are orthogonal. Thus, the choice of our volume of interest did not bias the statistical tests concerning the differences between temporal and spatial discrimination.

Finally, we assessed whether any of the activations obtained in the present auditory study overlapped with activations previously reported for discriminations in the tactile domain (Pastor et al., 2004). We defined volumes of interest according to the activations found in the tactile modality, and we tested for any corresponding auditory effect in the current study. Because the two studies (auditory and tactile) used equivalent procedures, we applied this procedure both for the overall effect of discrimination versus control, and for the two direct comparisons TD minus SD, and SD minus TD. Only regions activated both in the tactile study and in the present auditory experiment will pass this procedure, highlighting possible multimodal substrates common to audition and touch. Note that although two independent groups of subjects participated in the auditory and the tactile experiments, the use of statistical tests relying solely on between-subject variance (random effects analyses) allow us to combine data of the two groups, because both refer to population effects. Nonetheless, we should note that a within-subject design might in principle be more sensitive, possibly revealing additional multimodal effects.

Results

Behavioral data

Prior to fMRI scanning, we estimated the individual thresholds for TD and SD using a psychophysical procedure (see Experimental procedures). For the TD task at short ISIs (1–3 ms) subjects consistently reported the perception of a single sound and at long ISIs (50 ms) two clicks were reliably reported. For ISIs between 4 and 10 ms, subjects were less consistent, the same physical stimulus yielding different responses in different trials. Analogously, for the SD task as the higher intensity shifted from left to right ear the perceived stimulus location moved from left to right and the percentage of “left” responses decreased. For similar intensities in both ears (i.e., small IIDs; e.g., 20 dB SPL) responses were less consistent. For fMRI, two ISIs and two IIDs were chosen in the high response–consistency range, and two in the low response–consistency range for each subject.

Fig. 1 shows the group effect of consistency for both temporal and spatial discrimination tasks, as assessed in the fMRI experiment. A two-factor ANOVA with *discrimination task* (TD and SD) and *stimulus-type* (ISIs/positions yielding to different

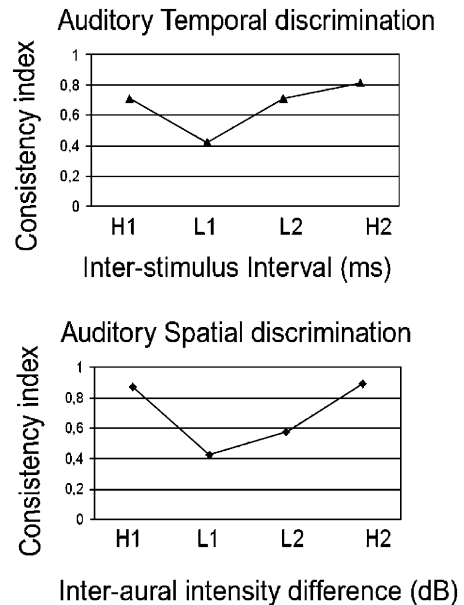


Fig. 1. Graphic showing behavioural performance during scanning. Grand average of the group consistency index for the spatial and the temporal auditory discrimination tasks. The units on the x axis on the bar graphs are ISI in ms for the temporal discrimination tasks, and inter-aural intensity difference in dB SPL. (H/L: High/Low response-consistency; 1: right position or short ISIs; 2: left position or long ISIs).

levels of response–consistency) as independent factors revealed the expected main effect of *stimulus-type* ($F = 4.2$; $P = 0.01$), with higher consistency-indexes for ISIs/positions at the extreme of the ranges compared with ISIs/positions in the intermediate range. There was no effect of *discrimination task* ($F = 0.26$; $P = 0.62$), and no interaction between the factors ($F = 0.56$; $P = 0.63$).

The mean reaction times were analysed similarly. There was no significant main effect of *discrimination task* (mean [SEM]: Temporal Discrimination = 860[18] ms; Spatial Discrimination = 803[43] ms; $F = 2.7$, $P = 0.19$). In addition, there was neither an effect of *stimulus-type* ($F = 2.7$, $P = 0.19$) nor an interaction between the two factors ($F = 2.6$, $P = 0.22$).

These data indicate that during fMRI scanning the tasks were well matched and that brain activity in the two discrimination tasks can be compared without behavioral confound. Moreover, the lack of significant main effect of task in the reaction time data suggests that subjects did not switch strategy in the two discrimination tasks. For example, subjects could in principle use the first stimulus to perform the spatial discrimination, while they had to wait for the second for temporal discrimination. However, note that this time difference could extend maximally to 25 ms (i.e., the longest ISI), which has no relevance for BOLD responses. Furthermore, we assessed the behavioural data looking for any effect of the congruency between the response-mapping of the attended and unattended feature (e.g., were subjects faster to respond to an ISI associated with “up”-button response, when the task-irrelevant stimulus-position was associated with the same [up] versus different [down] response?). This did not reveal any significant effect, indicating that subjects efficiently selected just one feature (temporal or spatial) and/or successfully inhibited the response associated with the unattended feature.

fMRI results

The analysis of fMRI data had three aims: (1) To highlight brain areas involved in both types of auditory discrimination, over and above simple auditory detection. (2) To investigate differences between the two types of auditory discrimination, with a specific interest in areas selectively activated during TD. (3) To verify whether any areas activated in the auditory experiment overlap with areas identified in a previous study that employed an analogous tactile discrimination paradigm (Pastor et al., 2004).

Common activations for temporal and spatial auditory discrimination vs. control

Using conjunction analyses (see Experimental procedures), we identified common areas that activated for both TD and SD tasks. These were located in cortical and subcortical regions (see Fig. 2). Cortical activations were found in right middle (x, y, z Talairach coordinates = 48, 20, 24; $z = 3.72$; P -corrected = 0.011) and inferior frontal gyri (x, y, z Talairach coordinates = 40, 46, -10; $z = 3.63$; P -corrected = 0.011), the right insula in its anterior aspect (BA 13) (x, y, z Talairach coordinates = 32, 22, -2; $z = 3.40$; P -corrected = 0.05) and the right anterior cingulate. At subcortical levels, the right putamen (x, y, z Talairach coordinates = 28, 4, 4; $z = 2.82$; P -corrected = 0.05) was activated by both discrimination tasks (Table 1a). Fig. 2 shows the anatomical location and pattern of activity for cortical regions, showing that these regions activated irrespective of *discrimination task* and *stimulus-type* (i.e., activity was independent of response–consistency). These results identify a common network

Table 1a

Main effect of auditory discrimination vs. control data include t statistic, Z scores, plus the coordinates of the maxima within the activated cluster (Talairach and Tournoux, 1988) (x, y, z)

	P -corrected	Z	x, y, z
Right middle frontal gyrus (BA 13 and 44) Insula	0.011	3.72	48, 20, 24
Right inferior frontal gyrus (BA 13 and 44) insula	0.011	3.63	40, 46, -10
Right anterior cingulate (BA 32)	0.02	2.89	16, 24, 26
Right insula (BA 13)	0.04	3.40	32, 22, -2
Right putamen	0.05	2.82	28, 4, 4

for auditory discrimination irrespective of the specific sensory attributes that had to be judged (temporal or spatial).

Activations specific for the auditory temporal discrimination

The critical aim of the study was to investigate brain areas specifically involved in TD relative to SD. For this, we compared directly activity during the two discrimination tasks, revealing activation of the anterior cingulate cortex (BA 32), with its peak located in the right hemisphere (x, y, z Talairach coordinates = 10, 26, 30; $z = 4.52$; P -corrected = 0.024) and a second cluster located in the medial aspect of the superior frontal gyrus (BA 6). This location corresponds to pre-SMA in the right hemisphere (x, y, z Talairach coordinates = 12, 16, 58; $z = 2.33$; P -corrected = 0.04)

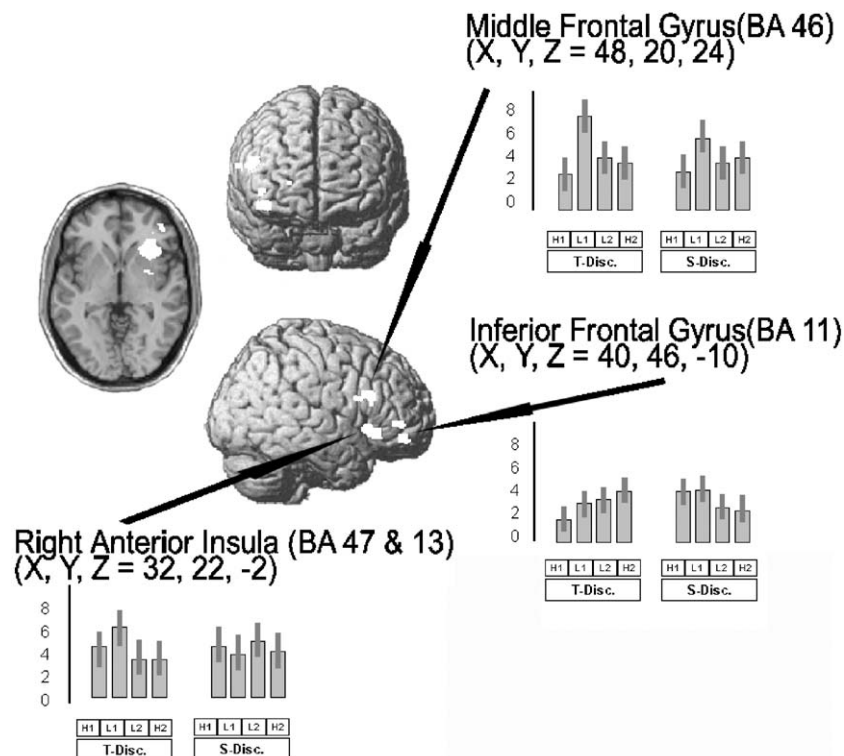


Fig. 2. Transverse sections on the canonical MR T1 template, showing anatomical details for the activations found in the right insula (all activations not visible in the surface rendered projections). Rendered view of the lateral surface of the right hemisphere and frontal view, showing regions activating for both SD and TD, versus control. The plots show the pattern of activation for the four conditions of TD and four conditions of SD. Effect sizes represent the activation for each condition compared to baseline. All areas were activated above control, irrespective of type of discrimination and consistency of response. SPM threshold P -corrected = 0.05. (H/L: High/Low response-consistency; 1: right position or short ISIs; 2: left position or long ISIs).

(Table 1b). Fig. 3 shows the location and pattern of activity for the two clusters in the medial frontal lobe.

The reverse comparison (SD versus TD) revealed no significant activations. However, sub-threshold activation was found in right superior parietal cortex and the precuneus (x, y, z Talairach coordinates = 20, -62, 56; $z = 4.67$; P -uncorrected = 0.0001) (Table 1c). This area is in good anatomical correspondence with another sub-threshold activation that we reported for the same comparison (SD versus TD) in our previous study using tactile stimulation (Pastor et al., 2004; see also below).

Finally, no brain region showed significant interactions between type of discrimination (TD or SD) and stimulus-type (i.e., ISIs/IIDs yielding to high or low response-consistency). This result suggests that the observed activation of the anterior cingulate and pre-SMA in temporal discrimination tasks cannot be attributed to non-specific task differences, such as task difficulty and/or attentional demand.

Multimodal activations for auditory and somatosensory discrimination: task-independent versus task-specific effects

We defined the location of activations of interest from our previous study in the tactile domain. We considered 3 effects in the tactile study: (1) Common activation by TD and SD versus a simple detection control; (2) specific activation by TD compared to SD; and (3) specific activation by SD compared to TD. We then assessed whether within regions activated by tactile comparisons there were corresponding effects in the present auditory experiment (anatomical overlap revealed using volumes of interest, see Experimental procedures).

The anterior cingulate cortex, inferior frontal gyri, insulae and the basal ganglia showing common activations for TD and SD versus simple detection in the current auditory task overlapped with regions activated for the same comparison in touch (Table 2a), thus indicating a possible supramodal role for these areas in sensory discrimination. We then investigated anatomical overlaps between touch and audition for the areas that activated specifically either for temporal or for spatial discrimination. Both the anterior cingulate cortex and pre-SMA that were activated in the present auditory study overlapped with areas activated by the analogous comparison in the tactile task (see Table 2b). Finally, the direct comparison of spatial versus temporal discrimination revealed that although below the chosen statistical threshold in both studies individually, an activation in the precuneus was present in both auditory and tactile spatial domains. This suggests a weak but consistent role for this region during discrimination of spatial characteristics of sensory stimuli, irrespective of the specific modality of presentation (Table 2c).

Discussion

The present study reveals several new findings concerning temporal discrimination of successive stimuli. First, a network of

Table 1b
Areas for auditory temporal discrimination vs. spatial

	P -corrected	Z	x, y, z
Anterior cingulate (BA 24 and 32)	0.024	4.52	10, 26, 30
Pre-SMA (BA 6)	0.04	2.33	12, 16, 58

Data include t statistic, Z scores, plus the coordinates of the maxima within the activated cluster (Talairach and Tournoux, 1988) (x, y, z).

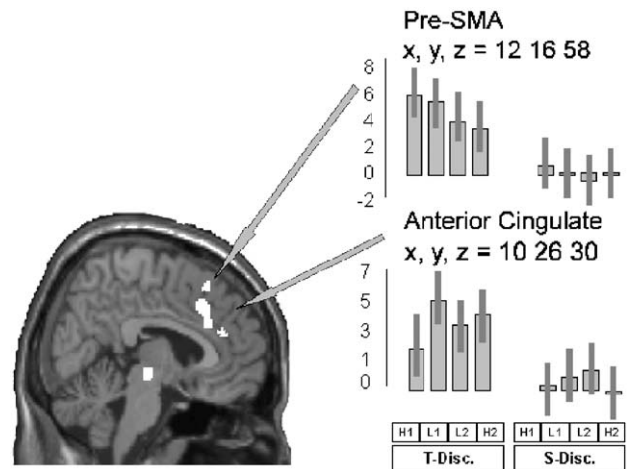


Fig. 3. Activations observed for the comparison of auditory TD versus SD rendered onto a sagittal section close to the midline. SPM threshold P -corrected = 0.05. The plots show the pattern of activation for the four conditions of TD and four conditions of SD. Effect sizes represent the activation for each condition compared to baseline. The plots illustrate that only the TD task activated above control, and that activations occurred irrespective of response-consistency. (H/L: High/Low response-consistency; 1: right position or short ISIs; 2: left position or long ISIs).

cortical and sub-cortical regions activates when discriminating attributes of a stimulus, as opposed to simply registering its presence (common for temporal and spatial discriminations). Second, anterior cingulate and pre-SMA are selectively recruited for processing temporal attributes. Third, the regions involved in auditory temporal discrimination substantially overlap with those previously associated with the same function in the tactile domain.

Areas activated for both temporal and spatial discriminations

When subjects made judgments about the properties of an auditory stimulus, a number of cortical and subcortical regions were activated irrespective of the relevant feature (i.e., temporal or spatial). At the cortical level, these included the middle and inferior frontal gyri, the anterior portion of the right insula and the right anterior cingulate gyrus. At subcortical levels, the basal ganglia activated for both types of discrimination task. The areas include activation of the head of caudate nucleus and putamen. Analogous regions were activated in our previous study that used equivalent conditions and comparisons in the tactile rather than auditory domain (Pastor et al., 2004). Although we should note that the cognitive demands of the detection task were smaller compared with the two discrimination tasks, the use of the control condition allowed us to highlight brain areas activated by both auditory discriminations (TD and SD). The finding of a common network for TD and SD, that also overlaps with regions activated for temporal and spatial discrimination in the tactile domain (see Pastor et al., 2004), reveals a common system processing sensory

Table 1c
Auditory spatial discrimination vs. temporal discrimination

	P -uncorrected	Z	x, y, z
Right superior parietal and precuneus (BA 7)	0.0001	4.67	20, -62, 56

Table 2a
Main effect of discrimination vs. control

	<i>P</i> -uncorrected	<i>Z</i>	<i>x, y, z</i>
Left inferior frontal gyrus (BA 13 and 44) Insula	0.0001	4.06	−26, −26 16
Right inferior frontal gyrus (BA 13 and 44) insula	0.0001	3.40	32, 22, −2
Right anterior cingulate (BA 32)	0.002	2.90	16, 26, 22
Right middle frontal gyrus (BA 46)	0.005	2.7	66, 14, 20
Left globus pallidus	0.005	2.55	−16, −10, 2

Common areas for discrimination in auditory and tactile experiments. Data include *t* statistic, *Z* scores, plus the coordinates of the maxima within the activated cluster (Talairach and Tournoux, 1988) (*x, y, z*).

input irrespective of modality, thus providing a possible candidate for a multi-modal network for feature discrimination.

Areas specific for auditory temporal discrimination

Several areas of the brain were specifically activated during the temporal discrimination task when directly contrasted with the spatial task. Note that for both tasks we used identical stimulus sets and motor responses. Moreover, the behavioural results indicated similar reaction times and no difference in the consistency indices. Therefore, the differential activation pattern is likely to reflect the specific processing of temporal attributes of the input, rather than any sensory, motor or difficulty-related processes. The chief areas activated here were located in anterior cingulate gyri including pre-SMA. There were also anatomical overlaps between these areas for the auditory and the tactile modality (see Table 2b). The peak activation in anterior cingulate and pre-SMA were found to be more anterior in the present auditory study than in our previous tactile study. This might be related to differences in the sensory modality explored, with somesthetic inputs having the richest and closest relationship to SMA. The pre-SMA peak activation was in the same cluster location and had the same maximum voxel as the tactile task (Pastor et al., 2004), but again the auditory cluster extended more anteriorly than the tactile activation. The results also revealed some lateralisation of activity in the right hemisphere for this specific type of temporal discrimination task. This pattern of lateralisation is consistent with previous work investigating different types of temporal perception that also revealed lateralisation of brain activity in the right hemisphere (e.g., Harrington et al., 1998; Pouthas et al., 2000; Macar et al., 2002; Lewis and Miall, 2003a,b).

Several fMRI studies have shown participation of mesial frontal structures including SMA in other timing tasks such as visual or auditory rhythm discrimination (Schubotz et al., 2000). Unlike the present experiment, the majority of previous studies on auditory temporal perception have used duration discrimination paradigms. However, the discrimination between two signals (judgement of simultaneity-succession, as here) constitutes a fundamental ele-

Table 2b
Temporal discrimination vs. spatial discrimination

	<i>P</i> -uncorrected	<i>Z</i>	<i>x, y, z</i>
Anterior cingulate (BA 24 and 32)	0.003	2.78	−14, 36, 26, 16, 36, 16
Pre-SMA (BA 6)	0.03	1.78	−4, 6, 64

Table 2c
Spatial discrimination vs. temporal discrimination

	<i>P</i> -uncorrected	<i>Z</i>	<i>x, y, z</i>
Right superior parietal and precuneus (BA 7)	0.009	2.36	2, −58, 60

ment of temporal processing that might be required also for estimation of interval duration. Rao et al. (2001) designed an fMRI study on auditory duration discrimination that allowed analysis of the motor response independently from the temporal task, with temporal slices of 2.5 s and found the earliest activation (2.5–5 s) in the right putamen and at a cortical level in prefrontal cortex. They also found activation in the anterior insula, SMA and pre-SMA, and anterior cingulate cortex, but these were common to both duration and pitch discrimination. Here we found activation of anterior cingulate and pre-SMA selectively for temporal discrimination. The higher selectivity observed in our study might relate to the fact that our task used discrimination between successive signals while Rao's tasks required more extensive encoding of stimuli and possibly a greater reliance on working memory. Duration discrimination was also used in Belin et al. (2002), again revealing enhanced activity in right prefrontal cortex, together with basal ganglia and cerebellum.

Several studies employed duration discrimination tasks in modalities other than audition (Maquet et al., 1996). In vision, Ferrandez et al. (2003) compared duration-discrimination versus luminance-discrimination revealing activation of prefrontal regions, basal ganglia and SMA. Combining EEG and PET Pouthas et al. (2000) also found increased activity in right prefrontal areas and anterior cingulate cortex during visual duration-discrimination. In the tactile modality, Macar et al. (2002) reported activation of a similar network during a tactile temporal reproduction task. Increased activation was found in the right dorsolateral prefrontal, anterior cingulate SMA and parietal cortices.

The combined activation of prefrontal areas and mesial frontal structures in time-related tasks raises the possibility of some functional link between the neural systems involved in temporal processing and those dealing with attentional control. However, the administration of noradrenergic agonists did not affect performance during duration-discrimination (stimulus duration around 50 ms), supporting the independence of the perception of short time intervals from attentional mechanisms (Rammesayer et al., 2001). On the other hand, recent findings by Lewis and Miall (2003a,b) support the hypothesis that timing of short time intervals is processed within the motor system. Further, in a recent fMRI experiment on visual attention to duration and to colour, Coull et al. (2004) demonstrated that activity in pre-SMA was parametrically related to time estimation. This result supports the hypothesis of a role for pre-SMA in providing an ordinal scale (or time-line) to quantify elements of a sequence, or beats in an interval (Coull et al., 2004). Our results complement these proposals, indicating that prefrontal structures traditionally thought to be involved in sequential motor programming might also sustain a multimodal system for time encoding and succession discrimination processing. Previous data (Pastor et al., 2004) and the present results show specific activation of pre-SMA during both tactile and auditory temporal discrimination tasks. Here, we additionally report activation of the anterior cingulate, a structure that is closely interconnected with pre-SMA (Wang et al., 2001).

Pre-SMA belongs to the prefrontal cortex because of its extensive connections with most prefrontal areas (46, 8A, 9, 10, 11, 12 and 13) (Inase et al., 1999; Middleton and Strick, 2002). Pre-SMA and anterior cingulate cortex share connections with the prefrontal cortex (Morecraft and Van Hoesen, 1993). Pre-SMA has been shown to serve a timing function during auditory-timed sequential movements (Ramnani and Passingham, 2001). Our findings in auditory temporal discrimination are compatible with the notion that a network comprising frontal cortex and basal ganglia is in charge of timing functions. One possibility is that the insular cortex (BA 13), anterior cingulate (BA 34) and pre-SMA (BA 6) play a role in tagging of temporal attributes for subsequent processing by SMA and other prefrontal and premotor regions. This does not imply, of course, that pre-SMA and anterior cingulate are the only areas involved in temporal processing, but both areas have a main role in succession discrimination of pairs when signals are similar, simple and brief.

Activation of anterior cingulate has been found in many different paradigms, including a PET study showing activation for both sustained attention and selective response to a visual target (Coull and Frith, 1998). While the role of prefrontal areas in the encoding of specific stimulus–response mapping is undisputed (Rushworth et al., 2004), we should note that this is an unlikely explanation for the activation reported here. In our design, temporal and spatial discriminations required equivalent stimulus–response mapping, both involving two alternative force-choices with button-presses. Another important function of this region of frontal cortex concerns its role in conflict monitoring and response adjustments (Botvinick et al., 2004; Kerns et al., 2004) and reward estimation (Walton et al., 2004). We should note that in our paradigm subjects never received any feedback concerning their performance, thus complex control processes should have been minimised. Further, any such process should be well matched in the two discrimination tasks (possibly less so in the control task), thus response-monitoring seems an unlikely reason for the activation that we observed when comparing directly temporal versus spatial discrimination. Instead, the finding of significant activation for the contrast TD versus SD, in both tactile and auditory modalities suggests an additional role for anterior cingulate cortex, here related to time discrimination.

Areas specific for auditory spatial discrimination

For completeness we also compared spatial versus temporal discrimination for the auditory task. This demonstrated a trend of activation located in the right precuneus. A similar region showed a related (also sub-threshold) pattern of activation in our previous tactile task (Pastor et al., 2004), suggesting a weak but consistent role of the precuneus in the judgement of spatial location of a stimulus (relative to the body). This area has been found by others to be activated in visuo-tactile discrimination tasks that involved reference to body coordinates (Misaki et al., 2002).

Relation to lesion studies

Patients with Parkinson's disease show increased auditory temporal discrimination thresholds with normal primary sensory perception (Artieda et al., 1992). The involvement of the basal ganglia, specifically the dopaminergic system, in both perceptual timing and timing of sequential movements, has been suggested by animal and human studies (Johnson and Harris-Warrick, 1990;

Lacruz et al., 1991; Artieda et al., 1992; Pastor et al., 1992; Gibbon et al., 1997; Harrington et al., 1998; Meck and Benson, 2002; Matell et al., 2003; Nenadic et al., 2003). However, in our study, basal ganglia activation occurs during both spatial and temporal discrimination. Thus, our results predict that patients with dysfunctional basal ganglia should not only be impaired in temporal tasks but also in tasks involving spatial judgements (Weder et al., 1999; Molloy et al., 2003). Moreover, our finding of overlap in the networks for both auditory and tactile modalities (see Tables 2a–2c) leads to a prediction of a multimodal deficit in patients with basal ganglia dysfunction (Lejeune et al., 1997; Weder et al., 1999; Molloy et al., 2003; Aglioti et al., 2003). Our findings permit us to hypothesise that damage to the basal ganglia should result not only in the loss of accurate motor control but also in an impairment of basic perceptual mechanisms. However, follow-up studies will need to systematically assess any modality-specific participation of particular sub-regions within the basal ganglia for temporal discrimination in one or another modality.

In conclusion, many of the areas that have previously been described as important for temporal processing were activated here for both temporal and spatial discrimination tasks in the auditory domain. These include basal ganglia, insulae and regions of the inferior frontal cortex. However, anterior cingulate and pre-SMA were selectively activated during discrimination of temporal attributes of the auditory stimuli. Furthermore, these areas overlap with regions previously activated using an analogous paradigm that employed tactile rather than auditory stimuli. These fronto-medial structures are directly and broadly connected with sensory and motor cortical areas, as well as subcortical regions, and they are thus strategically placed for a pivotal role in temporal processing across sensory modalities.

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