

Effect of task difficulty on the functional anatomy of temporal processing

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Temporal processing underlies many aspects of human perception, performance and cognition. The present study used fMRI to examine the functional neuroanatomy of a temporal discrimination task and to address two questions highlighted by previous studies: (1) the effect of task difficulty on neuronal activation and (2) the involvement of the dorsolateral prefrontal cortex (DLPFC) in timing. Twenty healthy subjects were scanned while either judging whether the second in a pair of tones was shorter or longer in duration than the standard tone or simply responding to the presentation of two identical tones as a control condition. Two levels of difficulty were studied. Activation during the less difficult condition was observed only in the cerebellum and superior temporal gyrus. As difficulty increased, additional activation of the supplementary motor area, insula/operculum, DLPFC, thalamus and striatum was observed. These results suggest the cerebellum plays a critical role in timing, particularly in gross temporal discrimination. These results also suggest that recruitment of frontal and striatal regions during timing tasks is load-dependent. Additionally, robust activation of the dorsolateral prefrontal cortex under conditions of minimal working memory involvement supports the specific involvement of this region in temporal processing rather than a more general involvement in working memory.

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Introduction

Temporal processing is a fundamental component of daily life activities that is involved in a variety of goal-oriented behaviors (Ferrandez et al., 2003; Mangels et al., 1998). The ability to process time has been associated with relatively simple tasks such as sequencing and planning events and more complex processes involved in driving or understanding cues that predict later events (Mangels et al., 1998; Tracy et al., 1998). Navon (1978) argued that our perception of the world consists of a hierarchy of dimensions and that time occupies the highest level of that

hierarchy (Navon, 1978). Considering its central involvement in perception and cognition, it is not surprising that timing is thought to influence a variety of processes, including speech–sound perception, receptive speech, working memory, learning, and academic achievement. In addition, dysfunction in temporal processing has been associated with many clinical disorders and/or clinical features, including attention-deficit hyperactivity disorder, dyslexia, and apraxia of speech (Barabasz, 1973; Bauermeister et al., 2005; Condray, 2005; Kaminsky et al., 2002; Kraus, 2001; Ziegler and von Cramon, 1986).

The key role of temporal processing in both normal cognition and disease states underscores the importance of understanding its neural underpinnings. Cognitive models of temporal processing have provided a groundwork for examining this process (Mangels and Ivry, 2001). One of the most influential models is scalar expectancy theory (SET), which differentiates three components of interval timing (Gibbon et al., 1984; Roberts, 1981). The first is the clock component which consists of a hypothetical internal clock which uses a pacemaker to produce temporal values representing objective time and an accumulator which sums these values to create a representation of time. In the memory component, these representations of current time are stored in a reference memory system. Finally, the decision component involves comparing the current representation of time to the reference interval that is stored in memory. Lesion studies, pharmacological studies with animals and recent neuroimaging studies suggest involvement of specific brain regions for these different processes. Much evidence points to the involvement of the basal ganglia and cerebellum in the pacemaker-accumulator component of temporal processing (Meck, 1996; Harrington et al., 1998a; Malapani et al., 1998; Roberts, 1981; Rao et al., 2001; Ivry et al., 2002; Ferrandez et al., 2003). Frontal and parietal regions have been implicated in memory and decision making components (Maquet et al., 1996; Mangels et al., 1998; Rao et al., 2001; Macar et al., 2002; Ferrandez et al., 2003; Coull et al., 2004; Pouthas et al., 2005).

A more detailed understanding of the neuronal mechanisms of timing is precluded, however, by the wide variety of tasks employed to study temporal processing. Different types of temporal processing tasks (e.g. temporal production, time perception) and even

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slightly different parameters used within similar temporal judgment tasks (e.g. 1000-ms tone duration versus 200-ms tone duration) are thought to recruit disparate cognitive processes (Casini and Ivry, 1999; Fuster, 1985; Gibbons and Rammsayer, 2004; Ingvar, 1985; Kagerer et al., 2002; Naatanen et al., 2004; Roy et al., 2005; Toplak and Tannock, 2005). While many of these timing tasks likely tap into the same neuronal mechanisms, the varying degree of cognitive resources required by various tasks complicates efforts to define the core substrates of temporal processing.

A common confound in many studies is working memory. Most temporal processing studies to date have required subjects to estimate, reproduce, or judge time over a range of a second or longer (Mangels et al., 1998; Smith et al., 2003; Toplak et al., 2003; Tracy et al., 2000). While temporal processing itself requires a memory component, maintaining information online for these long intervals requires a much heavier reliance on working memory, potentially leading to activation of brain regions such as the dorsolateral prefrontal cortex (DLPFC), well known for its involvement in this process. Although many studies have shown DLPFC activation during temporal processing (see Rubia and Smith, 2004 for review), the extent to which this region's involvement in timing is related to general working memory or to a function more specifically related to temporal processing is still uncertain. A goal of the present study was to evaluate temporal processing in the context of minimal working memory requirements to better understand the involvement of the DLPFC in temporal processing.

An additional issue that may be related to disparate findings between temporal processing studies is the role of task difficulty in the timing measure assessed. Research focusing on other types of cognition suggests that the level of difficulty selected for a task is crucial in determining the nature of cognitive resources needed for a task. Specifically, Fletcher and colleagues (1999) assert that disparate findings across studies when the same type of task is involved may be a function of the level of task difficulty employed (Fletcher et al., 1999). This hypothesis is supported by recent electrophysiological data in which brain activation is significantly modulated by the degree of change in task difficulty (Yucel et al., 2005; Davalos et al., 2005). These EEG studies, taken together with Fletcher and colleagues' functional neuroimaging data, strongly suggest that task difficulty modulates neuronal activation. A remaining question concerns whether different brain regions are involved at varying levels of difficulty in timing paradigms or whether difficulty-related differences reflect changing levels of activation of the same brain regions. The second goal of the present study, therefore, was to understand the effect of task difficulty on neuronal response during temporal processing.

The present study examines temporal processing with a simple duration comparison task, designed to minimize non-temporal confounds observed in previous timing studies. The paradigm utilizes a fixed tone throughout all trials in the study. Temporal judgments are based solely on changes in duration of the tone. The interstimulus interval was constant throughout testing, and visual stimuli were limited to a screen conveying simple directions that also was constant throughout the testing session. The study employs a temporal discrimination task with a very short (500 ms) delay between the standard and comparison tone. This minimal reliance on working memory, as well as an additional comparison of two levels of task performance in which working memory require-

ments should be the same, allows a test of the hypothesis that DLPFC involvement in temporal processing is related to a function other than working memory (Smith et al., 2003). Finally, the present study was designed to also test the hypothesis that modulation of the difficulty of a temporal judgment task would be associated with varying degrees of activation of the same brain regions.

Methods

Subjects

Twenty healthy subjects participated in this study. Mean age was 41.2 (SD = 9.7), 9 females, 11 males. Subjects provided written informed consent approved by the University of Colorado at Denver and Health Sciences Center Institutional Review Board.

Task design

Clustered volume fMR images were obtained, while subjects performed an auditory temporal discrimination task. The task consisted of two discrimination conditions, 'easy' and 'difficult', and a baseline condition (Fig. 1). These discrimination conditions were categorized as "easy" or "difficult" based on behavioral accuracy in a previous study (Davalos et al., 2005). In the 'easy' condition, subjects were presented with two tones, the first 200 ms, the second either shorter (70 ms, 100 ms) or longer (300 ms, 330 ms) than the first, separated by 500 ms. Subjects were asked to indicate via a button press whether the second tone was longer or shorter than the first tone. In the 'difficult' condition, the duration of the second tones was more similar to the standard tone, either shorter (160 ms, 170 ms) or longer (230 ms, 240 ms). In the baseline condition, both tones were 200 ms. Subjects were told the tones were identical and instructed to simply press either button after they heard both tones. Use of the clustered volume approach allowed stimuli to be presented and judgments made in the absence of scanner noise. Because of the delay in hemodynamic response, neuronal activity can be measured by acquiring volumes several seconds following timing processes of interest. This technique has been shown to substantially improve signal detection in fMRI experiments using auditory stimuli (Edmister et al., 1999).

Instructions to make a judgment or simply press a button were presented in the magnet via MR-compatible goggles (Resonance Technology, Inc.). The same screen, with simple judgment or no judgment instructions, was maintained throughout the run, with text highlighting indicating when subjects were to engage in each condition. MR-compatible headphones (Resonance Technology, Inc.) were used to present tones 500 ms after each echo-planar volume was acquired. Stimuli were complex tones composed from 5 frequencies (0.125, 0.25, 0.50, 0.75 and 1 kHz), each with a 50 ms attack and 25 ms decay. The paradigm was written and presented in E-prime (Psychology Tools, Inc.).

Timing for each discrimination/baseline event included 2-s scanning, 500 ms silence, 1-s stimulus presentation and 2.5 s to judge and/or respond, totaling 6 s (Fig. 1). Each of two runs contained 10 blocks (40 presentations) of each condition, "easy", "difficult" or baseline, presented in pseudo-randomized order across the run. Subjects were not informed of the "easy" versus "difficult" block distinction during the run, knowing only

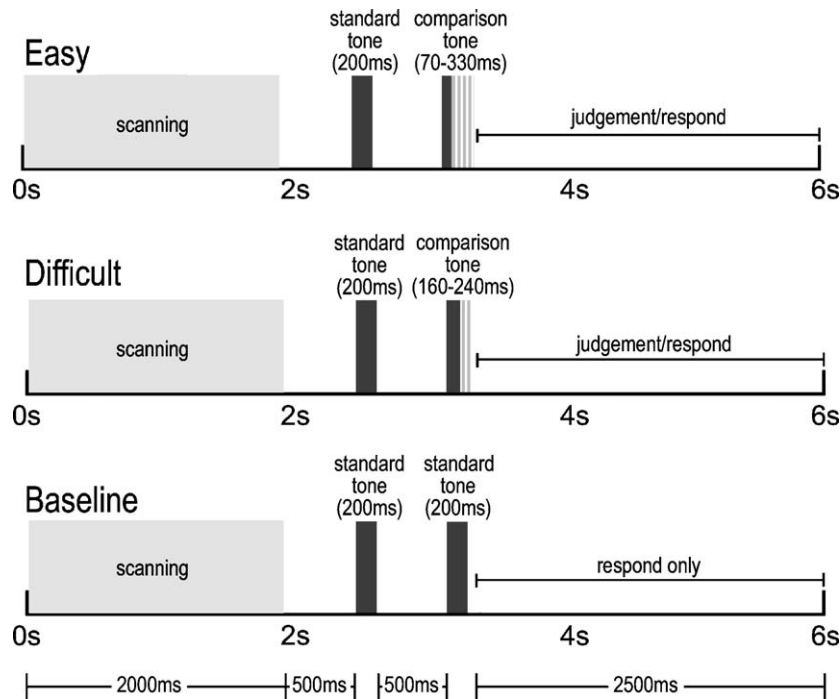


Fig. 1. Schematic representation of experimental design. During the “easy” condition, the 200 ms standard tone was followed by a comparison tone of 70, 100, 300 or 330 ms (± 50 or 65%). During the “difficult” condition, the comparison tone was 160, 170, 230 or 240 ms (± 15 , 20%). During “baseline”, subjects pressed a button, but did not judge, following presentation of two 200-ms tones.

ahead of time that task difficulty varied throughout the experiment.

MR parameters

Studies were performed with at 3 T GE MR system using a standard quadrature head coil. At the beginning of each scan, a high-resolution, T1-weighted 3D anatomical scan was acquired (IR-SPGR, TR = 9 ms, TE = 1.9 ms, TI = 500 ms flip angle = 10° , matrix = 256×256 , FOV = 220 mm^2 , 124 1.7-mm-thick coronal slices). Functional images were acquired with a gradient-echo T2* Blood Oxygenation Level Dependent (BOLD) contrast technique, with TR = 6000 ms (as a clustered volume acquisition of 2000 ms, plus an additional 4000 ms silent interval for task execution), TE = 30 ms, FOV = 220 mm^2 , 64^2 matrix, 31 slices, 4 mm thick, no gap, angled parallel to the planum sphenoidale. Additionally, one IR-EPI (TI = 505 ms) volume was acquired from each subject to improve coregistration between EPIs and the IR-SPGR.

Data analysis

Data were analyzed using SPM2 (Wellcome Dept. of Imaging Neuroscience, London). The first four image volumes were excluded for saturation effects. Data from each subject were realigned to the first volume, normalized to the Montreal Neurological Institute template, using a gray-matter-segmented IR-EPI as an intermediate to improve registration between the EPI and IR-SPGR, and smoothed with an 8-mm FWHM Gaussian kernel. Data were modeled with an HRF-convolved boxcar function, using the general linear model in SPM2. A 128-s high pass filter was applied to remove low-frequency fluctuation in the BOLD signal.

To account for both within-group and within-subject variance, a whole-brain random effects analysis was implemented. Parameter

estimates for each individual’s first level analysis (SPM contrast images) were entered into second-level t tests for each contrast of interest, “easy”–baseline, “difficult”–baseline and “difficult”–“easy”. To improve statistical power, results were masked with a gray matter mask, consisting of the average gray matter from all subjects obtained by their gray-segmented IR-EPIs. Functional results are overlaid onto the group average T1-weighted anatomical images. Data were corrected for multiple comparisons using the False Discovery Rate method, which controls the expected proportion of false positives among suprathreshold voxels (Genovese et al., 2002).

Results

Behavioral data collected during scanning indicated that subjects were significantly faster ($t = 9.4$, $df = 18$, $P < 0.001$) and made fewer errors ($t = 6.23$, $df = 18$, $P < 0.001$) during the easy compared to the difficult discrimination task. The mean % correct during easy discrimination = 98%, SD = 2, with a mean reaction time of 585 ms, SD = 160. The mean % correct during difficult discrimination = 89%, SD = 8.5, with a mean reaction time of 831 ms SD 227. Behavioral data were not available for one subject due to technical difficulties.

In the easy discrimination condition (easy–baseline), activation was observed only in cerebellum, bilateral superior temporal gyri (STG) and medial occipital cortex using a conservative, whole-brain, random effects analysis ($t = 5.40$, $df = 19$, $P < 0.05$ FDR-corrected). The MNI coordinates, voxel extents and statistics for these regions (Fig. 2) are shown in Table 1. At a less conservative threshold ($t = 1.75$, $df = 19$, $P < 0.05$ uncorrected), activation was observed in the SMA, premotor areas, DLPFC, insula/operculum, thalamus and basal ganglia, consistent with activation observed in the difficult discrimination condition.

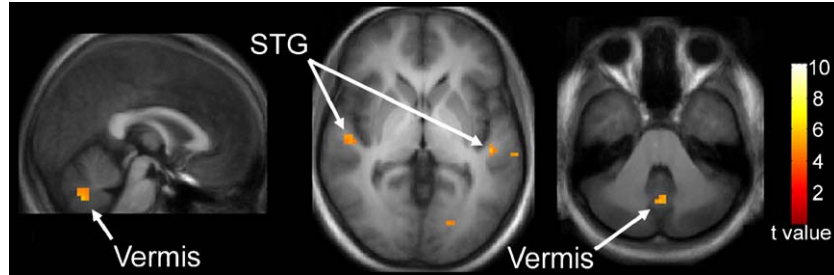


Fig. 2. Temporal processing during “easy” temporal processing. Activation of the cerebellar vermis, bilateral superior temporal gyrus (STG), was observed. Statistical parametric maps thresholded at $P < 0.05$, FDR-corrected, overlaid onto the average T1-weighted anatomy of all subjects ($n = 20$).

In the difficult discrimination condition (difficult–baseline), activation was observed in the SMA, bilateral insula/opercular cortex, bilateral dorsal premotor regions, bilateral STG, cerebellar vermis, bilateral DLPFC and ventral premotor regions, thalamus, bilateral putamen, caudate and medial occipital cortex ($t = 4.04$, $df = 19$, $P < 0.01$ FDR-corrected) (Fig. 3, Table 1). Fig. 4 shows results from the difficult–easy contrast. Increased activation was observed in frontal regions and basal ganglia, including robust activation of the SMA and bilateral activation of the insula/

operculum, DLPFC and putamen ($t = 3.99$, $df = 19$, $P < 0.01$ FDR-corrected).

Individual subject responses (% signal change, relative to the global mean, for the peak of activation in each region) for both the easy (easy–baseline) and difficult (difficult–baseline) conditions are shown in Fig. 5. These data show that mean hemodynamic responses during the different difficulty conditions were similar in the cerebellum and STG. More pronounced differences are observed in other brain regions, particularly in the insula/operculum, SMA and DLPFC. These data also show that the degree of inter-subject variability differs for different brain regions and is highest in the insula/operculum and DLPFC.

To examine the possibility that activation differences between conditions were due to differences in processing time, subjects’ reaction times were used as a regressor in an additional second-level regression analysis. No significant results were observed, suggesting that activation reported is not related simply to reaction (processing) time.

Table 1

MNI coordinates and statistics for brain regions active during temporal processing

	x	y	z	# voxels	t value	P value
Easy						
Cerebellum, vermis	0	-63	-39	22	5.48	0.048
Superior temporal gyrus (L)	-48	-24	-3	11	5.63	0.048
Superior temporal gyrus (R)	51	-18	-3	24	5.50	0.048
Medial occipital (L)	-21	-75	6	10	6.19	0.048
Difficult						
Insula/operculum (L)	-30	27	-3	151	7.28	0.002
Insula/operculum (R)	33	30	0	113	6.00	0.003
SMA	-9	15	51	333	7.16	0.002
Dorsal premotor (L)	-24	-12	57	71	6.18	0.003
Dorsal premotor (R)	24	-9	60	37	7.07	0.002
Superior temporal gyrus (L)	-48	-24	-3	5	4.63	0.005
Superior temporal gyrus (R)	60	-21	-6	50	6.22	0.003
Cerebellum, vermis	3	-57	-33	50	5.75	0.003
DLPFC (L)	-51	9	15	72	5.68	0.003
	-42	0	45	78	5.64	0.003
DLPFC (R)	54	12	27	112	5.42	0.004
	39	33	21	11	4.57	0.005
Thalamus (L)	-12	-21	12	60	5.57	0.004
Thalamus (R)	9	-12	12	7	4.52	0.001
Putamen (L)	-18	12	-3	22	3.74	0.005
Putamen (R)	21	-3	3	3	4.38	0.007
Caudate (R)	9	6	3	21	4.92	0.004
Medial occipital (L)	-18	-78	-6	6	4.61	0.005
Difficult–easy						
SMA	-9	18	48	484	9.27	0.000
Insula/operculum (L)	-30	27	-3	116	6.43	0.001
Insula/operculum (R)	33	27	3	239	6.26	0.001
DLPFC (L)	-54	18	24	26	5.72	0.001
	-33	57	12	22	4.97	0.003
DLPFC (R)	39	6	27	405	5.89	0.002
	30	57	9		5.60	0.002
	51	21	27		5.33	0.002
Putamen (L)	-21	15	-3	22	5.32	0.002
Putamen (R)	18	12	-3	29	4.83	0.004

Discussion

The primary goal of the present study was to elucidate the neuronal substrates of temporal processing, in the context of a low working memory load and varying task difficulty, factors which often complicate interpretation of timing studies. Activation of a network of cortical and subcortical regions, including the cerebellum, insula/operculum, DLPFC and premotor areas, SMA and basal ganglia was observed. In the following sections, results are discussed with regard to specific regions and their functions.

The results presented here suggest that the cerebellar vermis plays a fundamental role in temporal processing or a mechanism central to this process. This finding is consistent with previous suggestions of cerebellar involvement in timing processes, stemming from clinical observations, cerebellar lesion studies and neuroimaging data (Ivry et al., 2002). Clinically, dysmetria and dysdiadochokinesia, both hallmark symptoms of cerebellar dysfunction, have been attributed to a loss of coordinated timing between antagonist muscles (Hallett et al., 1975; Dichgans and Diener, 1984). Additionally, patients with cerebellar lesions show deficits in both motor timing and time perception tasks (Ivry et al., 1988; Malapani et al., 1998; Nichelli et al., 1996; Mangels et al., 1998). Although most previous studies have focused on the involvement of the cerebellar hemispheres in timing, activation of medial cerebellar vermis in the present study replicates findings from two prior neuroimaging studies in healthy controls. In a PET study, Jueptner and colleagues observed activation of the cerebellar

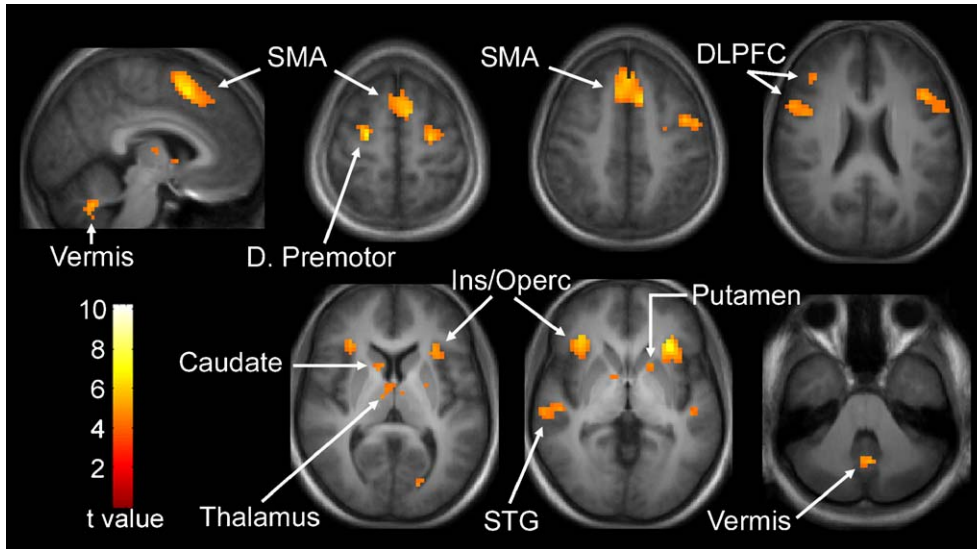


Fig. 3. Temporal processing during “difficult” temporal processing. Activation of the cerebellar vermis, superior temporal gyrus, as well as the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), insula/opercular cortex, caudate, putamen and thalamus was observed. Statistical parametric maps thresholded at $P < 0.01$, FDR-corrected, overlaid onto the average T1-weighted anatomy of all subjects ($n = 20$).

vermis and hemispheres during a timing task (Jueptner et al., 1995). The authors were able to further parse activation, showing that motor response was associated with cerebellar hemisphere activation, while the timing condition additionally activated the vermis. Cerebellar vermis activation has also been previously reported during tone duration comparison (Rao et al., 2001). In the same study, Rao and colleagues did not observe cerebellar vermis activation during pitch comparison, supporting the specific involvement of the vermis in timing. It should be noted, however, that a timing PET study by Maquet et al. (1996) reported vermis activation in both time and intensity comparison conditions, raising the possibility that cerebellar vermis may also be involved in other discrimination tasks.

The SMA activation observed in this study is consistent with prior reports of this region’s involvement during many different types of timing tasks (see Macar et al., 2002 for review, also Macar et al., 2002; Ferrandez et al., 2003; Macar et al., 2004; Coull et al., 2004). Activation was centered in the anterior portion of the SMA, subtending both the SMA proper and the pre-SMA, anterior to the Vca line. This sub-region of the SMA has been shown to be active in prior timing studies (Kawashima et al., 1999; Rao et al., 2001; Coull et al., 2004; Pouthas et al., 2005) and is thought to be involved in performing complex tasks, and early learning stages, as opposed to the performance of simple or overlearned tasks more likely to involve the SMA proper (Picard and Strick, 1996; Fujii et

al., 2002). Coull and colleagues (2004) recently demonstrated activation of the pre-SMA to be correlated with subjects’ level of attention to time (Coull et al., 2004). These results, in addition to other data describing the involvement of the pre-SMA in timing (Clower and Alexander, 1998; Shima and Tanji, 2000), led the investigators to propose that the pre-SMA is involved in invoking and attending to an imaginary time line against which “elements of a sequence, or ‘beats’ in a duration” can be measured. Results from the present study, in which pre-SMA activity was modulated by task difficulty, are consistent with this model.

The present study also detected robust activation of the insular/opercular cortex. The function of this region in the context of temporal processing is not well understood, possibly due to the fact that, unlike regions such as the cerebellum and basal ganglia which have long been implicated in timing, the insular/opercular cortex had not been thought to be involved in timing until the availability of PET and fMRI. Many neuroimaging studies have now shown this region to be involved in a wide variety of timing tasks, including attention to time (Coull et al., 2000, 2003, 2004), duration perception (Maquet et al., 1996; Rao et al., 2001; Ferrandez et al., 2003; Lewis and Miall, 2003; Hinton et al., 2004; Pouthas et al., 2005), auditory and visual rhythm perception estimation (temporal sequencing) (Schubotz et al., 2000), interval sequence encoding (Schubotz et al., 2000) and sensorimotor synchronization (Rubia et al., 2000).

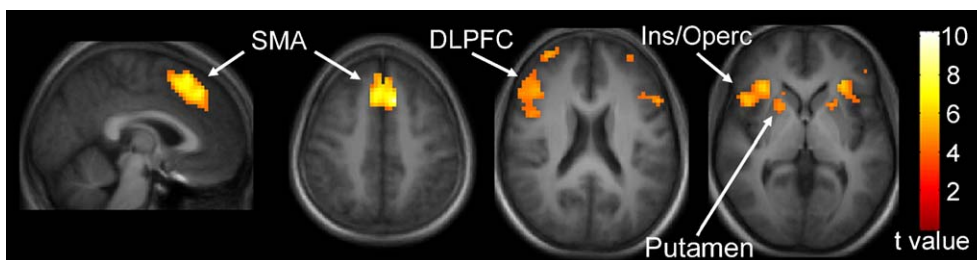


Fig. 4. “Difficult” compared to “easy” temporal processing. Increased activation was observed in the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), insula/opercular cortex and caudate. Statistical parametric maps thresholded at $P < 0.01$, FDR-corrected, overlaid onto the average T1-weighted anatomy of all subjects ($n = 20$).

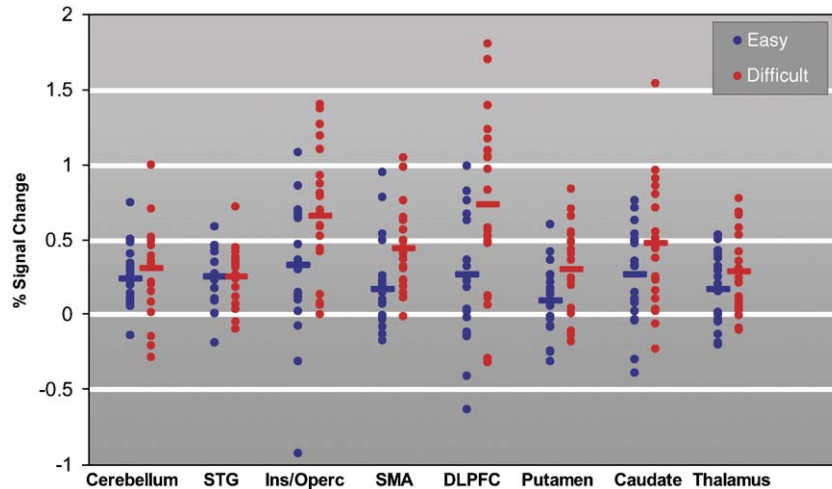


Fig. 5. Means and variability in subject responses during “easy” and “difficult” temporal processing.

While the opercular cortex has traditionally received much attention for its role in language, emerging evidence supports the idea that this region may play a more general role in the regulation of sequencing activity. Neuroimaging studies have revealed that the operculum is activated by both word and non-word temporal patterns (Fiez et al., 1995), melodic sequence recognition (Platel et al., 1997; Bey and Zatorre, 2003) and even the onset synchrony of geometric patterns (Lux et al., 2003). Given this evidence for the involvement of the inferior frontal cortex in sequencing, a similar function may subservise temporal processing, as suggested by Schubotz and colleagues (2000) in their study showing opercular activation associated with rhythm monitoring. Sequencing, i.e. attending to or processing order in time, is a key aspect of temporal judgment, in which an understanding of the temporal relationship of multiple items is necessary.

Activation of the basal ganglia in the present duration perception study supports proposals of this structure’s involvement in temporal processing (Meck, 1996). Prior evidence for basal ganglia’s role in timing has come from studies of patients with Parkinson’s disease, who are impaired in both motor timing and time perception and estimation of both short and long intervals (Harrington et al., 1998a; Artieda et al., 1992; Malapani et al., 1998). Further evidence has come from animal studies, which have shown that the dopamine agonist haloperidol slows down timing function, while the dopamine antagonist methamphetamine speeds it up (Maricq et al., 1981). Meck and colleagues (1986) have further demonstrated the selectivity of this response, showing that affinity for the dopamine D2 receptor predicts its ability to slow down timing functions, while affinity for related dopamine, noradrenergic or serotonergic receptors does not (Meck, 1986).

Prior neuroimaging studies in healthy controls have also demonstrated involvement of the basal ganglia in temporal processing (Schubotz et al., 2000; Rao et al., 2001; Schubotz and von Cramon, 2001; Ferrandez et al., 2003; Coull et al., 2004; Hinton et al., 2004; Shima and Tanji, 2000). Based on their data suggesting that activation of the putamen and caudate were uniquely associated with encoding time intervals, Rao and colleagues have suggested that the basal ganglia is involved early in temporal processing, formulating representations of time (Rao et al., 2001). Results from the present study not only support the involvement of the basal ganglia in temporal judgment but also

suggest this involvement is independent of motor responses. Although basal ganglia activation during the ‘easy’ condition was not statistically significant at a stringent whole-brain-corrected threshold, activation was observed at a less conservative threshold, suggesting that this region may have been active, though less so, during the easy condition. This suggests that, unlike the cerebellum, basal ganglia activity in the context of temporal processing is load-dependent, that is, it is modulated by task difficulty.

Under more difficult duration perception conditions, the present study revealed robust activation of the DLPFC, particularly the right DLPFC. Involvement of this region in temporal processing has been reported in prior studies of duration perception (Rao et al., 2001; Lewis and Miall, 2003; Smith et al., 2003), interval time estimation (Macar et al., 2002; Basso et al., 2003) and motor timing (Rubia et al., 1998; Jancke et al., 2000). Involvement of the DLPFC in temporal processing is also supported by lesion studies (Harrington et al., 1998b; Mangels et al., 1998; Casini and Ivry, 1999). The present findings shed new light on the debate of the role of the DLPFC in temporal processing. While studies of long-term (many seconds) timing tasks have suggested that the primary role of the DLPFC in timing tasks involves working memory components of the task, i.e. maintaining temporal representations online for later comparisons, studies which have minimized working memory requirements have suggested that this region plays a more primary role in temporal processing (Smith et al., 2003).

The task used in the present study involved a simple comparison of two tones, separated in time by only 500 ms, which is not likely to require a heavy reliance on working memory. Furthermore, the fact that the right DLPFC was robustly active in the ‘difficult–easy’ comparison strengthens this argument because the working memory requirements of both the ‘easy’ and ‘difficult’ tasks were nearly identical. Results of the present study therefore support the proposal that the DLPFC plays a specific role in temporal processing rather than a more general role in working memory function (Smith et al., 2003). One suggestion for a possible role of the DLPFC in timing comes from unit recordings of neurons in the DLPFC in primates. Constantinidis et al. (2002) have identified inhibitory circuitry in this region with predictable decay curves that could form the neural basis for a timing mechanism (Lewis, 2002; Constantinidis et al., 2002). It is also

possible, however, that DLPFC activation reported here is related to increased attentional load during difficult temporal processing, a possibility this study did not address. This seems unlikely, however, given results from a study by Smith et al. (2003) which reported DLPFC activation during a timing task that accounted for the effect of attention (Smith et al., 2003).

A goal of this study was to determine if different difficulty levels during temporal processing would be subserved by different neuronal mechanisms or involved modulation of the same brain regions. It is possible, for example, that because the tone duration difference during the easy condition was so large, timing could be accomplished using basic sensory processes. This interpretation would be appealing if the cerebellum and STG were clearly the only regions activated during the easy condition. While this may at first glance seem to be the case, a closer inspection of the data (Fig. 5) shows increased hemodynamic response during the easy condition in frontal and striatal regions as well. Responses in these regions are significant at a more liberal statistical threshold, suggesting that these regions were also likely active, though to a lesser degree, during easy temporal processing. This suggests that altering difficulty level during temporal processing results in changes in activation of the same brain regions rather than a fundamental change in brain regions used.

It is also important to consider the observed effect of task difficulty in the context of the difference between the difficult and easy conditions studied. Both conditions used the same standard tone and the same interstimulus interval. With the small number of presentations per block, the relatively long time between trials and the variation of stimuli within each condition, subjects were unable to discern the difficulty of upcoming comparisons, a condition verified in post-scan interviews. Therefore, early temporal processing, including encoding the standard interval, maintaining this information in memory, and encoding the comparison interval, should be nearly identical in both difficulty conditions. Activation observed in the DLPFC, SMA, insula/operculum and putamen, when comparing the two conditions, is likely related to late temporal processing components, mainly comparing durations and making the temporal judgment. This interpretation does not preclude involvement of these areas in early temporal processing components, however, as difficult temporal judgment likely involves increased attention to the timing mechanisms subserved by these regions. Future studies with additional non-temporal control tasks will be necessary to determine the involvement of different regions in these processes.

Conclusion

In summary, the present study demonstrates that temporal judgment is subserved by a distributed network of brain regions, including the cerebellum, insula/operculum, DLPFC and premotor areas, SMA, basal ganglia and thalamus. It is likely that the observed STG activation is related to attending to auditory processing, consistent with prior studies of attentional modulation of primary sensory areas (Alho et al., 1999; Haynes et al., 2005). While activation of the cerebellum remained constant, increased task difficulty was associated with greater activation of the SMA, DLPFC, insula/operculum and basal ganglia, supporting the hypothesis that difficulty-related differences in activation during temporal processing result from modulation of activity in brain regions that form a common network for temporal processing.

DLPFC activation under conditions of minimal working memory involvement supports the hypothesis that this region's role in temporal processing is independent of working memory function and suggests that the DLPFC may play a specific role in temporal processing.

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