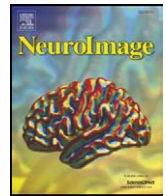


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The image of time: A voxel-wise meta-analysis

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ABSTRACT

Although there has been an explosion of interest in the neural correlates of time perception during the past decade, substantial disagreement persists regarding the structures that are relevant to interval timing. We addressed this important issue by conducting a comprehensive, voxel-wise meta-analysis using the activation likelihood estimation algorithm; this procedure models each stereotactic coordinate as a 3D Gaussian distribution, then tests the likelihood of activation across all voxels in the brain (Turkeltaub et al., 2002). We included 446 sets of activation foci across 41 studies of timing that report whole-brain analyses. We divided the data set along two dimensions: stimulus duration (sub- vs. supra-second) and nature of response (motor vs. perceptual).

Our meta-analyses revealed dissociable neural networks for the processing of duration with motor or perceptual components. Sub-second timing tasks showed a higher propensity to recruit sub-cortical networks, such as the basal ganglia and cerebellum, whereas supra-second timing tasks were more likely to activate cortical structures, such as the SMA and prefrontal cortex. We also detected a differential pattern of activation likelihood in basal ganglia structures, depending on the interval and task design. Finally, a conjunction analysis revealed the SMA and right inferior frontal gyrus as the only structures with significant voxels across all timing conditions. These results suggest that the processing of temporal information is mediated by a distributed network that can be differentially engaged depending on the task requirements.

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Introduction

Numerous neuroimaging studies investigating the neural correlates of time perception in the range of milliseconds to minutes have been published in the last decade. The results of these studies have led to a number of different theories about the roles of particular neural structures in time perception. For example, some investigators have emphasized the role of the basal ganglia in temporal processing (e.g., [Buhusi and Meck, 2005](#)), whereas others suggest a preferential role of the right prefrontal cortex ([Lewis and Miall, 2006a,b](#)). Still other accounts have assigned essential functions to the cerebellum ([Ivry et al., 2002](#)), supplementary motor area (SMA; [Macar et al., 2006](#)), right inferior parietal lobe (IPL; [Buetti and Walsh, 2009](#)), and insular cortex ([Craig, 2009](#)). Substantial differences in the nature of the tasks employed, the duration of the stimuli to be timed, the nature of the response and the baseline or control condition complicate comparisons between these studies and may account for the lack of consistency. In order to fully characterize the manner in which brain activity relates to temporal perception, quantitative methods may be necessary to search for concordance among neuroimaging studies. Here we present a quantitative, voxel-wise

meta-analysis of neuroimaging data designed to determine regions of concordance in the current literature on time perception.

Task variation in timing

Several factors may contribute to the variability in imaging studies reported to date. One factor may be the wide variety of tasks that have been employed. A dimension on which timing tasks vary is the degree to which they engage “motor” or “perceptual” timing routines. For motor timing tasks, the interval to be timed is defined by a motor response. The most commonly used task among motor timing studies is paced finger tapping, in which subjects are typically required to tap a response key in time with an isochronous metronome at a given rate (synchronization), and then continue tapping at the same rate without any external stimulation (continuation). In some studies, no continuation phase is employed, while in others the subject is required to tap at the midpoint between sets of pacing stimuli (syncopation). Another motor timing task is interval production/reproduction, in which subjects produce an interval from memory, by indicating in a stopwatch-like fashion when the interval begins and ends. A common variation in production/reproduction is the type of memory utilized, as investigators may require subject to produce an interval that was experienced recently (reproduction), or produce a prescribed duration (i.e., “produce 7 s”). Perceptual timing tasks, in contrast, require subjects to make judgments about temporal intervals. A task

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frequently employed in neuroimaging studies of perceptual timing is temporal discrimination, in which subjects compare the duration of successive stimuli by indicating whether the second stimulus is longer than or differs from the first.

A second factor that may contribute to variability is the duration of the stimulus to be timed. Neuroimaging studies have utilized test intervals ranging from 200 ms to 24 s. A number of distinct lines of evidence suggest that mechanisms and brain regions recruited in timing tasks differ as a function of the stimulus duration (Mauk and Buonomano, 2004; Buhusi and Meck, 2005; Lewis and Miall, 2003b). Evidence from neuropsychological studies in humans and investigations in animals suggest that timing of intervals above and below 1 s relies on different procedures (Harrington and Haaland, 1999; Buhusi and Meck, 2005; Gibbon et al., 1997). Lewis and Miall (2003b) suggested that sub-second intervals are embedded in motor action plans, while supra-second intervals require greater cognitive control. Additionally, Mauk and Buonomano (2004) suggest that the timing of sub-second stimuli may rely on sensory processes, wherein state-dependent networks may encode changes in duration (Karmarkar and Buonomano, 2007). Rammsayer (1997) proposed that timing of different durations may be dependent on different neurotransmitter systems; he reported, for example, that haloperidol, a non-specific D2 dopamine-receptor antagonist, altered timing performance in humans across both sub-second and supra-second ranges, whereas remoxipride, a D2 dopamine-receptor antagonist which primarily acts on mesolimbocortical projections (Gerlach and Casey, 1990), altered only supra-second performance.

Reviews of timing literature

Several reviews to date have attempted to characterize activations across the corpus of neuroimaging studies of timing. Macar and colleagues (2002) divided neuroimaging studies into rhythmic and perceptual categories; only activations resulting from control task subtractions were considered. The authors concluded that the basal ganglia (caudate and putamen), SMA, cerebellum, dorsolateral prefrontal cortex (DLPFC, Brodmann area [BA] 9/46), anterior cingulate and right IPL (BA 40) were often active across all timing tasks, suggesting that these regions formed the core network of time perception in the brain. However, in addition to studies employing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) techniques, the authors also included results from studies measuring surface Laplacians, electroencephalography (EEG) and scalp current densities. One potential weakness of the latter studies is that EEG and related techniques do not readily interrogate sub-cortical structures and may thus underestimate the role that these structures play in timing.

Lewis and Miall (2003b) reported a label-based meta-analysis of neuroimaging of timing. The authors considered three factors in partitioning the datasets for their analysis: interval duration (sub-second or supra-second intervals), nature of the response (motor vs. non-motor), and whether the motor response was continuous or discontinuous. The results taken from each study were from the least restrictive contrasts, the majority of which were [task – rest]. The results of their meta-analysis suggest different neural networks are recruited, depending on the task constraints. Sub-second tasks commonly activated the bilateral SMA, left sensorimotor cortex, basal ganglia and thalamus, as well as the right cerebellum, superior temporal gyrus and lateral premotor cortex. Supra-second tasks frequently activated the left cerebellum, as well as the bilateral prefrontal and parietal cortices, with the right DLPFC demonstrating more common activation than any other structure. Among all studies, the SMA and right cerebellum were the most commonly activated structures.

Two recent label-based reviews have also attempted to characterize common activations across timing tasks. Meck, Penney and

Pouthas (2008) reviewed a number of neuroimaging studies, concluding that the basal ganglia serve as a core timer across sub-second and supra-second timing tasks. Penney and Vaitilingam (2008) reviewed a larger corpus of neuroimaging timing studies; their review also divided experiments into sub-second and supra-second categories. The authors concluded that sub-second timing tasks most commonly activated the cerebellum, DLPFC, inferior frontal gyrus (IFG), superior temporal gyrus, premotor cortex, insula (BA 13), cingulate, pre-SMA, SMA, basal ganglia and thalamus, with the cerebellum being the most frequently activated. Supra-second timing tasks commonly activated the IFG, DLPFC, supramarginal gyrus (SMG), superior temporal gyrus, premotor cortex, cingulate, pre-SMA, middle temporal gyrus, basal ganglia and thalamus, with the IFG being the most frequently activated. However, this review included both activations subtracted from control tasks and from rest; as subtractions from rest do not control for other cognitive processes, activations in these studies may be related to a variety of cognitive operations in addition to timing procedures. Furthermore, the authors did not include any imaging studies employing paced finger tapping in their review.

Although these reviews have generated important and provocative findings, inconsistency across the studies persists, perhaps reflecting the fact that different studies were included, and discrepant procedures were employed to identify sites and extents of activation. Finally, although label-based reviews and meta-analyses may provide an overview of neuroimaging results, they do not provide any quantitative measure of the probability that a structure will be activated (Laird et al., 2005b).

Activation likelihood estimation

With the dramatic increase in functional neuroimaging studies, the need has arisen for quantitative methods to evaluate cross-study results. Activation likelihood estimation (ALE) is a powerful, well-validated technique for conducting meta-analyses that circumvents a number of problems inherent in previous techniques. Developed concurrently yet independently by Turkeltaub and others (2002) and Chein and others (2002), ALE is a quantitative technique for conducting a voxel-wise analysis of cross-study data.

The ALE technique involves several steps. First, data is pooled across the set of selected studies; the data consists of the activation peaks reported in each study. Next, each activation peak is modeled as a 3D Gaussian probability distribution in the brain; the width of the Gaussian models the uncertainty in localization. The overlap among these distributions is used to estimate the probability that at least one of the peaks from the literature should have fallen within a given voxel (ALE score). A permutation test is then conducted by computing voxel-wise ALE scores for randomly generated lists of activation peaks. The ALE scores from the literature analysis are compared to those from the random sets of foci to calculate the statistical significance of each ALE score. Since the inception of ALE, a number of improvements have been made to increase the flexibility and utility of the algorithm. Many of these improvements were borrowed from techniques used for the analysis of functional neuroimaging data, and include the introduction of false-discovery rate (FDR) thresholds and cluster analysis (Laird et al., 2005a).

While the ALE technique is a quantitative technique for characterizing large sets of neuroimaging data, several weaknesses also exist. First, the size and shape of activation clusters is not considered; the ALE algorithm determines the spread of activation as a user-defined full-width at half-maximum (FWHM) Gaussian. Second, the number of subjects tested in each study is not considered. Finally, the ALE technique does not consider the relative contribution of each study to each ALE value; because of this limitation, particularly strong data from a single study may identify voxels that are judged to be “significant” despite the fact that they are not activated in the vast

majority of studies included in the meta-analysis. We attempt to correct for some of these weaknesses with a new masking technique, described in more detail below.

Materials and methods

Activation likelihood estimation

The ALE algorithm models the probability that a particular focus will be located in a given voxel, using 3-dimensional Gaussian distributions. The probability that a focus should have been identified at a given location is calculated as

$$P = \frac{e\left(-d^2/2\sigma^2\right)}{(2\pi)^{3/2}\sigma^3}$$

where d is the Euclidean distance from the center of the voxel to the focus and σ is the standard deviation of a Gaussian distribution. The probability value, which ranges between 0 and 1, is multiplied by 8 mm^3 , to give the cumulative probability within a $2 \times 2 \times 2\text{ mm}$ voxel. The probability that any given focus should have been localized within a given voxel can then be expressed as the union of the probability distributions for all foci. A user-defined FWHM is chosen when generating the Gaussian distributions; this value is meant to represent the average localization uncertainty of the neuroimaging studies included in an analysis (Turkeltaub et al., 2002).

In order to calculate the significance for any given voxel, a whole-brain non-parametric permutation test is conducted (Good, 1994) under the null hypothesis that foci from the literature are randomly distributed throughout the entire brain. In the permutation test, x random foci are generated, where x corresponds to the total number of foci used in the experiment. This process is repeated for a user-defined number of permutations; generally, 5000 permutations are utilized. The ALE values generated from the randomly distributed foci form the null distribution of the test statistic, which may then be used to assign statistical significance to ALE values arising from experimental foci. Additional information about ALE methodology and the validation of ALE against label-based meta-analysis and fMRI is provided by Turkeltaub et al. (2002) and Laird et al. (2005a,b).

Literature searches were run using the PubMed and Medline databases in order to identify all studies conducted on timing that utilized PET or fMRI. Additionally, references from those articles and review articles of timing (Buhusi and Meck, 2005; Meck, Penney and Pouthas, 2008; Penney and Vaitilingam, 2008; Lewis and Miall, 2003b; Rubia and Smith, 2004; Harrington and Haaland, 1999; Witt et al., 2008; Macar et al., 2002) were reviewed for inclusion. Several inclusion criteria were used when considering studies for the meta-analysis. First, each study must have explicitly investigated timing; that is, for all studies included in the analysis time was the to-be-measured variable. Second, no studies using a-priori region of interest (ROI) based analyses were included; the validity of the ALE algorithm depends on equal coverage of all brain regions. Third, only studies with activations contrasted with a control task, or that employed a specific manipulation to elucidate timing mechanisms were included; those tasks that used passive monitoring as a control were excluded. Our rationale for including only higher-order contrasts was to reduce the possibility of non-timing related activations in our results.

After the corpus of timing studies was identified, stereotactic coordinates were chosen for the meta-analysis (see Table 1 for included studies and contrasts). We identified 41 manuscripts (32 fMRI, 9 PET; 45 experiments, 446 foci) that met our inclusion criteria (see Table 2 for excluded studies). We converted all MNI coordinates into Talairach space using the *icbm2tal* transform (Lancaster et al., 2007). When computing the transformed values, software-specific

conversions were utilized for those studies that used FSL or SPM analysis packages.

All experiments were categorized with respect to the sub- vs. supra-second and motor vs. perceptual dimensions previously described. Four distinct groups of studies were generated: sub-second motor (15 experiments, 206 foci), sub-second perceptual (8 experiments, 92 foci), supra-second motor (18 experiments, 98 foci), and supra-second perceptual (7 experiments, 50 foci). A boundary of 1000 ms was used to discriminate between sub- and supra-second studies. For those studies in which the intervals ranged across sub-second and supra-second stimuli, we determined whether a majority of the intervals tested were above or below 1000 ms. Separate ALE analyses were run for each of the four sub-groups. Additionally, the resultant maps from each sub-group analysis were overlaid onto a single template; a conjunction analysis then isolated those voxels that were significant across all four groups. Gaussian functions were modeled for each set of foci with a chosen FWHM of 12 mm, chosen to estimate the localization uncertainty of fMRI and PET studies (Turkeltaub et al., 2002). Permutation tests were run with 5000 permutations; we corrected for multiple comparisons in assigning statistical significance by using a FDR threshold of 0.05 (Laird et al., 2005a). All ALE analyses were carried out using the GingerALE software package (version 1.1, brainmap.org).

Masking of ALE values

The ALE score is calculated without considering which studies reported the contributing foci; it is possible for a voxel to achieve statistical significance even if only one study from the literature made a major contribution to the ALE value. To avoid potential false-positive results resulting from a small number of robust effects, we developed a new masking technique to ensure that statistically significant ALE values represent effects observed in multiple studies. This new masking technique was designed to control for differences in the number of experiments and foci between data sets in the present experiment. Following each meta-analysis, we used in-house C++ programs to calculate the contribution of each of the n experiments to the total ALE value at each voxel. We reasoned that, if ideal coherence were present in the dataset, each study would contribute $1/n$ of the voxel-wise ALE value. We therefore tallied the number of studies contributing at least $1/n$ of the ALE value at each voxel. We chose an arbitrary critical threshold (γ), such that only those significant voxels being contributed by γ or more experiments would be included in the mask. The ALE output was then thresholded using this mask, revealing those voxels that were significant by standard ALE FDR thresholding and represented coherence by γ or more of the n experiments. In the present study, we chose a threshold of 2 for each ALE analysis; in other words, for a voxel to be considered significant in the total meta-analysis, at least two experiments must have contributed at least $1/n$ of the ALE score at that voxel (see Supplementary Fig. S1).

Use of this masking technique allows one to calculate the relative contribution of each experiment to the voxel-wise ALE value. The result allows for a nuanced view of ALE values for any given data set, which can provide further insight about the relevant characteristics of chosen experiments.

Results

Sub-second motor timing

High areas of concordance for tasks involving sub-second intervals, as evaluated by a motor task, were found in the bilateral SMA, left middle frontal gyrus (BA 6) and precentral gyrus, right putamen and lateral globus pallidus, left thalamus, claustrum and

Table 1
Published studies explicitly investigating temporal processing.

Study	Sub-second ($n \leq 1$)	Supra-second ($n > 1$)	Perceptual	Motor	Contrast	Foci	Duration (ms)	Study #
Ortuno et al., 2002	x			x	Paced articulation—cued articulation	10	1000	1
Bengtsson et al., 2005	x			x	Paced finger tapping and articulation [complex]—paced finger tapping and articulation [simple]	6	375, 750, 1125	2
Jancke et al., 2000	x			x	Paced finger tapping—cued finger tapping	3	400	3
Jantzen et al., 2004	x			x	Paced finger tapping [syncopation]—paced finger tapping [synchronization]	10	800	4
Jantzen et al., 2005	x			x	Paced finger tapping [syncopation]—paced finger tapping [synchronization]	7	800	8
Jantzen et al., 2007	x			x	Paced finger tapping—cued finger tapping	9	800	5
Lewis et al., 2004	x			x	Paced finger tapping—cued finger tapping	42	500	6
Penhune et al., 1998	x			x	Paced finger tapping [novel]—paced finger tapping [learned]	16	250, 750	7
Oullier et al., 2005	x			x	Paced finger tapping [syncopation]—paced finger tapping [synchronization]	31	800	9
Lutz et al., 2000	x			x	Paced finger tapping [isochronous]—paced finger tapping [non-isochronous]	1	667	10
Mayville et al., 2002	x			x	Paced finger tapping [syncopation]—paced finger tapping [synchronization]	29	800	11
Bueti et al., 2008	x		x	x	Temporal reproduction—control button pressing (motor and perceptual components)	16	300, 600, 900, 1200	12a, 12b
Schubotz et al., 2001	x		x	x	Temporal reproduction—control button pressing; temporal monitoring—control monitoring	40	290–1450	13a, 13b
Ferrandez et al., 2003	x		x		Temporal discrimination—intensity discrimination	12	700	14
Maquet et al., 1996	x		x		Temporal discrimination—control monitoring	6	700	15
Schubotz et al., 2000	x		x		Temporal discrimination—[color discrimination; Pitch pitch discrimination]	27	300–1800	16
Tregellas et al., 2006	x		x		Temporal discrimination [difficult]—temporal discrimination [easy]	10	200	17
Shih et al., 2009	x		x		Temporal discrimination—control button pressing	5	100, 450	18
Jahanshahi et al., 2006	x	x		x	Temporal reproduction [long–short intervals; short–long intervals]	25	500, 2000	19a, 19b
Lewis and Miall, 2003a	x	x	x		Temporal discrimination—length discrimination	9	600, 3000	20a, 20b
Brunia et al., 2000		x		x	Temporal production [correct feedback–incorrect feedback]	4	3000	21
Garraux et al., 2005		x		x	Paced finger tapping—ordered finger tapping	1	2000	22
Jech et al., 2005		x		x	Temporal reproduction [parametric increase in duration length]	4	500–16,820	23
Kawashima et al., 2000		x		x	Paced finger tapping—cued finger tapping	4	1500	24
Larsson et al., 1996		x		x	Paced finger tapping—cued finger tapping	4	3800	25
Lejeune et al., 1997		x		x	Paced finger tapping—cued finger tapping	4	2700	26
Lewis and Miall, 2002		x		x	Temporal reproduction—control button pressing	9	3000	27
Macar et al., 2002		x		x	Temporal reproduction—control button pressing	6	2200–3200 and 9000–13,000	28
Macar et al., 2004		x		x	Temporal reproduction—force reproduction	2	2500	29
Shergill et al., 2006		x		x	Paced articulation—cued articulation	9	2000	30
Stevens et al., 2007		x		x	Paced finger tapping [syncopation/synchronization] (ICA)	12	750, 1500, 3500	31
Tracy et al., 2000		x		x	Temporal production—counting controls	3	1200–2400	32
Wittmann et al., 2008		x		x	Temporal reproduction—control button pressing	13	3000, 9000, 18,000	33
Rubia et al., 1998		x		x	Paced finger tapping [long–short intervals]	6	600, 5000	34
Basso et al., 2003		x		x	Temporal production working memory control	3	1500	35
Coull et al., 2004		x	x		Temporal discrimination [parametric increase in attention to time]	10	540, 1080, 1620	36
Livesey et al., 2007		x	x		Temporal discrimination—color discrimination	4	1000, 1500	37
Pouthas et al., 2005		x	x		Temporal discrimination [long–short intervals]	6	450, 1300	38
Rao et al., 2001		x	x		Temporal discrimination—control button pressing	15	1200	39
Smith et al., 2003		x	x		Temporal discrimination—order discrimination	7	1000	40
Jeupntner et al., 1996		x	x		temporal velocity discrimination—constant velocity stimulation	6	1000	41

Studies included in the meta-analysis; the contrasts (e.g., sub- vs. supra-second, motor vs. perceptual) for which each study is relevant are indicated. The relevant contrasts and corresponding number of foci from each study are also noted. The duration ranges are also listed: for temporal discrimination tasks, the duration(s) listed represent those used for the standard duration; for tasks in which a large number of possible durations were tested, the range is noted. ICA = independent component analysis.

posterior cerebellum. Additional clusters were found in the right IFG (BA 47), left middle frontal gyrus (BA 10), right posterior cerebellum, right middle frontal gyrus (BA 6), substantia nigra, IPL (BA 40), left superior temporal gyrus, right insula and precentral gyrus (see Table 3 and Fig. 1).

Sub-second perceptual timing

For studies employing sub-second stimuli with purely perceptual components, peak areas of high concordance were detected in the left IFG (BA 44), right insula, left SMA, superior frontal gyrus and putamen,

Table 2

Studies excluded from the present meta-analysis (reasons for exclusion are also presented).

Study	Reason for exclusion
Coull et al. (2008)	A priori ROIs
Hinton and Meck (2004)	No coordinates given
Gruber et al. (2000)	No dissociation between sub and supra-second
Sakai et al. (1999)	Passive viewing contrast
Belin et al. (2002)	Passive viewing contrast
Jeuptner et al. (1995)	Passive viewing contrast
Harrington et al. (2004a)	Rest contrast
Hinton et al. (2004)	Rest contrast
Nenadic et al. (2003)	Rest contrast
Rao et al. (1997)	Rest contrast

right caudate and IPL. Additional clusters were also detected in the left IPL, posterior cerebellum and parietal lobe (BA 7), as well as the right middle frontal gyrus (BA 6), posterior cerebellum, and precentral gyrus (BA 6) (see Table 4 and Fig. 1).

Sub-second conjunction

When both sub-second motor and perceptual maps were displayed on a single template, areas of overlap were detected in the bilateral SMA, bilateral middle frontal gyrus (BA 6), bilateral IPL (BA 40), bilateral IFG, right caudate and putamen, right insula and bilateral posterior cerebellum (see Fig. 1).

Supra-second motor timing

For supra-second intervals tested with motor timing tasks, our analysis revealed a number of distinct clusters of activation including the right SMA, bilateral cingulate gyrus (BA 24/32), right precentral gyrus (BA 44), claustrum, IPL, SMG and middle frontal gyrus (BA 10/9). Additional clusters were detected in the left precentral gyrus (BA 6/4), insula and superior frontal gyrus (BA 9) (see Table 5 and Fig. 2).

Supra-second perceptual timing

For studies investigating supra-second timing mechanisms with no motor component, strong areas of concordance were demonstrated in the right IFG (9/45), bilateral SMA, left precentral gyrus (BA 4) and left putamen. Additional clusters were detected in the right middle temporal gyrus (BA 22), thalamus, insula, claustrum and SMG (see Table 6 and Fig. 2).

Supra-second conjunction

When both supra-second motor and perceptual maps were displayed on a single template, areas of overlap were detected in the bilateral SMA, left precentral gyrus (BA 4), right cingulate gyrus, right IFG and bilateral insula (see Fig. 2).

Motor conjunction

When both sub-second and supra-second motor maps were displayed on a single template, areas of overlap were detected in the bilateral SMA, left insula, right IFG, left middle frontal gyrus and right IPL (see Supplementary Fig. S2).

Perceptual conjunction

When both sub-second and supra-second perceptual maps were displayed on a single template, areas of overlap were detected in the bilateral SMA, left putamen, right insula and right IFG (see Supplementary Fig. S3).

Total conjunction analysis

While the results of the individual analyses revealed a number of areas specific to timing conditions, we were also interested in determining if there were sites at which activation likelihood was identified in all four conditions. As such, the statistical maps for each individual condition were overlaid onto a single brain template in order to find regions that demonstrated significant ALE values in all

Table 3

Significant activation likelihood clusters for the sub-second motor timing analysis.

Location	x	y	z	ALE value	Volume (mm ³)	Studies
Left supplementary motor are (BA 6)	-2	6	50	0.015	6264	[2], [4], [6], [8], [9], [11], [12a], [13a]
Right supplementary motor are (BA 6)	6	0	56	0.012		
Left middle frontal gyrus (BA 6)	-26	-4	52	0.015	3496	[3], [4], [6], [8], [9], [11], [13a]
Left precentral gyrus (BA 6)	-30	-16	56	0.008		
Right putamen	20	8	10	0.010	2456	[1], [6], [11], [12a], [13a]
Right lateral globus pallidus	22	-10	6	0.007		
Left thalamus (VLN)	-16	-14	6	0.012	2312	[4], [7], [8], [9], [13a]
Left claustrum	-36	12	2	0.009	1960	[6], [11], [12a], [13a]
Left posterior cerebellum	-32	-62	-30	0.010	1760	[7], [8], [9], [11]
Right inferior frontal gyrus (BA 47)	38	24	0	0.009	1112	[5], [6], [7], [11]
Right inferior frontal gyrus (BA 47)	48	18	-10	0.007		
Left middle frontal gyrus (BA 10)	-28	40	24	0.010	912	[4], [8], [11]
Right posterior cerebellum	28	-62	-22	0.009	888	[6], [12a]
Right middle frontal gyrus (BA 6)	28	-2	50	0.009	672	[11], [13a]
Right posterior cerebellum	40	-52	-32	0.008	624	[2], [9]
Right substantia nigra	10	-20	-6	0.008	488	[7], [9]
Right posterior cerebellum	34	-44	-48	0.007	464	[2], [11]
Right inferior parietal lobe (BA 40)	38	-42	44	0.008	440	[6], [12], [13a]
Left posterior cerebellum	-26	-80	-24	0.007	416	[6], [7]
Left superior temporal gyrus (BA 22)	-46	-20	0	0.007	352	[11], [19a]
Right insula (BA 13)	46	8	16	0.008	296	[13a], [19a]
Right inferior parietal lobe (BA 40)	52	-34	44	0.007	184	[6], [9]
Right posterior cerebellum	4	-70	-44	0.006	176	[9], [11]
Right precentral gyrus (BA 6)	42	0	36	0.007	152	[9], [12a]

Higher ALE values represent greater concordance across studies and thus a higher probability of activation. The studies column includes the experiments primarily contributing to each ALE cluster, referenced from Table 1. BA = Brodmann area; VLN = ventral lateral nucleus.

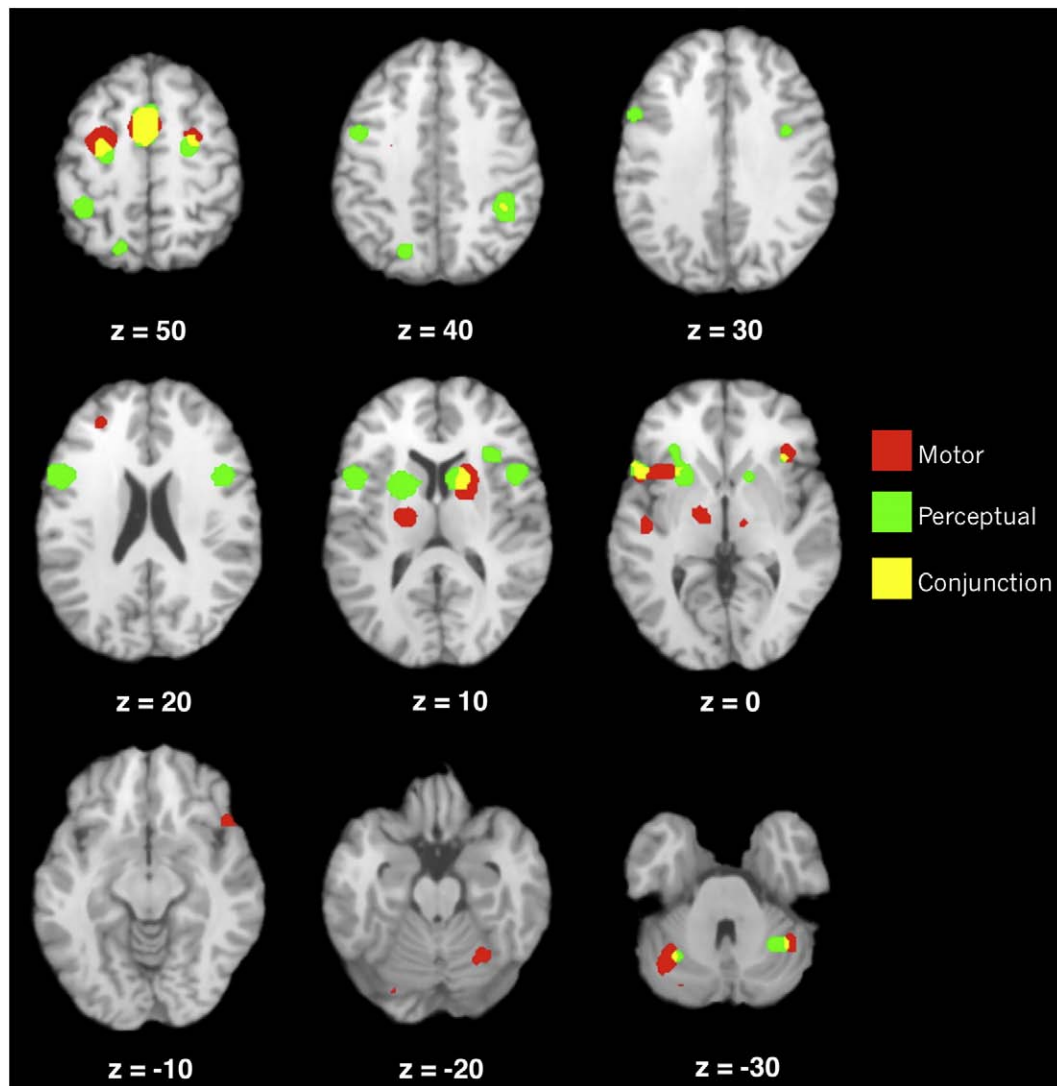


Fig. 1. ALE maps for sub-second timing studies. Axial slices are displayed with all significant voxels ($P < 0.05$; FDR-corrected). Conjunction areas represent voxels where statistical maps for motor and perceptual coincide.

four conditions. The results of our overlay revealed two regions: the right IFG (approximate Talairach coordinates: $x = 47$, $y = 10$, $z = 15$) and the bilateral SMA (approximate Talairach coordinates: $x = 0$, $y = 2$, $z = 53$) (see Fig. 3).

Discussion

The results of our meta-analysis revealed a number of distinct regions associated with the processing of temporal intervals.

Table 4

Significant activation likelihood clusters for the sub-second perceptual timing analysis.

Location	x	y	z	ALE value	Volume (mm ³)	Studies
Left inferior frontal gyrus (BA 44)	-48	8	14	0.011	5912	[12b], [13b], [14], [16], [17], [201]
Left supplementary motor area (BA 6)	-2	-2	54	0.012	5152	[13b], [15], [16], [17], [18]
Left supplementary motor area (BA 6)	0	10	48	0.008		
Left putamen	-20	4	10	0.013	4864	[12b], [13b], [14], [16], [17], [18]
Left claustrum	-28	24	4	0.008		
Right insula (BA 13)	46	10	16	0.011	4640	[13b], [14], [15], [16], [17], [20a]
Right insula (BA 13)	34	20	6	0.009		
Right caudate	14	8	8	0.012	2320	[13b], [16], [17]
Right inferior parietal lobule (BA 40)	40	-44	38	0.009	1888	[13b], [15], [16]
Right inferior parietal lobule (BA 40)	-38	-44	48	0.011	1584	[13b], [16]
Right posterior cerebellum	-28	-60	-36	0.010	1496	[20a], [16]
Left parietal lobe (BA 7)	-18	-70	44	0.009	1272	[13b], [16]
Right posterior cerebellum	32	-54	-32	0.009	1200	[12b], [16]
Left precentral gyrus (BA 6)	-24	-12	50	0.008	1184	[13b], [16]
Right middle frontal gyrus (BA 6)	24	-10	52	0.008	1176	[13b], [16]
Left middle frontal gyrus (BA 6)	-44	0	38	0.007	1144	[13b], [14], [18]
Right precentral gyrus (BA 6)	38	0	34	0.005	424	[13b], [17]

Table 5
Significant activation likelihood clusters for the supra-second motor timing analysis.

Location	x	y	z	ALE value	Volume (mm ³)	Studies
Right supplementary motor area (BA 6)	2	4	60	0.010	7480	[23], [25], [26], [27], [28], [29], [30], [31], [33]
Left cingulate gyrus (BA 24)	-6	2	42	0.008		
Right cingulate gyrus (BA 32)	6	20	34	0.008		
Right precentral gyrus (BA 44)	46	12	12	0.010	7400	[19b], [26], [27], [30], [31], [33]
Right claustrum	34	12	6	0.009		
Right precentral gyrus (BA 44)	58	-2	18	0.006		
Right inferior parietal lobule (BA 40)	46	-32	46	0.008	3832	[19b], [26], [27], [28], [30], [33], [35]
Right inferior parietal lobule (BA 40)	38	-54	42	0.006		
Right supramarginal gyrus (BA 40)	50	-46	44	0.006		
Right inferior parietal lobule (BA 40)	34	-46	44	0.005		
Right middle frontal gyrus (BA 10)	34	40	22	0.007	3648	[19b], [27], [28], [30], [33], [35]
Right middle frontal gyrus (BA 9)	36	26	30	0.006		
Left precentral gyrus (BA 6)	-52	4	12	0.008	2520	[23], [24], [25], [36], [35]
Left insula (BA 13)	-40	18	0	0.007		
Left precentral gyrus (BA 4)	-50	-8	44	0.010	2112	[19b], [23], [28], [29]
Left superior frontal gyrus (BA 9)	-36	38	26	0.006	1672	[23], [24], [25], [28], [35]

Furthermore, the likelihood that particular structures were activated depended on the duration of the interval to be timed and whether the task required predominantly motor or perceptual processing. Only the right IFG and bilateral SMA demonstrated significant activation likelihood across all conditions. These results support a number of conclusions. First, partially overlapping but distinct neural networks are recruited for the timing of sub-second and supra-second intervals.

Second, the conditions under which these structures activate may provide insight for neural theories of timing that postulate a cortico-striatal-thalamic network. Finally, the demonstration that some structures are activated across all timing conditions suggests that these structures form a part of the core network of temporal processing. We discuss each of these issues in turn, and relate the present results to prior reviews of the literature.

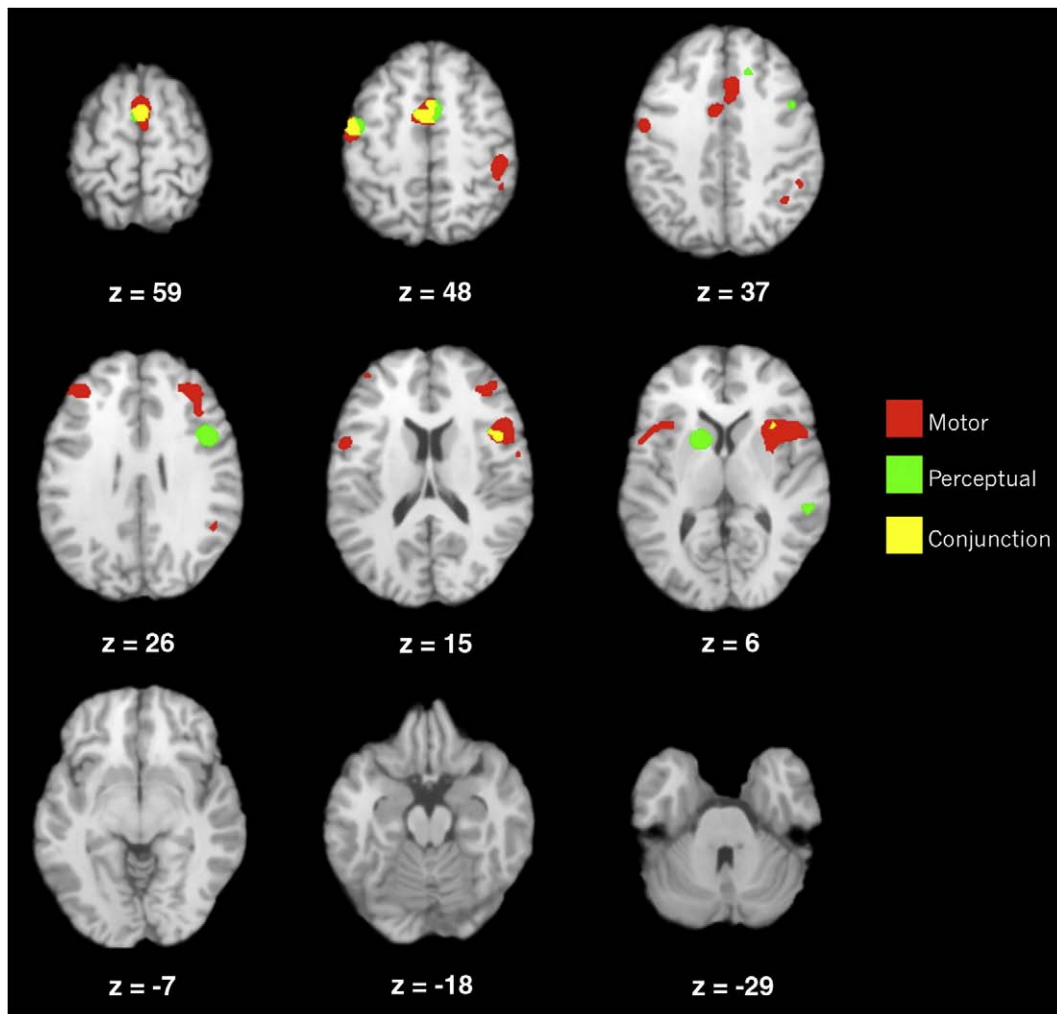


Fig. 2. ALE maps for supra-second timing studies.

Table 6
Significant activation likelihood clusters for the supra-second perceptual timing analysis.

Location	x	y	z	ALE value	Volume (mm ³)	Studies
Right inferior frontal gyrus (BA 9)	46	8	22	0.008	5088	[36], [37], [38], [39], [40]
supplemental motor area (BA 6)	0	0	54	0.008	3320	[36], [38], [39], [40]
Left putamen	-14	6	4	0.008	1760	[36], [37], [39]
Left precentral gyrus (BA 4)	-46	-8	46	0.007	1016	[38], [39]
Right middle temporal gyrus (BA 22)	54	-38	4	0.005	584	[36], [39]
Right middle frontal gyrus (BA 6)	18	28	36	0.004	448	[36], [38]
Right cingulate gyrus (BA 32)	10	24	32	0.004		
Left insula (BA 13)	-36	12	4	0.004	384	[36], [39]
Left inferior frontal gyrus (BA 47)	-40	14	-6	0.004		
Right claustrum	32	16	4	0.004	184	[37], [39]
Left supramarginal gyrus (BA 40)	-50	-48	28	0.004	112	[36], [37]

Sub-second and supra-second timing

The findings in the present study support the claim, first articulated by *Musterberg (1889)*, that there is a fundamental distinction between the procedures involved in the timing of sub- as compared to supra-second stimuli. Although this hypothesis has received considerable support (*Kagerer et al., 2002; Coslett et al., 2009; Mangels et al., 1998, Lewis and Miall, 2003b*), the issue remains controversial. For example, based on a review of the functional imaging literature until 2001, *Macar and others (2002)* concluded that the network involved in timing for sub-second and supra-second intervals did not differ. Our analysis of a larger corpus of studies with a relatively new and robust methodology, however, strongly supports the claim that sub- and supra-second timing are mediated by networks of brain structures that are at least partially distinct.

The result of the sub-second analyses revealed a set of cortical and sub-cortical structures. Notably, these structures are consistent with a number of findings in neuropsychological studies of timing. For example, consistent with studies of lesion-patients performing paced finger tapping tasks (*Ivry and Keele, 1989*) and perceptual timing tasks with sub-second intervals (*Nichelli et al., 1996; Mangels et al., 1998; Casini and Ivry, 1999; but see Harrington et al., 2004b*), we found significant ALE values in the bilateral posterior cerebellum. This result stands in contrast to the supra-second analyses, in which no regions of the cerebellum were implicated. Furthermore, the finding that the cerebellum is implicated in sub-second but not supra-second timing is consistent with several studies utilizing transcranial magnetic stimulation (TMS) of the cerebellum (*Lee et al., 2007; Koch et al., 2007; Del Olmo et al., 2007*). The finding that the regions of high activation likelihood are identified in the cerebellum across

motor and perceptual tasks for sub-second, but not supra-second intervals, is also consistent with the hypothesis of *Ivry and colleagues (2002)* that the cerebellum acts as an event timing system for intervals of brief duration.

Sub-second timing tasks also demonstrated a cluster of activation likelihood in the right IPL for both motor and perceptual timing tasks. Support for the role of the right IPL in sub-second timing has come from a variety of sources, including lesion studies in patients and TMS (*Bueti and Walsh, 2009*). *Harrington and others (1998)* first demonstrated that patients with right, but not left, IPL lesions showed increased variability on a sub-second temporal discrimination task. Two studies utilizing TMS have also demonstrated that disruptions of regions within the right IPL disrupt performance on sub-second timing tasks (*Wiener et al., in press; Bueti et al., 2008b*). The right IPL also demonstrated an overlap of significant ALE voxels for motor timing tasks. Less evidence from neuropsychological studies exists to implicate a specific role of the right IPL in this regard; a recent TMS study found that stimulation of the right IPL disrupted performance on a supra-second motor timing task (*Oliveri et al., 2009*).

Sub-second perceptual tasks demonstrated the highest activation likelihood in the left IFG. The left IFG has been seen as relevant to language production (*Heim et al., 2003*), semantic retrieval (*Demb et al., 1995*), and, more recently, response selection and inhibition (*Zhang et al., 2004; Kan and Thompson-Schill, 2004*). Activation in this condition was also highly associated with attending to timed sequences of stimuli, in which subjects must detect deviant durations among a series of repeating stimuli (*Schubotz and von Cramon, 2001; Schubotz et al., 2000*). This finding is consistent with earlier work demonstrating activation of the left IFG during auditory imagery of rhythmic sequences (*Halpern and Zatorre, 1999*). Furthermore, a

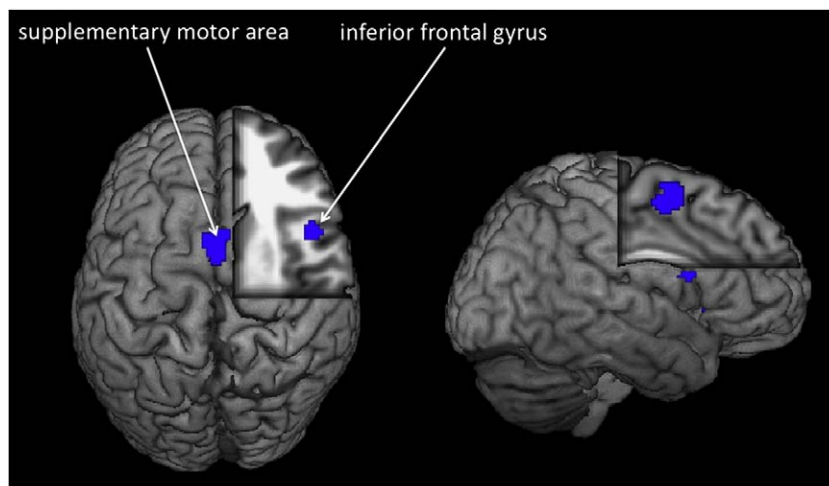


Fig. 3. ALE voxels representing the conjunction of all four separate meta-analyses on a single template. Only the right inferior frontal gyrus and bilateral supplementary motor area demonstrated concordance across all timing tasks.

recent study by [Grahn and McAuley \(in press\)](#) revealed that subjects performing a perceptual timing task with sub-second stimuli could be divided into those who perceived an implied beat and those who did not. Those subjects with implied beat perception were more likely to show activation of the left IFG, suggesting this structure underlies a beat-based strategy for timing.

Activation likelihood in the insular cortex was also found for sub-second and supra-second timing tasks. Both groups showed significant voxels across motor and perceptual tasks, with sub-second tasks only demonstrating significant voxels in the right insula, and supra-second tasks demonstrating significant voxels in the bilateral insula. Additionally, the overlap of significant voxels was found in the left insula for motor timing tasks and right insula for perceptual timing tasks. The insula is connected to the motor system and limbic system, and has been hypothesized to mediate interoceptive awareness ([Critchley et al., 2004](#)). Recently, [Wittmann and colleagues \(2008\)](#) have suggested that activation within the insula may contribute to the perception of time by accumulating information about physiological changes ([Craig, 2009](#); [Wittmann, 2009](#)). With regards to the asymmetrical activation likelihood pattern between durations, one possible interpretation is that left hemispheric activation likelihood during supra-second tasks is associated with counting strategies, as the left insula is hypothesized to underlie phonological processing ([Marien et al., 2001](#)); conversely, the right insula has been associated with melody, which may confer benefits during the timing of short intervals ([Ackermann and Riecker, 2004](#)). The left insular cortex is also associated with motor learning and the activation of planned motor movements ([Mutschler et al., 2007](#)), which may explain the overlap of significant ALE voxels in the left insula. The right insula overlap during perceptual timing tasks may be explained by a recent study by [Ho and colleagues \(2009\)](#), in which the right insula was shown to accumulate sensory evidence independently from a required motor response; this result is also consistent with the notion of the right insula as a temporal accumulator.

We also note that both sub-second and supra-second timing tasks demonstrated clusters of activation likelihood in the left precentral gyrus, yet not in the same location. Sub-second precentral gyrus activation likelihood appeared more medially and was commonly activated by tasks that required either paced finger tapping, or the monitoring of timed sequences. Supra-second precentral gyrus activation likelihood appeared more laterally and was associated with temporal reproduction and discrimination tasks. These results suggest that precentral gyrus activation likelihood cannot be explained by motor preparation alone, as the clusters were present across both motor and perceptual timing studies. The left precentral gyrus has been associated with information rehearsal ([Rao et al., 2001](#)) as well as directed attention ([Tzourio et al., 1997](#)), suggesting that these regions may be related to maintaining task-directed attention. In particular, the locations of precentral gyrus clusters also differ with respect to functional specificity; the cluster of sub-second task activation likelihood appears in the equivalent location of the hand area on the motor homunculus, while the supra-second cluster appears over the mouth region. The dissociation of functional location may help to explain interval range effects, as the hand activation likelihood for sub-second tasks may relate to real (or imagined) timed hand movements ([Oullier et al., 2005](#)), whereas mouth activation likelihood for supra-second tasks may relate to vocal (or subvocal) counting strategies ([Hinton et al., 2004](#)).

Perhaps the most prominent difference between regions implicated by sub-second as compared to supra-second intervals is the larger recruitment of right prefrontal regions in the latter. Specifically, the right IFG and middle frontal gyrus demonstrated the largest activation likelihoods for supra-second tasks; right IFG showed a slightly greater involvement in perceptual tasks while right middle frontal gyrus showed greater involvement in motor tasks. Both the right IFG and middle frontal gyrus have long been implicated in timing

tasks (for review see [Harrington and Haaland, 1999](#); [Rubia and Smith, 2004](#)). The role of these regions in timing, however, remains unclear. Some studies have argued that the right prefrontal cortex is linked to attentional demands ([Casini and Ivry, 1999](#); [Olton et al., 1988](#)), whereas others suggest the region may be crucial for reference memory ([Koch et al., 2003](#)) or working memory ([Jones et al., 2004](#); [Lustig et al., 2005](#); [Lewis and Miall, 2006a,b](#)). The results of the present study, however, allow for a more comprehensive view of the studies contributing to right IFG and middle frontal gyrus activation likelihood. Five studies were found to contribute to the right IFG cluster ([Rao et al., 2001](#); [Smith et al., 2003](#); [Coull et al., 2004](#); [Pouthas et al., 2005](#); [Livesey et al., 2007](#)) and an additional six studies contributed to the right middle frontal gyrus cluster ([Lewis and Miall, 2002](#); [Macar et al., 2002](#); [Basso et al., 2003](#); [Jahanshahi et al., 2006](#); [Shergill et al., 2006](#); [Wittmann et al., 2008](#)); nearly all of these studies attempted to control for activations resulting from attention or working memory processes, suggesting the activation cluster in the present study is the result of a more core timing process (see below).

Striatal beat frequency

In recent years the striatal beat frequency model has emerged as a biologically plausible account of the procedures underlying timing (SBF; [Matell and Meck, 2004](#)). According to this account, a putative 'internal clock' crucially depends on striatal integration of oscillating cortical activity. Memories of previously experienced durations are incorporated as cortico-striatal synaptic weights, while the decision process is carried out by striatal post-synaptic potentials reaching firing threshold, indicating that sufficient coincident cortical activity has occurred; as such, the striatum monitors the similarity of currently elapsing intervals with previously experienced ones. On this account, the substantia nigra signals the onset of a timed stimulus with a burst of dopamine to the striatum.

The results of the present study provide some support for the SBF model. The strongest support for the model comes from the sub-second motor timing results, in which clusters of activation likelihood were detected in regions of the cortex, basal ganglia (including the caudate, putamen and globus pallidus) and thalamus. Additionally, several regions with significant activation likelihood in the cortex, including the SMA, right IPL and right IFG, are known to have strong efferent projections to the basal ganglia ([Nachev et al., 2008](#); [Cavada and Goldman-Rakic, 1991](#); [Alexander et al., 1986](#)). As the SBF model proposes that timing is mediated by coincident detection of oscillatory neuronal firing from the cortex to medium striatal spiny neurons, with dopaminergic input from the substantia nigra at the onset of a timed interval, the fact that we found a small cluster of activation likelihood in the substantia nigra is particularly relevant.

The present data also speak to the relative contributions of different components of the basal ganglia regions to timing. Sub-second perceptual tasks showed activation likelihood in the bilateral putamen and right caudate, whereas sub-second motor tasks were associated with activation likelihood of the right putamen only. The ALE cluster in the right putamen was generated by studies in which subjects were required to produce a remembered duration ([Ortuno et al., 2002](#); [Mayville et al., 2001](#); [Buetti et al., 2008a,b](#)), suggesting a possible relation to either working memory ([Lustig et al., 2005](#)) or the precise timing of a motor plan ([Houk and Wise, 1995](#)). In contrast, studies in which subjects were required to detect deviant durations in patterns of stimuli ([Schubotz et al., 2000](#); [Schubotz and von Cramon, 2001](#)), or to perform a simple discrimination between two stimuli ([Tregellas et al., 2006](#)) contributed to the activation likelihood in the right caudate.

Although the SBF model is agnostic to differences between the caudate and putamen, the differential activation likelihoods across motor and perceptual timing tasks suggests that the basal ganglia recruits different neural circuits, depending on the task. Prior research

has demonstrated that regions of the striatum form segregated circuits with discrete regions of the cortex (Grahn et al., 2008). Efferent projections from the SMA to the putamen form the so called 'motor circuit,' whereas the caudate forms separate circuits with the frontal eye fields, prefrontal cortex and lateral orbital cortex; these connections suggest differential contributions of the caudate and putamen to behavior. Recent work suggests that activation of the motor circuit may relate to habit formation and stimulus-response learning (Graybiel, 2008), whereas the caudate is associated with goal-directed actions and the anticipation of reward (Tricomi et al., 2004). The activation likelihood of the putamen during sub-second motor tasks suggests these tasks engage the motor circuit, requiring subjects to form a precisely timed motor output. This stands in contrast to sub-second perceptual tasks, in which the activation likelihood of the caudate suggests the involvement of prefrontal circuits engaging higher-order processes, in order to complete the task.

Although the results of the sub-second analyses provide support for the SBF model, little support comes from the supra-second analyses. Supra-second motor timing tasks show no clusters of activation likelihood in the basal ganglia, thalamus or substantia nigra. For supra-second perceptual timing tasks, clusters of activation likelihood were detected in the left putamen and thalamus. This result is surprising, considering numerous studies demonstrate impaired supra-second temporal reproduction, a motor timing task, in unmedicated Parkinson's disease patients (Malapani et al., 1998, 2002; Koch et al., 2004a,b; Koch et al., 2008). When the studies contributing to these clusters were examined, we found that activation likelihood in the left putamen was provided by temporal discrimination tasks with discrete visual stimuli (Coull et al., 2004; Livesey et al., 2007; Rao et al., 2001). Additionally, overlap in the left putamen was detected for sub-second and supra-second perceptual timing tasks; notably, the majority of sub-second studies contributing to left putamen activation likelihood also utilized temporal discrimination tasks (Schubotz and Von Cramon, 2001; Schubotz et al., 2000; Ferrandez et al., 2003; Tregellas et al., 2006; Shih et al., 2009). Temporal discrimination requires a subject to compare a given duration to a previously experienced standard, and are heavily dependent on working memory. The left basal ganglia have been previously implicated in working memory function (McNab and Klingberg, 2008), suggesting the activation likelihood in the left basal ganglia may be related to the temporal demands on working memory.

We have recently reported data from subjects with extensive bilateral lesions of the basal ganglia that are consistent with this finding. Both subjects performed normally (or nearly so) on a variety of timing tasks with sub- and supra-second stimuli but performed quite abnormally on a paced tapping task (Coslett et al., submitted for publication). We argued that these data are broadly consistent with the view that there are multiple, distinct procedures for timing that are flexibly invoked as a function of task demands (Lewis and Miall, 2003a,b; Coslett et al., submitted for publication).

Common timing structures

Whereas the analyses discussed above provide important insights into the role of distinct brain regions in a number of different tasks, they do not speak to a question of fundamental import: are there brain regions common to all timing tasks? To address this issue we sought to determine if there are sites implicated in both sub- and supra-second tasks as well as motor and non-motor tasks. We identified two brain regions that were active across all conditions: the right IFG and bilateral SMA. As these two regions are evident regardless of the duration or task requirement, we suggest they are a part of the core network mediating time perception.

The right IFG has been implicated in a number of studies of timing. As noted above, previous reviews have suggested that the right IFG is preferentially recruited for supra-second timing operations. There is,

however, reason to think that the IFG plays a role in sub-second timing as well. Two prior neuropsychological studies have demonstrated that subjects with damage to the right prefrontal cortex exhibit deficits on timing tasks utilizing sub-second intervals (Nichelli et al., 1995; Harrington et al., 1998). Both studies involved temporal discrimination tasks. Additionally, two studies have implicated the prefrontal cortex in sub-second motor timing. Ivry and Keele (1989) demonstrated that subjects with unilateral prefrontal damage exhibit deficits on a paced finger tapping task; their analysis did not distinguish between subjects with right as compared to left hemisphere lesions. Additional evidence for the right IFG in sub-second timing comes from a study by Pfeuty et al. (2003), in which event-related potentials (ERP) were recorded while subjects performed a sub-second temporal discrimination task; ramping contingent negative variation (CNV) signals were detected over the right frontal lobe that correlated with comparison duration lengths, suggesting these signals represented directed attention to time.

The bilateral SMA contained the largest number of significant ALE voxels across all timing tasks. In light of its role in motor processing, it is perhaps not surprising that the region of concordance was larger and the ALE values were higher in the SMA in motor timing tasks; however, the SMA was implicated in perceptual timing tasks as well. Although the role of the SMA in timing remains to be fully elucidated, several studies utilizing electroencephalography (EEG) and magnetoencephalography (MEG) have also demonstrated ramping CNVs over the SMA during timing tasks (Macar et al., 1999; Macar and Vidal, 2002; Pfeuty et al., 2003; Noguchi and Kakigi, 2006), leading these authors to hypothesize the SMA serves as a temporal accumulator. Support for this account was recently provided by a study in monkeys in which neurons in the SMA demonstrated time dependent activity during a supra-second reproduction task (Mita et al., 2009).

Neuropsychological studies investigating the SMA in timing are rare. Only one study of which we are aware has directly explored timing resulting from SMA lesions in humans. Halsband and others (1993) tested two subjects with left SMA lesions on a paced finger tapping task with rhythmic stimuli. Both subjects were capable of maintaining rhythmic sequences when tapping in time with pacing stimuli, yet showed dramatic deficits when these stimuli were removed. The authors concluded that the SMA is necessary for planning and performing temporal motor sequences from memory. These results are in line with other work suggesting the SMA involves motor planning and implementation (Nachev et al., 2008).

Three studies have explored the role of the SMA in timing using TMS (Jones et al., 2004; Koch et al., 2004b; Del Olmo et al., 2007); no effects of TMS were noted. These null results must be interpreted with caution, however, in light of the fact that much of the SMA is distant from the surface coil employed in TMS and therefore may be difficult to stimulate effectively. Finally, we reported one subject with probable fronto-temporal dementia who exhibited a profound deficit on a variety of timing tasks (Wiener and Coslett, 2008); although brain-behavior relationships must be interpreted with caution in degenerative diseases, it is noteworthy that a resting PET scan demonstrated the greatest abnormality in the bilateral medial prefrontal cortex.

Although our data do not permit one to draw conclusions about the specific role played by the SMA in timing, the fact that the structure was active across all timing conditions is consistent with the claim that the SMA may be an element of the putative clock mechanism as other investigators have suggested (Macar et al., 2006).

Comparison with previous reviews

Our quantitative meta-analysis reveals both similarities and differences with previous reviews. The label-based meta-analysis performed by Lewis and Miall (2003b) noted that the SMA and cerebellum were the two most commonly activated structures in

studies of timing. Although we also found the SMA to be implicated in all types of timing tasks, cerebellar activation likelihood was exclusively linked to sub-second intervals. Additionally, we found numerous other structures with significant activation likelihood for sub-second and supra-second intervals in addition to those identified by Lewis and Miall (2003b). One clear difference between our study and that of Lewis and Miall is that we only included contrasts that utilized either a control task subtraction, or a different higher-order method (e.g., Coull et al., 2004; Jech et al., 2005; Stevens et al., 2007), to control for non-timing related activations.

An earlier review by Macar and others (2002) concluded that the basal ganglia, SMA, cerebellum, DLPFC, anterior cingulate, and right IPL were active across all motor and perceptual tasks, as well as across sub-second and supra-second intervals. Although each of these areas were implicated under some circumstances in our analyses, marked differences were found in their activation likelihood depending on the stimulus interval range and the nature of the response. One difference between our work and that of Macar and colleagues is that the latter study included contributions employing EEG and surface Laplacians, which do not provide any information regarding the activation of sub-cortical structures.

Penney and Vaitilingam (2008) reported that the cerebellum was the most commonly activated structure for sub-second timing tasks, whereas the right IFG was most often activated during supra-second timing tasks. Our results for supra-second tasks are consistent with their finding, but the cerebellum did not demonstrate the highest ALE values for sub-second timing tasks in our study. Additionally, Penney and Vaitilingam did not include any studies employing paced finger tapping.

There are a number of potential explanations for the differences between our study and previous reviews. One relates to the distinction between voxel-based and label- or structure-based analyses. In the former, significant activations require that the same voxels be activated across a number of studies whereas for the latter, activation in distinct and disparate voxels within the same named structure constitutes evidence of the participation of the brain region. The difference may be illustrated by considering the cerebellum, a relatively large, heterogeneous structure. For the purposes of label- or structure-based analyses, activations in the vermis and cerebellar hemisphere both constitute evidence of involvement of the cerebellum despite the fact that they are in brain regions with different functions and patterns of connectivity. In voxel-based procedures such as ALE, significant voxels in the vermis and cerebellar hemisphere are treated as independent. Thus, if activation is reported in different studies across multiple foci in a brain region, a label-based analysis is likely to implicate that brain region whereas a voxel-based approach will only treat them as related if the relevant voxels overlap. A second potential explanation for discrepancies between our study and prior investigations is that we have included a number of studies not incorporated in prior reviews. This difference is due to the publication of new investigations and the decision to include studies there were not included in at least some previous reviews (i.e., paced finger tapping).

Our study has a number of limitations. First, despite our efforts to control for the number of experiments contributing to a single study, we are unable to control for possible effects of discrepancies in the number of subjects tested or the rigor of the statistical thresholding. Second, like all meta-analyses, the data come from a disparate set of studies, each optimized to address specific – and often different – hypotheses about timing mechanisms.

Conclusions

The present study provides the first voxel-wise meta-analysis of the neuroimaging literature on time perception. Although our findings reinforce a number of previous observations about the roles

of brain structures such as the right IFG and the SMA, they provide a more nuanced perspective on the contributions of structures such as the cerebellum and basal ganglia to timing. Our results suggest that different neural regions are recruited between sub-second and supra-second intervals, with sub-second tasks relying more on sub-cortical structures than supra-second tasks. The results also constrain models such as SBF that postulate cortico-striatal networks underlying the neural basis of time; our findings suggest the basal ganglia are differentially engaged for sub-second and supra-second timing tasks. Finally, our analysis identified the right IFG and bilateral SMA as the only two regions to show consistent activation likelihood across all interval ranges and task requirements, suggesting these regions serve as part of a core network mediating timing in the brain.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.09.064.

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