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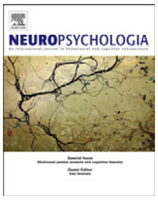

Functional anatomy of timing differs for production versus prediction of time intervals

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ABSTRACT

Timing is required both for estimating the duration of a currently unfolding event, or predicting when a future event is likely to occur. Yet previous studies have shown these processes to be neuroanatomically distinct with duration estimation generally activating a distributed, predominantly right-sided, fronto-striatal network and temporal prediction activating left-lateralised inferior parietal cortex. So far, these processes have been examined independently and using widely differing paradigms. We used fMRI to identify and compare the neural correlates of duration estimation, indexed by temporal reproduction, to those of temporal prediction, indexed by temporal orienting, within the same experimental paradigm. Behavioural data confirmed that accurate representations of the cued interval were evident for both temporal reproduction and temporal orienting tasks. Direct comparison of temporal tasks revealed activation of a right-lateralised fronto-striatal network when timing was measured explicitly by a temporal reproduction task but left inferior parietal cortex, left premotor cortex and cerebellum when timing was measured implicitly by a temporal orienting task. Therefore, although both production and prediction of temporal intervals required the same representation of time for their successful execution, their distinct neural signatures likely reflect the different ways in which this temporal representation was ultimately used: either to produce an overt estimate of an internally generated time interval (temporal reproduction) or to enable efficient responding by predicting the offset of an externally specified time interval (temporal orienting). This cortical lateralization may reflect right-hemispheric specificity for overtly timing a currently elapsing duration and left-hemispheric specificity for predicting future stimulus onset in order to optimize information processing.

1. Introduction

The on-line Merriam-Webster English dictionary (http://www.merriam-webster.com) gives two distinct definitions for the word "timing". The first is "the ability to select the precise moment for doing something for optimum effect". The second is the "observation and recording of the elapsed time of an act, action or process". These conventional, real-world definitions map neatly onto two of the main fields of timing research in the scientific literature, sometimes referred to as implicit and explicit timing (Coull & Nobre, 2008; Grondin, 2010; Jones, Malone, Dirnberger, Edwards, & Jahanshahi, 2008; Michon, 1980; Zelaznik, Spencer, & Ivry, 2002). Timing is measured implicitly by temporal prediction (or preparation) tasks, in which knowing when an event will occur in time optimises behavioural responses to that event (Niemi & Näätänen, 1981; Nobre, 2001). Here, accurate timing facilitates the sensorimotor task goal, which is to process the event as quickly or accurately as possible. Conversely, timing is measured explicitly by duration estimation tasks, which require the elapsed time of a motor act or sensory event to be measured and registered overtly (Grondin, 2010; Ivry & Schlerf, 2008; Wearden, O'Donoghue, Ogden, & Montgomery, in press). Here, the accurate estimate of timing is itself the task goal.

Temporal prediction tasks can be further subdivided as a function of the type of information that is used to predict when the event will occur. First, the unidirectional nature of the flow of time itself contains predictive power: the longer you wait for an expected event to occur (e.g., the shot from a starter's pistol), the greater is the conditional probability that it will occur at the next possible moment. This ever-heightening certainty of event occurrence translates empirically into faster response times for longer delays (Karlin, 1959; Niemi & Näätänen, 1981; Woodrow, 1914). Second, the environment can provide temporally informative

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sensory cues. For example, temporal regularities in sensory input, such as the beat of a metronome or the trajectory of a baseball, can generate predictions about when the event will occur. Targets appearing at times predicted by temporally regular auditory (Barnes & Jones, 2000) or visual (Correa & Nobre, 2008) contexts are processed more quickly and accurately than targets appearing before the predicted time. Temporally structured stimulus dynamics act as exogenous temporal cues, generating predictions in a bottom-up manner. By contrast, learned associations between sensory input and event timing (e.g., the 4 s delay before an amber traffic light turns red) serve as more endogenous temporal cues, generating predictions in a more top-down manner (Coull & Nobre, 2008; Coull, 2011). In the laboratory, the temporal attentional orienting task (Coull & Nobre, 1998; Nobre, 2001), a temporal analogue of the Posner covert spatial orienting of attention task (Posner, Snyder, & Davidson, 1980), demonstrates that temporal cues provide a behavioural advantage qualitatively similar to that of spatial cues (e.g., Coull & Nobre, 1998; Coull, Cheng, & Meck, 2011; Griffin, Miniussi, & Nobre, 2001). Specifically, temporally predictive symbolic cues allow targets to be processed both more quickly (Coull & Nobre, 1998) and accurately (Davranche, Nazarian, Vidal, & Coull, 2011).

In the temporal orienting of attention task, making use of endogenous cues to optimise behaviour depends upon a mnemonic representation of the learned cue–target interval. Mnemonic representations of learned intervals or durations are equally fundamental in duration estimation tasks in which the duration of an event is compared to a “standard” duration previously learned and stored in working or reference memory (Gibbon, Church, & Meck, 1984; Michon, 1985). In perceptual versions of these tasks, subjects typically compare the duration of a probe sensory stimulus to that of a previously learnt standard and provide a temporal judgement (e.g., same/different; shorter/longer). In motor versions of these tasks, subjects often reproduce the duration of a previously learnt (or entrained) standard, either by producing a sustained motor response whose duration corresponds to that of the memorised duration or a brief motor response after an inter-stimulus interval corresponding to the memorised duration. In both cases, an overt estimate of the duration of the currently elapsing event is sought, whether that estimate is provided by a perceptual comparison or by a motor response.

In both temporal prediction and duration estimation tasks therefore, subjects must initially access a stored representation of time. However, this temporal representation is ultimately used in quite different ways in the two tasks, or indeed in any tasks in which timing is measured implicitly versus explicitly (e.g., Zelaznik et al., 2002, 2005). In the former, the temporal representation is used to optimise sensorimotor processing, whereas in the latter it is used as a temporal template against which a currently elapsing duration is compared. These conceptual distinctions translate into measureable differences, both behaviourally and neurally. Implicit, predictive timing shows the same scalar properties as explicit timing, suggesting that implicit timing depends upon the same underlying temporal representation as explicit timing (Piras & Coull, 2011). However, patterns of temporal variability on implicit and explicit tasks do not correlate, suggesting a divergence in the way this representation is ultimately translated into behaviour (Merchant, Zarco, & Prado, 2008; Piras & Coull, 2011; Zelaznik et al., 2002, 2005). Additionally, although the electrophysiological characteristics of implicit, predictive timing are similar to those of explicit, duration estimation, their scalp distribution is neuroanatomically distinct (Macar & Vidal, 2003; Praamstra, Kourtis, Kwok, & Oostenveld, 2006; Pfeuty, Ragot, & Pouthas, 2003). This neuroanatomical distinction is further confirmed by the results of functional neuroimaging studies, in which explicit timing (i.e., duration estimation) generally activates a distributed, predominantly right-sided, fronto-striatal network (Wiener, Turkeltaub, & Coslett, 2010a; Coull et al., 2011), whereas implicit, predictive timing activates left-lateralised inferior parietal cortex (Coull & Nobre, 1998, 2008; Wiener, Turkeltaub, & Coslett, 2010b). Moreover, these patterns of activity are largely independent of the perceptual or motor nature of the duration estimation (Bueti, Walsh, Frith, & Rees, 2008; Wiener, Turkeltaub & Coslett, 2010a) or temporal prediction (Cotti, Rohenkohl, Stokes, Nobre, & Coull, 2011; Davranche et al., 2011) task.

So far, however, implicit predictive timing and more explicit duration estimation have almost always been examined independently, using very different paradigms. We therefore designed an fMRI experiment to identify and compare their neural correlates within a single experimental paradigm. Two previous fMRI studies have already directly compared explicit to implicit timing: in one, both forms of timing were measured by internally generated movement dynamics (Spencer, Verstynen, Brett, & Ivry, 2007) while in the other they were measured by linguistic discrimination of externally specified rhythms (Geiser, Zaehle, Jancke, & Meyer, 2008). By contrast to these studies of rhythmic timing, we used symbolic endogenous cues in the current experiment to index memorized representations of single (short or long) durations. Explicit timing was measured by an internally generated duration estimate, while implicit timing was measured by temporal prediction of an externally specified event. Neutral cue conditions controlled for the contribution of internally versus externally guided movement generally. In both explicit and implicit timing tasks, a temporal cue indicated the interval (short or long) to be estimated. Explicit duration estimation was indexed by a temporal reproduction task in which subjects internally generated the cued interval, making a brief response when they estimated that the cued interval had elapsed. Implicit, predictive timing was indexed by a temporal orienting task in which subjects responded as quickly as possible to the appearance of an externally specified event that appeared at the cued interval. Directly comparing these tasks allowed us to differentiate the neural substrates of timing when the same underlying temporal representation was used either to produce an overt estimate of currently elapsing time (temporal reproduction) or to predict future event onset in order to optimise sensorimotor processing (temporal orienting).

2. Material and methods

2.1. Subjects

Fifteen healthy, right-handed volunteers (mean age = 29.4 years), with normal or corrected-to-normal vision, participated in the experiment. All volunteers gave informed written consent to the study protocol, which had been approved by the local research ethics committee. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Tasks

Participants performed four experimental conditions: temporal production and its neutral cue control condition, plus temporal prediction and its neutral cue control condition. Conditions were blocked (6 trials per block), and each block of trials began with an instruction screen (8 s), stating the name of the condition and a brief reminder of the task to be performed. Each trial began with presentation of a visual cue, followed by a variable inter-stimulus interval, and then brief (130 ms) presentation of a response stimulus (Fig. 1). All visual stimuli were white, presented centrally on a black background. The visual cue comprised two concentric circles and the response stimulus comprised two horizontally aligned + symbols. Responses in all conditions were registered with a brief right index finger button press. Inter-trial intervals varied between 600 ms and 1500 ms.

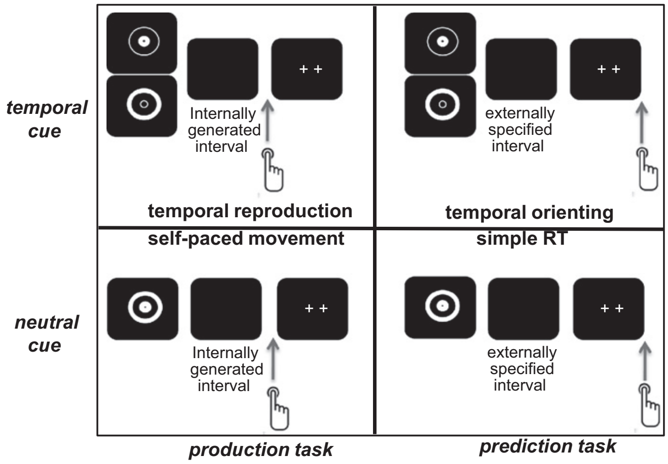

Fig. 1. Experimental conditions. Each trial began with presentation of a visual cue (two concentric circles) that either provided precise temporal information concerning the duration of the ensuing inter-stimulus interval (temporal cue) or acted simply as a trial onset signal, providing no temporally precise information (neutral cue). In temporal cue conditions (top row), a brighter inner circle indicated a short (600 ms) interval whereas a brighter outer circle indicated a long (1400 ms) interval. In neutral cue conditions (bottom row), the entire cue brightened, indicating a random inter-stimulus interval. For production tasks (left column), subjects internally generated the duration of the inter-stimulus interval, indicating their estimate with a motor response, which elicited presentation of the response stimulus. For prediction tasks (right column), the duration of the inter-stimulus interval was externally specified and presentation of the response stimulus elicited a speeded motor response. The temporal production condition was indexed by a temporal reproduction task, the temporal prediction condition by a temporal orienting task, the neutral production condition by a self-paced movement task, and the neutral prediction condition by a simple reaction time (RT) task.

The visual cue either provided precise temporal information concerning the duration of the ensuing inter-stimulus interval (temporal cue) or acted simply as a trial onset signal, providing no temporally precise information (neutral cue). Following presentation of either the temporal or neutral cue, participants then performed either a production or a prediction task. In the production task, participants made a brief button press to elicit the appearance of the visual response stimulus, whereas in the prediction task, participants made speeded responses to the response stimulus. These four conditions constituted a 2×2 factorial design, with cue (temporal/neutral) and task (production/prediction) as the experimental factors (Fig. 1). Participants performed a total of 48 trials per condition. All four conditions were matched for sensori-motor requirements, with the only difference between conditions being whether subjects had to produce or predict temporally precise or imprecise information. Prior to scanning, participants performed a training session (with feedback) to learn the association between the visual cues and inter-stimulus intervals. During this session, they performed 40 trials each of the temporal production and temporal prediction conditions (20 trials for the short cue and 20 trials for the long cue), and 20 trials each of the neutral production and neutral prediction conditions.

2.2.1. *Temporal production condition (temporal reproduction task)*

At trial onset, either the inner or outer circle of the cue was highlighted, indicating a short or long inter-stimulus interval, respectively. The short cue was presented for 600 ms and the long cue was presented for 1400 ms, to serve as additional reminders of the interval to be timed. At cue offset, the screen blacked-out then participants made a brief button press when they estimated that the cued interval (600 ms or 1400 ms) had elapsed. Upon responding, a response stimulus appeared on the screen. If participants failed to respond within 2400 ms of short cue offset or within 5600 ms of long cue offset the screen remained blank and the next trial began automatically. An equal number of short or long cues were intermixed within the block.

2.2.2. *Neutral production condition (self-paced movement task)*

At trial onset, both inner and outer circles of the cue were highlighted, providing no temporally precise information about the duration of the inter-stimulus interval. The neutral cue was presented for a relatively short and variable (400–650 ms) duration (average 510 ms). At cue offset, the screen blacked-out then participants made a brief button press after a random interval of their choosing. Upon responding, a response stimulus appeared on the screen. If participants failed to respond within 3000 ms of cue offset the screen remained blank and the next trial began automatically.

2.2.3. *Temporal prediction condition (temporal orienting task)*

At trial onset, either the inner or outer circle of the cue was highlighted, indicating a short or long inter-stimulus interval, respectively. The cue was presented for 500 ms. At cue offset, the screen blacked-out then the response stimulus appeared after the cued interval (either 600 ms or 1400 ms). Participants then made a speeded button press to the appearance of this stimulus. They were told to make use of the temporal information carried by the cue to predict when the stimulus would appear so as to respond to it as quickly as possible. An equal number of short or long cues were intermixed within the block.

2.2.4. *Neutral prediction condition (simple reaction time task)*

At trial onset, both inner and outer circles of the cue were highlighted, providing no temporally precise information about the duration of the inter-stimulus interval. The cue was presented for 500 ms. At cue offset, the screen blacked-out then the response stimulus appeared after a variable interval (600 ms, 1000 ms or 1400 ms). Participants then made a speeded button press to the appearance of this stimulus. They were told that the neutral cue did not allow them to predict when the stimulus would appear but that they still had to respond as quickly as possible upon its appearance (i.e., a simple reaction-time task). The inclusion of the medium length interval (1000 ms) served to increase the temporal uncertainty of stimulus onset. Moreover, we applied a positively skewed or "non-aging" probability bias to the distribution of the short, medium and long inter-stimulus intervals (0.5, 0.33 and 0.17, respectively). Skewing the prior probability distribution in this way serves to counteract the increasing conditional probability of event occurrence over time, rendering conditional probability effectively constant across the entire inter-stimulus interval (e.g., Baumeister & Joubert, 1969; Davranche et al., 2011; Granjon, Requin, Durup, & Reynard, 1973; Zahn & Rosenthal, 1966).

2.3. *fMRI scanning*

Scans were acquired using a 3-T Bruker Medspec 30/80 Advance whole body MRI system, equipped with a head coil. Echo-planar imaging (EPI) was used to obtain T2*-weighted fMRI images in the axial plan, using an interleaved slice acquisition sequence. The acquired image volume consisted of 40×3 mm transverse slices ($3 \times 3 \times 3$ mm resolution), with an inter-scan interval (TR) of 2.40 s. Four scanning runs (approximately 9 min per run) were acquired for each subject.

We used a blocked fMRI experimental design. Each block contained 6 trials of one of the four conditions, and began with a static instruction screen (8 s), stating the name of the condition and a brief description of the task. Each scanning run contained 2 blocks of each of the 4 conditions, presented in permuted order, which gave a total of 48 trials per condition across the entire experimental session. Scanning run order was counterbalanced across subjects. After one full permutation of the four conditions, a short (16 s) baseline condition was inserted, which comprised a central fixation point (++) identical to the response stimulus used in the experimental tasks. Subjects were asked simply to fixate the crosshairs during this time. A structural MRI was also acquired (using a standard T1 weighted scanning sequence, 1 mm^3 resolution) to allow anatomically specific localisation of significant areas of brain activation.

2.4. *Data analysis*

2.4.1. *Behavioural data*

Response times (RTs) in all four experimental conditions were recorded during the fMRI session. RT in the production tasks refers to the time between cue offset and motor response. RT in the prediction tasks refers to the time between onset of the response stimulus and the motor response. The presence of an accurate representation of time during the production tasks was assessed by repeated-measures ANOVA with condition (short/long/neutral) as a within-subjects factor. The presence of an accurate representation of time during the prediction tasks was assessed by repeated measures ANOVA, with cue (time/neutral) and inter-stimulus interval (short/long) as within-subjects factors. We also examined neutral-cue data from the prediction task for evidence of the hazard function, using a repeated measures ANOVA with inter-stimulus interval (short/medium/long) as a within-subjects factor. Post-hoc analyses were conducted using paired *t*-tests.

In addition, we examined the relationship between the temporal representations used in the production and prediction tasks by correlating temporal error in the temporal reproduction task to the RT benefit of temporal cueing in the temporal orienting task. Temporal reproduction errors were calculated separately for short and long cue trials and were defined as the unsigned difference between 600 ms and the RT produced during short cue trials, or between 1400 ms and the RT produced during long cue trials. Temporal orienting benefits were defined separately for short (600 ms) and long (1400 ms) interval trials and were calculated by subtracting RTs for temporal cue trials from RTs for neutral cue trials. Pearson correlations were conducted independently for short and long interval trials across subjects.

2.4.2. fMRI data

Image processing and analysis of fMRI data were conducted with SPM5 (http://www.fil.ion.ucl.ac.uk; Friston et al., 1995a,b). All functional images for each subject were slice-time corrected to adjust for temporal differences between slices acquired early, and those acquired late, in the image volume and then realigned to correct for head movement between scans. All images were then spatially normalised into a standard spatial reference frame by matching each image to the standard SPM5 EPI template, resampled to a 3-mm isotropic voxel size. Finally images were spatially smoothed to accommodate inter-subject differences in anatomy, using isotropic Gaussian kernels of 8 mm. Each participant's structural MRI was co-registered to the corresponding mean realigned functional image, in order to put structural images into the functional brain space.

Condition-specific responses were modelled as blocks (varying between, time-locked to the onset of cue in the first trial of the block. We modelled five regressors of interest, comprising the factorial combination of the four experimental conditions (temporal production, neutral production, temporal prediction, neutral prediction) plus the fixation baseline condition. We also included a separate regressor of no interest, which modelled the instruction screen for all four conditions. Condition effects were estimated according to the general linear model at each voxel in brain space in each of the 15 subjects. Images were adjusted for low-frequency physiological drifts, using a high-pass filter of 128 s.

We initially implemented 15 separate within-subject analyses, to define contrasts of interest. For each contrast of interest, each of the 15 maps (one per subject) were then entered into a second level of analysis, and statistical inferences for each contrast were derived using one-sample *t*-tests in SPM. The resulting group-level maps were characterised in terms of both peak amplitude and spatial extent. Maps were thresholded for significance at $p<0.05$, corrected (using false discovery rate) for multiple comparisons, with a cluster size of >5 voxels. All areas that survived this corrected threshold during interrogation of the entire brain volume are reported. We also report clusters that survive this threshold in selected regions of interest (small volume correction). Regions of interest for the temporal reproduction task were anatomically defined (using the anatomical automatic labeling (AAL) database; Tzourio-Mazoyer et al., 2002) and selected *a priori* on the basis of prior neuroimaging investigations of temporal reproduction (Bueti et al., 2008; Lewis & Miall, 2002; Macar, Anton, Bonnet, & Vidal, 2004) as well as a recent meta-analysis of explicit timing (Wiener et al., 2010a). Specifically, we further interrogated AAL-defined SMA, inferior frontal cortex bilaterally (incorporating frontal operculum and pars triangular), right inferior parietal cortex, basal ganglia, and cerebellum. Regions of interest for the temporal orienting task were also anatomically defined (AAL) and selected *a priori* on the basis of several neuroimaging investigations of temporal orienting (Coull & Nobre, 1998; Cotti et al., 2011; Davranche et al., 2011) and a recent meta-analysis of implicit timing (Wiener et al., 2010b). Specifically, we further interrogated AAL-defined left inferior parietal cortex, left ventral premotor cortex and left cerebellum.

The main aim of our study was to compare and contrast the neural substrates of temporal reproduction and temporal orienting within the same experimental paradigm, such that sensorimotor factors and the cued times were identical across tasks. Therefore, for each subject, we first defined contrasts to identify regions selectively activated by temporal reproduction i.e., [temporal production–neutral production] and temporal orienting i.e., [temporal prediction–neutral prediction]. To ensure that reported clusters were due to activations induced by the experimental conditions (temporal production or prediction), rather than deactivations induced by the control conditions (neutral production or prediction), these contrasts were inclusively masked by the maps of each temporal condition compared to the fixation baseline, thresholded at $p<0.05$, uncorrected for multiple comparisons (e.g., [temporal prediction–neutral prediction] was masked by [temporal prediction–baseline], thresholded at $p<0.05$). We expect these contrasts to largely replicate prior studies (e.g., Bueti et al., 2008; Coull & Nobre, 1998; Wiener et al., 2010a,b), with the added advantage that all sensorimotor aspects were matched across tasks.

We then identified those areas that were *selective* to temporal reproduction or temporal orienting by directly contrasting their patterns of brain activity i.e., [temporal production–temporal prediction] and [temporal prediction–temporal production]. To ensure that the contrasts did not simply identify the neural substrates of internally versus externally guided movement, we inclusively masked each contrast by the map of the relevant temporal condition compared to its neutral control condition (e.g., [temporal prediction–temporal production] was masked by [temporal prediction–neutral prediction], thresholded at $p<0.05$). Since each control condition engaged internally versus externally guided movement to the same degree as the relevant temporal condition, any clusters remaining after the masking procedure could not be due to internal versus external movement control. Parameter estimates (beta values) in significant clusters were extracted using the Marsbar region of interest toolbox (Brett, Anton, Valabregue, & Poline, 2002) and then plotted to aid data interpretation. We also directly compared temporal reproduction to temporal orienting whilst simultaneously controlling for whether the intervals had been internally (production) or externally (prediction) generated. To do this, we first contrasted each temporal condition to its neutral control condition, before then comparing each of these contrasts to one another i.e. [(temporal production–neutral production)–(temporal prediction–neutral prediction)] and [(temporal prediction–neutral prediction)–(temporal production–neutral production)]. Finally, we identified those areas that were common to temporal reproduction and temporal orienting tasks by masking areas selective to temporal production with those selective to temporal prediction (i.e., [temporal production–neutral production] masked by [temporal prediction–neutral prediction]). Both contrasts were thresholded at $p<0.001$. Note that the same network of areas was activated by the reverse masking procedure (i.e., [temporal prediction–neutral prediction] masked by [temporal production–neutral production] both thresholded at $p<0.001$).

3. Results

3.1. Behavioural data

3.1.1. Production conditions

In the temporal reproduction task, subjects produced good estimates of both the short 600 ms (mean=681.0 ms) and long 1400 ms (mean=1446.4 ms) intervals. As expected, and conforming to the scalar property of timing (Gibbon et al., 1984; Gibbon, Malapani, Dale, & Gallistel, 1997; Wearden & Lejeune, 2008), variability was more widespread during reproduction of long intervals than short ones (Fig. 2a). Estimates of short and long intervals in the temporal production condition were significantly different from the self-paced intervals in the neutral production condition (Fig. 2b), both in terms of mean response ($F(2,28)=52.34$, $p<0.001$) and variability ($F(2,28)=10.81$, $p=0.001$). Post-hoc testing revealed that the mean self-paced interval produced during the neutral production condition (998.9 ms) was significantly different from both the mean short ($t(14)=-3.84$, $p<0.005$) and long ($t(14)=5.305$, $p<0.001$) intervals reproduced during the temporal production condition. Crucially, variability was also significantly greater for self-paced responses in the neutral production condition than temporal reproduction of either short ($t(14)=-3.72$, $p<0.005$) or long ($t(14)=-3.38$, $p=0.005$) intervals in the temporal production condition. Fig. 2a illustrates that the spread of responses during the neutral production condition is wider than that of either the short or long trials of the temporal production condition.

3.1.2. Prediction conditions

RTs tended to be faster overall ($F(1,14)=4.22$, $p<0.06$) when the response signal was preceded by a temporal cue (temporal orienting task) than a neutral cue (simple RT task). Confirming results of prior studies (e.g., Coull & Nobre, 1998), this main effect was qualified by a significant interaction between cue-type and inter-stimulus interval ($F(1,14)=34.57$, $p<0.001$). Specifically, the speeding of RTs induced by temporal cues was evident at short ($t=-4.32$, $p=0.001$), but not long ($t=0.25$, ns), intervals (Fig. 3a). The differential benefit of temporal cues at short versus long intervals is due to the influence of the hazard function during neutral-cue trials. Even though subjects do not know when the target will appear in neutral trials, the unidirectional flow of time itself carries predictive power: the hazard function states that the conditional probability that the target will appear at the next possible moment, given that it has not yet appeared, increases over the inter-stimulus interval. Target onset can therefore be predicted with increasing certainty as the inter-stimulus interval lengthens, thereby diluting the benefit of temporal cues at longer inter-stimulus intervals. During neutral prediction trials, RTs were increasingly faster the longer the inter-stimulus interval ($F(1,14)=37.14$, $p<0.001$), providing evidence that the hazard function was indeed influencing performance, (Fig. 3b), despite our attempts to minimize its influence through the use of a non-aging probability distribution.

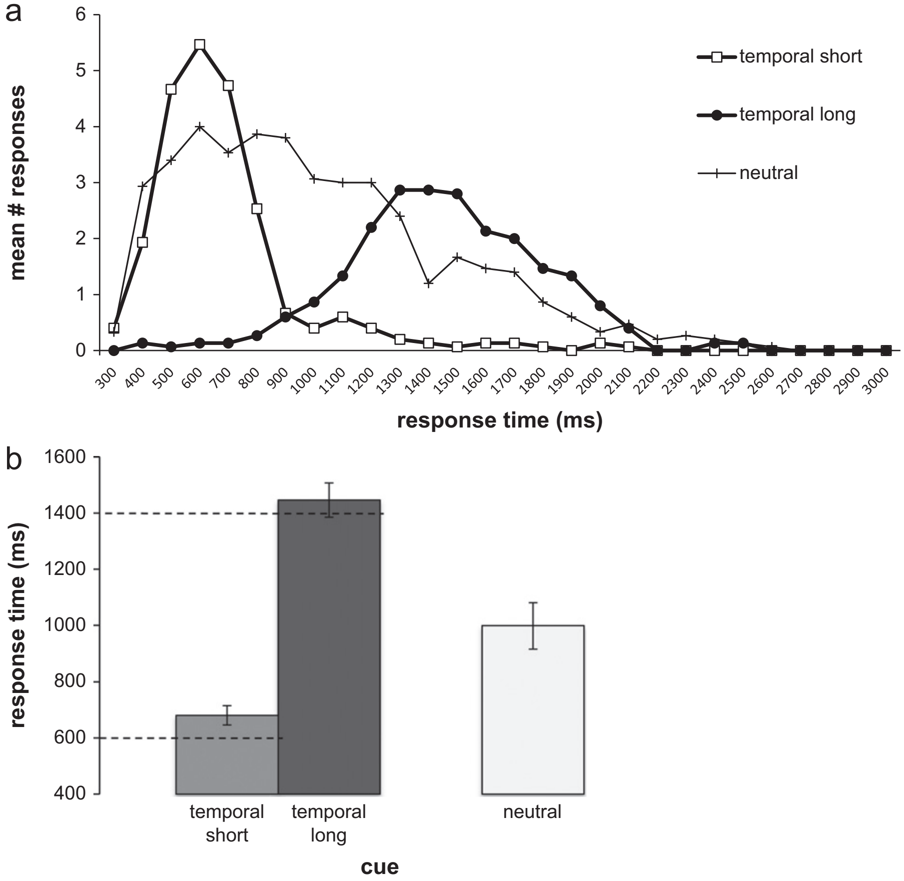

Fig. 2. Production performance. (a) Response distribution for reproduction of 600 ms (temporal short) or 1400 ms (temporal long) intervals, or for production of self-paced random intervals (neutral). Responses were sorted into 100 ms time-bins, ranging from 250 ms to 3000 ms. The spread (variability) of response times was greater for long than short timed intervals, conforming to the scalar property of timing. Moreover, the spread of response times was greater for random, self-paced intervals than either short or long timed intervals. (b) Mean response times produced for 600 ms (temporal short) or 1400 ms (temporal long) timed intervals were significantly different from those for self-paced, random intervals (neutral). The dashed lines indicate the 600 ms and 1400 ms target intervals. Error bars reflect standard errors.

3.1.3. Correlation between temporal production and temporal prediction

The RT benefit induced by temporal cues in the temporal orienting task was significantly correlated to the magnitude of temporal error in the temporal reproduction task, for long ($r=-0.581$, $p<0.05$), though not short ($r=0.34$, ns), intervals. Specifically, the more subjects benefitted from the long cue in the temporal orienting task, the more accurate they were in estimating the long interval in the temporal reproduction task.

3.2. fMRI data

3.2.1. Temporal production

The temporal reproduction task, when compared to the neutrally cued self-paced task (i.e., [temporal production–neutral production] masked by [temporal production–baseline]), significantly activated prefrontal and parietal cortices bilaterally, SMA, basal ganglia, and medial and bilateral cerebellum (Table 1), largely confirming prior reports (Bueti et al., 2008; Wiener et al., 2010a). When compared directly to the temporal orienting task (i.e., [temporal production–temporal prediction] masked by [temporal production–neutral production]), the temporal reproduction task activated just a sub-set of this network, in right-lateralised inferior frontal and parietal cortices, preSMA and left caudate (Fig. 4; Table 3a). The interaction between task (production/prediction) and cue (temporal/neutral) (i.e., [(temporal production–neutral production)–(temporal prediction–neutral prediction)] revealed significant activation of right inferior frontal cortex in three discrete clusters (51, 39, 18; $Z=3.99$); 54, 12, 21; $Z=3.83$); 42, 45, -3; $Z=3.63$).

3.2.2. Temporal prediction

The temporal orienting task, when compared to the neutrally cued simple RT task (i.e., [temporal prediction–neutral prediction] masked by [temporal prediction–baseline]), significantly activated prefrontal and parietal cortices bilaterally, SMA, and bilateral cerebellum (Table 2), generally consistent with prior reports (Coull & Nobre, 1998; Cotti et al., 2011; Davranche et al., 2011; Beudel, Renken, Leenders, & de Jong, 2009). When compared directly to the temporal reproduction task (i.e., [temporal prediction–temporal production] masked by [temporal prediction–neutral prediction]), the temporal orienting task activated a sub-set of this network, in left inferior parietal cortex, left premotor cortex and cerebellum bilaterally (Fig. 5; Table 3b). The interaction between task (production/prediction) and cue (temporal/neutral) (i.e., [(temporal prediction–neutral prediction)–(temporal production–neutral production)]) revealed no areas of significant activation.

3.2.3. Areas common to temporal production and temporal prediction

The network of areas common to both the temporal reproduction and temporal orienting tasks (i.e., [temporal production–neutral production] masked by [temporal prediction–neutral

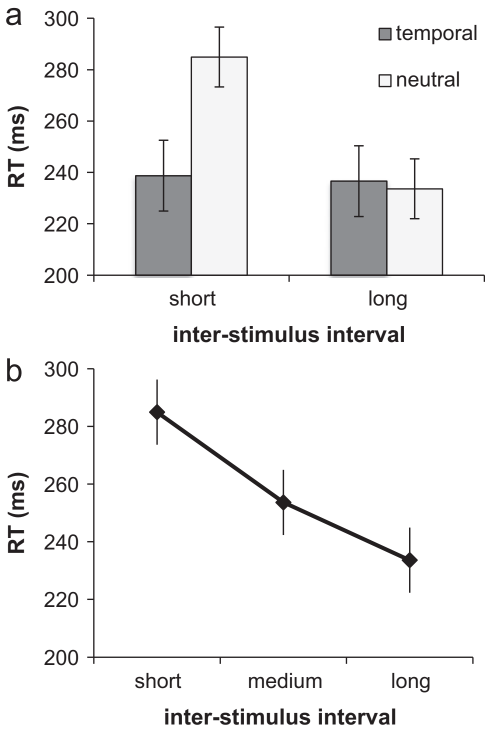

Fig. 3. Prediction performance. (a) Mean reaction times (RTs) were faster following temporal (temporal orienting task) than neutral cues (simple RT task), but only for short (600 ms), not long (1400 ms), inter-stimulus intervals. Error bars reflect standard errors. (b) Mean reaction times (RTs) for short (600 ms), medium (1000 ms), and long (1400 ms) intervals during the neutral prediction (simple RT) condition. Although the neutral cue carried no temporally specific information, RTs were significantly faster at longer inter-stimulus intervals due to increasing conditional probabilities of target appearance as a function of interval duration (the "hazard function"). Error bars reflect standard errors.

Table 1
Temporal production.

Anatomical structure	*x*, *y*, *z* co-ordinates (mm)	*Z* score
Right dorsolateral prefrontal cortex	45, 39, 21	4.86
Left dorsolateral prefrontal cortex	−39, 30, 21	4.03
	−51, 42, 3	3.59
Right inferior frontal gyrus	54, 12, 24	4.68
Left inferior frontal gyrus	−42, 3, 36	4.36
Right insula	36, 21, −6	5.49
Right premotor cortex	36, 3, 60	3.74
Pre supplementary motor area	9, 18, 48	4.68
Caudate	12, 9, 0	3.60
	3, −9, 12	3.71
Substantia Nigra	3, −15, −18	3.53
Thalamus	15, −9, 18	3.66
	−15, −18, 18	3.62
	3, −9, 12	3.71
Right inferior parietal cortex	39, −48, 45	5.36
Left inferior parietal cortex	−33, −48, 36	4.98
Posterior cingulate	−3, −27, 27	4.02
Right inferior temporal cortex	60, −39, −18	4.40
Medial cerebellum (vermis)	3, −63, −24	5.13
	3, −72, −12	4.13
Right cerebellum (VI)	21, −69, −33	4.43
Left cerebellum (Crus 2)	−30, −66, −39	3.54

Brain regions activated by the temporal reproduction task (temporal production condition) versus the self-paced movement task (neutral production condition). Activations are significant at $p < 0.05$, corrected for multiple comparisons across the whole brain.

prediction]), comprised right dorsolateral prefrontal cortex, bilateral inferior frontal gyri, SMA and inferior parietal cortices (Table 4).

4. Discussion

We directly compared two tasks, matched for basic sensorimotor requirements, in which timing of short (600 ms) or long (1400 ms) intervals was measured either explicitly, by a timed motor response (temporal reproduction), or implicitly, by speeded detection of a temporally predictable target (temporal orienting). In both tasks, a previously learnt visual cue indicated the duration of the subsequent inter-stimulus interval. Behavioural data confirmed that subjects had acquired accurate representations of the cued durations in both tasks. Moreover, these representations were correlated across tasks, at least for the long interval, with smaller temporal errors in the temporal reproduction task being associated with greater benefits of temporal cues in the temporal orienting task. In other words, an accurate representation of the cued interval in the reproduction task correlated with an accurate representation in the orienting task, suggesting the same temporal representation was being used in both tasks. Yet despite a common representation, or "temporal template", across tasks, this template was used in different ways according to task demands. When temporal templates were translated into overt estimates of interval duration in the temporal reproduction task, SMA, basal ganglia and right-lateralised frontal and parietal cortices were preferentially recruited. Conversely, when temporal templates were used to predict the onset of sensory events in the temporal orienting task, left inferior parietal cortex, left premotor cortex and cerebellum were preferentially engaged. Therefore, temporal reproduction and temporal orienting engaged discrete neuroanatomical substrates as a function of the way in which the memorised temporal template was ultimately used.

4.1. *Explicit measurement of timing by temporal reproduction*

In the temporal reproduction task, duration estimates were very close to the either the short (681 ms) or long (1446 ms) cued interval, indicating that accurate internal representations of the cued intervals could be faithfully reproduced. Moreover, these estimates displayed one of the hallmark features of timing, scalarity (Gibbon et al., 1984, 1997; Wearden & Lejeune, 2008), such that variability was greater for long intervals than for short ones (Fig. 2b). The average duration of the interval produced in the self-paced control task (999 ms), on the other hand, lay mid-way between those produced in the temporal reproduction task and responses were significantly more variable. It is, of course, possible that subjects were explicitly timing in the self-paced control task, since a strategy in which one produces 600 ms estimates on half the trials and 1400 ms estimates on the other half would produce a mean interval of around 1000 ms. However, inspection of the frequency distribution of responses (Fig. 2b) shows that subjects did not adopt this bimodal strategy, suggesting that even though they may have been timing in the self-paced control task at least they were not timing the 600 ms and 1400 ms cued durations. Yet subjects may still have been explicitly timing in this condition, deciding instead to deliberately produce an interval mid-way between the two cued intervals. Swanton, Gooch, and Matell (2009) have shown that when given a compound cue that integrated both short and long temporal cues (as is the case for the neutral cue in our own study), rats consistently responded at an interval that was the average of the previously reinforced short and long intervals. However, in our study, responses in the self-paced control task were significantly more variable than those in the temporal reproduction task, even when compared to reproduction of the longer 1400 ms interval, confirming that even if subjects were timing in the

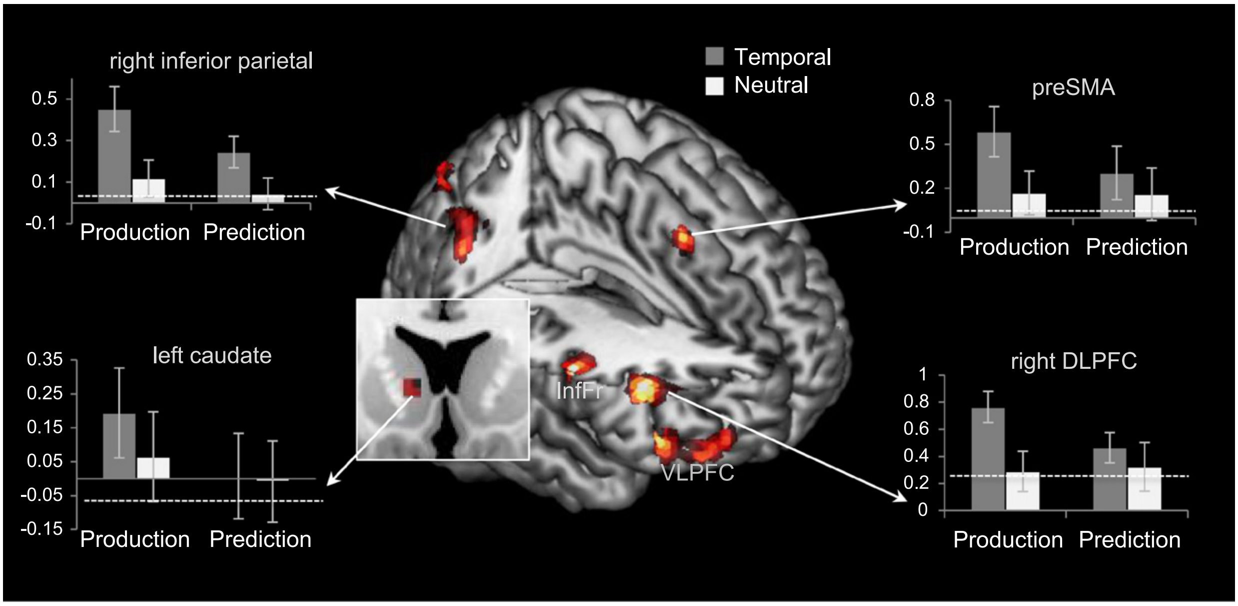

Fig. 4. Temporal production minus temporal prediction. The temporal reproduction task preferentially activated several regions of right prefrontal cortex (dorsolateral prefrontal cortex (DLPFC), inferior frontal gyrus (InfFr) and ventrolateral prefrontal cortex (VLPFC)), preSMA, right inferior parietal cortex and left caudate. Cortical activity is displayed on the template rendered brain from MRIcron (http://www.mricro.com) with a cut-out to better display the entire network of activation. Caudate activity (inset) is displayed on a coronal slice ($y=15$ mm) of the template MRIcron brain. Effects are thresholded at $p<0.001$ (uncorrected for multiple comparions). The accompanying plots illustrate the mean level of activity (beta values) in significant clusters during the production or prediction conditions, for temporal (grey) versus neutral (white) cue trials. Dashed lines show the level of activity in each brain area during the fixation baseline condition. Error bars reflect standard errors.

Table 2
Temporal prediction.

Anatomical structure	*x*, *y*, *z* co-ordinates (mm)	*Z* score
Left dorsolateral prefrontal cortex	−30, 39, 36	4.10
	−54, 9, 36	4.10
Right dorsolateral prefrontal cortex	45, 42, 27	4.78
	36, 27, 42	3.54
Left inferior frontal gyrus	−51, 9, 24	3.86
Right inferior frontal gyrus	51, 9, 21	3.68
Right premotor cortex	33, 3, 63	3.62
Left inferior parietal cortex	−54, −36, 45	5.09
	−33, −51, 39	4.22
Right inferior parietal cortex	39, −48, 45	4.77
Pre supplementary motor area	6, 9, 54	4.56
Posterior cingulate	−9, −72, 45	3.53
Left lateral cerebellum (VI)	−30, −69, −24	3.83
	−33, −54, −33	3.70
Right lateral cerebellum (VI)	33, −60, −30	3.65

Brain regions activated by the temporal orienting task (temporal prediction condition) versus the simple RT task (neutral prediction condition). Activations are significant at $p<0.05$, corrected for multiple comparisons across the whole brain.

self-paced control task they were not doing so in any temporally consistent way.

Behavioural data therefore confirmed that subjects were timing specific interval durations in the temporal reproduction task, but were producing non-temporally specific interval durations in the self-paced control task. Largely consistent with prior studies (e.g., Bueti et al., 2008; Lewis & Miall, 2002), fMRI data showed that SMA and bilateral fronto-parietal regions were activated when subjects reproduced temporally specific estimates. A recent meta-analysis of perceptual and motor timing has revealed that the two regions of the brain most consistently activated by duration estimation are right prefrontal cortex, in the region of inferior frontal gyrus, and SMA (Wiener et al., 2010a). Intriguingly, these areas have both also been implicated in self-paced, rather than externally triggered, movements (Cunnington, Windischberger, & Moser, 2005; Deiber, Honda, Ibanez, Sadato, & Hallett, 1999; Jahanshahi et al., 1995; Jenkins, Jahanshahi, Jueptner, Passingham, & Brooks, 2000; Rao et al., 1993). However, we find SMA and prefrontal cortex to be activated to an even greater extent by production of temporally specific, rather than random self-paced, intervals (see also Bortoletto & Cunnington, 2010), confirming the key role of these areas in timing of a previously acquired temporal template. Moreover, when the temporal reproduction task was contrasted directly to the temporal orienting task, we found more activation more specifically in the *pre*SMA and in *right*-lateralised inferior frontal and parietal regions, as well as another region consistently linked to duration estimation: the basal ganglia (Buhusi & Meck, 2005; Coull et al., 2011). Both temporal reproduction and temporal orienting depend upon learned temporal templates, but differ in the way in which these templates are used. Our data suggest that preSMA, basal ganglia and right-lateralised fronto-parietal cortices are preferentially engaged when subjects must provide an overt estimate of a learned temporal template.

It is important to note that these activations do not simply reflect the difference between internally generated and externally specified movement (e.g., Jahanshahi et al., 1995; Deiber et al., 1999; Cunnington et al., 2005): our masking procedure ensured they were also present in the comparison of the temporal reproduction task to its self-paced control condition, which similarly requires internal generation of intervals, but of random, rather than timed, intervals. Moreover, when temporal reproduction was compared both to externally specified time intervals (temporal orienting) *and* internally generated random intervals (self-paced control) simultaneously, the interaction analysis revealed selective activation of right inferior frontal cortex. Therefore, preSMA, basal ganglia, right parietal cortex and right inferior frontal cortex are linked not just to internal generation of movement but more specifically to the internal generation of *precisely timed* movement. Moreover, these areas are also activated by perceptual timing tasks (Coull & Nobre, 2008; Coull et al., 2011), in which timing is measured by the accuracy of

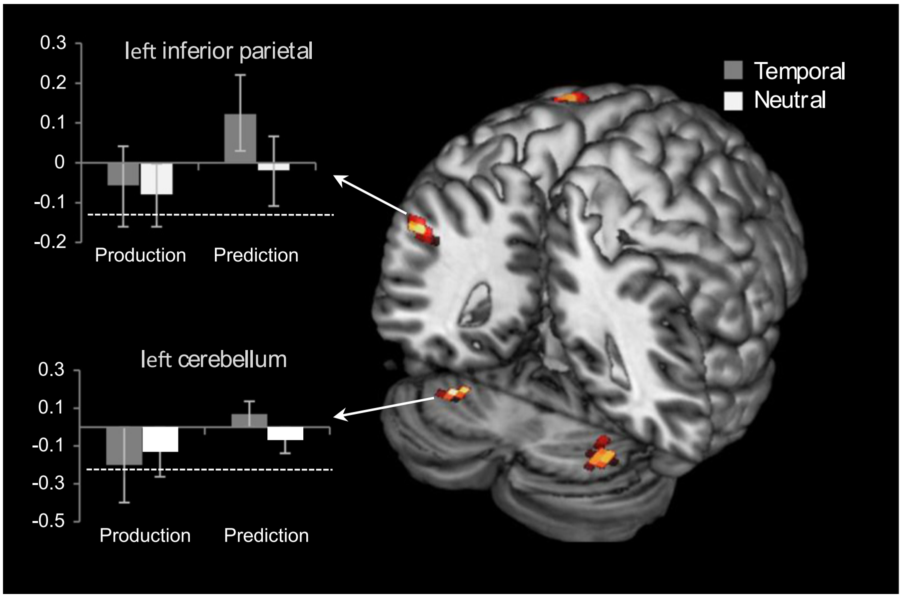

Fig. 5. Temporal prediction minus temporal production. The temporal orienting task preferentially activated left inferior parietal cortex and cerebellum bilaterally. Activity is displayed on the template rendered brain from MRIcron (http://www.mricro.com) with a cut-out to better display the entire network of activation. Effects are thresholded at $p < 0.001$ (uncorrected for multiple comparions). The accompanying plots illustrate the mean level of activity (beta values) in significant clusters during the production or prediction conditions, for temporal (grey) versus neutral (white) cue trials. Dashed lines show the level of activity in each brain area during the fixation baseline condition. Error bars reflect standard errors.

Table 3
Temporal production versus temporal prediction.

Anatomical structure	*x*, *y*, *z* co-ordinates (mm)	*Z* score
(a) Temporal production–temporal prediction		
Right dorsolateral prefrontal cortex	51, 39, 18	4.73*
	48, 36, 24	3.40*
Right inferior frontal gyrus	57, 12, 18	4.50*
Right ventrolateral prefrontal cortex	42, 42, −3	4.13*
Left ventrolateral prefrontal cortex	−51, 42, 6	4.03*
Right pre supplementary motor area	9, 21, 57	4.28*
Right inferior parietal cortex	48, −36, 48	4.00*
Left caudate	−12, 15, 3	3.46*
(b) Temporal prediction–temporal production		
Left dorsal premotor cortex	−21, 9, 69	3.81
Left inferior parietal cortex	−54, −48, 36	4.14
Left middle occipital cortex	−51, −69, −3	4.18
Left cerebellum (VI)	−33, −54, −27	4.19
	−30, −66, −21	3.82
Right cerebellum (VI)	33, −60, −24	3.88

Brain regions differentially activated by the temporal reproduction task (temporal production condition) versus the temporal orienting task (temporal prediction condition). To account for differences in internally-versus externally guided movement in the production versus prediction conditions, the temporal production–temporal prediction contrast was additionally masked by the temporal production–neutral production contrast and, similarly, the temporal prediction–temporal production contrast was masked by the temporal prediction-neutral prediction contrast. Activations are significant at $p < 0.05$, corrected for multiple comparisons across the whole brain or in an anatomically defined region of interest (*).

Table 4
Temporal production and temporal prediction commonalities.

Anatomical structure	*x*, *y*, *z* co-ordinates (mm)	*Z* score
Right dorsolateral prefrontal cortex	45, 39, 21	4.86
Right inferior frontal gyrus	54, 9, 21	4.23
Left inferior frontal gyrus	−51, 9, 39	3.63
Pre supplementary motor area	9, 15, 48	4.39
Right inferior parietal cortex	39, −48, 45	5.36
Left inferior parietal cortex	−33, −48, 36	4.98

Brain regions activated in common by temporal reproduction and temporal orienting ([temporal production–neutral production] masked by [temporal prediction–neutral prediction]). Activations are significant at $p < 0.05$, corrected for multiple comparisons across the whole brain.

non-motor perceptual discriminations. Indeed, timing activates SMA and right prefrontal cortex irrespective of the motor or perceptual nature of the task (Wiener et al., 2010a), suggesting these areas to be particularly crucial for a more general process of timing, rather than timed movement specifically.

4.2. *Implicit measurement of timing by temporal orienting*

In the temporal orienting task, subjects were faster to detect the target after a temporal cue that specified exactly when the target would appear, than after a neutral cue, which conveyed no temporally precise information. These data confirm numerous previous studies using this paradigm and indicate that memorised temporal representations can be used to predict when a future event will occur, thereby accelerating behavioural responses to that event. However, there are two additional behavioural findings that prompt a more subtle interpretation of the data. First, the RT benefit of temporal orienting was evident only at short intervals, not at long ones, consistent with prior studies (Coull et al., 2000; Correa, Lupiañez, & Tudela, 2006; Griffin et al., 2001). Second, the well-known variable foreperiod effect (Niemi & Näätänen, 1981) was evident in the neutral prediction condition, such that RTs were faster the longer the inter-stimulus interval. This pattern is indicative of the hazard function, which models the increasing conditional probability over time that an event will occur given that it has not already occurred. Taken as a whole, these RT data suggest that subjects were able to predict the appearance of the target at the long interval of the neutral prediction condition, when it had not yet appeared at either of the two shorter ones, thereby diluting the benefit of the temporal cue at long inter-stimulus intervals. Yet despite the fact that a degree of predictability was possible in the neutral prediction condition, fMRI contrasts nevertheless yielded significant differences between the temporally cued and neutrally cued prediction conditions, in frontal and parietal cortices bilaterally, SMA and cerebellum. Moreover, when compared directly to the temporal reproduction task, temporal orienting preferentially activated left inferior parietal cortex, left premotor cortex and cerebellum bilaterally. Left inferior parietal cortex and bilateral cerebellum in particular therefore were preferentially activated by a temporal orienting task as compared to either (1) a simple RT task, in which intervals were similarly externally specified but were less temporally predictable or (2) a temporal reproduction task, in which intervals were similarly specified by a temporal template but were internally generated. Our data suggest therefore that left inferior parietal cortex and bilateral cerebellum are preferentially engaged when a temporal template is used to predict the duration of an externally specified interval.

This pattern of activation is largely consistent with prior studies of this task (e.g., Coull & Nobre, 1998; Cotti et al., 2011; Davranche et al., 2011), and with a recent meta-analysis revealing left inferior parietal cortex to be the area most consistently activated by implicit, predictive timing (Wiener et al., 2010b). Left inferior parietal cortex has previously been implicated in motor preparation (Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998), motor intention (Lau, Rogers, Haggard, & Passingham, 2004), and selective orienting of attention to a particular motor act (Hesse, Thiel, Stephan, & Fink, 2006; Rushworth, Nixon, Renowden, Wade, & Passingham, 1997; Rushworth, Johansen-Berg, Gobel, & Devlin, 2003). It may be tempting therefore to interpret activation in the current study as simply reflecting the intention to make a specific motor response at some point in the future. However, we reject this hypothesis for three reasons. First left parietal cortex was activated more by the temporal prediction condition than either the neutral prediction or temporal production conditions, for which motor preparation/intention/attention would be similarly engaged. Second, temporal orienting has previously been shown to activate left inferior parietal cortex even when the laterality of the response, or even the response effector used to register the response, cannot be prepared in advance (Cotti et al., 2011). Third, temporal orienting activates left inferior parietal cortex whether temporally informative cues are used to improve accuracy of perceptual discriminations or speed motor responding (Davranche et al., 2011). Therefore, we believe the temporal orienting task measures a motor-independent attentional mechanism that directs attention to specific moments in time, in a manner analogous to the way that attention can be directed to specific locations in space (Posner et al., 1980), so as to optimise information processing. This notion of attentional selectivity ties in neatly with the first Merriem-Webster definition of timing noted earlier—“the ability to select the precise moment for doing something for optimum effect”.

In addition to left inferior parietal cortex, previous fMRI investigations have shown that lateral cerebellum is activated when the temporal consequences of sensory stimuli can be predicted, either by endogenous temporal cues in the orienting task (Coull & Nobre, 1998) or more exogenously by the dynamics of a moving stimulus (Beudel et al., 2009; O’Reilly, Mesulam, & Nobre, 2008). Moreover, in each of these investigations, the cerebellum was engaged selectively when subjects were predicting the temporal onset of a sensory stimulus, but not its spatial location. In other words, the *temporal* component of the predictive mechanism was crucial for its activation. The cerebellum has long thought to be crucial for more explicit measures of timing (Ivry & Keele, 1989), such as rhythmic movement (Spencer, Zelaznik, Diedrichsen, & Ivry, 2003) or temporal discrimination (Teki, Grube, Kumar, & Griffiths, 2011). Data from the current study however, suggest that the cerebellum, or more specifically lateral cerebellum, is activated to an even greater extent when current temporal information is used to predict the temporal characteristics of future events. Classically, the cerebellum is thought to implement feedforward mechanisms to predict the sensory consequences of motor behavior (Wolpert, Miall, & Kawato, 1998). In the temporal orienting task, by analogy, feedforward mechanisms can be used to predict the sensory (or more specifically sensori-temporal) consequences of visual cues. In other words, current sensory information can be forward modeled to predict when a future sensory event will occur (Schubotz, 2007; O’Reilly et al., 2008).

In the current study, we found activation of not only left inferior parietal cortex and cerebellum when comparing the temporal orienting task to its neutral-cue control condition but also prefrontal cortex bilaterally, right inferior parietal cortex and SMA, areas that are usually associated more with explicit, than implicit, timing (Wiener et al., 2010a,b). Moreover, an analysis of commonalities revealed that right dorsolateral prefrontal cortex, bilateral inferior frontal gyri, SMA, and bilateral inferior parietal cortices were activated not only by temporal reproduction but also by temporal orienting. One possible explanation for this unexpected pattern is that in previous studies subjects were performing orienting tasks only, during the experimental session. By contrast, in the current study, subjects were being asked to also perform more explicit temporal reproduction tasks. A rather general methodological question thus arises: does the global experimental context influence the pattern of activation elicited by a particular task? If one performs Task A interspersed with Task B in one session, but Task A with Task C in another, are the brain regions engaged by Task A identical in both sessions, or are they influenced by contemporaneous cognitive demands? It is already known that the same sensory stimuli can produce distinct patterns of brain activity depending on e.g., attentional (e.g., Corbetta et al., 1990) or mnemonic (Buckner, Koutstaal, Schacter, Wagner, & Rosen, 1998) context. By analogy, we speculate that the same task may produce distinct patterns of activity depending on the experimental context. This fundamental issue is crucial to the field of neuroimaging.

4.3. Conclusions

Although the same temporal representation is used to estimate the duration of a currently elapsing event or to predict the onset of a future event, their direct comparison reveals distinct neural signatures. A right-lateralised fronto-striatal network is engaged when timing is measured explicitly by a temporal reproduction task, in which the motor response marks the offset of an internally generated estimate of interval duration. Conversely, left parietal cortex, left premotor cortex and cerebellum are preferentially engaged when timing is measured implicitly by a temporal orienting task, in which the motor response indicates optimised responding to an externally specified temporally predictable interval. These distinct patterns of neural activity are strongly reminiscent of the anatomical dissociation proposed for action control (Goldberg, 1985), in which basal ganglia and SMA were suggested to underpin internally generated movement but parietal cortex, premotor cortex and the cerebellum to mediate externally triggered movement. By comparing temporal tasks to non-temporal control conditions in the current study, we show that these areas are in fact involved more specifically in the internal versus external control of *timed* movement.

We also highlight a cortical lateralization for the temporal reproduction and temporal orienting tasks in right and left hemispheres, respectively. This pattern of activation using motor timing paradigms complements earlier fMRI findings using a verbal timing paradigm, in which explicit timing of temporally predictable rhythmic speech patterns activated right-sided temporo-parietal areas, while implicit temporal processing of the same stimuli activated their left-sided homologues (Geiser et al., 2008). Electrophysiological data further confirm this hemispheric dissociation: when the contingent negative variation, an index of expectancy, was measured over right frontocentral electrodes it increased steadily with elapsing stimulus duration (Pfeuty et al., 2003) but if measured over left frontal (Pfeuty et al., 2003), parietal (Macar & Vidal, 2003) or premotor (Praamstra et al., 2006) electrodes, it increased only until the learned duration had been reached, even if stimulus presentation itself continued beyond this point. In other words, right-lateralised prefrontal cortex is engaged in timing of current stimulus duration, whereas left-lateralised motor structures are preferentially engaged in predicting future stimulus onset so as to optimize information processing.

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