21 Overview: An Image of Human Neural Timing

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CONTENTS

21.1 INTRODUCTION

The chapters in this book have described current ideas about the functional and neural mechanisms involved in timing behaviors and the temporal judgments of intervals. We optimistically conclude that current and future imaging techniques will soon allow a detailed understanding of the neural circuits involved in interval timing. We can, however, envisage two pitfalls that might slow progress if not treated with caution. The first is the probability that multiple mechanisms are involved in time measurement, and that these are functionally and anatomically discrete. If unrecognized, such duplicity of mechanisms could lead to extreme confusion regarding the locus and function of neural timing systems. The second pitfall is associated with the inherent limitations of neuroimaging techniques and the implications of these for investigations of time measurement. We believe that due to the sluggish and

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indirect nature of some techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), and the spatial imprecision of others, such as electroencephalography (EEG) and magnetoencephalography (MEG), neuroimaging results must be interpreted with great caution when used to investigate a delicate system such as that used for time measurement.

We will address these pitfalls by raising two general questions: First, does all human interval timing depend on the same basic neural system, or are fundamentally different processes used in different timing tasks? Second, to what extent can we expect functional imaging techniques to be useful in describing the detailed function of the mechanisms involved?

21.2 ARE THERE MULTIPLE SYSTEMS FOR INTERVAL TIMING?

Let us start by considering the evidence for multiple timers. A number of authors have suggested that different mechanisms may be used for different types of time measurement, including a distinction between implicit and explicit timing mechanisms (see Hopson, this volume). The length of a measured duration, whether it is timed or defined via movement, and the degree of awareness associated with the temporal judgment have all been suggested as factors that determine which system is used. Further, different authors have independently suggested that the degree of awareness involved in a timing judgment depends on the length of the duration measured, and that the extent to which the motor system is used is determined by the same factor (e.g., Ivry, 1996, 1997; Rammsayer, 1999). To our knowledge, however, no framework has yet combined all three factors into a unified model. We will here propose precisely such a model, adding one further important task characteristic: the *continuousness* of timing.

21.2.1 INTERVAL DURATION AS A DEFINING FACTOR

A variety of different observations have suggested that measurement of intervals in the milliseconds range draws upon a different timer than the measurement of intervals in the multiseconds range. These include differential psychophysical characteristics for temporal measurements at the two duration ranges (Gibbon et al., 1997), differential responses to pharmacological agents (Mitriani et al., 1977; Rammsayer, 1993, 1999; Rammsayer and Vogel, 1992), differential impairment by dual-task scenarios (Rammsayer and Lima, 1991), and differential impairment by specific brain lesions (Clarke et al., 1996). Most recently, some of our own neuroimaging data have shown that different brain regions are active during timing of 0.6- and 3-sec intervals using the same task (Lewis and Miall, in preparation).

21.2.1.1 Attention and Duration

A number of studies have suggested that the measurement of intervals longer than 1 sec requires cognitively controlled and attended processing, while measurement of intervals in the milliseconds range does not require direct attention. These include works showing that active processing in working memory is only required during the timing of longer intervals (Fortin, this volume; Fortin and Breton, 1995; Fortin et al., 1993; Rammsayer and Lima, 1991); temporal processing in the milliseconds range is unaffected by level of arousal (Rammsayer, 1989; Rammsayer and Vogel, 1992), but does depend on sensory processes (Rammsayer and Lima, 1991); and pharmacological agents, such as LSD and mescaline, know to interfere with cognitive processing, disrupting the timing of multiple seconds but not of milliseconds (Mitriani et al., 1977). On the basis of these findings, at least two authors (Mitriani et al., 1977; Rammsayer, 1999) have separately suggested that intervals in the milliseconds range are measured more or less automatically, while intervals in the multiseconds range require active processing under direct cognitive control.

21.2.1.2 The Motor System and Duration

Because the durations used in movement, for instance, in muscle phasing and coordination, fall within the subsecond range, it has been suggested that the timers used to measure these intervals may be located within the motor system. One candidate structure for such involvement is the cerebellum. Observations that the cerebellum is frequently active in tasks involving measurement of subsecond intervals (Belin et al., in press; Coull et al., 2000; Coull and Nobre, 1998; Jancke et al., 2000b; Jueptner et al., 1995, 1996; Kawashima et al., 2000; Lutz et al., 2000; Maquet et al., 1996; Parsons, 2001; Penhune and Doyon, 2002; Penhune et al., 1998; Rao et al., 1997; Roland et al., 1981; Schubert et al., 1998; Schubotz et al., 2000; Schubotz and von Cramon, 2001) and that cerebellar lesions lead to deficits in this type of movement-related timing (Ivry et al., 1988) have led to the idea that this structure may contain subsecond specific timers (see Diedrichsen et al., this volume; Hazeltine et al., 1997; Ivry, 1996). Further, network models of the cerebellum have shown that the structure could feasibly measure subsecond intervals in a number of different ways (De Zeeuw et al., 1998; Guigon et al., 1994; Medina et al., 2000; Perrett et al., 1993). However, the idea that the cerebellum is *exclusively* involved in movement-related timing, or for that matter, in the measurement of subsecond intervals, has been rejected due to evidence showing cerebellar involvement both in perceptual (i.e., nonmotor) timing (Casini and Ivry, 1999; Ivry and Keele, 1989; Nichelli et al., 1996) and in timing of intervals as long 21 sec (Malapani et al., 1998; Nichelli et al., 1996).

Other regions of the motor system, for instance, the premotor cortex, could also be involved in time measurement. One possible mechanism (Lewis and Miall, in preparation) for such involvement is the predictable activity of buildup cells, which has been shown by others (Matsuzaka et al., 1992) to increase or decrease during movement preparation. Central pattern generators (CPGs) offer another possibility. They are known to produce rhythmic activity with periods ranging from under 60 msec to several seconds (Arshavsky et al., 1997) for all manner of rhythmic motor activity, especially locomotor, respiratory, and chewing actions. Brain stem and spinal cord CPGs are modulated by top-down control (Armstrong, 1988) and have projections to cerebral regions (Arshavsky et al., 1978). They therefore have the potential to elicit fMRI-measurable activity in the cortex and cerebellum; cortical pattern generators are also a possibility.

21.2.2 HYPOTHESIS: TWO SYSTEMS FOR TIME MEASUREMENT

21.2.2.1 The Automatic Timing System

We propose that if an interval is measured again and again without change or interruption (as in self-paced finger tapping or perception of an isochronous rhythm), the temporal measurement can be performed by an automatic circuit, which does not require overt attention. This idea is in keeping with a loose interpretation of the motor program concept (Schmidt, 1982), which suggests that all of the information needed for an overlearned movement can be stored in such a way that, once selected and initiated, the movement is essentially performed automatically. Hence, it might be necessary to attend the first cycle or two of temporal production or perception in order to select the appropriate timing mechanism and set it running, but after that, attention should be required only when there is a mismatch between interval and expectation.

Studies of overlearned movement support this model because they have shown that explicit attention is not required for performance of these “automatic” movement tasks (Passingham, 1996). If attention is not required for the movement, then it cannot be required for the related temporal measurements. We therefore propose that a timing system exists for the measurement of brief intervals that are produced continuously and via movement, as in paced finger tapping or execution of other overlearned motor programs. This system likely recruits timing circuits within the motor system that can act without attentional modulation; we will therefore refer to it as the *automatic* timing system. CPGs would provide an ideal mechanism for the automatic system because they are characterized by continuous rhythmic output. The proposed timing mechanisms of the cerebellum would be similarly appropriate to measurement of intervals in automatic movement, as the cerebellum seems to have an important role in automated actions (Nixon and Passingham, 2000).

21.2.2.2 The Cognitively Controlled Timing System

Although the automatic system may be very handy for the nonattended measurement of time under certain very predictable conditions, it is unlikely to serve in all circumstances. For a start, automatic timing may only be possible when the interval in question is repeated over and over without stopping because unpredictable breaks in the sequence may mean that attention is required to restart or reset the timer for each new epoch. Furthermore, there may be limitations on the maximum duration length that the timers used by this system can conveniently measure (De Zeeuw et al., 1998; Guigon et al., 1994; Medina et al., 2000; Perrett et al., 1993). Finally, if the timers of the automatic system lie within the motor cortex or cerebellum, then they may be preferentially used for measurement of intervals that are part of a movement. We suggest, therefore, that intervals longer than a second or so, measured as discrete events rather than as part of a predictable sequence, and not defined by movement, are not appropriate for the automatic system and must draw instead upon a directly attended framework, which we will refer to as the *cognitively controlled* timing system.

Analogous to the overlapping use of the motor system for motor control and timing, we imagine that the cognitively controlled system may use neural circuits that are typically invoked for other cognitive operations, but can be recruited, when appropriate, for storing and processing information for temporal processes. Hence, we envisage that the cognitively controlled timing system draws on flexible, multipurpose cognitive modules within the prefrontal and parietal cortex, and thus shows overlap in functional imaging experiments with many other cognitive tasks. Following from the conclusions of Rammsayer (1999) and Mitriani et al. (1977) that cognitively controlled timing draws on active working memory and attention, we might therefore predict the involvement of the dorsal premotor cortex (PMC) or dorsolateral prefrontal cortex (DLPFC), both of which are known for working memory processing (Petrides, 1994; Smith and Jonides, 1999), and of some portion of the attentional system, currently thought to comprise the parietal, anterior cingulate, and frontal cortex (for a review, see Coull, 1998).

21.2.3 SUPPORTING EVIDENCE FROM THE NEUROIMAGING LITERATURE

If our hypothesis is correct and activity in the automatic and cognitively controlled systems can be measured using neuroimaging techniques, then an analysis of the existing neuroimaging literature should show dissociation in the brain areas activated by time measurement tasks with different characteristics. We have recently undertaken such an analysis, including all neuroimaging studies of human time measurement known to us (Belin et al., in press; Brunia and de Jong, 2000; Coull et al., 2000; Coull and Nobre, 1998; Gruber et al., 2000; Jancke et al., 2000a; Jueptner et al., 1995, 1996; Kawashima et al., 1999, 2000; Larasson et al., 1996; Lejeune et al., 1997; Lutz et al., 2000; Macar et al., 2002; Maquet et al., 1996; Matsuzaka et al., 1992; Onoe et al., 2001; Parsons, 2001; Penhune et al., 1998; Ramnani and Passingham, 2001; Rao et al., 1997, 2001; Roland et al., 1981; Rubia et al., 1998, 2000; Sakai et al., 1999; Schubotz and von Cramon, 2001; Tracy et al., 2000).

To test our hypothesis, it is necessary to examine how the pattern of activity observed in each study relates to the characteristics of the task performed. Accordingly, we have categorized the studies in three ways: (1) according to whether a duration greater than 1 sec was measured, (2) according to whether the measured duration was defined by movement, and (3) according to whether timing was continuous or occurred in discrete episodes. We listed all brain areas that were activated by these studies and recorded which studies showed activity in each. To be inclusive, we used the most lenient subtraction presented (for instance, test vs. rest) rather than a more rigorous control condition, as in Coull and Nobre (1998). In papers presenting multiple data sets, each independent set was included as a distinct study (Coull and Nobre, 1998; Jancke et al., 2000b; Lewis and Miall, in preparation; Rao et al., 1997; Rubia et al., 1998, 2000; Sakai et al., 1999). Finally, we performed a meta-analysis, using all of this information to determine the percentage of studies with certain task characteristics that showed activity in any given area.

The results of the meta-analysis are shown in Table 21.1. Brain areas are listed across the top row, with the laterality of each area listed just below. To reduce the complexity of this table, only those areas that were active in at least 40% of the studies in one of our categories are shown; thus many areas reported to be active in a minority of studies are not included. Different combinations of studies are dealt with in rows 1 to 9, with the relevant category of task characteristics indicated to the left of each row. Thus, row 1 deals with all studies in the review, while row 2 deals only with studies in which all three task characteristics are associated with the cognitively controlled timing system (i.e., temporal intervals of more than 1 sec were measured discretely and not defined by movement). Rows 3 to 5 deal with studies in which two of three task characteristics are associated with the cognitively controlled system; the specific pairings of task characteristics assigned to each row are indicated. Rows 6 to 9 follow a similar model, but deal with studies in which task characteristics are associated with the automatic system. The remainder of the table shows the percentage of the studies in each category (row) that report activity in each brain area, with more commonly activated regions shaded more darkly.

21.2.3.1 Significance of the Meta-Analysis

The first row of Table 21.1 shows no strong consensus regarding the areas involved in time measurement. Only the supplementary motor area (SMA) and right hemispheric cerebellum are active in more than 50% of studies, and no area is active in more than 55% of studies. The remainder of the table, however, shows clearly that a different set of areas is active during tasks associated with the automatic timing system than during tasks associated with the cognitively controlled timing system.

Tasks associated with the automatic timing system most commonly elicit activity in the bilateral SMA and sensorimotor cortex. The right hemispheric cerebellar hemisphere, frontal operculum, superior temporal gyrus, and left hemispheric basal ganglia are also frequently activated in these tasks, though they do not appear so commonly if intervals longer than 1 sec are measured (see row 9). Activity associated with these tasks is also frequently observed in the occipital cortex and left thalamus under some conditions, though these are not as consistent as the other areas. Interestingly, the DLPFC and parietal cortex rarely activate in tasks associated with automatic timing. In tasks associated with the cognitively controlled timing system, however, the right hemispheric DLPFC activates more often than any other area. The left hemispheric cerebellum is also very frequently active in cognitively controlled tasks, while the bilateral intraparietal sulcus (IPS), SMA, and right hemispheric cerebellum are frequently activated as long as the interval measured is longer than 1 sec (see row 4). Similarly, the right hemispheric ventrolateral prefrontal cortex (VLPFC) and inferior parietal lobe are commonly activated as long as timing occurs in discrete epochs.

Perhaps the most important observation to make regarding these results is that the patterns seen when studies are divided based on combinations of task characteristics produce a more coherent picture than when all studies are averaged together. If these studies truly all draw on the same time measurement mechanism, then we

TABLE 21.1
Summary of the Results from Our Meta-Analysis of the Neuroimaging Literature on Time Measurement[a]

	DLPFC	IPS	Insula	IPS	CB Lat.	F. Pole	Basal G.	Operc.	PMC	DLPFC	PMC	VLPFC	CB Med	VLPFC	Inf Par.	S. Par.	S. Par.	Operc.	CB Lat.	Basal G.	Thalamus	Occip.	Occip.	S. Temp.	SMA	SMA	M1	S1	
	R	R	R	L	L	R	R	L	R	L	L	L		R	R	R	L	R	R	L	L	L	R	R	L	R	L	L	**row**
All studies	36	25	25	25	48	25	26	25	33	28	36	25	28	42	47	15	18	31	55	34	20	29	23	28	53	59	47	34	**1**
Cognitively Controlled Timing System																													
Ig + n_mt + disc	100	67	67	33	33	100	33	33	33	33	33	33	67	33	33	50	50	33	33	33	0	0	0	33	0	0	0	0	**2**
Ig + n_mt	63	50	25	50	57	38	38	50	63	13	63	13	29	13	25	29	29	50	71	38	13	0	0	25	43	43	14	14	**3**
Ig + disc	60	60	60	50	50	30	20	30	40	40	40	50	25	60	50	22	22	20	50	30	20	30	30	30	56	56	33	0	**4**
disc + n_mt	63	38	38	13	63	63	50	25	25	50	25	25	63	50	63	17	17	38	38	38	13	13	0	13	17	17	0	0	**5**
Automatic Timing System																													
sh + mt + sq	0	0	0	0	14	14	0	0	14	0	14	0	29	14	29	29	29	43	57	43	43	43	43	71	86	86	100	100	**6**
sh + mt	0	0	0	0	14	14	0	0	14	0	14	0	29	14	29	29	29	43	57	43	43	43	43	71	86	86	100	100	**7**
sh + seq	22	0	0	0	25	22	13	11	22	11	22	11	25	33	33	22	33	44	63	50	38	38	38	67	67	67	89	89	**8**
mt + seq	7	0	14	7	18	21	7	7	14	14	21	14	27	29	43	14	14	21	45	29	21	43	36	36	64	79	83	75	**9**

Note: lg = interval longer than 1 sec; sh = interval shorter than 1 sec; n_mt = interval not defined by movement; mt = interval defined by movement; disc = interval measured noncontinuously (discretely); seq = interval measured continuously (sequentially); CB lat. = lateral cerebellum; F. pole = frontal pole; basal G. = basal ganglia; operc. = frontal operculum; inf. par. = inferior parietal lobe; S. par. = superior parietal lobe; occip. = occipital lobe; S. temp. = superior temporal lobe; M1 = primary motor cortex; S1 = primary sensory cortex.

[a] The table is explained in detail in the text.

might expect a stronger consensus regarding the areas involved than what is shown in row 1. Because different networks appear to be activated by tasks with different combinations of characteristics, this meta-analysis strongly supports the possibility of duplicitous mechanisms for time measurement.

Looking more closely at the specific areas activated, we see that several prefrontal areas believed to contain flexible cognitive modules (Ducan, 2001) are associated with the cognitively controlled tasks, but remain inactive during automatic tasks. These include the DLPFC, VLPFC, IPS, and inferior parietal. Also interesting is the observation that many regions of the motor system (the SMA, sensorimotor cortex, frontal operculum, basal ganglia, right cerebellum, and thalamus) commonly activate during automatic tasks. This pattern supports the hypothesis that what we have termed automatic timing may rely upon mechanisms located within the motor system itself. That some of these areas (SMA and right cerebellum) are also commonly activated in association with the cognitively controlled tasks suggests that use of the cognitively controlled system does not preclude involvement of modules from the automatic system. Before reading too much into these patterns, however, it is important to consider whether the observed activity is all truly associated with timing mechanisms, or whether some of it might be due to non-timing-related confounders.

21.2.3.2 Possibility of Confounders

Because we have reported the most inclusive contrast from each study in our analysis, much of the activity we describe may be due to movement or other task-related nontiming behaviors. Observations that the auditory, visual, and primary sensorimotor cortices are frequently activated in association with automatic timing tasks, for instance, should not necessarily be interpreted as support for the direct involvement of these areas in time measurement, because auditory or visual stimuli and movement in the tasks may have elicited this activity. Based upon the analysis presented thus far, it is impossible to determine whether activities are due to temporal processing or confounding factors. By looking more closely at some of the studies reviewed, however, we can begin to address this question.

If regions of the motor system are active even in those studies of timing where very little movement or movement preparation (or in some cases, no movement or movement preparation at all) occurred during scanning, then we can safely conjecture that their involvement is not merely motor associated, although we cannot rule out the possibility that motor imagery may be involved. This is the case for activity in the right cerebellar hemisphere (Belin et al., in press; Jueptner et al., 1996; Larasson et al., 1996; Roland et al., 1981; Sakai et al., 1999; Schubotz and von Cramon, 2001), right hemispheric frontal operculum (Belin et al., in press; Gruber et al., 2000; Larasson et al., 1996; Roland et al., 1981; Schubotz and von Cramon, 2001), SMA (Gruber et al., 2000; Larasson et al., 1996; Schubotz and von Cramon, 2001), and left hemispheric basal ganglia (Larasson et al., 1996; Parsons, 2001; Schubotz and von Cramon, 2001) during tasks requiring only covert decisions, memory encoding, memory rehearsal of rhythms, or detection of oddballs. Because this activity is not due to movement alone, it may be genuinely linked to timing.

Likewise, several studies have described activity in the temporal cortex during time measurement tasks involving no auditory cues (Coull et al., 2000; Larasson et al., 1996; Rao et al., 2001). Others have shown auditory activity during task phases that come after the cessation of auditory cues, such as continuation of tapping after auditory synchronization (Rao et al., 1997) or memory encoding after presentation (Sakai et al., 1999). It has been suggested (Rao et al., 1997) that this activity may be associated with auditory imagery used for the task, so the observation that the right hemispheric superior temporal cortex is one of the most commonly activated areas during tasks that would be expected to draw on the automatic timing system may well mean that the timing of these intervals frequently draws on auditory imagery. By contrast, the lack of studies in which the occipital cortex is activated in response to tasks that do not involve visual stimuli makes it unlikely that the activity observed here is associated with temporal processing.

Because the tasks associated with the cognitively controlled system are quite different from those associated with the automatic system, it could be argued that activity unique to these tasks is due to some form of confounder. Looking carefully at the literature, however, we see that these regions activate even when a more complete cognitive subtraction is used (Lewis and Miall, 2002, in preparation; Rao et al., 2001); hence, their involvement very likely relates directly to temporal processing. Because these areas include regions known for involvement in both working memory (DLPFC) and attention (IPS and inferior parietal lobe), this observation conforms to predictions regarding the cognitively controlled system (for further details concerning activations specific to interval timing, see Hinton, this volume; Hinton and Meck, 1997; Morell, 1996; Pouthas, this volume).

21.2.4 SUMMARY

This section has explained why we believe that different mechanisms are recruited for the measurement of time in different tasks. Both an automatic timing system, which is used to measure subsecond intervals when these are measured continuously via movement, and a cognitively controlled system, which is recruited for temporal measurements that cannot easily be performed by the automatic system (i.e., those of suprasecond durations, measured discontinuously, and not via movement), have been described. Evidence from lesion studies as well as from studies of motor circuitry suggests that the motor system could perform the task of the automatic system, while the flexible cognitive modules of the prefrontal and parietal cortices are more suited to the task of the cognitively controlled system. Hence, we have hypothesized that there may be a dissociation in functional locus for these two systems. A meta-analysis of existing neuroimaging studies of time measurement has shown that when the literature is taken as a whole, there is no strong consensus regarding the areas most commonly involved. If the studies are divided based on the characteristics of the task performed, however, a clear dissociation is seen between areas activated by automatic-associated and cognitive control–associated tasks. The former frequently activate parts of the motor system (SMA, sensorimotor cortex, cerebellar hemisphere, frontal operculum, and basal ganglia) as well as the superior temporal gyrus, but rarely activate the dorsal prefrontal cortex or parietal.

The latter frequently activate the frontal and parietal cortex (DLPFC, VLPFC, inferior parietal, and IPS), with additional activity in the cerebellum and SMA. This analysis supports the possibility that functionally and anatomically distinct systems for time measurement exist within the human brain and illustrates how failure to recognize this multiplicity can lead to confusion in the literature. Future attempts to investigate the neural locus of time measurement should therefore take the possibility of multiple systems into account, both when choosing a task to study and when interpreting their findings or the findings of others.

21.3 NEUROIMAGING AND THE TIME MEASUREMENT SYSTEM

We, like many others, are using functional magnetic resonance imaging as a tool to study human timing. Our survey of the literature shows that more than 25 imaging papers of interval timing have been produced so far, and like any other topic to which neuroimaging has been applied, we expect many more to follow in the next few years. Therefore, in this section we aim to discuss some of the conceptual limits to the imaging of human timing and explore ideas about what these studies may be expected to achieve. In the limit, any single functional imaging technique on its own (whether fMRI, PET, MEG, or EEG) is unlikely to be sufficient. As the bulk of this book has demonstrated, these imaging techniques must be complemented by patient studies, lesion experiments, drug interventions, and electrophysiological recording studies, spanning the range from system to cellular analyses. Nevertheless, neuroimaging by itself will prove an important tool (see Hinton, this volume; Pouthas, this volume).

21.3.1 The Functional Anatomy of Time Measurement

The first level of imaging analysis is to simply identify the areas involved in timing tasks (see Hinton, this volume; Meck, this volume; Meck and Benson, 2002; Sakata and Onoda, this volume). In many of the studies we have reviewed, this is achieved by using block analysis of timing tasks contrasted with nontiming control conditions. In these studies, activity is measured in blocks of 30 or more seconds at a time, so there is no real temporal resolution to the data. More specific localization of timing components can be achieved with event-related imaging techniques, but there are also clear limits on this technique, as we will describe below. The second level of attack is the use of imaging techniques to explore interactions between the timing subsystems or to approach the neural mechanism of their functions. At this level, we must consider whether the operation of each component in a time measurement system depends on neural mechanisms that we can actually detect. The most basic measures afforded by functional imaging studies are the changes in the activity of neural populations from one moment to another. In PET and fMRI, these are detected using the resulting changes in local blood flow or oxidation; thus, if a component of the time measurement system does not cause a significant change in metabolic cost, we may not detect its presence.

The most obvious example of this problem is the time-dependent process or “clock” central to the timing system, perhaps a “ticking” oscillator or similar circuit:

if the clock is always ticking, but other components (e.g., the accumulator) only intermittently use its output, it may be very difficult to detect this process using neuroimaging. One solution may be to selectively speed or slow the clock, independent of all other neural processes (Meck, 1996), and detect the changing activity that correlates with these alterations. However, it is possible that a neural clock circuit could be accelerated or slowed without leading to gross change in metabolic load: if the duty cycle (active to inactive states) is kept constant, then the main metabolic costs (e.g., dendritic processing and some contribution to ionic pumping across the membrane after spike activity) could be nearly identical in a cell or a circuit oscillating slowly or rapidly. Because we do not yet know what form of clock ticking, if any, is used in the timing process, we cannot predict whether the changes in neural activity associated with changes in clock speed would be imageable.

MEG and EEG techniques complement PET and fMRI with regard to temporal precision, as they can detect neural activity in the millisecond range (for a discussion of how EEG and PET techniques can be used to inform each other, see Pouthas, this volume). Hence, for example, these techniques would be invaluable for detecting a rhythmically active clock, as they could differentiate between the signals of different clock rates. However, these techniques also have their limitations, as both depend on the synchronous activity of a group of aligned neurons (or rather, their dendritic processes) and are insensitive to currents in tissue that are oriented perpendicular to the scalp. They are also insensitive to deep brain sources. One could certainly imagine time measurement processes that would be invisible to MEG or EEG.

21.3.2 IMAGING THE TIMER COMPONENTS

Bearing knowledge of the limiting characteristics of neuroimaging techniques in mind, let us think about the basic components of the scalar expectancy theory (or scalar timing) model (see Church, this volume; Gibbon et al., 1984) and ask how we can identify the mechanisms and the neural loci of each. The various components are the time-dependent process (the pacemaker), the local memory stores (the accumulator and the reference memory), and the comparator, as well as sensory input and modulatory output systems. Temporal information processing would also include the attentional system and the cognitive output structures or the motor systems using information from the timer.

For much of the imaging literature, the sensory input systems are treated as items of secondary interest. PET and fMRI depend on contrasting different behavioral states, and thus any process in common to the two states is not visualized. Hence, it is typical to attempt to balance the contribution of systems of secondary interest between the timing task and the control (baseline) task. Sensory inputs or motor outputs, if carefully balanced, do not confound the final results of the imaging study. However, this strategy has the implicit danger that it may obscure data suggesting that the timing functions actually depend on the specific sensory structure. Thus, if the time-dependent process is active from the start of the sensory stream, then it will be nearly impossible to distinguish between these two using functional neuroimaging. However, because interval timing is easily achieved across the gaps between delimiting stimuli, or by using stimuli in different modalities, this should not pose a real problem for the investigation of non-sensory-specific timing systems. The possibility that parts of the motor system may be obligatory components of some timing operations is less easy to dismiss.

In this vein, we have discussed above and other authors in this book have highlighted the fact that motor areas of the brain (cerebellum, basal ganglia, and premotor cortical areas) are strong candidates for involvement in interval timing tasks (see Diedrichsen et al., this volume; Hinton, this volume; MacDonald and Meck, this volume; Malapani and Rakitin, this volume; Matell et al., this volume; Pang and McAuley, this volume). If these circuits are recruited only for some timing operations, such as those in which repetitive motor outputs are needed (e.g., rhythmic tapping), then separation of motor timing and motor execution becomes very difficult. The wealth of evidence suggesting that imagined movement or mental rehearsal does activate the motor system compounds this difficulty because implicit use of motor systems to measure time, even without active movement, could cause neural activity. In the limit, we should perhaps ask if the attempt to separate timing from movement is sensible, if indeed the movement, or its internal rehearsal or planning, is what is actually used as the timing signal.

To approach this problem, it would be useful to know whether different motor timing circuits were selectively recruited for specific timing tasks. It seems likely that the neural operations involved in selecting or recruiting pattern-generating circuits during the first epoch of repeated, subsecond interval measurements would be detected by current functional imaging techniques. We have evidence (Lewis et al., under review) that this is the case, as areas known to be involved in movement selection show activity at the onset of different rhythm epochs, but appear inactive during the immediately following rhythm production. We believe that timing circuits are therefore actively recruited, or adjusted to the target intervals, but then continue to cycle with little additional cost.

Let us think about what this observation might mean at a finer level. In an earlier model of the neural mechanism of timing (Miall, 1989), it was suggested that different neural oscillators could be selected and combined to provide an interval timing system. Only the weighted output of the multiple oscillators could be said to encode a specific interval: many oscillators were active in each interval, and the selectivity of the system was generated by synaptic weighting of a subset of these to some output unit. Hence, the activity of this output unit, excited at the critical moment by the synchronous activity of its oscillating inputs, would easily be detectable, but the ongoing activity of the population of oscillators would not (for an extension of this model, see Matell et al., this volume; Meck, this volume). Miall (1989) proposed that additional neural machinery might be used to synchronize the oscillators at the start of each timed interval, but beyond that, the system could free-run with no additional metabolic cost. Again, this suggests that the neural activation required to start, select, or synchronize the oscillator system might be imageable, but its ongoing activity would be hard to detect. If the oscillator population itself became active at the start of each interval, from an inactive state, this should also be detectable, but this scenario seems unlikely.

The accumulator as described by Gibbon et al. (1984) is probably the most easily detectable timing element, as by definition its activation changes throughout each interval and must be reset. A naïve viewpoint might therefore be that the bulk of the imaging data produced so far reflects the activation of this accumulator circuit. However, using carefully designed baseline conditions, it should be possible to dissociate the accumulation process from related events such as the comparison or decision processes. The reference memory store in which the previous intervals are recorded might also seem easy to image, as it would accumulate traces of the previous intervals, changing with experience of the target interval. It is striking to us that cortical prefrontal areas are prominently active in cognitively controlled timing tasks: these may be the systems in which a trace of activity is set up and changes throughout the timed interval. Overlap of the observed regions with areas known to be involved in working memory is also important.

In contrast, it is likely that EEG and MEG techniques would be poor for studying the accumulator activity. A basic model of the accumulator (Miall, 1993) and a recent, more elaborate model (Koulakov et al., 2002) suggest that it may be made up of a population of independently active cells, and thus would not have the synchronous behavior necessary to cause a large signal. Some MEG analysis techniques have made use of the switch from synchronous activity in the idle state to desynchronized activity in an active state (Singh et al., 2002), and this could prove useful.

Lastly, the comparator function would appear to be difficult to detect. As a singular event at the end of each interval, comparison would contribute rather little to the overall signal within a typical block design imaging study. Event-related imaging designs would allow temporal separation of different events within the timing task if their occurrence could be varied with respect to each other. In such studies, the blood oxygenation signals are correlated with specific event times, for example, with the onset and offset of each interval, as long as these events are themselves uncorrelated (Buckner et al., 1996). Unfortunately, the comparator process will almost always be time-locked to other events, such as the initiation of whatever action is required at the end of the trial. For example, if the subject was asked to respond at the end of the target interval, the comparison operation, the transfer of that interval to reference memory, the resetting of the accumulator, possibly the stopping of the pacemaker clock, and the initiation of the response would all be very close in time. Better temporal differentiation using MEG or EEG, where events that cannot be decoupled could be temporally ordered, might provide a solution to this problem if it were clear what the order of their occurrence must be (see Sakata and Onoda, this volume).

21.4 CONCLUDING REMARKS

In summary, we can envisage some specific problems in functional imaging of human timing systems at present. Many of these are rooted in the intrinsic limits of PET and fMRI, with their dependency on sluggish and indirect measures of relative change in blood flow and oxygenation levels, rather than direct neural measures. EEG and MEG techniques in turn have limits in spatial resolution and are relatively insensitive to central brain structures. However, several features of the review presented in Table 21.1 encourage us. First, it is now clear that functional imaging can detect multiple areas of the human brain associated with time measurement tasks, and while the variation between different experiments is high, some areas activate consistently in association with timing tasks having specific characteristics and are thus strong candidates for further exploration. Second, we have argued that much of the variation between the experiments may be due to the diversity of timing tasks used — these tasks may even be drawing on quite separate systems. We can draw an analogy here with functional localization within the visual cortex. When an obvious, but inappropriate stimulus (such as a natural scene) is used, one gets the impression that the visual areas of the brain are horribly difficult to distinguish functionally. When a more appropriate stimulus is used (moving bars of light or drifting fields of dots), the organization becomes apparent. Thus, when appropriate timing tasks are used, the relationships between neural locus, neural mechanism, and timing behavior may become clear. Third, the enormous expansion of techniques now available to tackle the problem of time measurement, including imaging, multielectrode unit recording, drug studies, gene knockouts, transcranial magnetic stimulation, and the rest, means that a combined approach is both feasible and fruitful.

We believe that the most immediate future goal in the study of time measurement is to determine which timing systems are used under which specific circumstances. Once this has been established, the imposing arsenal of techniques at our command will facilitate further examination of the detailed functioning of each time measurement system. We therefore optimistically believe that with the aide of these methods, we will soon succeed not only in finding the timers for which we search, but also in understanding how they work.

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