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5-Hydroxytryptamine and interval timing behaviour

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Abstract

Interval timing behaviour is revealed by *prospective*, *immediate* and *retrospective* timing schedules. Prospective timing tasks are used to study intertemporal choice (choice between outcomes occurring after different delays), immediate timing tasks to study temporal differentiation (temporal regulation of the animal's behaviour) and retrospective timing tasks to study temporal discrimination (discrimination between the durations of external events). Central 5-hydroxytryptamine (5-HT) depletion promotes preference for small early reinforcers over large delayed reinforcers, possibly by facilitating the time-dependent degradation of reinforcer value. Central 5-HT depletion retards the learning of temporal differentiation, and increases the variability of timing in some immediate timing tasks; however, it does not impede (in some cases it facilitates) the acquisition of temporal discrimination. Attempts to ascribe all the effects of 5-HT depletion on timing to a single behavioural process have been unsuccessful, although disinhibition of switching between operant responses may account for some of the findings. Acute treatment with drugs affecting 5-HTergic mechanisms alters timing behaviour in qualitatively different ways in different timing schedules, casting doubt on the idea that the effects of these drugs are mediated by interaction with a unitary timing process. The receptors that mediate 5-HT's putative involvement in interval timing behaviour remain to be identified.

Keywords: 5-Hydroxytryptamine; Interval timing behaviour

1. Introduction

"Interval timing" refers to the ability of animals to adapt their behaviour in accordance with the temporal regularities in their environments. It is conventionally distinguished from endogenous rhythms, such as circadian and oestrus cycles. The principal differences between these two types of timing have been reviewed by Carr and Wilkie (1997) and Gibbon et al. (1997a). One feature of particular interest is the high level of adaptability, coupled with relatively modest precision, that characterizes interval timing, which stands in contrast to the relatively rigid, but very precise timing that characterizes biological timing. For example, animals can be trained to discriminate intervals whose durations range from milliseconds to hours, with a rather uniform coefficient of variation (a measure of precision: see below) of .1–.4, whereas the entrainment range of the circadian cycle is only about 20%, with a coefficient of variation of .01–.05 (see Campbell, 1997; Gibbon et al., 1997a).

In contrast to the wealth of knowledge that has accrued in recent years about the neural substrates of endogenous rhythms (see van Esseveldt et al., 2000), relatively little is known about the anatomy and physiology of interval timing. There is evidence that the cerebellum and the basal ganglia play important roles in interval timing (O'Boyle, 1997; Harrington and Haaland, 1998), possibly serving as components of an integrated "timing circuit" (Gibbon et al., 1997b). The ascending dopaminergic and 5-hydroxytryptaminergic (5-HTergic) pathways are believed to impose some "fine tuning" on the operation of this hypothetical timing circuit (Gibbon et al., 1997b; Hinton and Meck, 1997). This review deals specifically with the possible involvement of 5-HTergic mechanisms in interval timing behaviour; detailed reviews of the putative role of the dopaminergic projection in interval timing have been provided by Meck (1996), Hinton and Meck (1997) and Mattell and Meck (2000). We will start with a brief

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overview of some important features of interval timing behaviour, and then introduce some of the more influential theoretical models of timing processes. Then, we will review empirical findings on the effects of pharmacological manipulation of the 5-HTergic system upon timing behaviour. Finally, we will consider whether the extant data favour a significant involvement of the 5-HTergic projection in timing processes, and discuss possible implications of the data for current theoretical models of interval timing.

2. Basic phenomena of interval timing

Interval timing can be revealed by many types of reinforcement schedule. Killeen and Fetterman (1988) and Killeen et al. (1997) developed a taxonomy of timing schedules based on the relationship between the animal's timing response and the interval being timed. According to this taxonomy, the three main classes of timing schedule are (i) *retrospective* timing schedules, in which the subject is trained to emit discriminative responses depending upon the duration of an interval which has already elapsed when the response is made; (ii) *immediate* timing schedules, in which the subject's behaviour comes under the control of time during an ongoing interval and (iii) *prospective* timing schedules, in which the animal is trained to emit discriminative responses on the basis of intervals which follow the responses. Clearly, these different types of schedule entail widely differing reinforcement contingencies. However, timing behaviour maintained by these schedules has certain features which transcend the procedural differences by which the schedules are distinguished.

The interval bisection procedure (a retrospective timing schedule) is a convenient vehicle for illustrating the ubiquitous features of interval timing performance. The subject is trained to emit one response after a short presentation and a different response after a longer presentation of a stimulus. After accurate temporal discrimination has been acquired, the subject is tested with intermediate durations and, in each case, the percentage emission of the response appropriate to the longer duration (%L) is determined. The function relating %L to stimulus duration (the psychophysical or psychometric function) is generally sigmoid in shape (see Fig. 1), and may be used to derive two key indices of timing: a measure of central tendency (T_{50}) and a measure of variability (the limen). It is well established that, irrespective of the schedule used to generate it, interval timing performance conforms to Weber's law; that is, the Weber fraction (a measure of the relative precision of timing: limen/T_{50}) is approximately constant across a wide range of time intervals (Gibbon, 1977, 1991). This observation carries the implication that psychometric functions obtained using different reference durations are superposable when duration is rescaled according to the empirical value of T_{50} (the *scalar* property of timing). It should be noted, however, that superposability applies only to psychometric functions obtained using the same timing schedule. The exact form of the psychometric function, and the definition of the timing indices which it generates, differ somewhat between different types of timing schedule (Grondin, 2001; see below).

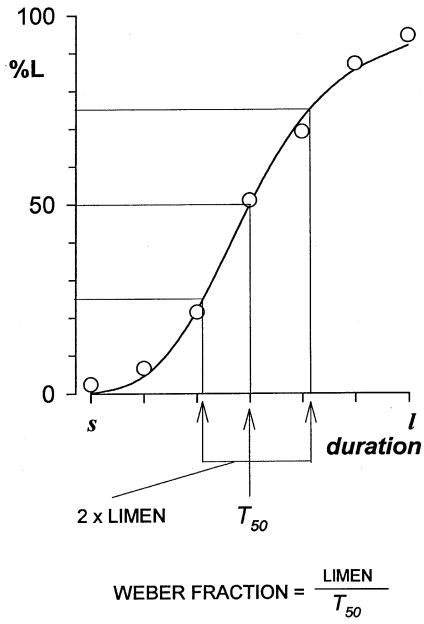

Fig. 1. Example of a psychometric function used to analyse interval timing behaviour ("interval bisection" task: see text for details). The subject is first trained to respond on one of two levers (A and B) depending on the duration of stimulus ("short" [s] vs. "long" [l]). After stable discrimination has been attained, probe trials are introduced using stimuli of intermediate durations and, in each case, percent choice of the lever appropriate to the "long" stimulus (%L) is recorded. *Ordinate*: %L; *abscissa*: stimulus duration. The curve is a logistic function, which is used to derive the indices of central tendency and variability of timing: (i) The bisection point (indifference point), T_{50}, is the duration corresponding to %L = 50; (ii) the Weber fraction is the ratio of the limen (half the difference between the durations corresponding to %L = 25 and %L = 75) to T_{50}.

3. Theoretical models of timing behaviour

Most current models of timing posit an "internal clock" whose operation underlies timing behaviour, and whose properties help to determine the quantitative features of timing performance. The hypothetical clock is deemed to constitute one part of a three-component system: the *clock* is assumed to produce an output which is related (not necessarily linearly related) to the interval duration; previously generated outputs are stored in *reference memory*; and a *comparator* assesses the similarity between the current output of the clock and the remembered duration (Wearden, 1999; Matell and Meck, 2000). The nature of the hypothetical clock differs between different timing models. Matell and Meck (2000) identify three principal types of hypothetical internal clock, based on (i) pacemaker–accumulator,

(ii) process–decay and (iii) oscillator/coincidence–detector mechanisms. Fig. 2 summarizes the pacemaker–accumulator model championed by Gibbon, Church and their associates, Scalar Expectancy Theory (SET: Gibbon, 1977, 1991; Gibbon and Church, 1990; Church et al., 1992). The hypothetical internal clock is deemed to consist of an endogenous pacemaker that generates pulses at a constant mean rate, and an accumulator that counts the pulses. The current status of the accumulator is copied to working memory. When timing an interval, the organism is assumed to reset the counter at the start of the interval, and then to make repeated comparisons between the current number of pulses in working memory and a sample of the number of pulses corresponding to the criterion interval, that has been laid down in the animal's reference memory during training. When the current number of pulses is approximately equal to the standard, the animal emits the appropriate timing response.

Wherein lies the source of variability of timing behaviour is a question that continues to exercise theoreticians in this area. Random fluctuations in pacemaker period cannot, on their own, account for scalar timing; such fluctuations would generate a coefficient of variation of timing behaviour that would decline as a function of the duration being timed, in contradiction of Weber's law (see Wearden, 1999; Killeen and Taylor, 2000). Proponents of SET have postulated variance in memory (Gibbon, 1992) or decision (Wearden, 1999) processes as the source of scalar variability of timing, whereas others have argued for a pivotal role of counter error (Killeen, 2001; Killeen and Taylor, 2000). Although the problem may appear esoteric, it is not irrelevant to the psychopharmacology of timing,

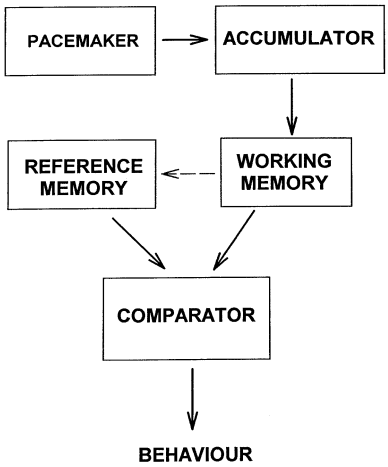

Fig. 2. Diagram of the "internal clock" purported to underlie interval timing. According to pacemaker-based models of timing, an endogenous oscillator generates pulses at a constant mean rate, and the accumulator counts the pulses. In timing an interval, the organism is supposed to compare the current number of pulses (in its working memory) to a sample of previously recorded numbers of pulses (stored in its reference memory). If the current number is approximately equal to the sample from reference memory, the organism emits the appropriate timing response.

because neurobiological interventions (including manipulation of 5-HTergic function: see below) can alter the variability of timing performance. An understanding of the mechanisms that determine variability could aid the interpretation of the effects of such interventions on timing behaviour.

A major competitor to SET is the Behavioural Theory of Timing (BeT: Killeen and Fetterman, 1988; Killeen et al., 1997; Machado, 1995). Like SET, BeT posits an endogenous pacemaker. However, unlike the essentially cognitive mechanisms proposed by SET, BeT assumes that the pacemaker's role is to drive the organism through a series of "behavioural states." During training under a timing schedule, particular behavioural states become associated with the criterion timing response; thus, a well-trained animal comes to emit the criterion response when it arrives at the appropriate behavioural state. A unique feature of BeT is its assumption that the period of the pacemaker is inversely related to the rate of reinforcement provided under the timing schedule; since a rapidly operating pacemaker should allow more accurate timing than a slowly operating one (Killeen et al., 1997), this feature of BeT correctly predicts that under steady-state conditions the Weber fraction should decline as a function of reinforcement density (Bizo and White, 1994a,b, 1997).

In contrast to pacemaker–accumulator theories, the clock posited by process–decay theories relies upon the time-course of decay of neural activation following a stimulus onset. For example, Staddon and Higa's (1999) Multiple Time Scales (MTS) model is based on a habituation process analogous to the sequential decay functions of a set of cascading resistor–capacitor integrators (see also Higa and Staddon, 1997). Another process–decay theory is the neural network model of Buhusi and Schajuk (1999), which proposes that salient stimuli evoke multiple memory traces of different amplitudes and time-courses. These models have been successfully applied to a wide range of timing phenomena in classical and operant conditioning. However, to date, they have not addressed the issue (some would say, the crucial issue: Gallistel, 1999; Gibbon, 1999) of the variability of timing.

Oscillator/coincidence detection models constitute a further class of timing theories. Church and his colleagues (Church and Broadbent, 1990, 1991; Collyer and Church, 1998) developed a connectionist model based on multiple oscillators with different periods; according to this model, time is represented by the vector of half-phases of several oscillators. According to Matell and Meck (2000), the multiple oscillator model lacks biological plausibility because of its requirement of unfeasibly long oscillator periods. Matell and Meck's (2000) striatal beat frequency (SBF) model, an elaboration of an earlier model proposed by Mial (1989), overcomes this problem. The model places the clock in a cortico-striato-thalamo-cortical circuit. Neurones in the corpus striatum are purported to respond to the coincident oscillating input from many

neocortical neurones. Matell and Meck (2000) have shown that such a mechanism, in which the input oscillations have periods in the range of tens or hundreds of mill-seconds, can generate timed output with periods of tens of seconds or more.

Two features of internal-clock models are especially pertinent to psychopharmacological analyses of timing behaviour. Firstly, it is assumed that during training in a timing task, the timed response is triggered by a particular status of the clock; if for any reason the clock is speeded up or slowed down, then the response will occur at an inappropriate time. This may be illustrated by reference to SET. According to this theory, the period of the pace-maker is crucial to timing performance only inasmuch as it determines the number of pulses that can occur within a given time period. At any given time-point, it is the accumulated number of pulses that determines whether an appropriate timing response will be emitted. Thus, if the period of the pacemaker is suddenly decreased or increased (for example, in response to an acute pharmacological intervention), the timing response will be emitted too early or too late, respectively. However, if the altered period of the pacemaker is maintained and training under the timing schedule continued, the timing response should gradually revert to its original point in time, due to readjustment of the accumulator criterion (see Hinton and Meck, 1997). This principle has been invoked to explain the transient effects of psychostimulant drugs (Maricq and Church, 1983; Maricq et al., 1981) and changes in reinforcement rate (Bizo and White, 1995; Machado and Guilhardi, 2000) on the locus of the psychometric function.

A second notable feature of the models mentioned above is that they generally posit a single integrated mechanism which subserves timing behaviour in all types of timing schedule. This is not to say that interval timing behaviour is not influenced by "nontiming" factors. As discussed above, internal-clock models contain mnemonic and decision components in addition to the hypothetical clock, which may be susceptible to the influence of sensory, motor, motivational and, no doubt, many other factors These influences may impinge on different components of the hypothetical timing apparatus. Nonetheless, as Zeiler (1998, p. 91) has observed, "a universal timing mechanism leads to the expectation that the laws of time estimation would be similar over a range of specific situations." Grondin (2001, p. 37) makes a similar point: "Weber's law is linked to the idea that there is one central timekeeping mechanism; it justifies the single-timing hypothesis." These authors have pointed to consistent differences between the psychometric functions, and, in particular, the sizes of the Weber fractions, obtained with different timing tasks, and argued that such differences indicate that different types of timing task may entail different types of timing process. We will have occasion to return to this argument in the final section of this review.

4. 5-HT and timing behaviour: review of empirical findings

4.1. Prospective timing schedules

Prospective timing schedules entail the control of behaviour by events that follow the response by a specified time interval. In most instances, the controlling event is reinforcement, and thus tasks of this type frequently take the form of *intertemporal choice* schedules, in which the subject chooses between reinforcers differing in magnitude and delay. Wogar et al. (1993a), Al-Ruwaitea et al. (1999a) and Mobini et al. (2000b) found that destruction of the ascending 5-HTergic pathways by intraraphe injections of the selective neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) promoted choice of the smaller and earlier of two reinforcers in discrete-trials lever-pressing tasks, and Thiébot (1992) found that the 5-HT depleting agent *p*-chlorophenylalanine had a similar effect in a T-maze task in which reinforcers of different sizes were presented after different delays in the two goal boxes. Acute treatment with drugs that interact with 5-HTergic mechanisms has also been found to affect intertemporal choice in some experiments. For example, Poulos et al. (1996) reported that the 5-HT-releasing agent *d*-fenfluramine promoted choice of the larger and more delayed of two reinforcers. Bizot et al. (1988) found that 5-HT uptake inhibitors had a similar effect; however, Charrier and Thiébot (1996) and Evenden and Ryan (1996) found that 5-HT uptake blockers did not alter choice between food reinforcers differing in magnitude and delay. Evenden and Ryan (1999) recently found that the 5-HT_2 receptor agonist (±)2,5-dimethoxy-4-iodoamphetamine (DOI) increased preference for the smaller and more immediate of two reinforcers, whereas selective antagonists of 5-HT_{1A}, 5-HT_2 and 5-HT_3 receptors had no significant effect upon choice. Interestingly, Brunner and Hen (1997) found that mice lacking 5-HT_{1B} receptors showed weaker preference for the smaller and earlier of two reinforcers than wild-type control mice, a difference which Brunner and Hen attributed to greater sensitivity to reinforcer size in the 5-HT_{1B} knockout mice.

A shortcoming of most of these studies is that they failed to clarify whether the effects of the pharmacological interventions reflected changes in sensitivity to *delay* of reinforcement or changes in sensitivity to reinforcer *size*. Ho et al. (1999) have proposed a method for distinguishing between these two possibilities. The method is based on the quantitative determination of indifference delays. For example, if a subject is required to choose between a small reinforcer delivered after a short delay and a larger reinforcer delivered after a longer delay, the latter may be varied systematically until the subject becomes indifferent between the two reinforcers, in other words, until it chooses the two reinforcers equally often. It is known that the indifference delay to the larger reinforcer is linearly related to the delay imposed on the smaller reinforcer

(Mazur, 1987), and this linear relation may be used to derive estimates of the subject's sensitivity to reinforcer magnitude and delay (Ho et al., 1999). Mobini et al. (2000a) adopted this approach in order to examine the effect of central 5-HT depletion on intertemporal choice. Mazur's (1987) adjusting-delay schedule was used to determine indifference delays to a large reinforcer (two food pellets) corresponding to a range of delays to a smaller reinforcer (one food pellet). The lesion produced a parallel displacement of the linear indifference function, shortening the indifference delay to the larger reinforcer at all delays to the smaller reinforcer. Since this pattern of effect is uniquely predicted by an increased sensitivity to delay (Ho et al., 1999), Mobini et al. (2000a) suggested that 5-HT depletion resulted in accelerated delay discounting (i.e., it increased the rate at which reinforcers become devalued as a function of delay).

4.2. Immediate timing schedules

Immediate timing schedules require the subject to respond differentially during an ongoing interval; accordingly, the behaviour maintained by these schedules is known as *temporal differentiation*. The start of the interval may be marked by the subject's own behaviour (as in the case of interresponse time schedules), or may be heralded by the onset of a signal (as in the case of the fixed-interval peak procedure).

4.2.1. Interresponse-time schedules

One of the best known immediate timing tasks is the delayed response task specified by *interresponse-time-greater-than-t* (IRT > *t*) schedules (also known as differential-reinforcement-of-low-response-rate [DRL] schedules). In these schedules, reinforcer delivery follows every response that is separated from the previous response by an interval of at least *t* s (see Zeiler, 1977). Convenient measures of IRT > *t* schedule performance include the overall response rate and reinforcement rate, which obviously tend to be inversely related (e.g., McGuire and Seiden, 1980), and the ratio of these two measures ("efficiency") (e.g., Fletcher, 1995). Although such measures can detect the effects of acute drug treatment and some brain lesions, they neglect the temporal structure that characterizes behaviour maintained by IRT > *t* schedules. This temporal structure is revealed by the frequency distribution of IRTs, which is most commonly bimodal, the lower mode representing very short ("burst") IRTs, and the upper mode approximating the criterion IRT, *t* (Harzem, 1969; Platt, 1979). The relation between the upper mode ("peak IRT"), and *t* is a power function (power ≈ 0.8), and the coefficient of variation (Weber fraction) is roughly constant across a wide range of values of *t* (see Harzem, 1969; Platt, 1979; Wearden, 1990). The peak IRT and coefficient of variation provide convenient measures of the central tendency and variability of temporal differentiation (e.g., Wogar et al., 1992, 1993b). More complex analytic methods have also been recommended, based on deviation of the IRT frequency distribution from randomness (Richards and Seiden, 1991) and exponential or Weibull-distribution functions fitted to the cumulative IRT probability data (Stephens and Voet, 1994).

Destruction of the 5-HTergic pathways by injection of 5,7-DHT into the cerebral ventricles (Jolly et al., 1999) or by direct injection into the median and dorsal raphe nuclei (Wogar et al., 1992, 1993b; Fletcher, 1995) impedes the acquisition of temporal differentiation and disrupts established temporal differentiation in well trained animals; this disruption takes the form of a shortening of the peak IRT and an increase in the size of the Weber fraction (Wogar et al., 1992, 1993b; Fletcher, 1995; Jolly et al., 1999). This effect has been observed with both short (15 s: Wogar et al., 1992, 1993b; 20 s: Fletcher, 1995) and long (72 s: Jolly et al., 1999) criterion IRTs. The effect of total ablation of the ascending 5-HTergic pathways can be reproduced by selective destruction of the median, but not the dorsal, raphe nucleus (Fletcher, 1995). Although both acquisition and steady-state IRT > *t* schedule performance are disrupted by 5-HT depletion, the acquisition of temporal differentiation appears to be especially vulnerable (e.g., Wogar et al., 1992, 1993b; see Al-Ruwaitea et al., 1997b). The slow development of temporal differentiation may reflect a more general difficulty that 5-HT-depleted rats encounter in learning to inhibit operant responses (Soubrié, 1986), and in this context it is of interest to note that Harrison et al. (1999) found that acquisition of accurate performance in a go/no-go task, which involved suppression of a prepotent response without any obvious timing component, was markedly retarded following 5-HT depletion, whereas steady-state performance was less severely affected.

Injection of the 5-HT_{1A} receptor agonist 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT) or the nonselective 5-HT_1 receptor agonist 5-carboxamidotryptamine directly into the median raphe nucleus reduced the peak IRT and increased IRT variability in an IRT >20-s schedule (Fletcher, 1993, 1994). This finding is consistent with 8-OH-DPAT's ability to inhibit 5-HTergic function via its agonist action at somatodendritic 5-HT_{1A} autoreceptors in the raphe nucleus (Hjörth and Magnusson, 1988). However, there is evidence that systemically administered 5-HT_{1A} receptor agonists may affect IRT > *t* performance predominantly by a postsynaptic action. Thus, Jolly et al. (1999) found that systemic treatment with 8-OH-DPAT or 5-methoxy-dimethyltryptamine increased the peak IRT and reduced IRT variability in an IRT > 72-s schedule; this effect was not attenuated, but rather enhanced, by central 5-HT depletion induced by intracerebroventricularly administered 5,7-DHT, consistent with denervation supersensitivity of postsynaptic 5-HT_{1A} receptors.

Tricyclic antidepressants and selective 5-HT uptake inhibitors (SSRIs) are well known for their ability to "improve" IRT > 72-s schedule performance, by reducing response rate and increasing reinforcement rate (O'Donnell and Seiden, 1983, 1992; Seiden et al., 1985; Marek and Seiden, 1988), and this effect has been attributed to an

enhancement of temporal estimation (Marek and Seiden, 1988). However, the current literature on IRT > 72-s schedule performance lends little support for this notion. Sokolowski and Seiden (1999), in one of the very few reports of the effects of SSRIs on IRT > *t* performance that have included quantitative timing indices, found that the SSRI paroxetine *increased* IRT variability (two other SSRIs, sertraline and fluoxetine had qualitatively similar, though nonsignificant, effects); sertraline and paroxetine, but not fluoxetine, increased the peak IRT.

4.2.2. Fixed-interval peak procedure

This procedure (Catania, 1970; Roberts, 1981) is a variant of the classical fixed-interval schedule (Ferster and Skinner, 1957). Each trial starts with the onset of a signal. In fixed-interval trials, reinforcement is scheduled to follow the first response emitted after a fixed time has elapsed since the onset of the signal. However, in "probe" trials, the reinforcer is omitted, and the signal continues for a period three or four times the length of the fixed interval. Behaviour in these probe trials consists of progressively increasing response rate up to the end of the criterion interval, followed by a declining rate of responding. The measure of central tendency of timing is the *peak time* (the time from the onset of the signal until response rate reaches its highest point), and the Weber fraction is usually calculated as the ratio of the *spread time* (conveniently measured as the time from when response rate reaches 70% of its maximum value until it first falls below that level) to the peak-time (Gibbon, 1977; Church et al., 1991). The fixed-interval peak procedure has been extensively used by Meck and his colleagues (Meck, 1996; Hinton and Meck, 1997) to examine the putative role of the dopaminergic projections in regulating pacemaker function. However, it has seldom been employed in studies of the involvement of 5-HTergic mechanisms in timing behaviour.

Morrissey et al. (1994) examined the effect of destruction of the ascending 5-HTergic pathways by intraraphe injection of 5,7-DHT on performance on a peak-interval 40-s schedule. The peak time exhibited by the lesioned group was virtually identical to that of the sham-lesioned control group. However, their spread time was greater than that of the control group, and this was reflected in a significant inflation of the Weber fraction. Acquisition of accurate temporal differentiation on the peak procedure entails a learned reduction of the rate of responding in the latter segment of the probe trials; it seems that 5-HT-depleted rats are slow to acquire this reduction of response rate, an effect of the lesion that may be related to the retarded acquisition of accurate IRT > *t* schedule performance noted earlier (Al-Ruwaitea et al., 1997b).

To best of our knowledge, there have been no studies of the effects of selective 5-HT receptor agonists or antagonists on peak fixed-interval schedule performance. Two studies have examined the effects of SSRIs. Ho et al. (1996) found that acute treatment with fluvoxamine did not affect either the peak time or the Weber fraction; chronic treatment produced a small reduction of the peak time but no change in the Weber fraction. Bayley et al. (1998) found that zimelidine (acute treatment) reduced both peak time and the spread time, but only at doses that severely reduced lever pressing rate; clomipramine had no effect on performance.

4.2.3. Free-operant psychophysical procedure

This procedure (Stubbs, 1976, 1980) consists of a series of trials in which reinforcement is provided, usually under a variable-interval schedule, for responding on one of two continuously available operanda, A and B. Reinforcer availability is allocated to A during the first half and to B during the second half of each trial. The typical pattern of responding consists of an increasing response rate on B, and a concomitantly declining response rate on A, during the course of the trial. This is reflected in the psychometric curve: relative response rate on B increases during the trial, passing the "indifference point" (50% responding on B) approximately midway through the trial, when reinforcer availability is transferred from A to B (Stubbs, 1976, 1980; Bizo and White, 1994a,b). The psychometric function may be used to derive the Weber fraction, as shown in Fig. 1. One feature of this procedure that is not shared by the other immediate timing schedules discussed above is the availability of an explicit measure of switching between response alternatives.

Destruction of the 5-HTergic pathways by intraraphe injection of 5,7-DHT does not prevent rats from acquiring accurate performance on this schedule, nor does it affect the steady-state values of the indifference point or Weber fraction; however, the lesion consistently increases the rate of switching between the two levers (Al-Zahrani et al., 1996a; Chiang et al., 1999). A facilitatory effect of 5-HT depletion on switching has been seen in other timing schedules (Al-Ruwaitea et al., 1997a). However, it does not appear to be specific for timing schedules, as it also occurs in concurrent operant schedules that do not entail explicit timing (concurrent variable-interval schedules: Al-Ruwaitea et al., 1999b).

Acute treatment with the 5-HT_{1A} receptor agonist 8-OH-DPAT produced a dose-dependent leftward displacement of the psychometric function obtained with the free-operant psychophysical procedure (i.e., it reduced the indifference point) (Chiang et al., 2000b; Body et al., 2001b). This effect appears to be mediated by a postsynaptic receptor population, since destruction of the ascending 5-HTergic projection did not prevent the effect of 8-OH-DPAT (Body et al., 2001b).

To our knowledge, there have been no other experiments on the effects of drugs affecting the 5-HTergic system on performance on the free-operant psychophysical procedure.

4.3. Retrospective timing schedules

In retrospective timing tasks, the datum of interest is the subject's behaviour after a specified interval has elapsed.

The usual format of tasks of this type is a conditional discrimination procedure, in which the subject is trained to emit one of two mutually exclusive responses following the offset of a signal, the two responses being differentially reinforced depending upon the duration of the signal (*temporal discrimination*). Retrospective timing tasks have been extensively employed in studies of temporal psychophysics in animals and man (see Allan and Gibbon, 1991; Fetterman, 1995; Fetterman and Killeen, 1992; Penton-Voak et al., 1996; Killeen et al., 1997).

4.3.1. Interval bisection task

In this task (Catania, 1970; Church and Deluty, 1977), the subject is first trained to discriminate two durations (''short'' and ''long'') in a discrete-trials conditional discrimination schedule. When accurate performance has been attained, probe trials, in which stimuli of intermediate duration are presented, are introduced into each session. In the case of each duration, the percentage of occasions on which the subject responds on the lever appropriate to the ''long'' stimulus (%L) is recorded. The logistic relation between %L and stimulus duration provides the basis for the psychometric function (Killeen et al., 1997). The measure of central tendency is the *bisection point* (the duration corresponding to %L = 50), which occurs at about the geometric mean of the two standard durations. The Weber fraction may be computed from the ratio of the limen (half the difference between the durations corresponding to %L = 25 and %L = 75) to the bisection point (Church and Deluty, 1977).

Morrissey et al. (1993) and Ho et al. (1995) trained rats with lesions of their 5-HTergic pathways and sham-lesioned control rats on the interval bisection task, using 2- and 8-s standard stimuli. The lesioned rats showed no deficit in discriminative precision as indexed by the Weber fraction; however, their psychophysical function was displaced to the left, this being reflected in a significant reduction of the bisection point compared to that of the control group. This effect of 5-HT depletion on the bisection point appears to reflect a facilitatory effect of the lesion on rats' tendency to move from the lever appropriate to the short stimulus to the lever appropriate to the long stimulus as the period of stimulus presentation proceeds (Chatlosh and Wasserman, 1987; Graham et al., 1994). Thus, the lesion-induced reduction of the bisection point was effectively prevented when movement across the chamber was ''discouraged'' by requiring the rat to make a nose-poke response on a panel placed midway between the levers prior to making a lever-press response (Ho et al., 1995). Moreover, when rats were trained to discriminate intervals that were too short to allow movement across the chamber within the period of stimulus presentation (200 vs. 800 ms), the lesion had no effect on the bisection point (Graham et al., 1994). An unexpected finding in both Graham et al's (1994) and Ho et al.'s (1995) experiments was that the acquisition of accurate temporal discrimination in the relatively demanding tasks employed in these experiments was actually faster in the 5-HT-depleted rats than in normal (sham-lesioned) rats (see below for discussion).

There have been few investigations of the effects of acute treatment with drugs affecting the 5-HTergic system on interval bisection performance. Chiang et al. (2000b) found that the 5-HT_{1A} receptor agonist 8-OH-DPAT increased the Weber fraction in this task without affecting the bisection point. Body et al. (2001a) have recently reported a similar effect of 8-OH-DPAT in another discrete-trials psychophysical schedule. However, Bizot (1997) reported that another 5-HT_{1A} receptor agonist, buspirone, failed to affect performance on a conditional temporal discrimination task. The discrepancy between the two studies may reflect differences between the efficacies of the two drugs, buspirone being a partial agonist and 8-OH-DPAT a full agonist at 5-HT_{1A} receptors (De Vry, 1995). On the other hand, procedural differences are also relevant; Bizot's (1997) schedule employed only a single intermediate duration in the probe trials, and was therefore unable to yield quantitative estimates of the timing indices.

Ho et al. (1996) found that the SSRI fluvoxamine had no significant effect on the bisection point, when given either acutely on chronically. Bizot (1997) reported that clomipramine altered performance on a temporal discrimination task in a manner consistent with a reduction of the bisection point, although their schedule did not yield quantitative timing indices (see above).

4.3.2. ''Temporal memory'' tasks

Retrospective timing tasks in which delays are imposed between the end of the stimulus whose duration is to be discriminated and the opportunity to make a discriminative response have been used to assess ''temporal working memory'' or ''memory for duration'' (Spetch and Wilkie, 1983). These tasks are essentially delayed matching-to-sample (DMTS) tasks, in which the sample stimuli are lights or sounds of different durations. As with other DMTS tasks, ''forgetting curves'' may be derived by plotting percent correct responses against delay interval (White, 1991). A consistent finding with intact animals performing these tasks is the ''choose-short effect,'' an increasing tendency for choice to become biased in favour of the response appropriate to the shorter of the two discriminanda as the delay interval is progressively increased (Spetch and Wilkie, 1983; Grant et al., 1997).

Al-Zahrani et al. (1996b) examined the effect of lesions of the ascending 5-HTergic pathways on memory for duration, using a conventional delayed conditional discrimination task, with stimuli (light presentations) of 2- and 8-s durations as the discriminanda, and poststimulus delays ranging from 2 to 32 s. The lesion did not affect overall accuracy of performance; however, it did enhance the choose-short effect. In a further investigation of this finding, Al-Zahrani et al. (1997) combined the interval bisection and DMTS tasks. Rats were trained to discriminate 2- and 8-s

stimuli; then, when accurate performance (>90% correct choices) had been attained, poststimulus delays were introduced in 50% of the trials, and stimuli of intermediate duration were presented in 10% of both the "no-delay" and "delay" trials. As expected, the rats showed poorer discrimination when a delay was interposed between the end of the stimulus and the opportunity to make a response, and this was reflected in a flattening of the sigmoid psychophysical function and an increase in the size of the Weber fraction. In addition, the bisection point was increased (i.e., the sigmoid function was displaced to the right) in the delay conditions compared to the no-delay condition. Central 5-HT depletion had no effect on discriminative precision (expressed by the Weber fraction), but significantly enhanced the delay-dependent increase in the bisection point (choose-short effect).

It has been proposed that the choose-short effect is inversely related to proactive interference: proactive influences suppress the choose-short effect, while elimination of such influences enhance it (see Spetch and Sinha, 1989). Therefore, a possible interpretation of the enhanced choose-short effect seen in 5-HT-depleted rats is that 5-HT depletion may reduce the impact of proactive interference on temporal memory. This is an attractive hypothesis, because it could explain not only the enhanced choose-short effect, but also the faster acquisition of temporal discrimination shown by 5-HT-depleted rats compared to their unlesioned counterparts (see above: Graham et al., 1994; Ho et al., 1995). It is possible that in normal rats acquisition of accurate conditional discrimination is hampered by proactive interference, choice accuracy on trial N being diminished by the influence of trial $N-1$. If this were the case, then reduced sensitivity to proactive interference could result in faster acquisition. Unfortunately, this hypothesis has not been supported by experiments designed to measure proactive interference directly. Al-Ruwaitea et al. (1997b) described two experiments employing the "intratrial interference" method, which allowed the effects of interfering short and long prestimuli upon subsequent delayed temporal discrimination to be quantified (Spetch and Sinha, 1989). Their results confirmed the influence of proactive factors on temporal working memory, but failed to identify any effect of central 5-HT depletion on proactive interference.

5. Some unanswered questions

5.1. Prospective timing schedules

The evidence reviewed above is consistent with a role for 5-HT in intertemporal choice. As discussed earlier, prospective timing schedules pose significant interpretative problems, because they nearly always confound delay of reinforcement with some other parameter of reinforcement (usually reinforcer magnitude). No simple way of disentangling the effects of delay and magnitude experimentally has yet been described; however, quantitative parametric analysis does allow *mathematical* separation of the effects of interventions on sensitivity to delay from their effects on sensitivity to other aspects of the reinforcing stimulus (Ho et al., 1997, 1999). Using this approach, Mobini et al. (2000a) identified a specific effect of 5-HT depletion on sensitivity to delay. Mobini et al.'s (2000a) results suggest that, in the intact organism, 5-HTergic mechanisms slow the rate of time discounting; when these mechanisms are absent, delay-dependent devaluation of reinforcers proceeds more rapidly.

In most current models of intertemporal choice, an inverse relation (usually an inverse *hyperbolic* relation; see Monterosso and Ainslie 1999) between the value of a reinforcer and the length of the prereinforcer delay is taken as an axiom, and the mechanisms underlying time discounting are seldom discussed. However, Mazur (1995, 1997, 2001) has proposed that time discounting arises from an inverse relation between the reinforcing efficacy of the stimuli present at the moment of choice and the duration of exposure of the subject to these conditioned reinforcing stimuli; in other words, the longer the subject is exposed to a conditioned reinforcer, the weaker the reinforcer becomes (Mazur, 2001). Whether impaired formation of conditioned reinforcing relations underlies 5-HT's role in time discounting is an interesting question for future experiments.

Which 5-HT receptor subtypes are involved in determining the rate of time discounting is still not known, although Brunner and Hen (1997) and Evenden and Ryan (1999) have recently initiated research into this question. Most currently available intertemporal choice schedules do not lend themselves well to addressing this question. One method, which allows rapid determination of indifference points, is the adjusting-amount schedule of Richards et al. (1997). In this schedule, two reinforcers of different sizes are provided after differing delays; the size of one is fixed, while the size of the other is adjusted up and down in accordance with the subject's choices, until an indifference point is attained. This method has been found to be sensitive to acute changes in reinforcer size and delay, and to generate stable indifference points in a single experimental session. Recently, the method has been exploited to examine the role of dopaminergic mechanisms in intertemporal choice (Richards et al., 1999; Wade et al., 2000); however, it has yet to be applied to an exploration of the putative role of 5-HTergic mechanisms. Another method, which may allow rapid determination of indifference points, was described by Evenden and Ryan (1996). In this schedule, the delay to the larger of two reinforcers is progressively increased in successive blocks of trials; the indifference delay may be estimated from the relationship between preference for the larger reinforcer and delay, by interpolation between the delays corresponding to proportional choices above and below 50%. This method has also proved sensitive to acute drug treatment (Evenden

and Ryan, 1996, 1999; Cardinal et al., 2000). It must be emphasised, however, that a drug-induced shift of a single indifference delay is not an adequate basis for drawing conclusions about the effect of the drug on the rate of time discounting (see above). There would seem to be no short cut to the laborious business of testing the drug of interest on a range of indifference delays, thereby allowing changes in the rate of time discounting to be revealed by appropriate function fitting (see Ho et al., 1999).

5.2. Immediate and retrospective timing schedules

Destruction of the 5-HTergic pathways does not prevent animals from acquiring accurate temporal differentiation and temporal discrimination. It does, however, alter the rate of acquisition. Interestingly, acquisition of temporal differentiation proceeds more slowly, whereas acquisition of temporal discrimination proceeds more rapidly, in the absence of central 5-HT. The slow development of temporal differentiation may reflect 5-HT-depleted rats' difficulty in learning to inhibit operant responses (Soubrié, 1986); however, the basis for the faster acquisition of temporal discrimination remains to be elucidated (see above).

Much of the interest in the effects of pharmacological interventions on steady-state timing behaviour centres on the supposed insights that these effects may provide into the neural basis of the ''internal clock.'' However, in attempting to interpret the effects of lesions in these terms, it is important to recognize that, according to current timing theories (Gibbon, 1977, 1991; Killeen and Fetterman, 1988; Killeen et al., 1997), a permanent change in clock speed is not expected to induce a permanent alteration of the index of central tendency of timing (i.e., the locus of the psychometric function), although it may alter the Weber fraction (Bizo and White, 1994a, 1995). In contrast, acute changes in pacemaker period should produce immediate shifts of the psychometric function without altering the Weber fraction (see Hinton and Meck, 1997; Gibbon et al., 1997b). Thus, for example, the leftward displacement of the peak IRT in IRT > t schedules and the reduction of the value of T_{50} in the interval bisection task induced by central 5-HT depletion cannot be accounted for in terms of a change in pacemaker period; an explanation for these findings must be sought among the other contingencies that are entailed by these schedules.

Ho et al. (1998) suggested that 5-HT depletion may facilitate (disinhibit) switching between behavioural states, and that this might explain many of the effects of the lesion on timing performance reviewed above, including the increased rate of switching between operanda seen in the free-operant psychophysical procedure and other concurrent reinforcement schedules, the leftward displacement of the psychometric function in second-range interval bisection tasks, and the increased Weber fraction seen in single-operandum timing schedules such as IRT > t and peak interval schedules. (In the case of single-operandum schedules, switching is assumed to occur between the hypothetical behavioural states of lever pressing and ''other behaviour'': see below.) However, although recent findings have confirmed the facilitatory effect of 5-HT depletion on switching, they have not supported the notion of a simple relation between facilitated switching and altered timing performance. For example, Chiang et al. (1999) found that while imposing a constraint on switching reduced the Weber fraction in the free-operant psychophysical procedure (see also Chiang et al., 1998), destruction of the 5-HTergic pathways did not affect temporal differentiation in either the ''constrained'' or the ''unconstrained'' version of the schedule. These findings indicate the need for further experiments to delineate the influence of switching on timing performance, and to identify the behavioural processes underlying the effects of 5-HT depletion on timing in schedules where switching is not involved. It must also be acknowledged that concept of switching is less than satisfactory from a theoretical point of view. In single-operandum schedules, in which switching is assumed to occur between the recorded operant and other unrecorded behaviour (Ho et al., 1998), enhanced switching is indistinguishable from facilitated or disinhibited responding (Soubrié, 1986). Switching in concurrent schedules may be viewed in the same light if ''switching'' is considered as an operant in its own right (see Davison and McCarthy 1988). In the context of 5-HT's role in switching and timing, two findings are worth emphasising. Firstly, 5-HT depletion results in enhanced switching even in aperiodic schedules, which do not entail any explicit timing contingency. Secondly, 5-HT depletion selectively enhances switching between concurrent operants; the rates of the concurrent operants themselves are often unaffected by 5-HT depletion (Al-Ruwaitea et al., 1999b).

The effects of acute treatment with drugs affecting the 5-HTergic system have also been found to differ between different types of timing schedule. Thus, SSRIs and other antidepressants consistently alter IRT > t performance, but do not affect performance on other immediate timing schedules. The 5-HT_{1A} receptor agonist 8-OH-DPAT, the only selective 5-HT receptor agonist to have been studied in different types of timing schedule, has qualitatively different effects in immediate and retrospective timing schedules; in both cases, 8-OH-DPAT's effects appear to be mediated by a postsynaptic receptor population (Body et al. 2001a,b). An important goal for future research in this area will be to specify the receptor subtypes involved in 5-HT's putative role in timing behaviour, and to identify their anatomical localization.

6. Implications for internal-clock models of interval timing

As discussed above, most current models of interval timing behaviour assume, either tacitly or explicitly, that a

unitary timing mechanism (the ''internal clock'') underlies the ability of organisms to regulate their own behaviour in time (temporal differentiation) and to make accurate discriminations of the durations of external events (temporal discrimination). According to Hinton and Meck (1997) and Gibbon et al. (1997b), the nigrostriatal dopaminergic projection serves to ''drive'' the pacemaker of such a clock, an action that may be opposed by an inhibitory influence of the raphe-striatal 5-HTergic projection. Unfortunately, for reasons given below, currently available data on the role of 5-HT in interval timing are not easy to reconcile with this notion.

Any model that posits a unitary internal clock would seem to imply that an intervention that alters its speed should produce qualitatively similar disruptions of temporal differentiation and temporal discrimination (Zeiler, 1998). Some of the findings reviewed above are inconsistent with this prediction. An example is the finding that 8-OH-DPAT selectively increases the Weber fraction in retrospective timing tasks without displacing the indifference point (Chiang et al., 2000b; Body et al., 2001a), whereas it dose-dependently displaces the indifference point in immediate timing tasks (Chiang et al., 2000b; Body et al., 2001b). According to Chiang et al. (2000a,b), such findings call into question the concept of a unitary internal clock, which subserves all forms of interval timing behaviour, and suggest that different timing processes, possibly involving different neural substrates, may underlie temporal differentiation and temporal discrimination. Interestingly, Chiang et al.'s (2000a,b) suggestion, based on pharmacological evidence, is echoed by Grondin's (2001) argument, based on psychophysical evidence (see also Zeiler, 1998). Against this suggestion, it may be argued that a unitary internal clock remains a viable construct; however, the drugs in question may not interact with this internal clock, but rather with some other processes (for example, reference memory, decision processes or switching between response alternatives: see above) that may be differently represented in retrospective and immediate timing schedules. In either case, it is clear that changes in the quantitative indices of timing derived from any one type of timing schedule cannot provide reliable information about the functioning of the hypothetical internal timing mechanism(s). In order to delineate and interpret 5-HT's role in interval timing, it will be important not only to increase the range of pharmacological interventions, but also to explore the effects of these interventions on a broad range of timing schedules.

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