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# Effects of Pharmacologically Induced Dopamine-Receptor Stimulation on Human Temporal Information Processing

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**Abstract**

According to the distinct-timing hypothesis, temporal discrimination of intervals in the range of seconds is cognitively mediated, whereas brief intervals in the sub-second range are processed automatically and beyond cognitive control. Although there is some evidence from neuropharmacological studies suggesting that temporal processing in the second and sub-second range is modulated by the effective level of dopamine (DA) activity in the brain, the findings are not conclusive. For the first time, the present experiment investigated the effect of a DA receptor agonist on timing performance in healthy human subjects. In a double-blind crossover design, placebo, 0.075 mg and 0.100 mg of pergolide were administered in a single oral dose. Performance on temporal discrimination of intervals in the sub-second range was significantly improved after 0.100 mg of pergolide compared to both placebo and the lower dose of pergolide. No reliable effect of pergolide could be observed for temporal discrimination of longer intervals. The overall pattern of results provides converging evidence for the validity of the distinct-timing hypothesis and for dopaminergic modulation of the neural mechanisms underlying automatic timing.

**Key Words:** Dopamine, temporal discrimination, time perception, time

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## Introduction

For more than four decades, internal clock models based on neural counting (cf., Rammsayer & Ulrich, 2001) provide a useful heuristic and conceptual framework for explaining animal timing and human time perception. According to this class of models, the internal clock mechanism is basically characterized by a neural pacemaker and an accumulator. The pacemaker generates pulses and the number of pulses relating to a physical time interval is recorded by the accumulator. Thus, the number of pulses counted during a given time interval is the internal representation of this interval. Hence, the higher the clock rate the finer the temporal resolution of the internal clock will be, which is equivalent to more accuracy and better performance on duration discrimination tasks. Two additional stages of temporal information processing have been assumed to translate clock readings into behavior (e.g., Creelman, 1962; Gibbon, Church, & Meck, 1984; Treisman, 1963). A memory stage enables storage of the output from the accumulator and, at the decision stage, previously stored information is compared with the current perceived duration. This final

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decision process yields an appropriate behavioral response, such as "second interval longer" when the duration of two temporal intervals have to be compared.

As an alternative theoretical framework, the distinct-timing hypothesis (Rammsayer, 2008) proposes two distinct timing mechanisms underlying temporal information processing in humans: a sensory mechanism for processing of durations in the range of milliseconds and a cognitive one for processing of longer durations. Michon (1985) argued that temporal processing of intervals longer than approximately 500 ms is cognitively mediated while temporal processing of shorter intervals is supposedly "of a highly perceptual nature, fast, parallel and not accessible to cognitive control" (Michon, 1985, p. 40). Converging evidence for the distinct-timing hypothesis has been provided by the finding that temporal processing of intervals ranging from 50 to 100 ms is unaffected by a secondary cognitive task, whereas temporal processing of intervals in the 1-second range was markedly impaired by the same secondary task (Rammsayer & Lima, 1991). Furthermore, the notion of two distinct timing mechanisms is also supported by neuroimaging studies on timing that suggest an automatic timing system for measuring brief intervals in the sub-second range and a cognitively controlled system for temporal processing of intervals in the supra-second range (Lewis & Miall, 2003a, 2003b, 2003c, 2006). It should be noted, however, that other imaging data may not fit neatly within this conceptual framework (for reviews see Meck, Penney, & Pouthas, 2008; Penney & Vaitilingam, 2008).

First scientific reports of pharmacologically induced effects on temporal information processing were published in the 19th century (cf., Rammsayer, 2008). In 1923, the French psychologist Henri Piéron introduced the idea that the finding that drugs affect human timing performance implies the involvement of basic physiological processes. More recently, increasing evidence for the neurochemical coding of behavior points to the significance of neuropharmacological approaches within the field of cognitive neuroscience. The ultimate aim of such an approach is to identify neurochemical brain systems that are mediating or controlling specific human behavior. This can be achieved by utilizing the specific pharmacological actions and action mechanisms of drugs for a better understanding of the neurobiological basis of a specific behavioral process. In this respect, drugs serve as research tools for elucidation of mechanisms underlying temporal information processing.

A large number of neuropharmacological studies on timing performance in animals are consistent with the notion of an internal clock based on neural counting. More specifically, the animal data suggest that the rate of the hypothesized internal clock used for temporal information processing is positively related to dopaminergic activity in the brain. Evidence for acceleration in pacemaker speed has been shown by numerous studies in rats using the indirect dopamine (DA) agonist methamphetamine (Buhushi & Meck, 2002; Çevik, 2003; Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; Matell, Bateson, & Meck, 2006; Meck, 1983, 1996). On the other hand, the DA receptor antagonist haloperidol has been shown to produce a deceleration in pacemaker speed (Buhushi & Meck, 2002; MacDonald & Meck, 2005; Maricq & Church, 1983; Meck, 1983, 1996). To what extent these findings also hold for human timing is still open to debate. Although dopaminergic activity in the brain apparently is somehow involved in human temporal information processing, the general notion of an internal clock based on neural counting seems doubtful in the light of the empirical data. It is important to note, however, that only very few neuropharmacological studies on the effects of dopaminergic activity in the brain on temporal information processing in humans appear to exist.

Unlike the animal studies, the available neuropharmacological data on human timing performance rather argue against the idea of a single internal clock as a general timing device. In humans, pharmacological interventions targeting at working memory seem to disrupt cognitively mediated timing processes. For example, benzodiazepines that interfere with working-memory performance impair temporal discrimination of intervals in the range of seconds, while timing of intervals in the sub-second range remained unaffected (Rammsayer, 1994, 1999). These neuropharmacological data in combination with experimental studies

employing a dual-task approach (e.g., Brown, 1997; Fortin & Breton, 1995; Rammsayer & Lima, 1991; Sawyer, Meyers, & Huser, 1994) support Zakay's (1993) view that processing of temporal information in the range of seconds occurs in working memory.

A large number of behavioral and neuropharmacological studies showed that working memory processes are modulated by dopaminergic projections to the prefrontal cortex (e.g., Goldman-Rakic, 1995; Arnsten, 1997). Recently, Lewis and Miall (2006) introduced the idea of a dual involvement of the neurons in the right dorsolateral prefrontal cortex in both working memory and timing of intervals in the supra-second range. Thus, these neurons, effectively modulated by the effective level of DA, may serve as a neural machinery for both working memory and cognitive time measurement. Therefore, it is not surprising that pharmacological substances such as haloperidol or remoxipride, that exert DA antagonistic effects in this region of the brain, produce impaired working-memory functioning as well as pronounced deficits in temporal discrimination in the second range (Lustig & Meck, 2005; Rammsayer, 2003). Taken together, these findings point to the conclusion that any pharmacological treatment that directly affects or effectively interferes with active information processing in working memory, results in impaired temporal processing of intervals in the range of seconds or longer (cf., Lewis & Miall, 2006; Rammsayer, 1997, 2003).

Unlike temporal processing of intervals in the range of seconds, from a pharmacological point of view, timing of extremely brief intervals in the range of milliseconds appears to be controlled by dopaminergic activity in the basal ganglia. In several studies with healthy human volunteers, performance on temporal discrimination was affected by the DA receptor blocker haloperidol that exerts its DA antagonistic effect on all dopaminergic neurons in the brain (Rammsayer, 1989, 1993, 1997). On the other hand, remoxipride, a DA receptor blocker that primarily acts on dopaminergic neurons projecting to the prefrontal cortex rather than on dopaminergic neurons in the basal ganglia, had no influence on the timing of extremely brief intervals in the sub-second range (Rammsayer, 1993, 1997). Additional converging evidence for the involvement DA activity of the basal ganglia in the timing of brief intervals is provided by clinical studies on Parkinson's disease (PD). PD patients are characterized by extremely low levels of dopaminergic activity in the basal ganglia (Hornykiewicz, 1972). Most interestingly, in studies comparing PD patients with age-matched healthy controls, performance on temporaomy

this type of DA supplementation does not enhance the neuron's firing rate (Paulus & Trenkwalder, 2006). From this perspective, to warrant maximum effectiveness at the behavioral level, DA agonistic pharmacological interventions should directly act on DA receptors rather than on other intraneuronal processes such as changes in rate of DA synthesis.

To our knowledge, there are no studies evaluating the effect of pharmacologically increased DA receptor activity on temporal discrimination in healthy human subjects. Such studies, however, would represent a worthwhile contribution to our understanding of the psychobiological mechanisms underlying temporal information processing. Therefore, the present study was designed to investigate the effects of the DA receptor agonist pergolide on temporal discrimination of intervals in the range of seconds and milliseconds. To assess duration discrimination performance in the second and sub-second range, difference thresholds were determined in relation to a 1,000-ms and a 50-ms base duration, respectively. The choice of both these base durations was motivated by the notion that the hypothetical shift from one timing mechanism to the other may be found at interval duration somewhere between 100 and 500 ms (cf., Abel, 1972a, 1972b; Buonomano, 2007; Buonomano & Karmarkar, 2002; Michon, 1985; Münsterberg, 1889; Rammsayer, 1996, 1997). Furthermore, when participants are asked to compare time intervals, many of them count out the required number of seconds. Since explicit counting becomes a useful timing strategy for intervals longer than approximately 1,200 ms (Grondin, Meilleur-Wells, & Lachance, 1999), the "long" base duration was chosen not to exceed this critical value.

In order to detect an existing dose-response relationship, in the present study, the DA receptor agonist pergolide was administered orally at two different, relatively low doses. A major reason for the obvious lack of recognized neuropharmacological timing studies involving dopaminergic drugs, poses the fact that administration of DA agonists in humans is followed frequently by considerable nausea, hypotension, and other adverse reactions. To reduce these potential side effects, the peripheral DA receptor blocker domperidone was administered at the beginning of each testing session.

## Method

### Participants

Participants were eight healthy male volunteers ranging in age from 20 to 25 years (mean ± SD = 22.5 ± 0.63 years). Four additional participants entered the study but had to be excluded because of severe side effects, namely nausea and hypotension, following pergolide intake. After filling in a health questionnaire, participants were selected according to the following inclusion criteria: non-smokers, no chronic drug intake, no past or present psychotherapy or psychiatric treatment, no allergy, no chronic endocrine or cardiovascular disease, no signs of present acute or chronic infections or gastrointestinal diseases. All subjects were informed about the study protocol andy

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across participants. Each block consisted of 64 trials, and each trial consisted of one standard interval (= base duration) and one comparison interval. The duration of the comparison interval varied according to an adaptive rule (Kaernbach, 1991) to estimate x.25 and x.75 of the individual psychometric function; that is, the two comparison intervals at which the response "longer" was given with a probability of .25 and .75, respectively.

For temporal discrimination of brief stimuli in the range of milliseconds, the standard interval was 50 msec and initial durations of the comparison interval were 15 msec below and above the standard interval for x.25 and x.75, respectively. To estimate x.25, the duration of the comparison interval was increased for Trials 1-6 by 3 msec if the participant had judged the standard interval to be longer and decreased by 9 msec after a "short" judgment. For Trials 7-32, the duration of the comparison interval was increased by 2 msec and decreased by 6 msec, respectively. The opposite step sizes were employed for x.75.

For temporal discrimination of longer durations, the standard interval was 1,000 msec and the initial values of the comparison interval were 500 msec and 1,500 msec for x.25 and x.75, respectively. To estimate x.25, the duration of the comparison interval was increased by 100 msec if the participant had judged the standard interval to be longer and decreased by 300 msec after a "short" response. For Trials 7-32, the duration of the comparison interval was increased by 25 msec and decreased by 75 msec, respectively. Again, the opposite step sizes were employed for x.75.

In each experimental block, one series of 32 trials converging to x.75 and one series of 32 trials converging to x.25 were presented. Within each series, the order of presentation for the standard interval and the comparison interval was randomized and balanced, with each interval being presented first in 50% of the trials. Trials from both series were randomly interleaved within a block.

Each participant was seated at a table with a keyboard and a computer monitor. To initiate a trial, the participant pressed the space bar; auditory presentation began 900 msec later. The two intervals were presented with an interstimulus interval (ISI) of 900 msec. The participant's task was to decide which of the two intervals was longer and to indicate his decision by pressing one of two designated keys on a computer keyboard. One key was labeled "*First interval longer*" and the other was labeled "*Second interval longer*". The instructions to the participants emphasized accuracy; there was no requirement to respond quickly. After each response, visual feedback ("+", i.e., correct; "-", i.e., false) was displayed on the computer screen. The next trial started when the participant pressed the space bar again.

As a measure of performance, half the interquartile range [(x.75 – x.25)/2], representing the difference limen, *DL* (Luce & Galanter, 1963), were determined for both duration discrimination tasks. In psychophysics, *DL* specifies the smallest difference in a given modality of sensory input that is detectable by a human observer. With this psychophysical measure, better performance on duration discrimination is indicated by smaller values of *DL*. In addition, decision time, i.e., the time from offset of the second interval until onset of participant's response, was obtained on each trial.

**Auditory fusion frequency task**

To control for possible drug-induced changes in sensory transmission of acoustic stimuli, an auditory fusion frequency (AFF) task was applied in addition to the duration discrimination tasks.

*Apparatus and Stimuli*. Apparatus was the same as for the duration discrimination tasks. The stimuli consisted of 25-msec noise bursts presented binaurally through headphones at an intensity of 88 dB.

*Procedure*. AFF threshold estimation consisted of 12 trials, and each trial consisted of two noise bursts separated by a variable ISI ranging from 1 to 40 msec. After each trial, the participant's task was to indicate by pressing one of two designated response keys whether he perceived the two successive noise bursts as one tone or two separate tones. The ISI was changed using an adaptive rule based on the Best PEST procedure (Pentland, 1980) to estimate the 75% fusion threshold. To enhance reliability of measurement, two AFF-threshold estimates were obtained for each participant. Thus, final individual threshold values represented the mean across both measurements.

**Self-rating scale of activation**

As a subjective indicator of cortical arousal, self-ratings on activation were obtained. The intensity of feelings of alertness, drowsiness, relaxation, concentration, and energy had to be marked on a rating scale ranging from 1 (i.e. "not at all") to 10 (i.e. "extremely pronounced").

**Pharmacological treatment and time course of the experiment**

In a double-blind crossover design, a combination of either 0.075 mg of pergolide and 30 mg of domperidone, 0.100 mg of pergolide and 30 mg of domperidone, or placebo and 30 mg of domperidone were administered orally in balanced order to each participant. Pergolide is a semisynthetic ergoline dopamine D1/D2 receptor agonist. Mean time to reach peak plasma concentrations is 2.5 to 3 hours after oral administration (Markham & Benfield, 1997).

Mostons46 Tc (d) Tj-0.12 T2 Tj-0.0ctmM aftafea Perafeur7r
nr (h) Tj3 Tj-0.1392 Tc (l ) Tj0 -13.44 TD 0 Tc 0.09792 Tc (.) 0.05808 Tc (o) Tj-0.036 Tc (n) 3.Tj Tj0 Tc (af) Tj(e) Tj0 Tc (a9
Tc (t)-0.036 Tc (46 Tc (d) TjTc (t) Tj -0.058Tj -0.1.74496 Tc ( ) T

**Table 1.** Means (M) and standard errors of the mean (SEM) of all dependent variables for the three experimental conditions.

| | Placebo | | Pergolide 0.075 mg | | Pergolide 0.100 mg | |
|---|---|---|---|---|---|---|
| | M | SEM | M | SEM | M | SEM |
| TD sub-second range | | | | | | |
| DL [msec] | 7.2 | 0.31 | 7.7 | 0.72 | 5.9 | 0.43 |
| Decison time [msec] | 872 | 0.78 | 880 | 111 | 829 | 101 |
| TD second range | | | | | | |
| DL [msec] | 141 | 18.2 | 173 | 32.1 | 162 | 13.3 |
| Decision time [msec] | 744 | 95 | 730 | 88 | 690 | 82 |
| Auditory fusion threshold [msec] | 11.8 | 4.1 | 15.4 | 5.2 | 13.1 | 5.9 |
| Subjective activation | 5.5 | 0.16 | 5.5 | 0.18 | 5.9 | 0.19 |

Note. TD = temporal discrimination, DL = difference limen

The absence of a statistically significant effect of pergolide on temporal discrimination of intervals in the second range does not in itself show that administration of an acute dose of 0.100 mg of pergolide differentially influences temporal processing in the sub-second and second range. To directly compare timing performance of both these ranges, *DLs* were converted into Weber fractions by dividing each *DL* by the duration of the respective standard interval. As can be seen from Figure 1, under placebo, Weber fractions were virtually identical for the second and sub-second range but clearly differed after administration of 0.100 mg of pergolide.

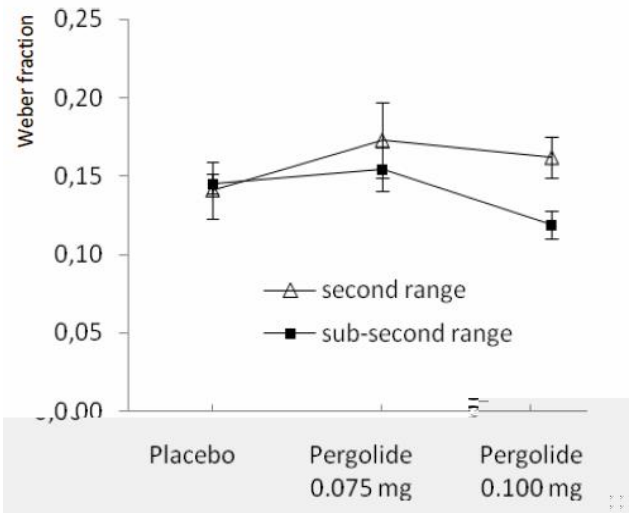


**Figure 1.** Mean Weber fractions (± SEM) for temporal discrimination of intervals in the second and sub-second range under placebo, 0.075 mg of pergolide, and 0.100 mg of pergolide, respectively. * $p$<.05

This was corroborated by a two-way analysis of variance with Drug (placebo vs. 0.100 mg of pergolide) and Base Duration (duration discrimination in the sub-second vs. duration discrimination in the second range) as two repeated-measurement factors. Although a statistically significant main effect could be shown neither for Drug [$F(1,7) = 0.14$, $p = .72$, $^2 = .019$] nor for Base Duration [$F(1,7) = 3.79$, $p = .09$, $^2 = .351$], the interaction of both factors became significant [$F(1,7) = 8.15$, $p = .025$, $^2 = .538$]. A post-hoc test yielded a reliable difference between Weber fractions for temporal discrimination of intervals in the second (0.162 ± 0.013) and sub-second range (0.119 ± 0.009; $p < .01$) after 0.100 mg of pergolide, while no significant difference could be revealed under placebo. For the placebo conditions, Weber fractions were 0.145 ± 0.006 and 0.141± 0.018 for discrimination of intervals in the second and sub-second range, respectively.

**Discussion**

The outcome of the present experiment shows that temporal discrimination of brief intervals in the range of milliseconds was reliably improved by 0.100 mg of the DA receptor agonist pergolide, whereas temporal discrimination of intervals in the 1-second range remains unaffected. Moreover, a closer inspection of the effect of 0.100 mg of pergolide compared to placebo revealed an apparent, albeit nonsignificant, performance decrement for temporal discrimination of the long intervals (see Figure 1). These findings provide converging evidence for the distinct-timing hypothesis suggesting two qualitatively different timing mechanisms involved in temporal processing of intervals in the sub-second and supra-second range, respectively. The statistical analysis of Weber fractions also supports the notion of two distinct timing mechanisms.

Sure enough, with an increasing dose of pergolide, a point will be eventually reached where any sensory or cognitive functions will be severely impaired. Within the framework of the pharmacopsychological approach, however, differential sensitivity of temporal processing of intervals in the sub-second and second range to

relatively low doses of a specific pharmacological treatment is indicative of different neurocognitive processes underlying temporal discrimination of intervals in the millisecond and second range, respectively. In other words, if both timing functions were based on the same timing mechanism, they should be likewise affected by a given dose of the pharmacological substance administered.

In the present study, AFF thresholds proved to be insensitive to changes in dopaminergic activity produced by 0.075 and 0.100 mg of pergolid. This indicates that the improvement in temporal discrimination in the sub-second range cannot be explained by unspecific, non-temporal sensory improvement in auditory sensitivity. Similarly, the absence of a pergolide-induced effect on self-rated feelings of activation argues against the possible explanation that increased performance on temporal discrimination observed with 0.100 mg of pergolide may be caused by drug-induced elevated levels in vigilance and cortical arousal. Rather, this superior performance in comparison to placebo and the low dose of pergolide appears to represent a highly specific DA-agonistic effect on the automatic timing system involved in temporal processing of intervals in the sub-second range. According to Lewis and Miall (2003a, 2003b) the automatic timing system is closely linked to components of the motor system and does not draw much upon the prefrontal cortex.

Clinical studies with PD patients (Artieda et al., 1992; Rammsayer & Classen, 1997) as well as neuropharmacological studies with healthy subjects (for a concise review see Rammsayer, 2008) provided converging evidence for the basal ganglia as a major biological substrate of this automatic timing system. Despite this evidence, the definitive neural basis for timing in the sub-second range remains unclear (cf., Buonomano, 2007; Mauk & Buonomano, 2004; Rammsayer, 2008). Nevertheless, regardless of what kind of internal timing mechanism one assumes (cf., Karmarkar & Buonomano, 2007; Rammsayer & Ulrich, 2001), the existing neuropharmacological findings indicate that DA receptor activity in the basal ganglia effectively modulates temporal sensitivity in the sub-second range. While pharmacological blockade of DA receptor activity results in severely impaired timing performance (e.g., Rammsayer, 1989, 1993, 1997, 1999), the present study provided first evidence for enhanced temporal discrimination performance in the sub-second range following a pharmacologically induced increase in DA receptor activity.

Within the framework of neural counting models, another major component, besides the pacemaker-counter device, represents the decision unit. At this stage, neural representations of two intervals will be compared to each other. Theoretically, the beneficial effect of DA agonistic pharmacological treatment on temporal discrimination of intervals in the sub-second range could also have been brought about by a more efficient or more sensitive decision process. The lack of a dopaminergic effect on decision time as observed in the present study, however, may suggest that the decision stage has not been influenced by DA agonistic pharmacological treatment.

Unlike temporal discrimination of intervals in the sub-second range, temporal processing of longer intervals was not improved by the DA receptor agonist pergolide. Rather, there seems to be a tendency for a slight deterioration of timing performance after pergolide treatment. In humans, temporal discrimination of intervals in the second-range represents a cognitively controlled process depending on the right dorsolateral prefrontal cortex (Lewis & Miall, 2006). This cortical region is modulated by dopaminergic afferent input from the ventral tegmental area. Therefore, it would be reasonable to expect an effect of pergolide on temporal discrimination of intervals in the range of seconds.

Previous studies on the effects of pergolide on working memory performance yielded a rather puzzling picture of positive and negative results (cf., Bartholomeusz, Box, van Rooy, & Nathan, 2003; Kimberg & D'Esposito, 2003; Müller, von Cramon, & Pollmann, 1998; Roesch-Ely et al., 2005). These inconsistent findings may be due to DA *antagonistic* effects produced by low doses of pergolide. While the DA agonistic effect of pergolide is a consequence of the stimulation of postsynaptic DA receptors, the DA antagonistic effect of pergolide observed at lower doses depends on activation of presynaptic autoreceptors. At low doses, DA

receptor agonists, such as pergolide, have been shown to preferentially stimulate DA autoreceptors (Di Chiara, Porceddu, Vargiu, Stefanini & Gessa, 1977; Tissari, Rossetti, Meloni, Frau, & Gessa, 1983). DA autoreceptors are presynaptic D2 receptors (Creese, 1987) and their stimulation by low doses of DA agonists decreases dopaminergic neurotransmission either by reducing the firing rate (Mercuri et al., 1997) or the amount of DA released per spike (L'Hirondel et al., 1998). From this perspective, the slight tendency of pergolide to impair cognitively mediated timing performance may have been caused by stimulation of DA autoreceptors. Although there is some indication of differential sensitivity of dopaminergic pathways within the basal ganglia and dopaminergic projections to the prefrontal cortex, this is a rather tentative interpretation.

To sum up, the present study was the first to show that a pharmacologically induced direct increase in DA receptor activity in the brain results in improved temporal discrimination of intervals in the range of milliseconds. The concomitant failure to observe a similar effect on temporal discrimination of longer intervals in the second range provides converging evidence for the distinct-timing hypothesis suggesting different timing mechanisms underlying temporal processing of intervals in the second and sub-second range, respectively. Further research utilizing psychophysical, psychophysiological, pharmacopsychological, neuroimaging, and computational approaches is considered necessary to identify the very nature of these timing mechanisms.

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