What Can Be Inferred from Multiple-task Psychophysical Studies about the Mechanisms for Temporal Processing?

Hugo Merchant, Ramón Bartolo, Juan Carlos Méndez, Oswaldo Pérez,
Wilbert Zarco, and Germán Mendoza

Instituto de Neurobiología, UNAM, Campus Juriquilla.
Boulevard Juriquilla No. 3001 Querétaro, Qro. 76230 México
`hugomerchant@unam.mx`, `merch006@umn.edu`

Abstract. We used different tools from experimental psychology to obtain a broad picture of the possible neural underpinnings of temporal processing in the range of milliseconds. The temporal variability of human subjects was measured in timing tasks that differed in terms of: explicit-implicit timing, perception-production, single-multiple intervals, and auditory-visual interval markers. The results showed a dissociation between implicit and explicit timing. Inside explicit timing, we found a complex interaction in the temporal variability between tasks. These findings do not support neither a unique nor a ubiquitous mechanism for explicit timing, but support the notion of a partially distributed timing mechanism, integrated by main core structures such as the cortico-thalamic-basal ganglia circuit, and areas that are selectively engaged depending on the specific behavioral requirement of a task. A learning-generalization study of motor timing also supports this hypothesis and suggests that neurons of the timing circuit should be tuned to interval durations.

Keywords: Interval perception and production, circle drawing, multidimensional statistics, learning and generalization.

1 Introduction

Time is among the most crucial magnitudes that living beings must quantify in order to survive. From microseconds to circadian rhythms, temporal information is used to guide behavior and specific brain mechanisms have been suggested for the time processing in different time scales covering twelve orders of magnitude. Even though there is not a time sensory organ, organisms are able to extract temporal information from stimuli of all sensory modalities, whether it is the interval between two notes in a symphony or the duration of an eclipse. In addition, during music execution and dancing human beings can generate complex sequences of time intervals with their movements. In some behaviors, an explicit representation of the interval to be timed is used as in tapping with a rhythm,

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while in others time processing is covertly present or implicit as during continuous drawing, where timing is an emergent property of the trajectory produced [1]. Also, time intervals can be produced or estimated just once or as many times as it is needed. Therefore, some of the key elements of temporal processing include the time scale being quantified, the modality of the stimulus, whether time is being measured for a movement or for a perceptual decision, whether the task involves single or multiple intervals, and the implicit or explicit nature of timing.

A central question among time researchers is whether a single neural mechanism is employed for the measurement of time across all kinds of behaviors or if, on the contrary, different areas and encoding strategies are employed by the brain depending on the behavioral context in which time is processed. These two opposing views regarding the mechanism of explicit timing are mainly used for the range of hundreds of milliseconds, a time scale that has been investigated in our laboratory. Although many behaviors that are essential for survival require the temporal processing in this range, the search for the brain mechanisms for time measurement in the scale of milliseconds has not been investigated until recently. In contrast, the psychophysics of temporal quantification started as early as the late XIX century (see [2]), and many timing tasks have been used to test the existence of one or multiple neural clocks. As a natural extension of the psychophysical experiments, a large amount of neuroimaging studies have been conducted recently to describe the brain circuits that are activated in a number of timing tasks.

The present chapter is divided in two sections. The first one is devoted to the comparison between the neuroimaging results and the predictions made by the psychophysical measurements performed in our laboratory regarding the functional organization of a dedicated timing mechanism. The last section focuses on the predictions generated by our study on learning and generalization of time intervals that states that the timing mechanism is multimodal and that at least a fraction of the neurons of the timing circuit should be tuned to different interval durations. The last prediction is supported by neural network simulations.

2 fMRI of Temporal Processing

Functional brain imaging studies have yielded useful information about the structures that participate in time measurement. Numerous perceptual or motor tasks using single or multiple time intervals in the hundreds of milliseconds range have consistently found that structures like the striatum of the basal ganglia and the supplementary motor areas are activated, regardless of the non-timing factors involved in the task, such as the modality of the stimuli used to define the intervals [3, 4, 5, 6, 7, 8, 9]. This has led some to conclude that the same structures are always recruited for temporal processing in this range and that different task features, such as the perceptual or motor nature of the task, or if single or multiple intervals are involved, do not significantly modify which brain regions are activated [10]. In this regard, it has been proposed that some interconnected structures, like the dorsal premotor and supplementary motor areas, the basal ganglia and the thalamus, which are essential for movement planning and execution, also form a timing circuit [11, 12]. This is an appealing view, since time perception and production go hand by hand while interacting with the environment. Indeed, various perceptual studies, using auditory [3,6,8], visual [7,9,13,14] and tactile [10] stimuli have reported consistent activation of some or all of the structures of this hypothetical timing circuit. Importantly, humans are not the only primate species that has been investigated. A PET study by Onoe and collaborators [15] using macaque monkeys trained to discriminate between two visually defined time intervals found some of these areas, like the basal ganglia, to be activated. This is a relevant finding, because it implies that these animals can be good models for the neurophysiological study of timing.

However, these are not the only regions that have been reported to increase their activity while timing. A relevant example is the cerebellum, a structure known to have profuse connections with the neocortex. While a group of investigators have reported activation of medial cerebellar structures [6] during timing tasks, others have found activation in the lateral part of the hemispheres [13,16], and still others have not reported their activation at all [3]. The cerebellar activation is regarded by some investigators as an evidence for its involvement in timing but others propose that it may simply reflect its role in sensorimotor integration. A similar example is the dorsolateral prefrontal and the inferior parietal cortices. These structures have also been considered as candidates for a dedicated timing network, albeit more frequently in the seconds range [9]. Some research groups claim that the parietal and prefrontal cortices are activated because they are important nodes in the temporal processing network. Nevertheless, since these regions have important roles in attention and working memory, their activation may reflect that these cognitive processes are needed to solve the tasks. Additionally, some of these studies have also pointed out that a bias seems to exist towards the activation of right hemispheric structures [13], although results from other studies can be considered as a challenge to such view [17].

Fewer studies have focused on interval production rather than perception, but the majority has found again the supplementary motor area, the basal ganglia, the thalamus and the cerebellum to be involved [5, 14, 17]. In fact, Bueti and collaborators [14] directly investigated whether different regions were activated for perceptual or for motor timing. They found that in both conditions the basal ganglia and the cerebellum increased their signal, but a more complex network that included the supplementary motor areas and the inferior parietal cortex, was preferentially activated during production tasks. Finally, a recent meta-analysis using an activation likelihood estimation algorithm on the data of 20 fMRI studies showed that when maps of both motor and perceptual tasks in the sub-second range are displayed on a single template, the following overlapping areas were detected: SMA, middle frontal gyrus (BA 6), IPL (BA 40), IFG, right caudate and putamen, right insula and the posterior cerebellum [12].

Overall, these findings point out that no single brain structure can be considered as the sole responsible for time quantification. Furthermore, temporal estimation can be viewed as the result of the interaction of multiple cortical and subcortical areas. However, there are some regions that consistently appear to participate conforming the main core timing network that includes the supplementary motor area and the basal ganglia, while others are not that consistent, like the cerebellum, the dorsolateral prefrontal cortex, and the inferior parietal cortex. Other structures may also be recruited depending on particular task demands such as the primary sensory cortical areas. Nevertheless, the functional imaging literature does not support the notion that the representation of time could be ubiquitous, arising from the intrinsic dynamics of non-dedicated neural mechanisms, as suggested by modeling studies [18,19,20]. Thus, these results can begin to shed light on our main question. While there's no unique brain clock, some of its structures definitely seem to conform a partially distributed timing network devoted to the scale of hundreds of milliseconds.

3 Psychophysics of Temporal Processing Across Behavioral Contexts

We have addressed these issues in our laboratory by testing human volunteers on different perceptual and production timing tasks [21, 22]. In order to study the effects of factors other than timing on the performance variability of human subjects we designed four tasks that differed in their sensorimotor processing, the number of intervals, and the modality of the stimuli used to define the intervals (Fig. 1). Importantly, in all the tasks the subjects temporalized their behavior in the range of 350 to 1000 ms. Using these factors we could group the tasks as follows: If timing was required for the guidance of movements, they were classified as time-production tasks, whereas time-perception tasks were those in which perceived intervals had to be compared. Depending on the number of time intervals being produced or compared, they could be categorized as single or multiple-timing tasks. Finally, the stimuli used to cue the subjects could be either visual or auditory [21].

Two tasks could be considered as perceptual. In the time interval Discrimination Task (Dis), subjects were presented with five stimuli that created four isochronous base intervals which were immediately followed by a sixth stimulus that produced a comparison interval. This could be shorter or longer than the base and subjects had to tell which it was by pressing one of two keys on the computer keyboard. The Categorization Task (Cat) had two phases, training and execution. In the training phase, two single intervals were presented to the subjects, an extremely short one and an extremely long one. After 20 trials were performed in this fashion, subjects were presented with six intermediate intervals additionally to the trained ones and subjects were instructed to categorize them as short or long using the prototypes acquired during training (Fig. 1).

In the other two tasks, time intervals were produced with movements. The Multiple Tapping Task (MTap) consisted on producing multiple isochronous intervals by tapping on a button. The first intervals were produced in synchronization with stimuli, which were immediately eliminated after the completion of four intervals and the subjects had to produce four additional internally-timed

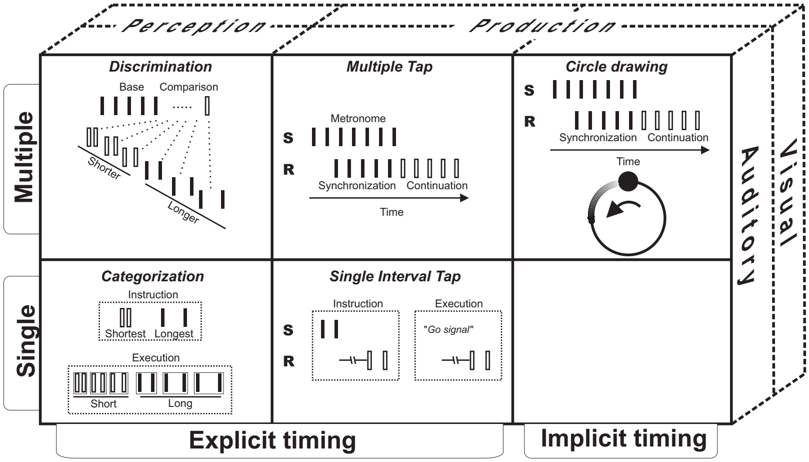

Fig. 1. Timing tasks. Five timing tasks, performed with auditory or visual interval markers, were used to evaluate the influence of four factors on timing performance: explicit vs. implicit, visual vs. auditory modality, single vs. multiple intervals, and perception vs. production of the intervals. Modified from [21,22]

intervals. The second production task, named Single Tapping Task (STap) had also two phases, instruction and execution. In the instruction phase two stimuli were presented sequentially, creating an interval that the subject was required to reproduce by tapping twice in the push-button. After five instruction trials, subjects did ten trials in the execution phase, in which no interval was presented and only a go signal indicated the subject to produce the instructed interval (Fig. 1).

An important feature of this study is that all subjects performed all the tasks, which increased the ability to detect intra- and inter-task differences in the temporal and non-temporal components of the behavior (Fig. 1). The first crucial observation in this study was that in all tasks the temporal variance increased as a function of the interval, following the scalar property of interval timing [23]. However, as it can be seen in Fig. 2, this relation differed across tasks and modalities. Experimental psychologists have used different analytical strategies to decompose the total variability of task performance into temporal and non-temporal elements. Such methods include the Wing-Kristofferson model [24] and the Slope model [25]. According to the Slope model, variability can be decomposed into time-dependent and time-independent processes from a linear regression between the variability and the squared interval duration. The former correspond to the slope in the regression, since it is directly related with the scalar property of interval timing, and the latter to the intercept. The intercept can be associated with the inherent sensorimotor and memory components of a particular task, which are constant across all the processed interval durations [25]. We used this analysis to test the difference in time-dependent variability between the tasks and found that perceptual, visual and single interval

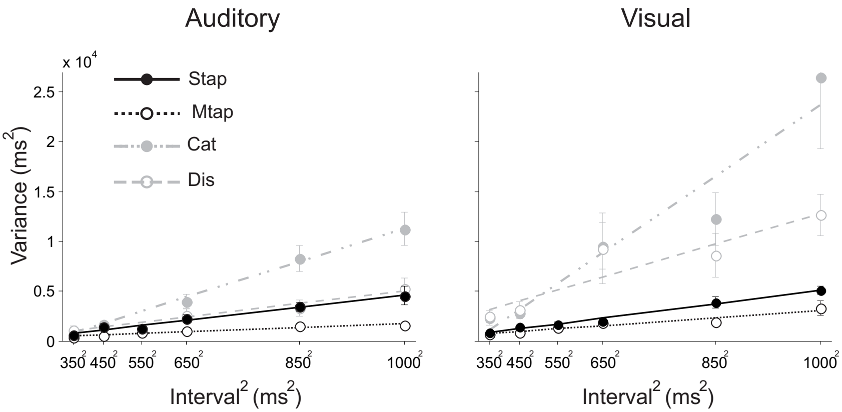

Fig. 2. Mean variances plotted as a function of the interval duration squared for the 4 different tasks in the auditory and visual conditions. Taken from [21].

tasks had significantly larger slopes than the production, auditory and multiple tasks (Fig. 2). These results have at least two interpretations: whether different mechanisms are being used for each task and modality or a common timing system is being modulated by the nature of the task.

We reasoned that if a common timing mechanism was being used to solve all the tasks, then a subject with small timing variability in one task would also have small variability in the other three behavioral paradigms [26]. Consequently, we performed a correlation analysis to compare the performance variability of each subject between pairs of tasks for all interval durations. Indeed, the results are graphically presented in Fig. 3 and show that subjects' performance showed a complex set of significant correlations between many tasks, with consistent correlations between the same task across modalities. These data cannot be interpreted as evidence for multiple timing mechanisms specific for each task context, nor as evidence for a common timing mechanism that functions equally every time a subject quantifies time. Hence, in concordance with the neuroimaging observations, we suggest the existence of a partially distributed timing mechanism, integrated by main core interconnected structures such as the cortico-thalamic-basal ganglia circuit, and areas that are selectively engaged depending on the specific behavioral requirement of a task. These task-dependent areas may interact with the main core timing system to produce the characteristic pattern of performance variability in a paradigm (Fig. 2) and the set of intertask correlations described in Fig. 3. Nevertheless, a precautionary note is in place here, since significant correlations could also be due to common individual cognitive strategies across many tasks.

In the tasks described above time was explicitly present. However, it has been shown that timing variability differs depending on the temporal goals of the task and whether time is guiding behavior directly or if it is an emergent property of the actions [1]. To tackle whether our explicit timing tasks differed from a task

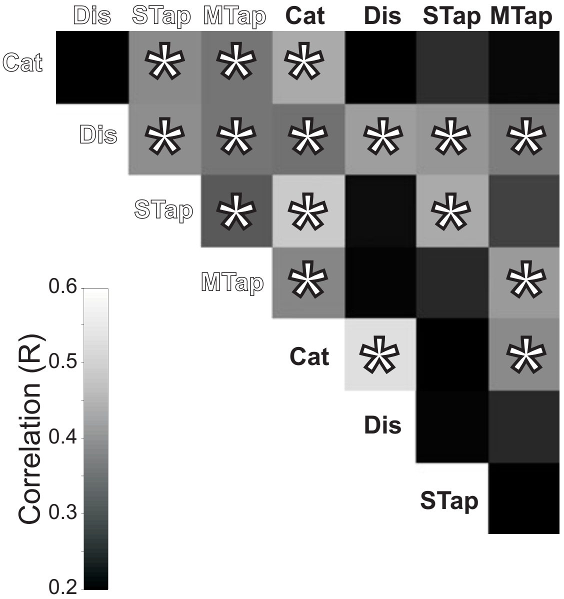

Fig. 3. Correlation matrix showing the Pearson R value in a grayscale (inset, bottom left) for all possible pairwise task comparisons. Asterisks indicate significant correlations ($P < 0.05$) between specific pairs of tasks. Open and closed fonts correspond to tasks with auditory and visual markers, respectively. Modified from [21].

where time processing is covertly present, we tested the same group of subjects on a Circle Drawing (CirD) task. This task has been regarded as an implicit-timing task, since the kinematic properties of continuous drawing can generate temporal behavior without engaging a neural explicit-timing clock [27]. By manipulating a joystick, subjects controlled the position of a cursor displayed in a monitor and were required to draw a circle following a path of 5 cm of diameter with it. Importantly, subjects were instructed to attempt to pass the cursor through a window in the path in coincidence with the presentation of isochronous auditory or visual stimuli. Once the subjects drew four circles, stimuli were extinguished and four additional circles had to be drawn at the same rate. Hence, the CirD task has the same structure of the MTT but instead of tapping, subjects continuously drew circles in a rhythmic fashion (Fig. 1).

With the subjects' performance variability we constructed a 9x9 dissimilarity matrix, which quantifies the distances in variability between all pairs of tasks [22]. This matrix was initially used for a hierarchical clustering analysis. This analysis accommodates the tasks in a representative spatial configuration known as dendrogram, which reflects how much of the variability in one task is related to the variability in the others. The clustering pattern we obtained is depicted in Fig. 4A and shows three important relationships between the tasks. First of all, the only implicit timing task we tested, circle drawing with both modalities, is

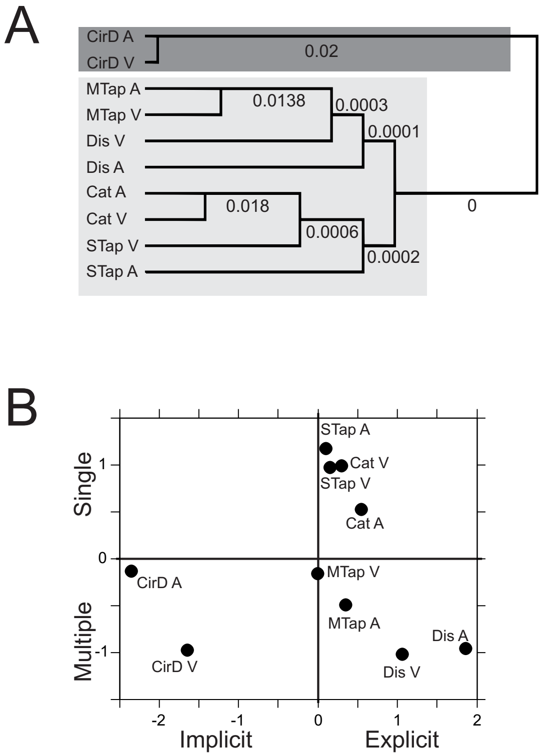

Fig. 4. A. Dendrogram for the temporal variability in the five tasks with both marker modalities, auditory (A) and visual (V). **B.** Two dimensional representation of the performance in the same tasks using multidimensional scaling analysis. Modified from [22].

isolated from the rest of the tasks that require explicit timing. Second, the two single interval tasks (STap and Cat), again with both modalities, are separated from the two multiple interval tasks by the next big branch. Finally, the same tasks with the different modalities are clustered together. The number on the top of the figure is the probability that each tree ramification was a random event. All the branches have a chance likelihood of $p < 0.05$.

Finally, we performed a multidimensional scaling analysis, a method that reduces the dimensionality of a data set, in our case the dissimilarity matrix, to create a two or three dimensional representation of the complex relation between the data. In this way we can obtain the most important underlying dimensions of our data set [22]. Fig. 4B presents our results, where it can be seen that the most important dimension, the abscissa, again separated the circle drawing task from the rest, whereas the second dimension, the ordinate, separated single from multiple interval tasks. Thus, explicit and implicit timing, as well as cyclic or multiple and single interval tasks generate clear differences in performance. The statistical significance of our results is less than 0.0087.

The results of these psychophysical comparisons suggest that the neural underpinnings of implicit timing is different from the dedicated mechanism for explicit timing. Indeed, the performance dissociation of explicit and implicit timing in repetitive tapping and drawing tasks has been meticulously documented using correlation [1, 27, 28] and slope [29] analyses. For example, the temporal consistency during a continuous circle drawing task (very similar to our circle drawing) is not correlated with the timing variability during multiple interval tapping, discrimination, or a task where circle drawing is intermittent [1, 27]. Therefore, it has been suggested that the neural mechanism for implicit timing depends of the motor and premotor areas that control the kinematic properties of continuous rhythmic movement behaviors, such as the circle drawing task, and is not quantifying the passage of time but controlling the velocity of the continuous movement [28]. The present results also showed an important segregation in the performance variability between single and multiple interval timing. This suggests that the activation of a cyclic pattern of behavior not only confers an advantage regarding temporal variability and accuracy in multiple interval tasks as reported before [21,25,30], but also may engage a distinctive neural substrate that can be discriminated from the single interval mechanisms using multivariate analytical approaches. Finally, the marker modality did not create superordinate dimensions in the resulting MDS axes. These results are at odds with studies showing that, in both perceptual and production tasks, visual stimuli produce more variable time estimates than auditory ones [21,31,32]. However, our present MDS results may reflect the fact that the explicit-implicit and number of timed intervals functional distinctions are more important than the task modality. In fact, the dendrograms obtained (Fig. 2), which showed a more comprehensive picture of the grouping between behavioral parameters, demonstrated the relevance of task modality.

Our results are in close agreement with those of the neuroimaging literature. They imply that the brain may use some common resources for explicit timing in the hundreds of milliseconds range, but that there are factors that can modify the processing of these intervals, probably by recruiting different structures depending on behavioral constrains. Future studies could measure the changes in the intensity of BOLD signal as a function of some of the mentioned non-temporal factors and the range of intervals that we used, and thus could help in the clarification of these issues. Indeed, multidimensional statistics could be used in order to test whether the structure of the multi-task temporal variability observed in our studies can be replicated using the changes in both the timing circuit configuration and the magnitude of the BOLD signal across brain areas. Needless to say that through neuroimaging and psychophysical studies we can only speculate about the cellular mechanisms behind time quantification. These mechanisms can be addressed with neurophysiological studies that have the spatial and temporal resolution needed to determine the neural codes behind time quantification. Some laboratories, including our own, are beginning to investigate this interesting problem in behaving non-human primates, that seem to be a promising animal model for this research area [33, 34, 35].

4 Contribution of Learning Studies to the Knowledge of Timing Systems

Learning experiments have been another useful tool, although indirect, for the study of different cognitive processes including temporal processing. The characterization of the properties of learning can provide important insights about the neural underpinnings of the behaviors being studied. The changes in behavior induced by training in a controlled context are informative per se, but if we also assess changes in non trained conditions, varying the behavioral context in a systematic way, we can get important additional information about the organization of the underlying neural systems.

Several studies have shown that timing can be improved by practice [36, 37, 38, 39, 40, 41]. In addition, most of these studies have also shown that these improvements can generalize to other timing behaviors. Thus, in this section we review the findings of timing learning-generalization literature including our recent experiment on the matter, which explored other information processing properties of the timing system engaged in the hundreds of milliseconds scale.

The rationale of the learning approach is the following. Let's imagine a network that processes the gray level of a visual stimulus, and that this network has to discriminate a specific gray level (50%-black) from a gradient ranging from 10% to 100%-black, producing a categorical output-signal every time that 50%-black is presented to the network (Fig. 5A). Then, let's assume that this network is able to perform this function from the beginning with a certain precision degree, giving an incorrect output in some trials. Next, we can train the network and produce an increase in its precision for the 50%-black stimulus, promoting a change in the network dynamics every time the output is incorrect while reinforcing correct responses. Finally, after training we can evaluate the precision for the discrimination not only for the 50%-black trained stimulus but also for the complete gray-gradient. This strategy allows to test whether the processing of other gray levels can also profit from the training, suggesting a functional overlap in how the network responds to the trained and non-trained conditions. We would expect that the discrimination errors will decrease with training, producing an output discrimination function that will be more precise for the gray levels surrounding and including the 50%-black, compared with the initial behavior of the network (Fig. 5A). Thus, these effects give us an idea of how the network processes information around the trained parameter, as well as its processing limits. This strategy is followed frequently in the artificial neural network literature. In the specific case of timing, an improvement in time perception induced by training would generalize toward untrained conditions if the time information is processed by the same network. Thus, the amplitude of the generalization window will be determined by the processing capabilities of a dedicated timing network under different timing contexts, which is another psychophysical tool to address the problem of one or multiple clocks, discussed above.

One of the first timing studies that used this approach reported a gradual improvement in a temporal discrimination task across a series of practice sessions [36]. Human subjects were requested to discriminate a standard interval,

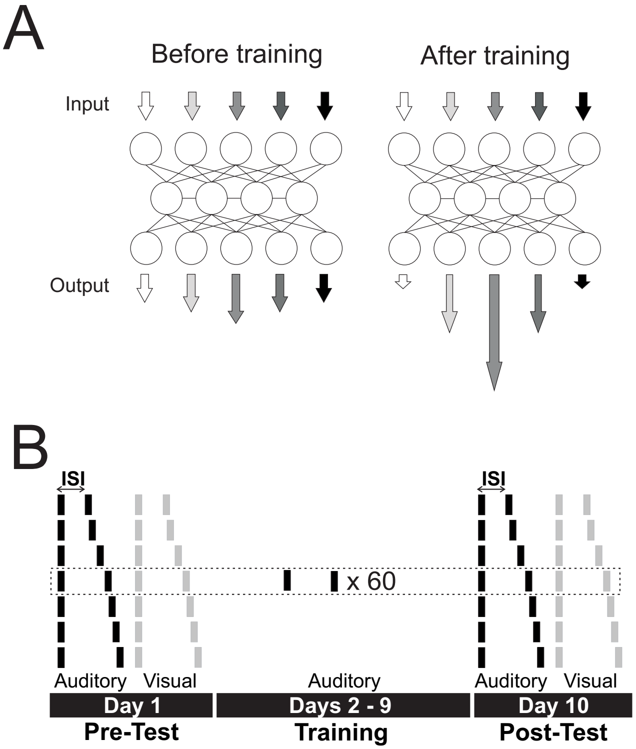

Fig. 5. A. Schematic representation of the learning generalization approach. A network that responds to the presentation of a gray-level stimulus, represented by the input arrows, with a probability of response represented by the size of the output arrow. **B.** Experimental design. The number of days is showed for each of three phases of the experiment (pre-test, training phase, and post-test). ISI - inter-stimuli interval. Modified from [44].

delimited by two tones of a given pitch, from comparison intervals in order to estimate the discrimination threshold. It was observed that the threshold gradually decreased with training, and that the total decrease of the threshold was statistically significant. Additionally, the subjects were tested in non trained conditions, in which the frequency of the tones or the duration of the standard interval were changed. Interestingly, it was observed that the learning effect was transferred to the discrimination of time intervals defined by stimuli with different pitch. However, there was no transfer of learning to standard intervals with different durations [36]. These results revealed that the temporal features are extracted from the auditory stimuli independently of the frequency, and suggest that a common timing network is recruited for time processing regardless of features of the auditory stimuli. On the other hand, the results also imply the existence of interval specific networks, since no learning transfer was observed between the durations of the trained and non-trained standard intervals. It has been suggested that the learning transfer depends on the improvement of temporal processing and not on more efficient memory or decision processes, at least for auditory interval discrimination [40].

In confirmation to the previous study, it has been observed that learning induces an improvement in the discrimination of intervals delimited by tactile stimuli, and that this learning generalizes: (1) across untrained skin locations on the trained hand, (2) to the corresponding untrained skin location in the contralateral hand, and (3) to a timing discrimination task of auditory stimuli [37]. The learning transfer in this study occurs again only in the trained duration [37]. In addition, it has also been observed that intensive learning in a time perception task can cause an improvement in a motor timing task that is restricted to the trained duration, suggesting that motor and perceptual timing share a common neural substrate, and that this substrate is duration-specific [39, 41]. The learning transfer from a perceptual to a motor task has been demonstrated with auditory [39] and tactile [41] interval markers, emphasizing the multimodal nature of the timing mechanism.

On the other hand, some studies suggest that early sensory areas play an important role on temporal processing. For example, it has been shown that learning to discriminate temporal modulation rates was accompanied not only by a specific learning transfer to a temporal interval discrimination (and not to a frequency discrimination task), but also by an increase in the amplitude of the early auditory evoked responses to trained stimuli [42]. This learning induced enhancement of early bilateral auditory evoked responses occurred in conjunction with an increase in the power of gamma oscillations in the inferior frontal cortex, suggesting that plasticity is not confined to auditory cortices and rather engages a distributed timing network [42]. Furthermore, a recent TMS study reported that the disruption of the auditory cortex impaired not only time discrimination of auditory stimuli but also impaired that of visual stimuli to the same degree. In contrast, TMS over the primary visual cortex impaired performance only in visual time discrimination. These asymmetric contributions of the auditory and visual cortices in time perception may be explained by a superiority of the auditory cortex in temporal processing [43]. Hence, these studies emphasize the role of sensory areas in time quantification, showing that auditory areas have a privileged status on temporal processing.

Overall, these studies support the idea of a common timing network that has access to multimodal information, with no topographical organization in the auditory (frequency based) or somatosensory (somatotopic organization) modalities, and that shares resources during time perception and time production. Therefore, this area of timing research also confirms our hypothesis of the existence of a partially distributed timing circuit, where the core network is affected by sensory areas in a context dependent fashion. In addition, these studies show a consistent duration specificity in the learning transfer of timing abilities, which suggest that timing neurons in the partially distributed timing circuit should be tuned to interval durations with relatively sharp tuning curves.

Regarding the latter point, the studies that have reported no learning generalization across interval durations have tested intervals with very different magnitudes (more than 50% of the trained interval), and, therefore, their sensitivity to measure learning transfer in the temporal domain has been low. Hence, one of the questions we had was whether the hypothetical groups of cells that are tuned to different interval durations show sharp or broad tuning curves, and whether the specificity of interval tuning depends on the magnitude of the processed interval. In order to study the learning of motor timing and the transfer of learning in the time domain, we designed an experiment in which several durations surrounding a standard interval (Fig. 5B) were used as targets in the Single Tapping Task (STap), described in the previous section (Fig. 1). Three groups of human subjects were submitted to extensive training (8 days) in one out of three standard Inter-Stimuli Intervals ([ISI] 450, 650 or 850 ms). The subjects completed 60 blocks of trials per day, and each block consisted of 5 instruction trials plus 15 execution trials (900 execution trials per day) using only the standard interval delimited by auditory stimuli [44]. With the purpose of evaluating the transfer of learning across intervals, the performance variability (standard deviation of the produced intervals) of a set of seven target ISI's was assessed using auditory and visual marker stimuli independently, before and after training (Fig. 5B). Therefore, this design allowed us to evaluate the transfer of motor timing learning across different intervals and modalities [44].

The first finding in our study was that human subjects showed a learning process for motor timing (Fig. 6). Learning was manifested as a gradual reduction in performance variability across training sessions, describing a decaying function similar to those observed in perceptual timing tasks [36, 37, 40, 45]. In fact, we found a significant decrease in intertap variability during the execution phase of the STap across training days (ANOVA, $p < 0.01$). In addition, we studied the learning dynamics for each subject by fitting the following power function:

$$SD = bT^m \tag{1}$$

where SD is the Standard Deviation of the produced intervals (dependent variable), T is the training day (independent variable), m is the time constant (slope) of the function, and b is the intercept, an estimate of the initial value of the curve. We found a significant difference in the intercept b but not in the slope of the power function across trained intervals. These results suggest that the initial value of the curve follows the scalar property of interval timing with a larger variability for larger interval magnitudes, a finding expected from the results reported above. In addition, our findings suggest that the learning dynamics is independent of the trained interval.

The next step was to characterize the transfer of learning in the temporal domain (transfer towards untrained intervals) and between sensory modalities. To this end, we constructed transfer curves where the difference in temporal variability before and after training (Pre-test - Post test) was plotted as a function of the interval magnitude. In addition, we performed one-sample t tests to determine whether the variability reduction was significantly different from

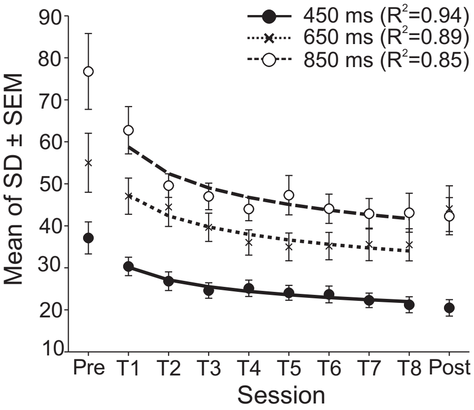

Fig. 6. Learning curves for motor timing. SD (mean ± SEM) of the produced intervals plotted as a function of the training day (T1-T8). Filled circles, crosses, and open circles are data for 450ms, 650ms, and 850ms, respectively. Lines are predicted curves from the fitting to a power function. Modified from [44].

zero for each interval. A clear transfer of learning was observed within the time domain for the three different trained intervals (Fig. 7). However, the generalization pattern (e.g. the intensity of transfer across intervals or modalities) was different for different trained intervals, as follows. For the trained interval of 450ms, we observed a strong generalization of learning only for intervals close to 450ms, whereas for the trained interval of 850ms we found a large learning transfer across a wide range of interval durations. The generalization pattern for the trained interval of 650ms showed intermediate values in terms of magnitude and interval spread; however, the transfer was less organized that the previous two intervals, with contiguous intervals showing inconsistent effects (Fig. 7). Interestingly, the transfer pattern was cross-modal across the three trained intervals. Although subjects were trained using only auditory stimuli, significant improvements were observed for the visual modality.

We performed Gaussian function fittings to the generalization patterns in Fig. 7. High coefficients of determination (R^2) were observed for the transfer curves of 450ms and 850ms, as it would be expected for an organized, gradually decreasing transfer of learning. In contrast, for the 650ms standard a low R^2 was found, in concordance the scattered pattern revealed by the t tests. More importantly, we found that the amplitude of the Gaussians (at the half height) showed a linear increase with the duration of the standard interval, following the scalar property of timing. Finally, the peak of the curves (the mean) was not centered on the trained interval, showing a bias between modalities. Indeed, the bias in the transfer functions might be related to the fact that auditory stimuli tend to be judged longer than visual stimuli [31,46]. Overall, these findings give indirect support for the presence of two important properties of the brain network involved in time quantification during the execution of the STT. First, at least a

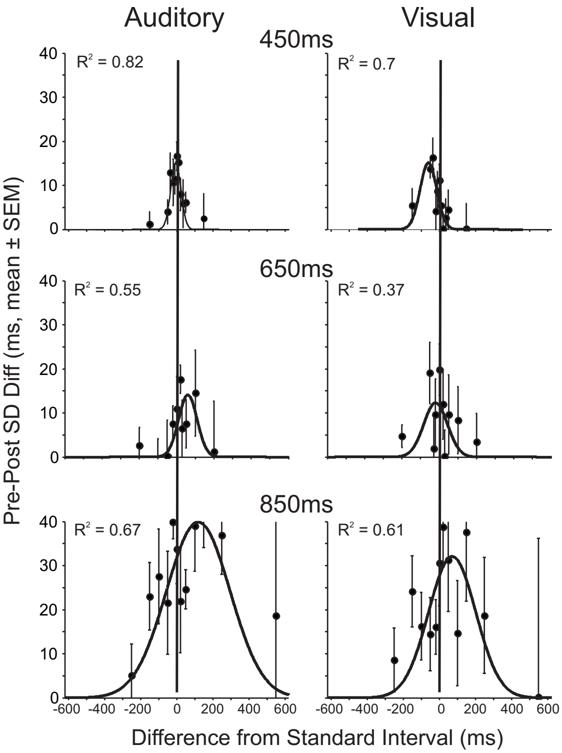

Fig. 7. Transfer curves. Mean (± SEM) difference in performance (Pre-training SD - post-training SD) is plotted as a function of the difference of the target interval with respect to the trained standard. Gaussian fittings were applied to the data and the coefficient of determination (R^2) is showed for each fitting. Taken from [44].

group of neurons in the timing circuit may be tuned to interval durations. The tuning curves of such neurons probably show an increase in tuning dispersion as a function of the preferred interval. This increase in tuning specificity could be one of the neural correlates of the scalar properties of interval timing [47]. Furthermore, our results give additional support for the existence of a multimodal timing circuit that shows a bias towards auditory stimuli (see also Figures 2 and 4). The asymmetrical effects of auditory and visual stimuli on temporal processing are probably due to the privileged access of auditory information [42,43,48] to the core timing network. During intensive learning, however, it is possible that not only the auditory areas but also part or the entire main core timing structures are subjected to plastic changes that increased their information processing [42]. Hence, the complete generalization from the auditory to the visual condition observed in our data could be the result of plastic changes in the main core explicit timing network.

The inconsistent transfer of learning for the 650ms standard is very peculiar and should give us a hint about the organization of the duration-specific or tuned neuronal populations. Previous studies have shown that the preferred (unpaced) tapping rate of humans has a bimodal distribution, with peaks around 270ms and 450ms [49, 50]. In addition, a language timing study showed that the distribution of pauses between phrases or paragraphs has also a bimodal distribution with peaks around 400ms and 1200ms, and where the intervals between 600ms and 750ms are the less frequent [51]. Hence, the interval of 650ms could be a duration that is not processed in a common fashion. Based on this evidence we can speculate that the properties of the timing network are shaped by the occurrence of the intervals present in our everyday life, so that the neurons that are tuned to interval durations show a distribution of preferred intervals that reflects the most common processed durations. Thus, we predict that the number of cells with preferred intervals around 650ms should be smaller than the cells with preferred intervals around 450ms and 850ms. An additional thought is that the sculpting of the preferred interval distribution by the environmental temporal patterns should be limited by the innate properties of the timing mechanism, in such a way that our abilities to quantify time across behavioral contexts should depend on the interaction between these two phenomena.

5 Interval Tuning Properties of an Artificial Neural Network

Previous neural network studies have suggested that neural circuits with dynamical changes in their excitatory-inhibitory interactions are able to process temporal information [18, 19, 52]. Consequently, in order to test some of the tuning properties of timing cells predicted by the previous learning and generalization study, we simulated a recurrent neural network. This neural network model was constructed using integrate-and-fire (I&F) units that are simple models of the electrical behavior of a single neuron. The I&F units are characterized by their passive integration in the subthreshold voltage range and the generation of stereotypic spikes above threshold [53]. In addition, we modeled three different time dependent properties of the postsynaptic integration: the paired-pulse facilitation of monosynaptic excitatory postsynaptic potentials (EPSPs), paired-pulse depression of fast inhibitory postsynaptic potentials (IPSPs), and the slow IPSPs produced by the activation of GABAb receptors (Fig. 8A). This network included 400 excitatory units and 100 inhibitory units, with a 20% of random recurrent connectivity and has a similar structure of the network reported by Buonomano in 2000 [18] (Fig. 8B). We used as input stimuli the same intervals included in the generalization experiment in humans: 450, 650, and 850 ms. In fact, two short bursts of activity separated by these durations were used to simulate the input intervals. In addition, we used a layer of perceptron units with backpropagation learning as the reading output of the network. The perceptron layer was connected to the excitatory neurons of the recurrent network and included 3 perceptron units, each associated with the discrimination of our tested intervals (450, 650 and 850 ms; Fig. 8B).

It is important to clarify that this neural network was designed to understand some basic principles of interval tuning in the hundreds of milliseconds range

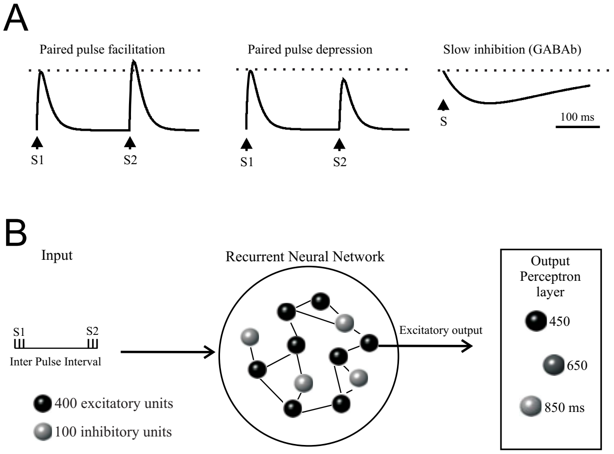

Fig. 8. A. Simulated pair-pulse facilitation of excitatory postsynaptic potential and pair-pulse depression of inhibitory postsynaptic potential in response to pairs of stimuli using a transmitter release probability $\tau_\alpha \frac{dP_\alpha}{dt} = P_\alpha - P_0$, and slow inhibition simulated with a double exponential $\frac{d^2I}{dt^2} + (\tau_r + \tau_d)\frac{dI}{dt} + (\tau_r \tau_d) I = \sum_j \sum_{ispike} w_{i,j} \delta (t_i - t)$. **B.** The recurrent neural network is composed of 400 excitatory and 100 inhibitory I&F neurons, with a 20% random connectivity. A layer of perceptron units with backpropagation learning was used as a reading output. We have 3 perceptrons corresponding to intervals 450, 650 and 850ms, which received inputs from the excitatory neurons of the recurrent network.

and how these tuning mechanisms could explain the patterns of generalization observed in our experiments. Hence, we are assuming that tuning is an important element used by the main core timing network to encode explicit temporal information. We are not addressing the multimodal or context-independency of interval tuning with these simulations. In fact, we are currently implementing a more sophisticated neural network in order to test how the main core timing areas can generate the scalar property of interval timing and how the specific areas that are engaged depending on the behavioral constrains can produce, in conjunction with the core areas, the patterns of temporal variability observed in the multitask and the learning-generalization studies. Seminal modeling work has suggested that an ubiquitous [19,54] or a centralized timing mechanism, like the Striatal Beat Frequency (SBF) model [55], can explain a range of temporal behaviors.

Interestingly, we found that the recurrent network was able to show interval tuning, characterized by selective neural responses to pairs of input stimuli separated by a particular duration (see the inset of the left panel of Fig. 9A). The tuning specificity depends on the weights of the set of inhibitory and excitatory inputs, as well as the time dependent properties that these inputs produce on the tuned cells. Changing systematically the weights of the excitatory connections with paired-pulse facilitation, as well as the weights of the GABAb connections

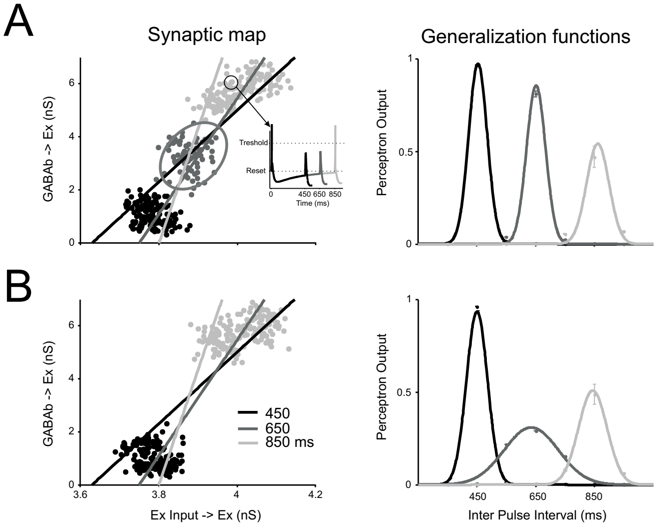

Fig. 9. A. *Left panel*: Synaptic map of the efficacy of GABAb connections (ordinate) and excitatory connections (abscissa) to excitatory neurons in response to pairs of input pulses separated by 450 (black dots), 650 (dark gray dots), or 850 (light gray dots) ms. Thus, depending of the strength of synaptic weights the excitatory neurons respond selectively to inter pulse intervals. The inset panel shows an excitatory neuron that responds selectively to 850ms due to the specific combination of input weights. Lines show the threshold for the interval specific response to the second input pulse stimulus. Black line: 450ms, dark gray line: 650ms, and light gray line: 850ms. *Right panel*: Probability of correct classification by perceptron units to inter pulse interval ranging from 350 to 950 ms. **B.** The same than A but with a synaptic map configuration that does not include the weights for the 650ms selective responses.

to the excitatory cells of the network, we were able to determine a synaptic space where different interval specificities were produced (Fig. 9A, left panel). For example, when both the excitatory and the GABAb inputs weights are high, the circuit produces tuned responses to the 850ms interval. In contrast, when the excitatory weight is moderate, and the facilitation of the excitatory input over-weights the GABAb low input, the circuit shows a selective activation for the 450ms interval (Fig. 9A, left panel).

Initially, we tested the generalization pattern of the recurrent network using a homogenous distribution of weights in the synaptic map (Fig. 9A, left panel). The generalization function for each trained interval was obtained once the perceptron layer was trained to discriminate that interval, and the network was tested to a wide range of intervals without allowing for further learning. Indeed, the right panel of Fig. 9A shows the probability of correct classification by the perceptron units to interval durations ranging from 350 to 950 ms after the network was trained to the 450, 650 and 850 ms intervals independently. It is evident that the width of the generalization curve increased as a function of the duration of the trained interval, following the same organizations observed in the learning and generalization study in human subjects. Therefore, these results suggest that interval tuning can be generated in the timing network through a combination of inhibitory and excitatory weights that show different time dependent properties, such as paired-pulse facilitation of EPSPs, paired-pulse depression of fast IPSPs, and slow IPSPs.

The learning transfer of the interval specificities in the recurrent network showed similar properties observed in the generalization study of motor learning in the STap task. However, an important difference in our network simulations was that the 650ms trained interval showed a strong and systematic generalization across neighbor intervals. In contrast, human subjects showed an inconsistent transfer pattern for interval surrounding the trained 650ms interval. The final question, then, was what is the configuration of weights in the synaptic map that could produce generalization functions in the recurrent network that follow more closely the results obtained in the human subjects study. After testing different synaptic map configurations, we found that a synaptic map with two discrete distributions of weights, one in the lower left quadrant of the map (around the 450ms selective weight area), and another in the upper right quadrant (around the 850ms selective weight area; see the left panel of Fig. 9B), produced generalization functions that were closer to the human timing performance. In fact, the generalization functions depicted in the right panel of Fig. 9B show that the learning transfer for the interval of 650ms was smaller than the 450 and 850 ms trained intervals. Therefore, these findings suggest that the deficient learning transfer for the 650ms in human subjects could be due to a decrease in the frequency of the synaptic weights that lead to the interval specificity to this duration. The decrease in the frequency of specific synaptic weight combinations could be imposed by the occurrence of the intervals processed in our daily life behaviors, as discussed in the previous section.

Overall, our simulation experiments showed that a recurrent network that includes synaptic time dependent properties can produce interval selective responses with a pattern of generalization that was similar to the one observed in the psychometric study in human subjects, with an increase in the width of the generalization function as a function of the duration of the trained interval and a dip in the transfer height for the 650ms interval. The latter effect can be produced by a synaptic map that shows a strong bias towards the synaptic weights associated with the tuning of the 450 and 850 ms intervals.

6 Concluding Remarks

Learning and generalization studies, including our own, provide evidence for the existence of a dedicated general timing mechanism that has access to multimodal information and is engaged in the perception and production of time intervals. Furthermore, our multiple-task psychophysical studies suggest that these behavioral parameters, together with the number of processed intervals, can influence in a specific fashion the performance of the timing mechanism. These latter observations have refined our hypothesis, suggesting that time quantification in the hundreds of milliseconds depends on a partially distributed circuit of interconnected brain areas. In addition, our learning and generalization study gave support to the notion that at least a fraction of the neurons of the time processing neural circuit should be tuned to different interval durations, and that the width of their tuning curves may increase as a function of their preferred intervals. Artificial neural network simulations demonstrated that interval tuning can be produced in a simple recurrent network that includes different time dependent synaptic properties. Indeed, preliminary neurophysiological studies performed in our laboratory on behaving monkeys, have shown that a portion of neurons in the supplementary motor cortex are tuned to interval durations during the execution of different timing tasks.

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