



Time and number: the privileged status of small values in the brain

Catalin V. Buhusi^{1*} and Sara Cordes²

¹ Department of Neurosciences, Medical University of South Carolina, Charleston, SC, USA

² Department of Psychology, Boston College, Boston, MA, USA

*Correspondence: buhusi@musc.edu

When dancing, one follows the rhythm without much conscious control, while also singing, entertaining a conversation, planning intricate sequences of steps, or estimating the time until the end of the song. Processing of rapid beats, in the sub-second range seems to be done automatically and doesn't appear to interfere with timekeeping in the range of seconds or minutes, required for planning the steps, or estimating the duration left until the end of the song. This may be because the processing of rapid beats and slow sequences is split between different timing mechanisms and/or the left and the right hemispheres of our brain (Hancock, 2011).

Relatively distinct brain circuits process time in the millisecond, seconds-to-minutes, or circadian range (Buhusi and Meck, 2005), but the distinction blurs around 1-s intervals. Circadian timing, which operates over roughly 24 h, and controls functions such as the sleep-wake cycle and the metabolic processes, is based on a molecular clock in the suprachiasmatic nucleus (Gallego and Virshup, 2007; Allman and Meck, 2011). Millisecond timing engages a variety of specialized local circuits in the cerebellum (De Zeeuw et al., 2011), for fast and fine movement control, or in the auditory cortex, for speech processing (Nourski and Brugge, 2011). Finally, planning and motor control in the seconds range engages the cortico-striatal circuits, motor, parietal, and prefrontal cortices, both in animals (Meck et al., 2008; Buhusi and Meck, 2009) and humans (Coull et al., 2004, 2011; Stevens et al., 2007). The relative separation of these circuits explains why one can deal with different attributes simultaneously, but also raises the possibility of conflicts or cooperation between these circuits for time intervals around 1 s.

The question of whether sub- and supra-second timing engages distinct brain circuits was recently investigated in patients with unilateral hemispheric lesions

(Gooch et al., 2011). Rather than selecting patients by lesion, the study used voxel-based lesion-symptom mapping (Bates et al., 2003) in patients with various lesions, and evaluated the contribution of each voxel for the overall performance in all patients, thus tapping into the circuits critical for timing without using *a priori* assumptions regarding the location of interest.

Three findings bear noting. First, patients with lesions in the frontal or parietal cortices were less accurate than controls, thus supporting neurobiological models of timing suggesting that cortico-striatal circuits (Matell and Meck, 2004; Buhusi and Meck, 2005; Oprisan and Buhusi, 2011) and parietal circuits (Leon and Shadlen, 2003) develop neural representations of time. Second, the right hemisphere was involved in timing both sub- and supra-second timing, consistent with previous studies implicating right cortical regions in interval timing (Schubotz et al., 2000; Rubia et al., 2003; Smith et al., 2003; Coull et al., 2004; Meck and Malapani, 2004; Lewis and Miall, 2006; Bueti et al., 2008), and supporting the hypothesis that right dorsolateral prefrontal cortex is crucial for timekeeping (Lewis and Miall, 2006; Meck et al., 2008). Instead, the left temporal lobe was involved in timing sub-second durations only, consistent with its implication in processing fast, auditory information. Thus, whereas all durations required the same circuitry in the right hemisphere, only the shortest intervals (<1 s) involved additional left-hemisphere structures, suggesting millisecond timing may have a special status in the brain.

This distinction between short (sub-second) and longer intervals (supra-second) is not unique to time. Remarkable parallels exist between counting and timing, such that it has long been thought that counting may tap into similar cognitive and neural mechanisms as that of time (Meck and Church, 1983; Walsh, 2003; Feigenson,

2007; Cantlon et al., 2009). Timing and counting abilities are found in a diverse range of non-human animal species, from honeybees and rats to dolphins and monkeys (Meck and Church, 1983; Cantlon and Brannon, 2007; Cordes et al., 2007; Dacke and Srinivasan, 2008), and they share striking similarities, including Weber's law: The ease with which two durations or numbers are discriminated is based upon their ratio, not their absolute difference (Meck and Church, 1983; Cantlon and Brannon, 2007). All species share a system for representing time and number that must have arisen early in evolutionary history and is present early in development (Xu and Spelke, 2000; vanMarle and Wynn, 2006; Brannon et al., 2007, 2008 – see Gallistel, 1990). In fact, time and number may even be represented using a common metric, in which the representation of one count is equivalent to 200 ms of time (Meck and Church, 1983; but see Balci and Gallistel, 2006). Support for the claim that representations of time and number are derived from the same mechanism is also provided by neurobiological studies of numerical processing, which like those of temporal processing, implicate parietal areas and, at least early in development, this activation is unique to the right hemisphere (Rivera et al., 2005; Cantlon et al., 2006) as in the case of time.

Furthermore, whereas both behavioral and neural evidence suggests a distinction between sub-second and supra-second timing, a similar distinction exists between representations of small (<4 or 5) sets and larger sets. Behavioral data from adults, infants, non-human primates, and even mosquitofish reveal that small sets are treated differently than large sets (e.g., Trick and Pylyshyn, 1994; Hauser and Carey, 2003; Agrillo et al., 2008; Cordes and Brannon, 2009a,b). For example, when asked to rapidly identify the number of items in a set, adults reveal little to

no reaction time cost for each additional item in a small set (termed “subitizing”), but once set sizes exceed 4 or 5 items, the slope of the reaction time function markedly increases. More strikingly, despite strict adherence to Weber’s law for large set discriminations, infants and non-human animals reveal sharper discrimination abilities when sets are exclusively small (e.g., discriminating 2 from 3 but not 4 from 6, despite similar ratios; Feigenson et al., 2002) yet consistently fail to discriminate small from large sets despite a favorable ratio (e.g., failing to discriminate 2 from 4 or 3 from 6, despite successfully detecting twofold changes in number for larger sets, e.g., 4 vs 8 or 8 vs 16; Xu, 2003; Cordes and Brannon, 2009b). Lastly, infants with Williams syndrome discriminate small sets (2 from 3) but fail in large set discrimination (4 vs 8), suggesting these distinct numerical systems can be selectively affected (Van Herwegen et al., 2008). Whereas, unlike in the case of time where sub-second and supra-second durations are presumably both represented via a common currency of continuous mental magnitudes, evidence suggests that small numerical values may be represented in a distinctly different fashion from large ones (discrete object files for small sets and noisy analog magnitudes for large). Regardless, striking similarities in discontinuities are observed across both systems suggesting there may be something special about these small quantities.

Neural activation patterns for small numbers also selectively involve secondary brain areas distinct from those for large sets. Like time, small and large numerosities alike activate similar neural circuitry, however, again as in the case of time, additional activation is found in distinct structures (the right temporo-parietal junction) when small sets are encountered (Ansari et al., 2006). Interestingly, activation in this additional small-number structure is negatively correlated with reaction times during large number judgments suggesting that it is through the inhibition of this small-number system that large sets are processed. Therefore, much like the case of sub-second timing, additional neural circuitry appears to be dedicated to small numerosities, indicating the ability to process small values may have been favored throughout evolution.

Why is this the case? Processing short durations and small sets are critical to survival. In the case of time, a number of important skills, including speech production and comprehension, motor planning and even musical performance, are dependent upon sub-second timing (e.g., Shannon et al., 1995; Merchant and Georgopoulos, 2006; Tallal and Gaab, 2006). Differences in the order of tens of milliseconds can lead to dramatic differences in phonological processing (in the case of language), motor coordination, and even rhythm perception. In fact, millisecond timing is so crucial for speech that basic training in rhythm and intonation has been found to help patients with non-fluent aphasia regain their speech through singing words they cannot speak (Melodic Intonation Therapy: Naeser and Helm-Estabrooks, 1985; Popovici, 1995; Norton et al., 2009). Similarly, the ability to track small sets of objects can also make the difference between life and death when those objects are predators, prey, or even offspring. Presumably, attending to more than one item at a time should also subserve proper functioning in more complex situations such as social interactions and multi-tasking.

Although much has been learned regarding the behavioral and neural signatures across the time and number spectrums, many questions remain unanswered. How does the brain negotiate timing and counting conflicts at these small/large boundaries? Since evidence suggests large numbers are efficiently processed through the inhibition of the small-number brain area, does a similar inhibitory mechanism underlie the processing of durations longer than 1 s? Despite distinct localizations and functions of small set processing and sub-second timing, are there common features to their behavioral or neural make-up? Understanding the competition and cooperation between brain regions involved in interval timing and counting (Lewis and Meck, 2011) may lead to a better understanding of the mechanisms disregulated in disorders such as schizophrenia, dyslexia, Parkinson’s disease, Williams syndrome, and dyscalculia – all characterized by timing and/or counting deficits – and the development and refinement of behavioral therapies to alleviate them (e.g., Sparks et al., 1974; Overy, 2003; Wilson et al., 2006; Breier et al., 2010; Wan et al., 2010; Vines et al., 2011).

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health grants MH65561 and MH73057 to Catalin V. Buhusi, and an Alfred P. Sloan Research Fellowship to Sara Cordes. We would like to thank Warren H. Meck for insightful comments on an earlier version of this manuscript.

REFERENCES

- Agrillo, C., Dadda, M., Serena, G., and Bisazza, A. (2008). Do fish count? Spontaneous discrimination of quantity in female mosquitofish. *Anim. Cogn.* 11, 495–503.
- Allman, M. J., and Meck, W. H. (2011). Pathophysiological distortions in time perception and timed performance. *Brain*. doi: 10.1093/brain/awr210
- Ansari, D., Lyons, I. M., van Eimeren, L., and Xu, F. (2006). Linking visual attention and number processing in the brain: the role of the temporo-parietal junction in small and large symbolic and nonsymbolic number comparison. *J. Cogn. Neurosci.* 19, 1845–1853.
- Balci, F., and Gallistel, C. R. (2006). Cross-domain transfer of quantitative discriminations: is it all a matter of proportion? *Psychon. Bull. Rev.* 13, 636–642.
- Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., and Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nat. Neurosci.* 6, 448–450.
- Brannon, E. M., Libertus, M. E., Meck, W. H., and Woldorff, M. G. (2008). Electrophysiological measures of time processing in infant and adult brains: Weber’s law holds. *J. Cogn. Neurosci.* 20, 193–203.
- Brannon, E. M., Suanda, S., and Libertus, K. (2007). Temporal discrimination increases in precision over development and parallels the development of numerosity discrimination. *Dev. Sci.* 10, 770–777.
- Breier, J. I., Randle, S., Maher, L. M., and Papanicolaou, A. C. (2010). Changes in maps of language activity activation following melodic intonation therapy using magnetoencephalography: two case studies. *J. Clin. Exp. Neuropsychol.* 32, 309–314.
- Bueti, D., Walsh, V., Frith, C., and Rees, G. (2008). Different brain circuits underlie motor and perceptual representations of temporal intervals. *J. Cogn. Neurosci.* 20, 204–214.
- Buhusi, C. V., and Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nat. Rev. Neurosci.* 6, 755–765.
- Buhusi, C. V., and Meck, W. H. (2009). Relative time sharing: new findings and an extension of the resource allocation model of temporal processing. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 364, 1875–1885.
- Cantlon, J. F., and Brannon, E. M. (2007). Basic math in monkeys and college students. *PLoS Biol.* 5, e328. doi: 10.1371/journal.pbio.0050328
- Cantlon, J. F., Brannon, E. M., Carter, E. J., and Pelphrey, K. A. (2006). Functional imaging of numerical processing in adults and 4-year-old children. *PLoS Biol.* 4, e125. doi: 10.1371/journal.pbio.0040125
- Cantlon, J. F., Platt, M. L., and Brannon, E. M. (2009). Beyond the number domain. *Trends Cogn. Sci. (Regul. Ed.)* 13, 83–91.
- Cordes, S., and Brannon, E. M. (2009a). The relative saliency of discrete and continuous quantities in infants. *Dev. Sci.* 12, 453–463.
- Cordes, S., and Brannon, E. M. (2009b). Crossing the divide: infants discriminate small from large numerosities. *Dev. Psychol.* 45, 1583–1594.

- Cordes, S., King, A. P., and Gallistel, C. R. (2007). Time left in the mouse. *Behav. Processes* 74, 142–151.
- Coull, J. T., Cheng, R. K., and Meck, W. H. (2011). Neuroanatomical and neurochemical substrates of timing. *Neuropsychopharmacology* 36, 3–25.
- Coull, J. T., Vidal, F., Nazarian, B., and Macar, F. (2004). Functional anatomy of the attentional modulation of time estimation. *Science* 303, 1506–1508.
- Dacke, M., and Srinivasan, M. V. (2008). Evidence for counting in insects. *Anim. Cogn.* 11, 683–689.
- De Zeeuw, C. I., Hoebeek, F. E., Bosman, L. W., Schonewille, M., Witter, L., and Koekkoek, S. K. (2011). Spatiotemporal firing patterns in the cerebellum. *Nat. Rev. Neurosci.* 12, 327–344.
- Feigenson, L. (2007). The equality of quantity. *Trends Cogn. Sci. (Regul. Ed.)* 11, 185–187.
- Feigenson, L., Carey, S., and Hauser, M. (2002). The representations underlying infants' choice of more: object files versus analog magnitudes. *Psychol. Sci.* 13, 150–156.
- Gallego, M., and Virshup, D. M. (2007). Post-translational modifications regulate the ticking of the circadian clock. *Nat. Rev. Mol. Cell Biol.* 8, 139–148.
- Gallistel, C. R. (1990). *The Organization of Behavior*. Cambridge, MA: MIT Press.
- Gooch, C. M., Wiener, M., Hamilton, A., and Coslett, H. B. (2011). Temporal discrimination of sub- and supra-second time intervals: a voxel-based lesion mapping analysis. *Front. Integr. Neurosci.* 5:59. doi: 10.3389/fnint.2011.00059
- Hancock, P. A. (2011). On the left hand of time. *Am. J. Psychol.* 124, 177–188.
- Hauser, M., and Carey, S. (2003). Spontaneous representations of small numbers of objects by rhesus macaques: examinations of content and format. *Cogn. Psychol.* 47, 367–401.
- Leon, M. I., and Shadlen, M. N. (2003). Representation of time by neurons in the posterior parietal cortex of the macaque. *Neuron* 38, 317–327.
- Lewis, P. A., and Meck, W. H. (2011). Does sleep contribute to degeneracy in neural timing? *The Psychologist* (in press).
- Lewis, P. A., and Miall, R. C. (2006). A right hemispheric prefrontal system for cognitive time measurement. *Behav. Processes* 71, 226–234.
- Matell, M. S., and Meck, W. H. (2004). Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes. *Brain Res. Cogn. Brain Res.* 21, 139–170.
- Meck, W. H., and Church, R. M. (1983). A mode control model of counting and timing processes. *J. Exp. Psychol. Anim. Behav. Process.* 9, 320–334.
- Meck, W. H., and Malapani, C. (2004). Neuroimaging of interval timing. *Brain Res. Cogn. Brain Res.* 21, 133–137.
- Meck, W. H., Penney, T. B., and Pouthas, V. (2008). Cortico-striatal representation of time in animals and humans. *Curr. Opin. Neurobiol.* 18, 145–152.
- Merchant, H., and Georgopoulos, A. P. (2006). Neurophysiology of perceptual and motor aspects of interception. *J. Neurophysiol.* 95, 1–13.
- Naeser, M. A., and Helm-Estabrooks, N. (1985). CT scan lesion localization and response to melodic intonation therapy with nonfluent aphasia cases. *Cortex* 21, 203–223.
- Norton, A., Zipse, L., Marchina, S., and Schlaug, G. (2009). Melodic intonation therapy: shared insights on how it is done and why it might help. *Ann. N. Y. Acad. Sci.* 1169, 431–436.
- Nourski, K. V., and Brugge, J. F. (2011). Representation of temporal sound features in the human auditory cortex. *Nat. Rev. Neurosci.* 22, 187–203.
- Oprisan, S. A., and Buhusi, C. V. (2011). Modeling pharmacological clock and memory patterns of interval timing in a striatal beat-frequency model with realistic, noisy neurons. *Front. Integr. Neurosci.* 5:52. doi: 10.3389/fnint.2011.00052
- Overy, K. (2003). Dyslexia and music. From timing deficits to musical intervention. *Ann. N. Y. Acad. Sci.* 999, 497–505.
- Popovici, M. (1995). Melodic intonation therapy in the verbal decoding of aphasics. *Rom. J. Neurol. Psychiatry* 33, 57–97.
- Rivera, S. M., Reiss, A. L., Eckert, M. A., and Menon, V. (2005). Developmental changes in mental arithmetic: evidence for increased functional specialization of the left inferior parietal cortex. *Cereb. Cortex* 15, 1779–1790.
- Rubia, K., Smith, A. B., Brammer, M. J., and Taylor, E. (2003). Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage* 20, 351–358.
- Schubotz, R. I., Friederici, A. D., and Von Cramon, D. Y. (2000). Time perception and motor timing: a common cortical and subcortical basis revealed by fMRI. *Neuroimage* 11, 1–12.
- Shannon, R. V., Zeng, F. G., Kamath, V., Wygonski, J., and Ekelid, M. (1995). Speech recognition with primarily temporal cues. *Science* 270, 303–304.
- Smith, A., Taylor, E., Lidzba, K., and Rubia, K. (2003). A right hemispheric frontocerebellar network for time discrimination of several hundreds of milliseconds. *Neuroimage* 20, 344–350.
- Sparks, R., Helm, N., and Albert, M. (1974). Aphasia rehabilitation resulting from melodic intonation therapy. *Cortex* 10, 303–316.
- Stevens, M. C., Kiehl, K. A., Pearlson, G., and Calhoun, V. D. (2007). Functional neural circuits for mental timekeeping. *Hum. Brain Mapp.* 28, 394–408.
- Tallal, P., and Gaab, N. (2006). Dynamic auditory processing, musical experience, and language development. *Trends Neurosci.* 29, 382–390.
- Trick, L., and Pylyshyn, Z. (1994). Why are small and large numbers enumerated differently? A limited capacity preattentive stage in vision. *Psychol. Rev.* 101, 80–102.
- Van Herwegen, J., Ansari, D., Xu, F., and Karmiloff-Smith, A. (2008). Small and large number processing in infants and toddlers with Williams syndrome. *Dev. Sci.* 11, 637–643.
- vanMarle, K., and Wynn, K. (2006). Six-month-old infants use analog magnitudes to represent duration. *Dev. Sci.* 9, F41–F49.
- Vines, B. W., Norton, A. C., and Schlaug, G. (2011). Non-invasive brain stimulation enhances the effects of melodic intonation therapy. *Front. Psychol.* 2:230. doi: 10.3389/fpsyg.2011.00230
- Walsh, V. (2003). A theory of magnitude: common cortical metrics of time, space, and quantity. *Trends Cogn. Sci. (Regul. Ed.)* 7, 483–488.
- Wan, C. Y., Uber, T. R., Hohmann, A., and Schlaug, G. (2010). The therapeutic effects of singing in neurological disorders. *Music Percept.* 27, 287–295.
- Wilson, A. J., Dehaene, S., Pinel, P., Revkin, S. K., Cohen, L., and Cohen, D. (2006). Principles underlying the design of “The Number Race,” an adaptive computer game for remediation of dyscalculia. *Behav. Brain Funct.* 2, 1–14.
- Xu, F. (2003). Numerosity discrimination in infants: evidence for two systems of representations. *Cognition* 89, B15–B25.
- Xu, F., and Spelke, E. S. (2000). Large number discrimination in 6-month-old infants. *Cognition* 74, B1–B11.

Received: 06 October 2011; accepted: 06 October 2011; published online: 31 October 2011.

Citation: Buhusi CV and Cordes S (2011) Time and number: the privileged status of small values in the brain. *Front. Integr. Neurosci.* 5:67. doi: 10.3389/fnint.2011.00067

Copyright © 2011 Buhusi and Cordes. This is an open-access article subject to a non-exclusive license between the authors and Frontiers Media SA, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and other Frontiers conditions are complied with.