



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

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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).

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