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The neuroscience of time and number: untying the Gordian knot

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Many aspects of the neuroscience of time and number (NEUTIN), as well as its associated psychophysics, have objective, absolute qualities reminiscent of Newtonian physics. For example, both time and number representations have been hypothesized to be based on the absolute value of a pulse-accumulation process generated by a neural pacemaker whose temporal integration is linear with the duration and/or number of events (Gibbon et al., 1984; Buhusi and Meck, 2005; Allman et al., 2011). Moreover, it has been shown that a single "count" within such a pacemaker/accumulator equals a fixed amount of time (e.g., 200 ms). This finding suggests that "pulses" have a uniform size and serve as a common currency for both time and number as long as the pulse-accumulation process can be operated simultaneously in "event" (count) or "run" (time) modes (Meck and Church, 1983; Meck et al., 1985; Meck, 1997; Breukelaar and Dalrymple-Alford, 1998; Roberts et al., 2000; Brannon and Roitman, 2003; Cordes et al., 2007; Roitman et al., 2007). On the other hand, our experience of time and number evokes another well-known characteristic of physics, relativity theory. This aspect is captured by the scalar property: Temporal and numerical judgments are based on the proportional relationships among the durations being timed and/or the objects or events being counted (Gibbon, 1977; Gibbon et al., 1984; Brannon et al., 2001, 2008; Cheng and Meck, 2007; Buhusi and Meck, 2009a,b).

Information processing models of time and number magnitude describe the scalar property as deriving from cognitive processes such as attention, short-term memory, and reference memory (e.g., the mode-control model of counting and timing; Meck and Church, 1983; Meck et al., 1985). Distortions in numerical and temporal cognition occur in neurological and psychiatric conditions that disrupt these processes (e.g., attention deficit hyperactivity disorder, autism, dyscalculia, Parkinson's disease, and schizophrenia) – see Allman and Meck (2011). However, our understanding of the mechanisms underlying NEUTIN and their specific relations to the brain mechanisms underlying other aspects of cognitive processing remains in its infancy.

One barrier to understanding the intricate, intertwined nature of the relations among temporal, numerical, and other aspects of cognitive processing is that researchers have often adopted an Alexandrian solution – that is, divided these aspects into different fields of study. This has led to a lack of consistent agreement on terminology, creating further obstacles to a unified understanding (Paule et al., 1999; Meck and Benson, 2002; Buhusi and Meck, 2005; Meck, 2005; Meck et al., 2008; Coull et al., 2011). There is also a need for technological advances to improve the spatial and, especially critical in this context, temporal resolution of current neuroimaging methods. However, if these efforts are undertaken, the exploration of how the brain performs temporal integration across multiple time scales is expected to be among the premier topics to unite systems, cellular, computational, and cognitive neuroscience over the next decade (Buonomano, 2007).

Questions concerning the impact of development, sensory modality, sleep-dependent memory consolidation, stimulus field/whole-body motion, and genetic predispositions toward increased/decreased neurotransmitter activities of dopamine, glutamate, and serotonin systems in cortico-striatal circuits will be important components in future studies of numerical and temporal cognition (Libertus and Brannon, 2009; Dehaene and Brannon, 2010; Sysoeva et al., 2010; Agostino et al., 2011; Wiener et al., 2011). Meanwhile several theoretical and empirical developments promise a more integrated view. In particular, we have suggested that the identity properties of an item (color, shape, size, location, etc.) may be coded by which cortical neurons are firing while temporal properties are coded by the oscillatory properties of that firing (Lustig et al., 2005). Attention serves to modulate and maintain the integrity of this representation, and striatal neurons act as "coincidence detectors" first encoding and then responding to behaviorally relevant patterns of identity and oscillatory inputs. This approach brings together feature-based views of representations in short- and long-term memory (e.g., Oberauer and Kliegl, 2006; see Jonides et al., 2008; Lustig et al., 2009 for discussion) with views that emphasize oscillatory processes and the detection of specific oscillatory patterns for working memory and timing (e.g., Matell and Meck, 2004; Hazy et al., 2006).

Recent findings from Harrington et al. (2010) are interesting from this perspective. Cortico-striatal activation patterns differed at encoding depending on whether participants attended to the pitch or the duration of a tone; in particular, the striatum was especially active during duration encoding, possibly reflecting its role in integrating oscillations across cycles to represent the passage of time (Matell and Meck, 2004; Meck et al., 2008; Allman and Meck, 2011; Harrington et al., 2011a,b; Portugal et al., 2011). However, during retention, striatal activation was equivalent for the two stimulus classes (and greater than a control task), consistent with a striatal role in modulating thalamocortical structures to recurrently maintain the activation patterns associated with relevant stimuli. Another study (Manning et al., 2011) found direct evidence for the role of oscillations in encoding temporal-order information using intercranial recording methods. When patients recalled items they had previously studied, not only were oscillatory patterns present at encoding recapitulated, but the similarity between the oscillatory patterns associated with different items at retrieval varied linearly with the distance between those items at encoding. In addition, those patients that had stronger reinstatement patterns in neural oscillations were also more likely to show temporal clustering in their behavioral recall. Interest in fMRI and EEG measures of oscillatory activity in both resting-state and task-oriented neural networks is also rising (e.g., Laufs et al., 2003; Achard et al., 2006) and presents an exciting opportunity for integration with NEUTIN.

The translational impetus to further integrate NEUTIN with other aspects of basic and cognitive neuroscience is compelling. First, accurate estimation of time and number is an essential component of organized behavior (Gallistel and Gibbon, 2000). Disruptions in NEUTIN-related processes are characteristic of and may even be causal in the symptoms of disrupted organization or synchronization present in several neuropsychiatric disorders including dyslexia, aphasia, Parkinson's, and schizophrenia (Eagleman et al., 2005; Wojtecki et al., 2011). Second, timing and counting involve several fundamental cognitive processes (e.g., attention, working memory, long-term memory) for which a long tradition of research has identified dissociable behavioral signatures and neural substrates. These tasks may thus provide, within a single testing session, well-validated measures of multiple cognitive constructs important for diagnosis and treatment. Third, many timing and counting tasks can be administered similarly across species, increasing confidence when extrapolating from animal models to human neurophysiological and cognitive function in the testing and development of drugs for the treatment of schizophrenia, Alzheimer's disease, and other forms of dementia (Meck and Church, 1983; Church et al., 1994; Rakitin et al., 1998; Roitman et al., 2007; Penney et al., 2008; Gu et al., 2011; Meck et al., 2011; Ward et al., 2011). Targeting NEUTIN tasks that have demonstrated cross-species behavioral validity (e.g., Penney et al., 2008) for further development in psychometrics, genetic and pharmacologic manipulations, exploration of neural substrates, and sensitivity to disease models will be an important step in bringing this potential to fruition (for a related example of task development in the control of attention, see Demeter et al., 2008, 2011; Nuechterlein et al., 2009; Luck et al., 2011).

Finally, the ability to use temporal and numerical processing tasks both across species (e.g., Penney et al., 2008) and across the lifespan (Lustig and Meck, 2001, 2011) makes them attractive tools for helping to elucidate the evolutionary and ontogenetic development of cognitive processes. As noted above, basic temporal and numerical processing abilities appear to be present even in relatively simple organisms and in very young children, but NEUTIN-related tasks also seem quite sensitive to irregularities in the functioning of attention and memory. They may therefore be useful in screening children at a very young age to identify those at-risk for difficulties in important educational activities (especially mathematics; Libertus et al., 2011) and even provide a basis for training and intervention (Shaffer et al., 2001; Cosper et al., 2009).

To summarize, temporal and numerical processing is both fundamental and complex. These two domains have often been studied separately from each other, and from other cognitive domains such as attention, memory, and emotion. However, recent developments including a new appreciation of the importance of oscillatory processes in neural function and of the translational value of temporal/numerical processing tasks hold great promise for a better understanding of both NEUTIN *per se* and how the brain produces organized behavior more generally.

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