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Glutamate – a forgotten target for interval timing

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Since the early 1980s, dopamine and acetylcholine have received much interest in research on the neural substrates of interval timing (e.g., Meck, 1983, 1996; Meck and Church, 1987; Cheng et al., 2007a,b). The information-processing component of scalar expectancy theory (SET) formed the theoretical basis for many of these pharmacological studies (Gibbon et al., 1984). Alternative theories, including the Behavioral Theory of timing (Killeen and Fetterman, 1988), the Learning-to-Time model (Machado, 1997), the Multiple-Time-Scale model (Staddon and Higa, 1999), and the Striatal Beat Frequency (SBF) model (Matell and Meck, 2004) have been proposed for overcoming some of the deficiencies of SET. Evaluation of the similarities and differences of these models has been undertaken elsewhere (Matell and Meck, 2000). From a neuroscientific perspective, however, the SBF model is the most appealing, because it is the only model that deals with the specific neural substrates of interval timing. The SBF model was developed to elucidate the role of glutamate (Glu), a forgotten target for the neural substrate of interval timing, emphasizing the role of cortico-striatal Glu on behavior. However, few studies have focused on the role of Glu in the temporal control of behavior in the seconds-to-minutes range (Cheng et al., 2006; Bhave et al., 2008). This article seeks to identify important points to consider when examining the role of Glu in interval timing guided by the SBF model.

In psychopharmacological studies, a direct injection of drugs such as Glu receptor antagonists into the dorsal striatum is preferable to systemic injection, because the model assumes that the cortical Glu input to the medium spiny neurons (MSNs) in the dorsal striatum, in which neural plasticity occurs, is important for "coincidence detection" underlying duration discrimination. Pioneering work by Miller et al. (2006) revealed that the NMDA receptor antagonist MK-801 increased the peak time and variance of the response rate function in the peak-interval procedure. Unfortunately, this study did not conclusively demonstrate the importance of the Glu in the dorsal striatum, because the drug was injected systemically.

In future studies, the role(s) of two distinct types of ion channel Glu receptors (AMPA and NMDA) should be examined in two distinct phases; acquisition (memory formation for specific target durations) and performance (accuracy and precision of timing behavior following acquisition). Glu synapses predominantly act through AMPA-type receptors to produce fast synaptic excitation (i.e., normal synaptic transmission). However, striatal long-term potentiation (LTP), a representative form of neural plasticity, requires activation of NMDA-type Glu receptors (Lovinger, 2010). Therefore, the role of AMPA and NMDA receptors may differ between the acquisition and performance phases of interval timing. Not only ion channel-type receptors, but also the role of metabotropic Glu receptors 1 and 5 should be clarified during the acquisition phase, because these receptors are thought to be important for neural plasticity among MSNs (Surmeier et al., 2007; López de Maturana and Sánchez-Pernaute, 2010).

In order to examine drug effects on memory formation for target durations, we propose the adoption of a "time-shift paradigm." In this paradigm, once the discrimination for the first required target duration (e.g., 20 s) is acquired in, for example, the peak-interval procedure, the required target duration is then changed (e.g., to 40 s), and behavioral training is continued (second phase). The drug effect is examined during the formation of memory for the target duration in the second phase. This "time-shift paradigm" can dissociate the effects of the drug on the formation of the memory for the target duration from the effect on other processes (e.g., learning task rules, which may be included in the first stage of learning). Recently, Höhn et al. (2010) adopted a version of the "time-shift paradigm" in delayed classical conditioning and immunohistochemical analysis against Arc protein was used to test whether a change in the CS–US interval (resulting in a new memory formation for duration) triggers plasticity in the dorsal striatum. In a similar fashion, the "time-shift paradigm" provides a powerful tool for isolating the role of Glu in the formation of memory for target durations.

Recently, we examined the effect of intraperitoneal injection of a non-competitive NMDA receptor antagonist, MK-801, on the formation of the memory for the target duration in a "time-shift paradigm" version of peak-interval procedure. Contrary to our expectations, the peak time in MK-801 group was immediately shifted in the earliest sessions of the second phase (unpublished observation). A previous study (Miller et al., 2006) reported that systemic injection of MK-801 immediately increased the peak time, which can mask the possible effects of MK-801 on memory formation in our study. The effect of intra-dorsal striatum injection of drugs should be examined in the "time-shift paradigm" in future studies. Taken together, the role of Glu in interval timing will be clarified more precisely by considering the above three points: injection routes, receptor subtypes, and learning phases.

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