



Sex differences in counting and timing

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It is generally agreed that there are significant and reliable sex differences in human cognition that can be revealed using laboratory based tasks (reviewed by Kimura, 1996; Loring-Meier and Halpern, 1999; Weiss et al., 2003). Animal models have shown that for at least one type of cognitive process, visual-spatial navigation, these sex differences are organized by exposure to gonadal steroids early in life (Williams et al., 1990; Williams and Meck, 1991, 1993) and are modulated by exposure to activational estrogens after puberty (Rapp et al., 2003; Sandstrom and Williams, 2004) as well as androgens (Bimonte-Nelson et al., 2003). Moreover, hormonally induced alterations in the hippocampus, and in the basal forebrain cholinergic projections to the hippocampus (Gould et al., 1991; Ragbetli et al., 2002; Berger-Sweeney, 2003; Veng et al., 2003; Gibbs, 2010) appear to be the neural mechanisms underlying these sex differences in spatial cognition.

Interestingly, there are a number of studies that suggest that men outperform women on tests of temporal discrimination and reproduction when the interval being timed is short, in the milliseconds to seconds range (Roeckelein, 1972; Strang et al., 1973; Rammesayer and Lustnauer, 1989; Wittmann and Szegal, 2003). It is less clear whether there are sex differences in the perception or production of longer intervals (seconds to minutes – see Friedman, 1977, but also see Block et al., 2000). These data suggest that there may be hormonally organized or activated differences in interval timing, a fundamental property of brain that is important for many behaviors (e.g., motor control, optimal foraging, spatial navigation, and higher-level cognition). To date, relatively little work has been done to examine possible underlying neuroendocrine development and modulation of interval timing. An examination of the neural and neuroendocrine underpinning of timing and time perception is particularly important because there are well known sex differences in the expression of developmental disabilities in learning and cognition (e.g.,

autism), as well as psychiatric illness (e.g., depression and schizophrenia) and neurodegenerative disease (e.g., Alzheimer's and Parkinson's disease).

Meck and colleagues (Meck and Church, 1983; Meck et al., 1985) developed a model-control model of temporal integration in which the same analog magnitude estimation system is used in different modes of pulse accumulation for both timing (run mode) and counting (event mode). In such a system, a count is equivalent to the amount of time that the accumulation process is active during the enumeration of the event. As a result, the final accumulation of counts in the event mode is functionally equivalent to the final accumulation of pulses during the run mode used for the timing of signal durations. Consequently, if counting and timing are considered basic building blocks for symbolic cognition (Cordes and Gelman, 2005; Cordes et al., 2007; Lustig, 2011), and if the temporal integration processes common to both abilities would be affected by neuroendocrine mechanisms, then one might be able to use deficits in temporal integration as early predictors of these disorders (see Allman, 2011; Allman and Meck, 2011; Allman et al., 2011; Falter and Noreika, 2011).

These findings raise several interesting questions. First, what is the extent of sex differences in temporal integration as related to timing and counting? Are sex differences in temporal integration seen only at short (small), millisecond intervals (counts) or across all temporal intervals (counts) as discussed by Buhusi and Cordes (2011)? Is the smallest unit of temporal integration (e.g., quantal unit) similar in male and female rats? While the behavioral data from male rats using signal durations over 2 s suggest that time and number are represented in the same fashion (Meck, 1997), similar procedures suggest differences between counting and timing in male rats when using intervals in the milliseconds range (Clarke et al., 1996) as well as differences between counting and timing in female rats (Breukelaar and Dalrymple-Alford, 1998).

A second issue is whether sex differences in timing and counting are modulated by organizational and activational effects of gonadal steroids? To date only a few studies have evaluated the effect of estradiol on timing and counting in adult female rats. Ross and Santi (2000) found that systemic administration of estradiol for 2 weeks impaired the ability of ovariectomized rats to use both time and number as discriminative stimuli. Two more recent studies have reported an increase in clock speed following the administration of estradiol to ovariectomized females (Sandstrom, 2007), but not to castrated males (Pleil et al., 2011), suggesting a sex difference in responsiveness to estradiol replacement. There is also some evidence that organizational actions of gonadal hormones may modify clock speed of adult rats (Pleil et al., 2011). A third unresolved issue is the determination of the neural representation of time and number in males and females. Current data indicate that cortico-striatal circuits, as well as dopaminergic afferents from the substantia nigra pars compacta, play a central role in interval timing (Harrington et al., 1998; Harrington and Haaland, 1999; Matell and Meck, 2000, 2004; Matell et al., 2003; Coull et al., 2011) and these circuits and their response to estrogen and dopaminergic agonists are sexually dimorphic (e.g., Becker, 1990, 1999; Bazzett and Becker, 1994; Xiao and Becker, 1994). In fact, the striatum is sexually dimorphic even during embryonic development, when the striata of females are more densely packed with dopamine axons and the GABAergic neurons that form striatal synapses than those of males (Ovtscharoff et al., 1992). To date most studies of the neural representation of time and number have used male subjects. Male rats with lesions of the dorsal striatum or substantia nigra pars compacta behave as though they have a severely impaired perception of time (Meck, 2006a,b). Dopaminergic drug administration either systemically (Meck, 1996, 2007; Cheng et al., 2007a,b,c) or intrastrially (Neil and Herndon, 1978) alters the speed of interval timing processes. Moreover, male

Parkinson's disease patients show deficits in reproducing durations when they are off of their dopaminergic medications (Malapani et al., 1998, 2002; Jahanshahi et al., 2010; Jones and Jahanshahi, 2011; Jones et al., 2011). Brain imaging studies in humans show the cortex and striatum are activated during timing tasks (Rao et al., 1997, 2001; Harrington et al., 1998; Hinton and Meck, 2004; Meck and Malapani, 2004; Meck et al., 2008; Allman and Meck, 2011; Coull et al., 2011). To date, no studies have compared neural activations during timing and counting tasks in males versus females.

Male–female differences have also been reported in the likelihood temporal information versus number information are used to solve discriminations. For example, when durations are larger than 2 s male rats readily and equally use both time and number to solve discrimination tasks (Meck and Church, 1983) while females preferentially use temporal cues over counting (Breukelaar and Dalrymple-Alford, 1998). Possible sex differences between temporal integration and numerical ability using durations in the order of hundreds of milliseconds remain to be investigated. The procedure that has been used to collect these data is the bisection procedure (Church and Deluty, 1977; Meck, 1983) and the specific variant of this procedure used to study counting and timing was developed by Meck and Church (1983) and has several features that make it ideally suited for these sex differences studies. The bisection procedures can be used to study counting and timing simultaneously (Breukelaar and Dalrymple-Alford, 1998; Paule et al., 1999), in a variety of species (rat: Meck and Church, 1983; Pleil et al., 2011; mouse: Penney et al., 2008; monkey: Merritt et al., 2010; human: Allan and Gibbon, 1991; Roitman et al., 2007) and across developmental stages (children: Droit-Volet and Meck, 2007; Droit-Volet et al., 2007; Lustig and Meck, 2011; aged adult: Lustig and Meck, 2001, 2011). As well, these procedures have the advantage of being able to dissociate timing at the short (millisecond to second) and long (seconds to minutes) durations as demonstrated by Breukelaar and Dalrymple-Alford (1998) and Melgire et al. (2005). Briefly, male and female rats can be trained to discriminate between four standard stimuli (sequences of on/off auditory events) which are either “time-relevant” or “number-relevant”; the

“number-relevant” standard stimuli have a total duration of 4.0 s with either two or eight sound-on events, whereas the “time-relevant” standard stimuli have a total duration of 2.0 or 8.0 s with the total number of events held constant at four. After the discrimination is acquired, the four periodic standards are pseudorandomly mixed with probe (test) signals with variable duration (3.0, 4.0, 5.0, and 6.0 s) but constant number of events, four, and probe signals of constant duration (4.0 s) consisting of either 3, 4, 5, and 6 events (see Cordes et al., 2007). By using continuous or segmented stimuli in this procedure it is also possible to compute the equivalent time interval corresponding to one increment in counting, also known as “quantal unit” (Meck et al., 1985). The quantal unit has been shown to be about 200 ms in male rats (Meck and Church, 1983) and humans (Whalen et al., 1999). As yet, separate quantal units for males and females tested in the same procedures remain to be determined.

SEXUAL DIFFERENTIATION OF TIMING AND COUNTING

As has been suggested recently (McCarthy and Arnold, 2011), there are a number of ways that sex differences in timing and counting might develop. The classic model (Phoenix et al., 1959) is that adult brain and behavior become sexually differentiated or organized during early development by gonadal hormones, which are released at high levels by male but not female fetuses. Thus, as a first step in exploring the underlying neuroendocrine basis of sex differences in timing and counting the early hormone environment of males and female can be manipulated and their adult behavior examined. This comparison allows for the determination of whether gonadal steroid exposure soon after birth hormonally organizes sex differences in timing/counting. To date, no study has manipulated hormones early in development and examined the consequences for both adult counting and timing, although as mentioned previously, clock speed appears to be organized by early gonadal hormones (Pleil et al., 2011).

It is also possible that sex differences in counting and timing might emerge because of sex differences in the effects of circulating estrogens in the adult female versus testosterone in the male. While this potential

sex difference has never been explored, one study has evaluated the effect of estradiol on timing and counting in females (Ross and Santi, 2000) and revealed that low dose exposure to estradiol in females decreases both timing (in the 2–8 s range) and counting accuracy, but does not dissociate performance on timing and counting tasks. However, this study did not study male rats, and did not examine timing in the millisecond range. Future work should manipulate hormone exposure both developmentally and in adulthood in both males, and females across several cycles and compare the accuracy and precision of their timing and counting performance (see Pleil et al., 2011).

Recent evidence suggests that some sexually dimorphic pathways and behavior emerge because of direct genetic sex differences, rather than a cascade of hormonal events that stem from male–female genetic differences. For example, only males express the *Sry* gene, which is known to cause the differentiation of the male testes. Interestingly, *Sry* is also expressed in dopaminergic neurons in the substantia nigra that project to the striatum and have direct male-specific effects (Dewing et al., 2006). When *Sry* expression is reduced in adult rats, the expression of tyrosine hydroxylase in the substantia nigra and striatum are reduced and motor performance declines. Thus it is possible that direct, sex-specific effects of a sex chromosome gene may cause sex differences in the neural pathways underlying counting and timing. This possibility also remains unexplored.

THE NEURAL REPRESENTATION OF TIME AND NUMBER

Future studies should explore the representation of time and number by a network of neural substrates (including the basal ganglia, frontal cortex, and parietal cortex) in males and females using ensemble recordings at multiple sites (Vodolazhskaya and Beier, 2002; Varga et al., 2010; Coull et al., 2011). We hypothesize that the same neural substrates are involved in processing both temporal and numerical information, but that sexual dimorphisms in the neural substrates in temporal processing underlie differences in temporal integration and synchronization of the timing pattern as well as learning and memory for time in males and females (see Cheng et al., 2008).

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