Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Phasic Estradiol Levels and Bias for Immediate Rewards

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Review of Smith et al.

Some of life's greatest challenges involve denying oneself short-term rewards in the pursuit of long-term goals. Deciding to enroll in a PhD program in lieu of taking a high-paying job out of college, with the hopes of a more rewarding career in the future, is one such decision. On a day-to-day basis, similar yet less consequential decisions are continuously being made, like resisting a tempting chocolate cake or refraining from drinking a superfluous glass of wine. The ability to resist immediate rewards to achieve long-term goals has cumulative effects on quality of life (Lopes et al., 2005). Activity in various structures within the prefrontal cortex (PFC) are strongly associated with these inhibitory processes (Thayer and Lane, 2000; Wager et al., 2008), and recent work suggests that circulating estradiol, which enhances dopamine (DA) activity (Jacobs and D'Esposito, 2011), may additionally affect an individual's propensity for choosing greater, future rewards over lesser, immediate ones.

In a recent article published in *The Journal of Neuroscience,* Smith et al. (2014) investigated the effects of ovarian cycle phase (an indicator of circulating estradiol levels) on a delayed discounting task. Additionally, the authors analyzed how the effects of estradiol levels interact with variations in the gene encoding the catechol-*O*-methyltransferase (COMT) enzyme, which metabolizes released DA and accounts for >60% of total DA turnover in the PFC (Männistö and Kaakkola, 1999). The influence of allelic variation in the *COMT* gene on the "Now" bias, that is, choosing immediate rewards over larger future ones, has been demonstrated in multiple studies. Its influence is thought to partially result from its effects on tonic DA levels within the PFC: *val/val* carriers, who have low DA levels, have a stronger Now bias than *met/met* carriers, who have higher DA levels (Boettiger et al., 2007). Because Jacobs and D'Esposito (2011) found a positive interaction between circulating estradiol levels and variation in the *COMT* gene on a working memory task, Smith et al. (2014) postulated that estradiol may also exert an effect on delayed discounting through modulation of dopaminergic PFC functioning. Accordingly, they hypothesized that women with lower estradiol levels, which occur at the beginning of the menstrual phase, will have a stronger Now bias than women who are in their follicular phase and thus have elevated estradiol levels. Furthermore, they hypothesized that these effects would be modulated by variation in the gene that codes for *COMT*.

Smith et al. (2014) had women (18–40 years old) perform the experimental procedure twice, once during days 1–2 of their menstrual cycle and again at days 11–12. A subset of the women had their estradiol levels directly measured via saliva assay. The paradigm consisted of a standard delayed discounting task in which participants had to choose between smaller but immediate monetary rewards and larger but delayed ones. The authors' results were consistent with their hypothesis: women exhibited a stronger Now bias during days 1–2 as compared with days 11–12, and this was especially true in women who had identifiable increases in salivary estradiol. Furthermore, Val carriers (*val/val* and *val/met*) of the *COMT* gene were found to have significantly greater mid-cycle declines in the Now bias and rises in estradiol as compared with Met homozygotes, suggesting that Val carriers may have driven the effect observed in the sample as a whole.

Might there be an evolutionary advantage to the influence of estradiol on Now bias? Given that the ostensible reason for ovarian cycling of estradiol is reproductive, cyclic changes in impulsivity may be of value by affecting mating decisions. Female primates tend to be most fertile mid-cycle (Dixson, 2012), so whom they decide to mate with during this time can have especially important consequences. For example, during early estrus, chimpanzees copulate promiscuously with many different males, yet when they are close to ovulation, they copulate frequently with high-ranking males (Matsumoto-Oda, 1999) and are more selective about choosing mates, independent of male behavior (Stumpf and Boesch, 2005). This increase in mate selectivity may be a type of real-world proxy for the Now bias—trading in the immediate pleasure of indiscriminate promiscuity for the greater long-term reward of higher genetic fitness of offspring by mating with fewer but higher status

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males. Thus, in addition to preparing the uterus for implantation, the mid-phase spike in estradiol may also increase fitness by modifying PFC activity, decreasing delayed discounting, and modifying mate choices.

Smith et al.'s (2014) finding of a potential role of circulating estradiol in delayed discounting raises the possibility that the exogenous estrogens included in hormonal contraceptives may modulate variations in the Now bias by suppressing mid-cycle fluctuations in steroid hormones (Roumen, 2007). Many contemporary low-dose hormonal contraceptives work by mimicking the hormonal state of pregnancy, which results in an endocrinological profile similar to that reported of women at days 1–2 of their menstrual cycle in Smith et al.'s (2014) study and thus may influence DA modulation of the Now bias. Such findings would be consistent with a growing body of literature suggesting that hormonal contraceptive treatment can have subtle, yet potentially important influences on a range of behaviors and psychological processes (Alvergne and Lummaa, 2010). Considering how many decisions one must make in a day, from hitting the snooze button one extra time to deciding to forgo the pleasure of watching late night TV, the putative effects of the estrogens in hormonal contraceptives may be affecting day-to-day decision making in subtle ways. There are very few studies investigating the effects of hormonal contraceptives on decision-making, and results like those found in Smith et al. (2014) emphasize the need for a better understanding of this relationship.

With that said, it is not clear that estradiol was the causative factor influencing the Now bias in Smith et al.'s (2014) study. Previous studies have shown that higher levels of testosterone are associated with increases in the Now bias (Takahashi et al., 2006), and whether variations in testosterone levels affected the results in Smith et al.'s (2014) study was not investigated. Testosterone in women is at its peak during the beginning of the menstrual cycle and is at significantly lower levels during most other times (Bui et al., 2013). Thus, even though Smith et al. (2014) measured estradiol directly in some participants, it is possible that estradiol levels served as a proxy for circulating testosterone, which may have contributed to the effects reported in the manuscript. Future work will be necessary to determine the precise causal role estradiol plays in the Now bias of cycling females.

Finally, the results by Smith et al. (2014) raise the question of whether previous studies that used delayed discounting tasks had controlled for menstrual cycle phase. It may be of interest to researchers in the field to consider adding menstrual cycle phase to experiments dealing with various cognitive tasks, as this might yield more veridical results as well as shed light on other potential tasks that may be effected by such hormonal fluctuations.

The decisions we make sculpt the life we create for ourselves. How the virtue of patience guides us to choose the greater reward over the immediate one is influenced by a number of factors, including hormonal fluctuations. While Smith et al. (2014) have illustrated estradiol's potential role in altering delayed discounting in an experimental setting, it will be interesting to see whether future studies are able to extrapolate such findings to everyday decisions.

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