Sex differences in cognitive development following adolescent amphetamine exposure

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Teenagers are vulnerable. Illicit drug use during adolescence significantly increases the risk of developing and struggling with addiction throughout life.[1,2,3] Addiction is a chronic, relapsing brain disease associated with deficits in cognitive functions mediated by the prefrontal cortex (PFC).[4] The PFC is amongst the last regions in the brain to fully mature – its development persists through adolescence and into early adulthood.[5,6]

Sex specific hormones play a critical role in shaping the neural circuitry underlying behavior.[7,8,9] Ongoing neurodevelopmental processes in adolescence coincide with puberty, the period of peak sexual maturation.[10] At the onset of puberty in female mice, ovarian hormones regulate circuit development in the frontal cortex.[11] Neuronal and synaptic development in the PFC progress at different rates in male and female rodents.[12,13] Similarly, adolescent human MRI studies report differences between sexes in the timing of both gray and white matter development.[5,14,15,16]

Drug use during adolescence might disturb PFC development and lead to cognitive impairments that increase vulnerability to addiction. Previous research from our lab suggests that exposure to amphetamine during development leads to neuroanatomical and behavioral changes in male mice.[17,18] Specifically, repeated high dose amphetamine exposure during early adolescence disrupts both the maturation of medial PFC circuitry and relevant cognitive functions.[17] At the preclinical level, there is a paucity of investigation on how drug use affects females. Given known sex differences in numerous neurodevelopmental processes during puberty, drugs likely affect the developing PFC differently between males and females. However, the role of sex in the effects exerted by adolescent drug exposure remains unreasonably ambiguous.

Here, we sought to identify sex differences in the long-term cognitive effects of repeated exposure to high doses of amphetamine during early adolescent development. We compared differences in behavioral inhibition, cognitive flexibility, and motivation between adult C57BL/6 male and female mice following repeated exposure to the equivalent of recreational amphetamine doses in early adolescence.

Beginning postnatal day 21, mice were injected with a sensitizing regimen of amphetamine (4 mg/kg) or volume-matched 0.9% NaCl saline control, every other day for a period of ten days (PND 22±1 - 31±1) (Figure 1a). Locomotor activity, defined as distance traveled in a given period of time, was measured for 90 minutes following each saline or amphetamine injection. We found that both male and female mice exhibit robust sensitization of drug-induced locomotor activity over the 90 minutes following treatment (Figure 1b). Amphetamine seemed to acutely affect both sexes similarly. Following this ten-day regimen, mice were left undisture

In adulthood, we administered a Go/No-Go Task adapted to mice in operant conditioning chambers.

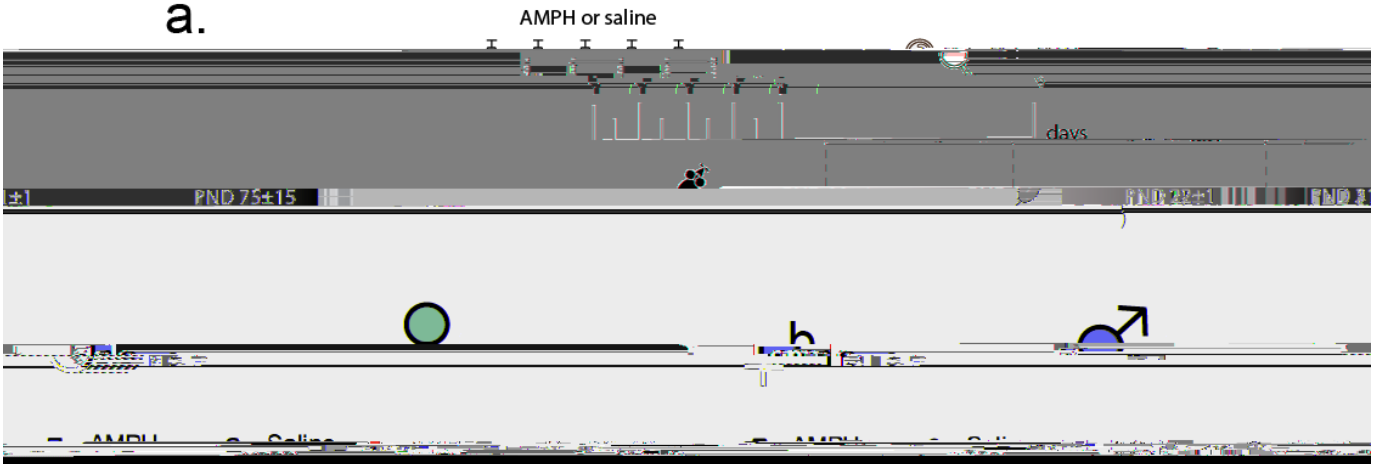
a.
AMPH or saline
days
±1
PND 75±15
b.

Figure 1. (a) Experimental timeline of pre-treatment and behavioural assessments in female and male mice (AMPH: amphetamine). **(b) (Left panel)** Female mice treated with amphetamine showed robust drug-induced locomotor activity (two-way ANOVA; main effect of treatment, $F_{1,68} = 77.97$, $p < 0.0001$; main effect of time, $F_{4,68} = 17.62$, $p < 0.0001$; interaction effect, $F_{4,68} = 14.41$, $p < 0.0001$). **(Right panel)** Male mice treated with amphetamine showed robust drug-induced locomotor activity (two-way ANOVA; main effect of treatment, $F_{1,72} = 80.73$, $p < 0.0001$; main effect of time, $F_{4,72} = 21.28$, $p < 0.0001$; interaction effect, $F_{4,72} = 18.18$, $p < 0.0001$). **(c)** Behavioral inhibition is not impaired in adult female mice treated with amphetamine in early adolescence. **(Left panel)** Adult male mice that received amphetamine during early adolescence make more commission errors across the 10 days of the Go/No-Go (two way mixed-design ANOVA, significant main effect of treatment, $F_{(1, 18)} = 4.839$, $p = 0.0411$; significant main effect of time, $F_{(9, 162)} = 5.491$, $p < 0.0001$; significant interaction, $F_{(9, 162)} = 2.584$, $p = 0.0083$. Amphetamine n = 8, Saline n = 12). **(Right panel)** Go/No-Go task commission error r/MCID 31>ET EET EMC /P <</MCID 93>BDC /MCID 38>Br)

References

1. Anthony, J. C., & Petronis, K. R. (1995). Early-onset drug use and risk of later drug problems. *Drug and Alcohol Dependence*, *40*(1), 9–15. doi:10.1016/0376-8716(95)01194-3
2. Jordan, C. J., & Andersen, S. L. (2017). Sensitive periods of substance abuse: Early risk for the transition to dependence. Developmental Cognitive Neuroscience, 25, 29-44. http://dx.doi.org/10.1016/j.dcn.2016.10.004
3. McCabe, S. E., West, B. T., Morales, M., Cranford, J. A., & Boyd, C. J. (2007). Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Results from a national study. *Addiction*, *102*(12), 1920–1930. doi:10.1111/j.1360-0443.2007.02015.x
4. Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Publishing Group*, *12*(11), 652–669. doi:10.1038/nrn3119
5. Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., et al. (2004). Dynamic mapping of h(V)5(o)-ETBT11n. c58 Tmþ

Neuroscience : the Official Journal of the Society for Neuroscience, *21*(22), 8819–8829.

7. Schulz, K. M., & Sisk, C. L. (2016). The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. *Neuroscience & Biobehavioral Reviews*, *70*, 148–158. doi:10.1016/j.neubiorev.2016.07.036
8. Sisk, C. L. (2017). Development: Pubertal Hormones Meet the Adolescent Brain. *Current Biology*, *27*(14), R706–R708. doi:10.1016/j.cub.2017.05.092
9. Sisk, C. L., & Zehr, J. L. (2005). Pubertal hormones organize the adolescent brain and behavior. *Frontiers in Neuroendocrinology*, *26*(3-4), 163–174. doi:10.1016/j.yfrne.2005.10.003
10. Van Swearingen, A. E. D., Walker, Q. D., & Kuhn, C. M. (2012). Sex differences in novelty- and psychostimulant-induced behaviors of C57BL/6 mice. *Psychopharmacology*, *225*(3), 707–718. doi:10.1007/s00213-012-2860-4
11. Piekarski, D. J., Boivin, J. R., & Wilbrecht, L. (2017). Ovarian Hormones Organize the Maturation of Inhibitory Neurotransmission in the Frontal Cortex at Puberty Onset in Female Mice. *Current Biology*, *27*(12), 1735–1745.e3. doi:10.1016/j.cub.2017.05.027
12. Drzewiecki, C. M., Willing, J., & Juraska, J. M. (2016). Synaptic number changes in the medial prefrontal cortex across adolescence in male and female rats: A role for pubertal onset. *Synapse*, *70*(9), 361–368. doi:10.1002/syn.21909
13. Willing, J., & Juraska, J. M. (2015). The timing of neuronal loss across adolescence in the medial prefrontal cortex of male and female rats. *Neuroscience*, *301*, 268–275. doi:10.1016/j.neuroscience.2015.05.073

14. Giedd, J. N., Raznahan, A., Mills, K. L., & Lenroot, R. K. (2012). Review: magnetic resonance imaging of male/female differences in human adolescent brain anat

20. Gourley, S. L., Zimmermann, K. S., Allen, A. G., & Taylor, J. R. (2016). The Medial Orbitofrontal Cortex Regulates Sensitivity to Outcome Value. *The Journal of Neuroscience*, *36*(16), 4600–4613. doi:10.1523/JNEUROSCI.4253-15.2016
21. Fillmore, M. T., Rush, C. R., & Marczinski, C. A. (2003). Effects of d-amphetamine on behavioral control in stimulant abusers: the role of prepotent response tendencies. *Drug and Alcohol Dependence*, *71*(2), 143–152.
22. Millan, M. J., Agid, Y., Brüne, M., Bullmore, E. T., Carter, C. S., Clayton, N. S., et al. (2012). Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nature Reviews Drug Discovery*, *11*(2), 141–168. doi:10.1038/nrd3628
23. Greenfield, S. F., Back, S. E., Lawson, K., & Brady, K. T. (2010). Substance Abuse in Women. *The Psychiatric Clinics of North America*, *33*(2), 339–355. doi:10.1016/j.psc.2010.01.004
24. Kuhn, C. (2015). Emergence of sex differences in the development of substance use and abuse during adolescence. NCBI. *Pharmacology & Therapeutics*, *153*, 55–78. doi:10.1016/j.pharmthera.2015.06.003
25. Shulman, E. P., Harden, K. P., Chein, J. M., & Steinberg, L. (2014). Sex differences in the developmental trajectories of impulse control and sensation-seeking from early adolescence to early adulthood. Journal of Youth and Adolescence, 44(1), 1–17. doi:10.1007/s10964-014-0116-9