

# Methylphenidate Exposure in Late Adolescent Mice Leads to Adult Cross-Sensitization

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Use, misuse, and diversion of attention deficit hyperactivity disorder (ADHD) stimulant drugs has significantly increased especially in adolescent populations. Adolescence is a key stage of development in which the brain undergoes sexually dimorphic changes brought about by synaptic pruning, and further structural modification. The psychostimulant methylphenidate (MPD), commonly prescribed as Ritalin® for ADHD, causes an overall increase of dopamine concentration within the mesocorticolimbic pathway, and may result in neuroplastic alterations in adolescence leading to neurobehavioral alterations in adulthood. Previous studies in our lab demonstrated that there are female-specific effects in behavioral cross-sensitization caused by a methylphenidate exposure during early adolescence (P22-31). Behavioral cross-sensitization is a hallmark of addiction and manifests as locomotor activity, which stems from neuroplastic changes. We hypothesize that methylphenidate exposure during late adolescence (P42-51) will result in unique sex-specific behavioral cross-sensitization effects in adulthood compared to early adolescence and saline controls. Male (n=41) and female (n=51) C57Bl/6J mice were injected (i.p.) with 1.0mg/kg MPD during late adolescence followed by a subacute challenge dose of 0.5mg/kg methamphetamine or saline during adulthood (P90). At P90, behavioral cross-sensitization was assessed using an open field chamber. Behavioral sensitization was operationalized by analysis of XY ambulation and fine motor movements. Preliminary analysis indicates cross-sensitization in MPD-exposed males and females but not between them, as was demonstrated after early adolescent exposure. Therefore, these data suggest the developmental boundary for male MPD-induced cross-sensitization exists in a critical developmental window between early and late adolescence. These collective results support the importance of considering both sex and developmental stage in clinical prescription practices, especially since we report an adolescent MPD-induced increase and subsequent adult addiction susceptibility.