Webinar Q&A Report:
Reductions in Impulsivity in an Animal Model of Attention Deficit Hyperactivity Disorder (ADHD)

1. **How long is the training?**

   F. Scott Hall: For the traditional 5-CSRTT/CPT the training is long, many months. For the modified versions, the training takes only 10 days, although it is very intensive. Testing 3x per day and up to 100 trials per session. The IGT on the other hand is only 3 days, but does not necessarily provide the same information.

2. **Do you expect the PPI deficits to be related to PFC dysfunction (as opposed to early sensory areas)? If so, how?**

   F. Scott Hall: My expectation is that PPI deficits are related to dopamine overactivity in the NAC or resultant changes in the PFC or elsewhere. That is based upon previous studies showing that these structures were important in modulating PPI, and in particular the role of dopamine in inducing PPI deficits (see the question on cannabinoids as well about this). However, this is simply based on that expectation and I think that other alternatives should also be explored, including early and late sensory processing (including cortical sensory processing).

3. **With FDA approval of CBD for epilepsy: Is there a role for the endocannabinoid system in ADHD? What is the effect of cannabinoids in the DAT knockout mice?**

   F. Scott Hall: There is certainly a strong relationship between ADHD and cannabis use, although there is a strong relationship for ADHD and all drug use. This has largely been put down to ADHD phenotypes that also may contribute to initial drug use, or subsequent drug misuse. Nonetheless, the possibility should not be excluded that a portion of this is an attempt (even if a poor one) at self-treatment of some kind. With respect to rodent studies, cannabinoids (and endocannibinoids) affect both DRD2 receptors and DAT. Tzavara et al., Biol Psychiatry (2006) showed that several drugs that potentiate endocannabinoid signalling alleviated DAT KO induced hyperactivity, but this was associated with the TRPV1 receptor, not the CB1 receptor. A recent interesting study, Melnick et al, Neuropsychopharmacology, 2021, showed that a CB1 allosteric modulator reduces hyperdopaminergia and associated behavior (including PPI deficits) in DAT KO mice and another mouse model of hyperdopaminergia. So, there is certainly some degree of evidence for this relationship, although I do think that much remains to be done, particularly to relate these preclinical findings to clinical findings.

4. **The presented results with 5CSRTT are in strict concordance with previous results from Italy (https://pubmed.ncbi.nlm.nih.gov/28855580/)**

   F. Scott Hall: Thank you, I should have mentioned this study in my talk. Actually, our results with the 5-CSRTT were not presented in my talk. Generally, we did not find deficits in the 5-CSRTT in adult animals, although I am not certain that we did the correct manipulations to identify more subtle deficits. The results we showed were primarily in the CPT in adult animals. There are interesting differences between your study and ours, including age. Your study examined adolescent animals. We have another unpublished study that confirms that finding in the 5CSRTT.

5. **Do the DAT KO mice have normal cannabinoid receptor expression (protein and mRNA) levels?**

   F. Scott Hall: The Tzavara et al (2006) study mentioned in response to another question found that there were reduced anandamide levels in the striatum in DAT -/- mice. They also found elevated levels of TRPV1 in the striatum, but unaltered levels of CB1. However, like many studies of DAT KO mice, they did not examine DAT +/- mice in that study, so it is not known whether these changes might be applicable to behavioral consequences of the heterozygous deletion, including the ones that I discussed.

6. **Does thigmotaxis indicate anxiety? Can the orients or meanders reflect risk assessment?**

   F. Scott Hall: Thigmotaxis is often taken as an indication of anxiety. I would not say that mean meander reflects risk assessment, I would probably say that it more likely represents the complexity of the locomotor pattern. In addition, what appears to happen is more a matter of habituation. The initial locomotor/exploratory response includes more longitudinal movements and less meander (and other elements of complexity). The DAT KO mice take longer to transition to later exploratory stages, that includes more variable and local patterns of exploratory behavior. This is most likely to be a matter of habituation though, because DAT KO mice do not show elevated anxiety in standard tests. I think the CAR test really assesses risk assessment; whether this cognitive process affects other types of behavioral tests is hard to determine, but it is an interesting question that deserves further inquiry.

7. **You have a fair amount of anxiety behavior potentially confounding some of these behaviors. Do you have a way of testing this out?**

   F. Scott Hall: I think that this possibility has been largely eliminated. Although largely from unpublished data, because it was negative, DAT KO mice have not shown any evidence of anxiety in standard tests of anxiety, at least in our hands, but I think for many others as well. Indeed, one study, Carpenter et al., Dev Neurosci (2012) actually found reduced anxiety in DAT KO mice. I do wonder whether the hyperactivity might have been a confounding factor in the measurement of anxiety, particularly in DAT -/- mice, but it is at least hard to argue that they are more anxious. Again, DAT +/- mice were not examined in that study, although we have not found any differences in DAT =/- either in standard tests of anxiety.

8. **How long does it take to train mice for 5CT?**

   F. Scott Hall: In the modified version, the training takes only 10 days, although it is very intensive. Testing 3x per day and up to 100 trials per session.

9. **Do the heterozKOs show the same changes in circuitry as the homozKOs?**

   F. Scott Hall: Interesting question. This is unknown, but it would be important to find out as we are presuming that the basis of the impairments in DAT +/- mice is similar to the DAT -/- mice.

10. **Are you sure that after several minutes in the platform is it still impulsivity?**

    F. Scott Hall: Actually, I do not think it is. This was a matter of great debate with the reviewers of our first CAR paper (the responding author on that paper acquiesced to the demands of reviewers that we treat the results as impulsive behavior during the publishing process, after a few versions went back and forth to the journal). I think that the deficits really reflect differences in risk assessment.

11. **Do you think that cliff avoidance reaction task could be a model of reflection impulsivity rather than motor impulsivity?**

    F. Scott Hall: I definitely do not think that the CAR task really measures motor impulsivity, as they take too long to fall. An argument could certainly be made for reflection impulsivity, but again, they consider the consequences for long time, they just make a risky decision, so I really think that the deficit lies in some other aspect of executive function, which I usually refer to as risk assessment.

12. **Will you explore the different neurocognitive domains of impulsivity (Finberg, 2014)?**

    F. Scott Hall: I would like to very much. If I can get NIH to pay for more work on this topic, and additionally it would be nice to further dissect other aspects of executive function, where I think the greatest impairments in DAT KO mice lie. I also think that deficits in executive function are clear in ADHD, and it will be interesting to see how strong the changes in DAT KO mice resemble those deficits.

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