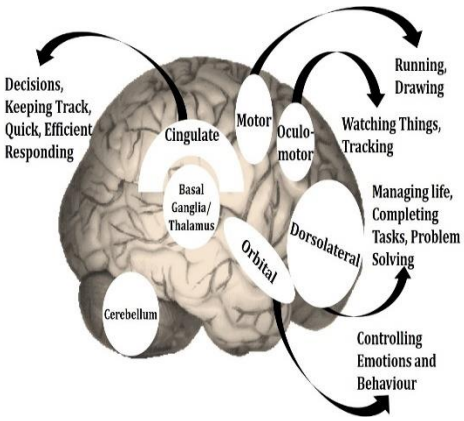
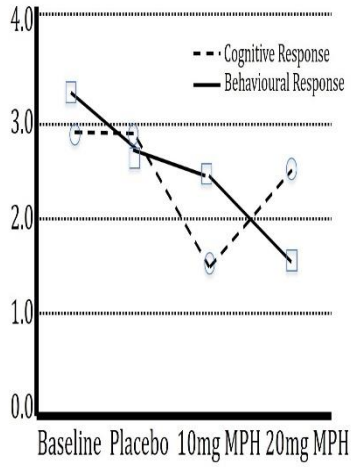
ADHD Medication Trials

Most children with emotional/behavior disorders have attention problems (Hale et al., 2018), but do they equally benefit from stimulant medication, the most common treatment for Attention-Deficit/Hyperactivity Disorder (ADHD)? The medication wakes the "brain boss" so it can control the rest of the brain. Through medication trials with colleagues, Dr. Hale has shown that his test battery reliably determines neuropsychological and behavioral medication response in children with ADHD (Carmichael et al., 2015; Hale et al., 2011; Kubas et al., 2012). Children with ADHD have executive function deficits that interfere with academic and/or behavioral functioning (Hale et al., 1998; 2002; 2005; 2009; 2011; 2012; 2013, 2014, 2015, 2018; Hoeppner et al., 1997; Kubas et al, 2012; Reddy et al., 2007; see figure to left), so it is important to examine both neuropsychological and behavioral medication response. (For a complete listing of the research, please consult Dr. Hale's curriculum vitae and the research tab found on this website).



Open, single, or double-blind trials of stimulant response are offered for physicians to help monitor treatment effects. It is important to note that *clinical referral and clinical decision making are entirely made by the referring physician*. The goal of the ADHD medication trial is only to provide neuropsychological and behavioral data to the referring physician to aid in their clinical decision making, but it is up to the physician to choose whether the medication is clinically useful, and what dose to pick.

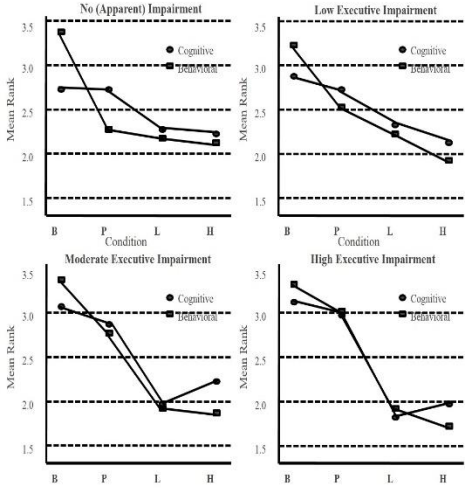
In our research, the medication trial was typically a 4-week trial, with 60-minute neuropsychological testing sessions each week. Behavior ratings were collected from the parent(s), teacher(s), and allied professionals that worked directly with the student. Observational data in a school setting was conducted, but was not required. After the trial is completed, neuropsychological and behavioral data were rank ordered across conditions (lower ranks = better neuropsychological and behavioral functioning) and then the ranks were then subjected to nonparametric randomization tests for statistical comparison across conditions.



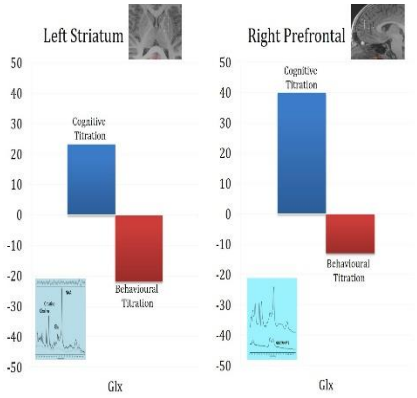
Note. Lower Ranks = Better performance and behaviour; Order of conditions = Baseline, Low Dose, Placebo, High Dose

The data and graph depicting neuropsychological and behavioral response are shared with the referring physician and parent, and the referring physician makes a judgment of how to proceed with further treatment. *It should be noted that a significant statistical response does not mean there is a*

significant clinical response – that is the referring physician's decision. Thus, unlike pediatric neuropsychological evaluations discussed in other links on this website, there is no clinical interpretation of the data, just a reporting of the trial, any side effects found, a table showing the results, and then a graph is produced to show the results (see above figure).



Prior double-blind placebo-controlled research conducted by Hale and colleagues (2011) has revealed that not all children diagnosed behaviorally (e.g., DSM-5) with ADHD show a significant response to methylphenidate (MPH; i.e., Ritalin; see figure to the left). Their research also found that the best dose for neuropsychological functioning is often lower than the best dose for behavior. In particular, subsequent research showed that working memory was impaired on high dose stimulants, even in good responders (Kubas, et al., 2012). Working memory is very important for learning in the classroom (e.g., reading comprehension, math problem solving, written expression, following directions, taking notes). This research suggests that choosing the best stimulant dose based on behavior alone may be problematic, because even if the child appears to show a good medication response for behavior, the child's working memory may be impaired on this "best" dose. This is entirely consistent with prior animal research (e.g., Berridge & Arnsten, 2015), but this is the first time the differential neuropsychological and behavioral response was shown in children. It is interesting to note that preliminary findings from a follow-up medication trial study suggest the problem may be with glutamate, an important neurochemical involved in memory (see figure to right).



In addition, research by Dr. Hale's graduate student (Carmichael et al, 2015) showed that although neuropsychological data and behavior ratings were only modestly related, a direct comparison of DSM-IV ADHD criteria with neuropsychological factor scores in predicting medication response revealed DSM-IV Inattentive criteria were completely unrelated to medication response. In particular, DSM-IV ADHD Inattentive criteria were completely unrelated to medication response, but the "cool" dorsolateral factor score (derived in Hale et al., 2005) and "hot" orbital factor score were highly related to response. This suggested to the research team that we

Measure	Cognitive Medication Response r (r^2)	Behavioural Medication Response r (r^2)
DSM-IV Inattention Ratings (Parent Report)	.09 (.008)	.03 (.000)
DSM-IV Hyperactivity-Impulsivity Ratings (Parent Report	.30* (.090)	.25 (.063)
Dorsolateral-Dorsal Cingulate "Cool" Circuit Functions Factor	.44** (.194)	.33* (.109)
Orbital-Ventral Cingulate "Hot" Circuit Functions Factor	.45** (.203)	.31* (.097)

need to reconsider “inattention” in ADHD diagnosis and determining treatment effects. Please see Table table for results.