Supplemental Methods

Of the 78 potential ADHD subjects, 44% (N=34) were excluded from this current study (largely because of current psychotropic medication use or chronic histories of substance abuse or dependence).

To assess ADHD, we used the standard methods employed in ADHD studies published previously by this group (see 1 and 2 for more details). Briefly, we used a module derived from the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (K-SADS-E) (3). We first ascertained whether a subject met criteria for a childhood diagnosis by asking the subject to report retrospectively whether he or she experienced each symptom "as a child" and at what age it began. An item was scored as positive if 1) the answer to an item was "yes" and 2) the subject reported experiencing it more than other individuals the same age. Subsequently, we asked whether the subject experienced that same symptom within the past month. This assessment systematically acquires information on all DSM-IV ADHD symptoms, measures, and domains of impairment, age at onset, and whether the symptom still persists. Previous work shows that retrospective childhood diagnoses of ADHD can be made in a reliable and valid manner by using this method (4, 5). For this study, we considered a subject positive for ADHD only if DSM-IV diagnostic criteria were met in childhood and persisted into adulthood.

Regarding the reliability of our ADHD measure, we computed kappa coefficients by having child and adult psychiatrists and licensed clinical psychologists diagnose subjects from audiotaped interviews, assigning one of two possible classifications: no diagnosis or full diagnosis. Based on 500 assessments from interviews of children and adults, the kappa coefficient for ADHD was 0.88.

To assess current depression and anxiety, we administered the Profile of Mood States (POMS) (6) on the day of the scan. Subjects were asked to rate how they had been feeling in the past week, including the current day. The POMS is an adjective checklist of 72 items using a scale ranging from 0 ("not at all") to 4 ("extremely") to indicate how well the adjective describes the subject's state. The POMS is a dimensional measure of current mood that has been demonstrated to be valid and reliable, and it is typically used to assess subtle changes in mood that otherwise may not be detected in a yes/no clinical diagnosis (6).

Working Memory and Control Tasks for fMRI

We used a variant of the sequential-letter visual N-back task (7) that has been used in neuroimaging studies of working memory (e.g., 2) and previously described by us (2). Briefly, subjects were instructed to respond to every stimulus using a button box, pressing one button to signal targets and another for nontargets. In the vigilance control "X-task," the target was the letter "X." In the working memory 2-back task, a letter was a target if it was the same as the letter that was presented two trials (i.e., letters) previously, or "2 back." To perform the task accurately, a subject was required to remember the letter presented two trials previously, compare it to the current letter, and decide whether the two letters were the same. Each subject participated in three runs of the task lasting 5.6 minutes each. Each run incorporated a block design with 12 epochs: 1) three 36-second epochs of the X-task, 2) three 36-second epochs of the 2-back task, and 3) six 20-second epochs of "fixation" (to provide a prestimulus baseline and recovery period for the hemodynamic response between the X-task and 2-back task blocks). Condition order was randomized across runs and subjects. Percent correct responses and mean reaction time for correct responses were used as performance measures. Because ADHD subjects often demonstrate greater within-subject variability than do normal comparison subjects (for instance, 8), we assessed for group differences in intrasubject variability of the reaction time data.

Supplemental Analyses

Given the relative scarcity of imaging data for females in the literature, we examined the simple effects for the women (comparison women – ADHD women; ADHD women – comparison women) and found that there were no significant differences.

We tested for effects of stimulant medication history by comparing neural activation in our contrast of interest for the ADHD subjects who were currently prescribed stimulants but had undergone a washout period (N=18) to activation for the ADHD subjects who had been prescribed stimulants in the past (N=9) and for the ADHD subjects who were stimulant naive (N=17). We also compared subjects with any past or current history of stimulant treatment (N=27) to those who were stimulant naive (N=17). There were no differences in neural activation for any of these comparisons.

Since there were significant differences between groups in levels of depression and tension/anxiety, we re-ran the interaction analyses with these variables included as covariates. The results of these ANCOVAs were virtually identical to the results of the original analyses, indicating that these variables were not accounting for the

observed interaction effects. Because there was a nonsignificant difference in overall age between the ADHD and comparison groups, we also conducted an ANCOVA with age as the covariate. This demonstrated that age was not accounting for the interaction effects either. (Results available upon request.)

To assess whether the interaction effects were accounted for by differences between comparison groups, we tested for and found no significant differences between male and female comparison groups. There were also no regions for which the men with ADHD showed greater activation than the women with ADHD. However, the female ADHD group showed significantly greater activation than the male ADHD group in several regions, including the bilateral occipital lobe, cerebellum, and left insula. (Results available upon request.)

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