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What is This?
Latent Inhibition in ADHD Adults On and Off Medication: A Preliminary Study

R. E. Lubow\(^1\), Oren Kaplan\(^2\), and Iris Manor\(^3\)

Abstract

Objective: To determine the effects of stimulant medication on performance of ADHD adults on a selective attention task that assesses the processing of irrelevant stimuli. Method: ADHD patients and matched controls were given two sessions of a two-stage visual search-latent inhibition (LI) task. In stage-1, they detected the location of a unique shape presented with homogeneous distractors. In stage-2, target detection response time was examined as a function of the stage-1 experience with the target or distractor, or both, providing a within-subject measure of LI. In Session-1, the ADHD subjects were off their customary stimulant medication. In Session-2, they were on medication. Results: Off-medicated ADHD subjects exhibited similar LI to that of controls; medicated ADHD subjects exhibited less LI than controls. Group differences in LI were mediated by RTs to the previously task-irrelevant distractor stimulus. Conclusion: The attenuated LI of the on-medication ADHD group is attributable to drug action that reduces attentional resources allocated to distractors. (J. of Att. Dis. 2012; XX(X) 1-XX)

Keywords
ADHD, adults, stimulants, latent inhibition, task-irrelevant stimuli

ADHD (American Psychiatric Association, 2000) is a neurodevelopmental cognitive disorder that is present in children and, in many cases, continues into adolescence and adulthood (Barkley, 1998). Characterized by impaired attention, impulsivity, and overactivity, ADHD frequently causes difficulties in academic and work performance and in emotional and adaptive functioning in social situations. Monotonous and effortful activities appear to exacerbate ADHD symptoms, particularly in the allocation of attention to task-irrelevant stimuli (Solanto, 2001). Because the pathophysiology of ADHD includes dysregulation of biogenic amines, especially of norepinephrine and dopamine (e.g., Pliszka, McCracken, & Maas, 1996), many ADHD patients benefit from psychostimulant drugs with noradrenergic-dopaminergic agonistic activity (see Greenhill, 2001; Wilens, Morrison, & Prince, 2011, for reviews).

The attentional dysfunctions that accompany ADHD have been widely studied, and there is general agreement that sustained attention (vigilance) is improved with the administration of psychostimulant medication (see Advokat, 2010, for a review). The picture for selective attention, however, is more controversial. Many reports have failed to find benefits, such as with response times (RTs) in a visual search word-matching test (Malone & Swanson, 1993), in visual search under conditions of parallel or serial processing (Taylor, Sunohara, Khan, & Malone, 1997), and in measures of interference and processing time on the Stroop test (Biederman et al., 2008).

In a study that did obtain an effect of stimulant drug on selective attention, Lubow, Braunstein-Bercovitz, Blumenthal, Kaplan, and Toren (2005) compared two groups of older ADHD children (8-15 years old), one being treated with several medications based on methylphenidate and the other not, with matched controls on a two-stage visual search task. The task assessed the effects of changing a previously irrelevant stimulus (distractor) into a target. Such a procedure, related to latent inhibition (LI; poorer performance to a previously task-irrelevant stimulus than to a novel one) indicated that ADHD children processed the task-irrelevant stimuli differently than the control children. Although all three groups exhibited the LI effect, the nonmedicated ADHD group exhibited less LI, at least for left side targets, suggesting an attentional deficit in the untreated ADHD group that was normalized by methylphenidate.

However, since medication status was a between-participant variable, the nonmedicated ADHD group may...
have been composed of children who did not benefit from methylphenidate or who had side effects from the treatment. Consequently, the medicated and nonmedicated ADHD groups may have differed on non-drug-related aspects. The present research focused on determining whether there are visual search LI differences between an ADHD group tested on and off medication and a control group. Such a within-participant design ensures the comparability of the ADHD participants in the two medication conditions (off medication/on medication). In addition, because of the paucity of investigations with mature ADHD participants, particularly with a visual search paradigm that assesses selective attention, we conducted the research with young adults. Thus, the present study comprised two groups of young adults, one diagnosed with ADHD and the other a matched control group. Both groups took part in the two-stage visual search LI task (described above), which was administered in two sessions. In Session 1, the ADHD participants were tested in the absence of their usual medication. In Session 2, the same participants were tested while under the influence of their medication. The LI visual search task was administered to the two groups in both Sessions 1 and 2 but with different targets and distractors.

We expected that the control group would show robust LI effects in Sessions 1 and 2, as had been repeatedly demonstrated with the visual search procedure (see Lubow & Kaplan, 2005, for a review), as well as with other tasks (see Lubow, 2005, for a review). As opposed to this, the off-medication ADHD participants (Session 1) should exhibit less than normal LI (Lubow et al., 2005), which should be normalized by the psychostimulant administered prior to Session 2.

Method
Participants

A total of 35 clinically diagnosed ADHD patients and 35 controls, matched on gender, age, and education level (see Table 1), completed the experiment. One participant from the ADHD group was excluded because of RTs that were almost 10 times more than the group average. Consequently, the matched control was also excluded. None of the participants had a history of psychotic symptoms, head injury, epilepsy, or a diagnosis of autistic/pervasive developmental disorder symptoms.

In all, 16 patients had ADHD Combined-type, Inattentive, as well as Hyperactivity and Impulsivity. A total of 19 patients had ADHD Predominantly Inattentive (ADHD-PI). The ratio of the two types is similar to that reported in the literature, indicating that the study population was a representative one. In regard to comorbidity, two ADHD-PI patients were diagnosed with an anxiety disorder and two more with depression. One ADHD-combined patient was bulimic. The low percentage of patients with comorbidities reflects a study population of functioning young adults, mostly students.

ADHD patients were recruited from the ADHD Unit of Geha Hospital after signing an informed consent agreement. They were diagnosed as ADHD on the basis of Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV; American Psychiatric Association, 1994) criteria, a comprehensive psychiatric examination, and scores on the Wender Utah Rating Scale and the Adult ADHD Self-Report Scale (ASRS). A senior psychiatrist from the unit (I.M.) verified that participants’ diagnostic data were available and valid.

All ADHD patients were currently being treated with stimulants, either methylphenidate or mixed amphetamine salts (Adderall), 21 with immediate release MPH (IR-MPH), 7 with MPH extended release (LA-MPH), 5 with once-a-day MPH (MPH-OROS), and 2 with Adderall. The mean duration of treatment was 17.4 months (SD = 4.11; range = 14-32 months).

ADHD patients were requested to take their customary medication on the morning of the preceding day of the experiment but not to take it on the morning of the experiment. Instead, they were asked to bring their medication with them to the laboratory.

Control group participants were volunteers from the hospital staff and the college. During the recruitment phase, control participants were administered the ASRS to exclude those with possible ADHD.

Apparatus

All experimental events were presented on a laptop computer. On any given trial in the practice, preexposure, and test stages of the visual search task, the computer screen
displayed 20 white figures on a dark gray background. In all, 19 of the figures were identical in shape and size (distractors), and one figure was unique (the target). All figures were constructed from five randomly connected straight lines generated from a 3 × 3 matrix measuring 1.5 × 1.5 cm.

Procedure

Participants, run individually, were seated in front of the computer keyboard, at normal viewing distance from the screen. They were informed that they would see a series of displays with 20 figures, one of which was different from all of the others. Participants were told to press the left arrow key if the unique figure appeared to the left of the screen midline and to press the right arrow key if the unique figure was to the right of the midline. The figures remained on the screen until the participant responded. The interval between the response and the next display was 1.5 s.

On half of the trials, the target appeared on the left side of the screen, and on half on the right side. Targets and distractors could appear in any one of 96 positions created by an imaginary 12 × 8 matrix. The positions of the 20 figures were randomly determined for each trial, and the target appeared in a different position on each trial.

Session 1

Practice stage. The experiment began with 12 practice trials that were constructed in a similar manner to the trials in the preexposure and test stages, but with different figures. The target and distractor figures remained unchanged during the 12 trials. After each trial, a message appeared on the screen indicating whether the response was correct or incorrect. In the subsequent stages of the experiment, feedback was omitted.

Preexposure stage. The preexposure stage immediately followed the practice session. Participants were told that they would see a new series of displays and that their task was the same as in the practice phase. The preexposure stage consisted of 96 trials, each of which contained the same target figure and the same distractor figures. The position of the target was randomized, but it appeared only once in each of the possible 96 screen positions. Columns, rows, and left–right positions were counterbalanced. On each trial, display presentation was terminated when the participant responded.

Test stage. The 96-trial test stage began immediately after the preexposure phase without any interval or notice. Participants had to continue their previous task, identifying whether the unique shape was on the right or on the left of the midline. However, the targets and distractors varied from trial to trial. The test stage was composed of four trial types: (a) The target and distractors were the same as in preexposure; (b) the target and distractors were novel; (c) the target and distractors were the same as in preexposure, but with reversed roles—the previous target became distractors, and the previous distractors became the target (preexposed [PE] condition); and (d) the test target was novel, and the PE target became the distractor (non-preexposed [NPE] condition). The first trial type provides a retrieval cue for the preexposure stage and by that enhances the L1 effect. Each of the four trial types appeared 24 times in a random order, with the restriction of no more than two successive identical trial types. Figure shapes were completely counterbalanced across participants and across status as target and distractor. In addition, half of the participants in each group viewed stimuli from one set of stimuli (Set A) and half from a second set of stimuli (Set B). In Session 2, the stimulus sets were reversed for the participants.

The dependent variables were RT, as measured from the onset of the display to the key press response, and errors. For statistical analyses, mean RTs for correct responses were computed for each trial type.

On completion of Session 1, ADHD participants took their customary ADHD medication. Participants from the ADHD and control groups were asked to leave the experimental room and to return in 1.5 hr. They were instructed to remain in the building, where they could spend their time in any way that they chose. However, they were requested neither to drink beverages with caffeine (coffee and colas) nor to have a large meal.

Session 2. Session 2 was identical to Session 1, with the exception that the visual search shapes were different from those in Session 1. Participants who had shapes from Set A now had shapes from Set B, and those who had Set B now had Set A.

Results

Session 1

Preexposure stage. The difference between the mean target detection RTs for the off-medications ADHD participants and the control group (M = 2.10, SEM = .14; M = 2.07, SEM = .11, respectively) was not significant, t(68) = 0.19, p > .10. However, the difference in the mean percentages of errors for the two groups (M = 4.40, SEM = .54; M = 2.29, SEM = .49, respectively) was significant, t(68) = 2.92, p = .005. Pearson correlations between mean RTs and mean percentages of errors were calculated separately for the nonmedicated ADHDs and controls. The correlations were negative but not significantly different from zero, r(35) = −.18 and r(35) = −.16, ps > .10, respectively, demonstrating a negligible trade-off between response speed and accuracy.

Test stage. Figure 1A displays mean RTs for the off-medication ADHDs and the control group as a function of target stimulus preexposure (PE vs. NPE). As can be seen,
RTs were consistently slower to the PE stimulus than to the NPE stimulus, reflecting the basic LI effect.

This observation was supported by a $2 \times 2$ mixed ANOVA (Group $\times$ Preexposure). The preexposure effect was significant, $F(1, 68) = 30.96, p < .001, \eta^2 = .31$. The Group effect and the Group $\times$ Preexposure interaction were not significant, $p > .20$. Thus, LI was present in the off-medication ADHD participants and the control group, and the size of the two LI effects was not significantly different.

**Session 2**

**Preexposure stage.** The mean target detection RTs for the on-medication ADHD participants and the control group were $M = 1.66, SEM = .10; M = 2.04, SEM = .24$, respectively. The difference between the groups was not significant, $t(68) = 1.52, p > .10$. The mean percentages of errors for the on-medication ADHD participants and the control group were $M = 4.49, SEM = .48; M = 1.88, SEM = .40$, respectively. As in Session 1, the difference between the groups was significant, $t(68) = 4.18, p < .001$. Pearson correlations between the mean RTs and the mean percentages of errors were calculated for the on-medication ADHD participants and the control group. The correlations were positive but not significantly different from zero, $r(35) = .24$ and $r(35) = .18, p > .10$, respectively.

**Test stage.** Figure 1B displays mean RTs for the on-medication ADHDs and the control group as a function of target stimulus preexposure (PE and NPE). As can be seen, and as in Session 1, RTs were slower to the PE target than to the NPE target (LI effect). Unlike in Session 1, Figure 1B suggests that the control group exhibited a larger LI effect than the on-medication ADHD participants.

These observations were supported by a $2 \times 2$ mixed ANOVA. As in Session 1, the main effect of preexposure (LI) was robust, $F(1, 68) = 26.25, p < .001, \eta^2 = .28$, whereas that of group was not, $F(1, 68) = 2.03, p = .16$. Unlike in Session 1, the Group $\times$ Preexposure interaction was significant, $F(1, 68) = 4.83, p = .03, \eta^2 = .07$, confirming a larger LI effect for the on-medication ADHDs than for the control group.

Between-participant contrasts compared RTs of controls and on-medication ADHDs to the PE stimulus and to the NPE stimulus. For the PE stimulus, but not for the NPE stimulus, the difference was significant, $t(68) = 1.82, p = .04$; $t(68) = 0.75, p > .10$, respectively, indicating that the larger LI effect for the controls when compared with the on-medication ADHDs, as seen in Figure 1B, was the result of differences in processing the PE stimulus.

**Comparing LI in Sessions 1 and 2**

As can be seen by comparing Figures 1A and 1B, and more clearly in Figure 2, the LI effect (PE minus NPE) for the
control group was greater in Session 2 than in Session 1, whereas for the ADHD group the LI effect was smaller in Session 2 than in Session 1. These observations were supported by a $2 \times 2$ ANOVA (Group × Session), in which only the interaction was significant, $F(1, 68) = 8.43, p = .005, \eta^2 = .11$. Within-participant contrasts indicated that the increase in LI for the control group, from Session 1 to Session 2, was significant, $t(34) = 2.31, p = .02$, whereas for the ADHD group the decrease in LI across sessions approached significance $t(34) = 1.72, p = .095$.

**Discussion**

In Session 1, the control group exhibited the visual search LI effect, as in many earlier studies (see Lubow & Kaplan, 2005, for a review). Although we also predicted that the ADHD patients who had withheld taking their usual medication would have less LI than the control group, they displayed more LI than the control group, although not significantly.

In Session 2, the control group again demonstrated an LI effect. It was also predicted that when the ADHD participants were administered their regular medication 1.5 hr prior to the session, the LI effect would be normalized, that is, it would be like that of the control group. Indeed, the LI effect for the on-medication ADHD participants in Session 2 was not different from that of the control group in Session 1, but it was less than that of the control group in Session 2.

Although drug administration may be the source of the Session 2 attenuation of LI in the ADHD group, when compared with their performance in Session 1 and with the control group in Session 2, there are other explanations, most of which arise because drug conditions, with appropriate placebo controls, were not counterbalanced across sessions. Additional explanations include possibly higher motivation in the ADHD group than in the control, particularly in Session 2, when the delay and the repetition of the procedure may have contributed to a lackadaisical attitude in the control group. As opposed to this, the reintroduction of medication in the ADHD group may have induced motivational demand characteristics that affected performance independently of the drug action.

Relatedly, the ADHD group may have been affected differently than the control group by the test–retest procedure. Although the stimuli in Session 1 were not the same as those in Session 2, they may have been a greater source of interference for the ADHD group than for the control group, particularly because the stimuli were complex meaningless shapes. However, ADHD participants in Session 2 not only responded faster than in Session 1 but also responded faster than the control group in Session 2, indicating that they were less affected by interference from Session 1 than the controls, an effect that is compatible with the administration of a stimulant.

Indeed, stimulants increase general response speed, including in ADHD participants (see Advokat, 2010, for a review). However, this by itself cannot account for the finding that the attenuated LI in the on-medication ADHD participants when compared with the control group is derived from differences in RTs to the PE stimulus. Such an effect indicates that the putative drug action was specific to the Stage 1 task-irrelevant stimulus. Similarly, in between-group (drug, no-drug) experiments with healthy adults, low doses of stimulants, such as the indirect dopamine agonist, d-amphetamine, attenuate LI (e.g., Gray, Pickering, Hemsley, Dawling, & Gray, 1992; see Kumari & Ettinger, 2010, for a review). These data support the position that the results of Session 2 were, in spite of the alternative explanations, primarily due to the medication. However, the size of the drug effect may have been influenced by the fact that more than 24 hr intervened between the last “home” administration of the drug and the administration after Session 1, thereby postponing the usual time of drug ingestion.

At first glance, it seems paradoxical that when the ADHD group was off medication, the LI effect was not different from that of the control group, but that with medication, the LI effect was attenuated compared with the control group. Such an “abnormal” effect, however, is not necessarily a negative attribute. Although low LI has been reported in some subgroups of schizophrenia and in normal participants who score high on schizotypal questionnaires (see Lubow, 2005; Lubow & Kaplan, 2010, for reviews), low LI also is associated with creativity and openness to experience (see Carson, 2010, for a review). The magnitude of the LI effect is simply an expression of the degree to which the previously exposed task-irrelevant stimulus has been processed or attended. Thus, whether attending to the task-irrelevant stimulus in the preexposure stage is beneficial or detrimental to performance with that stimulus depends, in part, on the nature of the test stage. If the test-stage task requires attending to the previously irrelevant stimulus, as
in the present experiment, then performance will be diminished (LI effect). If, however, the test stage requires the participant to attend to a new stimulus that is accompanied by a previously irrelevant one that remains irrelevant, then, of course, performance will be enhanced.

Within this framework, we attribute the attenuated LI of the ADHD group in Session 2 to a drug action that reduces attentional resources allocated to the distractors in the pre-exposure stage. As such, the encoding of stimulus features of the task-irrelevant distractors would be impaired (Lubow, 2010). Consequently, when the previous distractors appear as targets in the test stage, they would be functionally novel and attract attention, giving them a similar status to the objectively novel NPE target, and thereby reducing LI.

The results of the present study are different from those of Lubow et al. (2005), who reported that an unmedicated ADHD group can exhibit less LI than a medicated ADHD group or a control group. Although the two studies used the same preexposure and test-stage procedures, the differences in experimental designs and compositions of the ADHD groups precludes a viable explanation of the differences in the results. Nevertheless, the present study provides preliminary evidence that stimulant drugs administered to adult ADHD patients after 1 day of drug deprivation reduces the LI effect when compared with control participants. Furthermore, the attenuation of LI derives from differences in responding to the previously task-irrelevant stimulus, and not to the NPE novel stimulus, suggesting that ADHD medication specifically affects the processing of task-irrelevant stimuli, in this case the PE distractors that were later made into targets.

If, indeed, test-stage performance is affected by prior (Stage 1) processing of a task-irrelevant stimulus, then the drug-produced LI attenuation must be the result of impaired retrieval of task-irrelevant stimuli, which, as noted above, may well be due to diminished processing of task-irrelevant stimulus features (Lubow, 2005, 2010). Future studies that assess the role of stimulants on the performance of ADHD participants should look directly to the task-irrelevant stimuli for effects, as in the present experiment, or indirectly, as in how task-irrelevant stimuli, which are always present, may affect performance on a task-relevant stimulus.

**Declaration of Conflicting Interests**

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**Notes**

1. A more complete description of the procedure, including pictures of the stimuli, can be found in Lubow and Kaplan (2005).

2. Sessions 1 and 2 were analyzed primarily with separate ANOVAs. Although Session 2 was a repeated test for the ADHD and control groups, the ADHD group was not medicated in Session 1 but medicated in Session 2, whereas the control group was not medicated in either session, thereby precluding a factorial design.

3. The magnitudes of the significant and marginally significant effects are indicated by eta squared ($\eta^2$). The $\eta^2$’s reported here and elsewhere are partial values.

4. The size and direction of the effects of preexposure to a task-irrelevant stimulus on subsequent performance are also dependent on number of preexposures and difficulty of the Stage 1 masking task (for reviews, Lubow, 2005, 2010).

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Bios

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