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ORIGINAL INVESTIGATION

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Dopamine agonists disrupt visual latent inhibition in normal males using a within-subject paradigm

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Abstract Latent inhibition (LI) is the delayed learning of an association when the conditioned stimulus has previously been experienced out of the context of that association. LI can be measured across species and has been used to understand the neurobiology of schizophrenia, since some reports suggest that schizophrenia patients exhibit LI deficits. One challenge of LI studies in humans has resulted from the fact that LI paradigms have almost uniformly involved between-subject comparisons. We now report a new within-subject paradigm that detected LI in normal adult male subjects after ingestion of a placebo. After amphetamine (20 mg p.o.) or bromocriptine (1.25 mg p.o.), LI was not evident, suggesting that the LI detected by this paradigm is sensitive to disruption by dopamine agonists. The apparent advantages and limitations of this paradigm are discussed with regard to its future use in understanding the neural basis of reported LI deficits in schizophrenia.

Keywords Amphetamine · Bromocriptine · Latent inhibition · Schizophrenia

Introduction

Latent inhibition (LI) is a cross-species model that may be used to study the neural substrates of complex associative deficits in schizophrenia. LI is most commonly defined as the normal decrement in the rate of association of a conditioned stimulus (CS) and an unconditioned stimulus (UCS) that occurs when the to-be-conditioned stimulus is initially pre-exposed to the subject without the UCS (Lubow and Moore 1959; Lubow 1973). Conceptually, it is believed that LI occurs when a subject learns to ignore a stimulus that does not predict an important event ["pre-exposure" (PE) phase]. When the stimulus subsequently starts to predict an important event ("test phase"), the learned "ignore" response must be overcome before a new CS–UCS association can be acquired. While the true learning mechanism responsible for LI may actually reflect something other than "learning to ignore" the pre-exposed stimulus, LI is demonstrated operationally by a reduction in acquisition, or rate of acquisition, of a CS–UCS association in which the CS is the pre-exposed stimulus, compared with the acquisition, or rate of acquisition in which the CS is a non-pre-exposed (NPE) stimulus. In most published reports, LI is demonstrated in a between-subject design, in which one group of subjects is pre-exposed to the CS, while another group is not pre-exposed to the CS.

Baruch et al. (1988a) reported that some schizophrenia patients exhibit deficits in LI when tested with an auditory LI task. In the initial phase of an acute psychotic episode, schizophrenia patients learned the test phase association as if they had not been exposed to the CS during the PE phase. These investigators suggested that pre-exposed schizophrenia patients actually learn the test phase association more rapidly than expected because they cannot adequately "gate" or suppress the cognitive response to an irrelevant stimulus. In other words, in this paradigm, impaired gating actually resulted in "better" than expected performance in schizophrenia patients. This original observation of LI deficits in acutely hospitalized schizophrenia patients has been replicated by the same group (Gray et al. 1992a), who also have reported (Gray et al. 1992b) that LI is disrupted in normal controls after treatment with a low dose of amphetamine (5 mg) but not a higher dose of amphetamine (10 mg).

Over the past decade, a number of attempts to replicate and extend these findings with LI have met with mixed success. Using the identical paradigm described by Baruch et al. (1988a), in addition to a different visual LI paradigm, we failed to detect LI deficits in a large sample of schizophrenia patients (n=73) versus controls (n=107) (Swerdlow et al. 1996). Others have found normal levels of LI in schizophrenia patients (Lubow et

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al. 1987), while others reported that LI deficits might be attributed to the effects of antipsychotic medications (Williams et al. 1998). Interestingly, while the central finding of LI deficits in schizophrenia has been somewhat elusive, the "derivative" LI models have continued to expand, including findings of antipsychotic-potentiated LI in rats (Weiner et al. 1987, 1990, 1996) and LI deficits in normal populations labeled "high schizotypy" based on questionnaire response patterns (Baruch et al. 1988b).

Several factors may have contributed to difficulties in detecting robust LI deficits in schizophrenia patients. First, LI deficits appear to be highly "state" dependent: they sometimes (Baruch et al. 1988a; Gray et al. 1992b) but not always (Swerdlow et al. 1996) occur in patients within 2 weeks of an acute schizophrenia exacerbation, but not at any other stage of the illness. Obviously, this rather precise clinical criteria, and the nature of acute psychosis, complicates the study of a large number of suitable test subjects. Second, positive reports of LI deficits utilized between-subject paradigms, in which performance in schizophrenia patients "pre-exposed" in the CS was compared to performance of patients who were not pre-exposed to the CS. This between-subject design, necessitated by complexities of the LI paradigm, demanded more than twice the number of subjects than would be required by a within-subject design, and carried the disadvantage of the extra variability associated with between- versus within-subject studies.

A within-subject visual LI paradigm was reported recently that detected different amounts of LI in normal males and female students with low versus high median scores on a "schizotypy" questionnaire (de la Casa and Lubow 2001). Measures of LI in this paradigm were based not on rates or amounts of learning – the dependent measures in all of the studies that have identified LI deficits in schizophrenia patients – but instead, were based on response latency. The results were complex and included interactions between sex and questionnaire-based groups. We previously reported the use of a computerized between-subject visual LI paradigm that failed to detect LI deficits in schizophrenia patients (Swerdlow et al. 1996), but which detected increased LI in patients with OCD (Swerdlow et al. 1999). In the present study, we modified this visual LI paradigm to permit a within-subject LI comparison. The major focus of this study was to assess the sensitivity of this new, within-subject LI paradigm.

As a secondary focus, this paradigm was used to test the effects of dopamine (DA) agonists on within-subject visual LI in normal control subjects. Both direct (bromocriptine) and indirect (amphetamine) DA agonists were tested. If this paradigm is sensitive to LI changes similar to those detected by between-subject paradigms with schizophrenia patients and DA agonist-challenged normals (Baruch et al. 1988a; Gray et al. 1992b), then it should be able to detect slowed acquisition of a pre-exposed CS-UCS association under placebo conditions, but not under conditions of amphetamine ingestion. Based on the recent reports of de la Casa and Lubow (2002), in addition to the cumulative number of correct responses, response times of correct responses were also recorded.

Table 1 Reasons for subject disqualification

	n
Withdrew prior to test day	10
SCID-NP: major depressive episode	6
SCID-NP: self-reported illicit drug use*	5
Positive toxicology screen on pre-test day**	2
Medical problem/medication	2
Hearing impairment	1
Total	26

* Self-reported illicit drug use within past year (MDMA, psilocybin), or past month (marijuana), after denying drug use during phone screen
** Drugs detected: benzodiazepines

Methods and materials

The methods used in these studies were approved by the UCSD Human Subjects Institutional Review Board (IRB no. 011202), and were approved and supported by the National Institute of Mental Health (MH 59803). Fifty-five right-handed males participated in a series of studies that included testing on a number of different psychophysiological measures, the results of which are reported elsewhere (Swerdlow et al. 2002a, 2002b). In total, the study involved phone contact and two laboratory visits, and subjects were paid US $140 for study completion. Phone screening procedures were identical to those described in previous reports from our group (Swerdlow et al. 2000, 2002a). Enrollment in studies was sequential over 6 months, with bromocriptine (n=12) and matched placebo (n=13) groups enrolled first, followed by amphetamine (n=15) and matched placebo groups (n=15) enrolled second.

Subjects who passed phone screening criteria were screened a second time at our laboratory facility. During this session the principle investigator (N.R.S.) informed each subject of the potential risks and benefits of the study. Subjects also read and signed a consent form for study participation and completed a urine toxicology test with exclusion for any identified drug, and underwent a physical and psychological examination that included a structured clinical interview (SCID-NP; First et al. 1997). Subjects also completed the tridimensional personality questionnaire (TPQ; Cloninger et al. 1991) to assess the relationship between novelty seeking (NS) and sensitivity to the effects of DA agonists, based on reports of increased sensitivity to amphetamine in individuals scoring high on this measure (Hutchison et al. 1999). Harm avoidance (HA) and reward dependence (RD) scores were also determined.

Reasons for subject disqualification prior to testing (not included in "final" sample; n=55) are seen in Table 1. Subjects who passed the second screening returned for a test day 7–10 days later; subjects were instructed not to alter their normal patterns of caffeine consumption prior to the test. On the drug test day, subjects arrived at 0830 hours, received a standardized breakfast and underwent a second urine toxicological examination. At 0915 hours, subjects consumed either active [bromocriptine, 1.25 mg (n=12) or amphetamine 20 mg (n=15)] or inactive (placebo (n=28) pills; neither subjects nor experimenters knew the pill identity. Subjects then underwent psychophysiological testing including measures of acoustic and tactile startle (preliminary results reported in Swerdlow et al. 2001, 2002b). LI testing began 2 h after pill consumption.

For LI testing, subjects were seated approximately 60 cm in front of a 28×21-cm monochrome computer screen. Six geometric

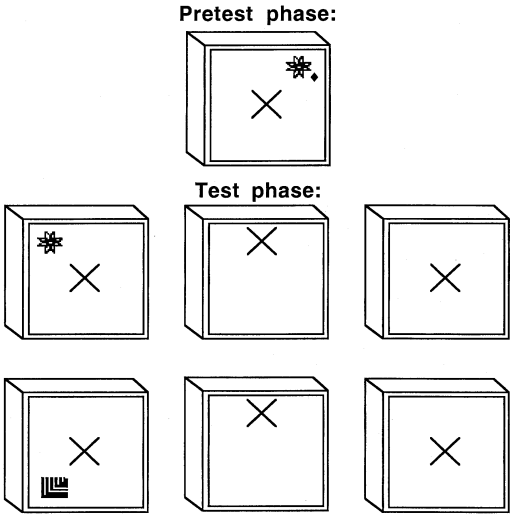

Fig. 1 Schematic representation of latent inhibition (LI) paradigm. During the pretest phase (*top*), subjects are pre-exposed (PE) to one of the two conditioned stimulus (CS) symbols (the PE symbol, shown) in addition to non-target symbols (not shown). A *diamond shape*, shown here, appears in 14 of the total 84 trials, and is counted by subjects. During the test phase, subjects attempted to predict the movement of an "X", signaled by both the PE symbol (*middle*) and by a non-pre-exposed (NPE) symbol (*bottom*). Details are found in Methods

symbols (approximately 30×30 mm; Fig. 1) were visible on the screen [five of the symbols were irrelevant (IR) symbols and one was the PE symbol]. Subjects were told that there would be two phases to the experiment. During the first phase (pretest) they would see an "X" that would remain in the center of the screen at all times. The six symbols would appear on the screen, one at a time, in different corners of the screen, and a small solid diamond would appear occasionally to the right of each symbol. Subjects were instructed to count the number of times the diamond appeared. The experimenter cleared the screen for the pretest phase. An "X" (40×40 mm) then appeared in the center of the screen. Four seconds later, subjects were exposed to presentations of each of the six symbols, in pseudorandom order, balanced for screen quadrant. The five IR symbols were each presented 8 times and the PE symbol was presented 24 times. Only one design was on the screen at any time (duration =1 s). Interpresentation intervals were 3.5 s (onset-to-onset). Each of the six symbols was accompanied twice by the diamond (total number of solid diamond presentations =12, total presentations with and without the diamond =64). At the end of the session, subjects reported their diamond count (group means: placebo =12; amphetamine =11.91; bromocriptine =11).

The second phase (test phase) followed thereafter. Subjects were told that during this portion of the task they would again see a series of symbols, the diamond, and an "X" on the screen, and that something on the screen would signal that the "X" was going to move from the center of the screen to the top of the screen, and then back to the center. The subject's task was to determine when the "X" was about to move and to press the "space bar" on the keyboard as soon as possible, prior to the movement of the "X". Once the subject indicated that the directions were understood, a 10-s delay began, followed by the test phase and the appearance of the "X" at the center of the screen. All stimuli were then presented in a manner identical to the pretest phase, but an additional symbol was added (NPE symbol). All symbols (PE, NPE and IR) appeared 12 times and the diamond appeared twice directly to the right of each symbol (total number of solid diamond presentations =14, total presentations with and without the diamond =84). Each appearance of either the PE or the NPE symbol (with or without the diamond) was followed 2.5 s later by the movement of the "X", described above. "Space bar" presses during the design presentation or the 2.5-s interval prior to the movement of the "X" were scored automatically by the computer as "correct", without any feedback provided to the subject, and the reaction time (RT) to key press was recorded. On completion of the test phase, the screen was cleared and a tone sounded. Subjects were then asked whether they had a strategy for pressing the space bar; if the strategy was correct, they were asked whether they could identify the two target shapes (PE and NPE symbols) from a printed compilation of all shapes used in the study.

Heart rate and blood pressure were determined (sitting position, brachial cuff), and subjects completed a symptom rating scale, before pill ingestion and throughout the morning, including immediately after LI testing. Symptom rating scales were designed to assess general somatic and psychological symptoms and level of consciousness (modified from Norris 1971; Bond and Lader 1974; Bunney et al. 1998), and were identical to those described by Swerdlow et al. (2002a). Ratings were treated as continuous variables and were analyzed using mixed-design ANOVAs, with a difference score that reflected the change between measures collected pre-drug ("baseline") and post-LI testing.

LI was assessed by analyzing the rate and number of cumulative correct responses to both the PE and NPE symbols. To demonstrate the sensitivity of this within-subject paradigm, performance in placebo group subjects was examined first. Because cumulative responses violate the ANOVA assumption of independent samples, we assessed acquisition rate by determining the trial number by which each subject achieved a learning criterion (>50% correct responses) for the NPE and PE associations. For example, if a subject achieved their second correct NPE response on trial 3, their NPE score was "3"; if they achieved their fourth correct PE response on trial 7, their PE score was "7". If a subject failed to exceed a 50% correct response rate, their score was "13" (one greater than the maximum number of 12 trials). Because the nature of these data required non-parametric analyses, NPE versus PE acquisition (no. of trials to reach criterion) were compared using a Wilcoxon Sign Rank test, which did not take advantage of the power afforded by the within-subject design. To accommodate for this, a paired *t*-test was used to compare the number of correct NPE vs PE responses at the trial corresponding to the median NPE score (trial 8). Once the sensitivity of the LI paradigm was established in placebo group subjects, the above analyses were applied to bromocriptine and amphetamine groups, and an ANOVA was used to compare the total correct responses using condition (NPE vs PE) as a within-subject variable and drug group as a between-subject variable. Drug effects on LI were demonstrated by a significant drug × condition interaction, and appropriate post-hoc comparisons. Based on studies in humans (Gray et al. 1992a) and rats (Weiner et al. 1987), the a priori prediction was that LI would be reduced or eliminated by amphetamine; the caveat in this prediction is that Gray et al. (1992a) reported LI-disruptive effects of amphetamine with 5 mg, but not 10 mg p.o., and the present study utilized an even higher dose of amphetamine (20 mg). No clear a priori prediction was available for the effects of bromocriptine on LI. Based on human studies with other "gating" measures (Abduljawad et al. 1997, 1998), one might predict that bromocriptine should disrupt LI, while animal studies with other direct DA agonists (Weiner et al. 1990) would lead to a prediction of no significant effect on LI. Alpha was 0.05.

Other exploratory measures were also assessed. Based on recent reports of RT changes associated with LI (Lubow and de la Casa 2002), we assessed RTs for correct responses in all subjects. Unlike the study of Lubow and de la Casa (2002), the present design did not include a "forced response" (i.e., in the study by Lubow and de la Casa 2002, "The trial terminated when the subject pressed one of the six keys"); instead, the trial terminated automatically with the movement of the "X". Thus, RTs in the present study were not recorded if subjects did not perform the key press during the design presentation or the 2.5-s interval prior to the movement of the "X". Mean RTs for correct responses in each condition were calculated and compared across drug groups. Finally, LI measures were

assessed using grouping factors based on low versus high median scores on TPQ subscales.

While a selective failure to respond correctly to the PE symbol might be viewed as evidence of LI, a failure to respond correctly to the NPE symbol was interpreted as a generalized learning difficulty that precluded any simple interpretation of LI data. For this reason, data from some subjects was excluded based on a failure to achieve two correct NPE responses (i.e., evidence that they "learned" the NPE association). These "non-learners" were distributed relatively equally among active drug (7 of 27) and placebo groups (5 of 28). Demographic, personality and response characteristics of non-learners and learners were compared in an attempt to understand the basis for failure to acquire the NPE association. Two subjects (1 placebo, 1 active) were excluded because they reached the criteria for cumulative correct responses by pressing the space bar at a high rate, even when non-CS symbols appeared. This resulted in the highest number of errors [19 and 20, >3.8 SD above mean errors (mean±SD errors = 3.12±4.14)]. The final test sample thus included 41 subjects. Importantly, inclusion of the 12 "non-learners" and the 2 "high error" subjects increased the variance, but did not change the overall pattern of results.

Results

Relevant characteristics of placebo, bromocriptine and amphetamine group subjects are seen in Table 2. Groups did not differ significantly in age, caffeine intake or TPQ subscale scores. Mean bromocriptine dose was 0.017 mg/kg, and mean amphetamine dose was 0.283 mg/kg. Across the three drug groups, a total of five subjects were self-identified smokers: two smoked five cigarettes or fewer per week, and three smoked one to five cigarettes per day.

Cumulative correct responses for PE and NPE symbols in placebo, amphetamine and bromocriptine groups are seen in Fig. 2. To assess the sensitivity of this paradigm to LI effects, data were first analyzed from all placebo group subjects. Wilcoxon Sign Rank test revealed that subjects reached the learning criteria (>50% correct responses) faster for NPE than PE associations ($z=2.10$, $P<0.04$; median trials to criterion: NPE=8, PE=11). Post-hoc paired t-test at trial 8 revealed significantly greater total correct responses for NPE than PE associations ($t=2.22$, df 21, $P<0.04$); similar comparisons revealed significant group separation earlier in the test session ($P<0.05$, 0.007, 0.015, and 0.02 for trials 4–7, respectively) and later in the session ($P<0.04$ for trial 9), that waned toward the end of the session (n.s. for trials 10–12), suggesting a differential rate of acquisition, rather than an absolute difference in ability to acquire the PE versus NPE association. The magnitude of the LI effect was modest:

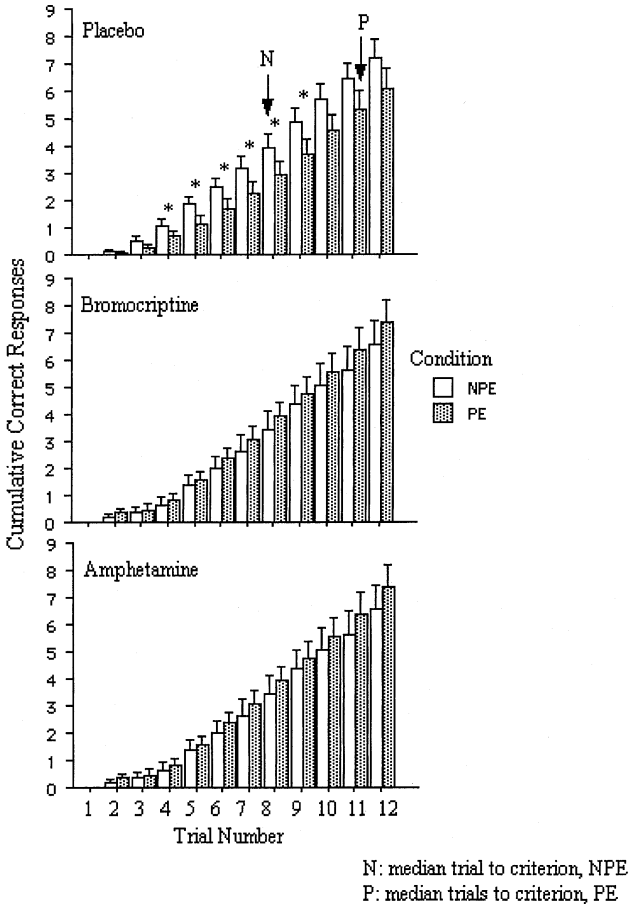

Fig. 2 Cumulative correct responses in the test phase in subjects pretreated with placebo (*top*), 1.25 mg bromocriptine (*middle*), or 20 mg amphetamine (*bottom*). Latent inhibition (LI) is seen in placebo-group subjects, who register more correct responses to the non-pre-exposed (NPE) symbol than to the pre-exposure (PE) symbol. "*P*" and "*N*" indicate median trials-to-criterion for NPE (trial 8) and PE (trial 11) conditions. The bias toward correct responses to the NPE symbol is evident early in the test session and reaches statistical significance for trials 4–9 (*). In contrast, learning in bromocriptine and amphetamine group subjects occurs at comparable rates for NPE and PE symbols; in other words, they do not exhibit LI

at the point of greatest separation (trial 5), the effect size (d) of PE relative to NPE responses was 0.54, consistent with a moderate effect (Cohen 1988).

Because placebo groups exhibited essentially identical performance across the two enrollment cohorts, they were combined for comparison versus amphetamine and bro-

Table 2 Subject characteristics

Drug group	Age (years) Mean (SD)	Mean drug dose (mg/kg)	Ethnicity (C:A:H)*	Daily caffeine (mg) Mean (SEM)	TPQ subscale score; mean (SEM)		
					NS	HA	RD
Amphetamine n=11	22.55 (1.32)	0.283	9:1:1	61.06 (14.47)	18.91 (1.42)	6.64 (1.25)	19.82 (0.98)
Bromocriptine n=8	21.63 (0.71)	0.017	4:2:2	62.06 (19.68)	18.38 (1.27)	5.38 (1.78)	19.13 (1.58)
Placebo n=22	22.09 (0.89)	N/A	12:8:2	43.63 (12.03)	19.14 (0.97)	9.00 (1.29)	20.09 (0.82)

* Caucasian:Asian:Hispanic

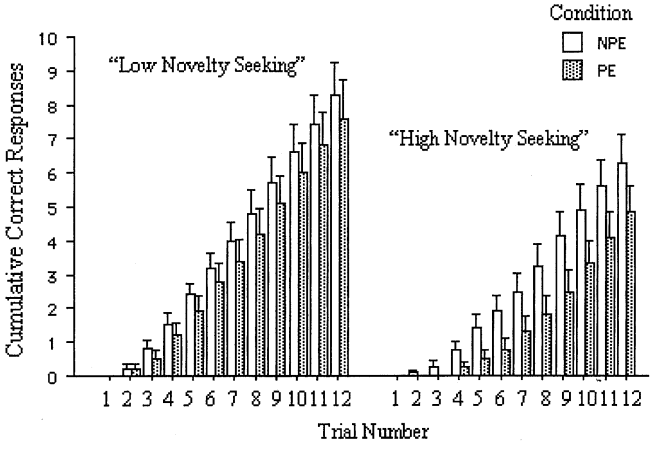

Fig. 3 Cumulative correct responses in the test phase in placebo-group subjects. Latent inhibition (LI) was not significantly different in subgroups distinguished by low versus high median scores on the tridimensional personality questionnaire scale for novelty seeking. High novelty seekers exhibited fewer overall correct responses, and while they appeared to also exhibit more robust LI than did low novelty seekers, this was not supported by statistical comparisons

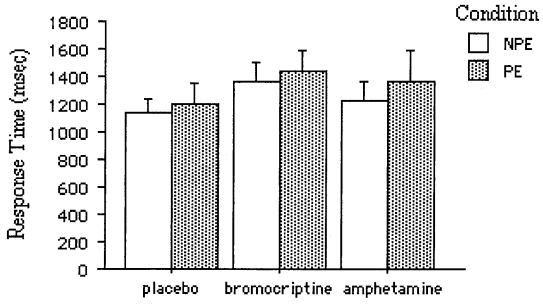

Fig. 4 Time (ms) for correct responses to pre-exposure (PE) and non-pre-exposed (NPE) symbols in placebo, bromocriptine and amphetamine group subjects. No evidence of latent inhibition was detected using this variable, and no differences in reaction times were noted across drug groups

mocriptine groups. Analyses revealed a blockade of LI in both amphetamine and bromocriptine group subjects. Wilcoxon sign rank test revealed no difference in rate to achieve criterion between NPE and PE associations for either amphetamine (z=0.54, n.s.; median scores to criterion: NPE=9, PE=9) or bromocriptine (z=1.41, n.s.; median scores to criterion: NPE=10, PE=8) groups. ANOVA of cumulative correct responses at trial 8 (median trial for >50% correct rate in placebo group subjects) revealed no significant effect of group (F<1) or condition (F<1), but a significant interaction of group × condition ($F_{2,38}$=3.66, P<0.04). In contrast to the findings in placebo group subjects (above), there was no evidence of LI in either amphetamine or bromocriptine group subjects (NPE versus PE correct scores: t values =1.10 and 1.49, respectively; Fig. 2). Similar ANOVA results emerged from comparisons earlier and later in the test session. Cumulative correct responses for PE and NPE symbols in the active drug groups were essentially indistinguishable, and no effects of condition approached significance for any trial in either bromocriptine or amphetamine groups subjects. There were no significant differences in the numbers of "missed" targets (omissions) or pressing errors across the placebo and active drug groups. Finally, the lack of significant LI was evident in active drug groups, independent of whether they correctly reported the task strategy ("got it").

Analyses of TPQ scores revealed no clear relationship to LI or drug sensitivity. Placebo group subjects exhibited LI independent of whether they were in the low or high median of NS, HA or RD scores [at trial 8, significant effects of condition for all comparisons (P<0.05), and no significant interactions with low versus high median group for any comparison; cumulative data from NS split seen in Fig. 3]. Low NS score subjects achieved significantly more total correct responses than did high NS score subjects [significant effect of median group ($F_{1,20}$=6.37, P=0.02), but no group × condition interaction (F<1)]. No such relationship was observed with either HA or RD scores. For both amphetamine and bromocriptine groups, LI was not detected, independent of whether subjects scored in the low or high median for NS, HA, or RD scores.

No evidence for LI could be seen in the analyses of RTs on correct key-press responses (Fig. 4). ANOVAs of mean RT for PE and NPE symbols revealed no significant effect of condition in placebo group subjects (F<1), and inclusion of active drug groups revealed no significant effects of drug or drug × condition interactions.

One concerning feature of this LI paradigm was the high number of subjects who failed to acquire the NPE association (12 of 53 subjects). In an attempt to understand the basis for "failed" NPE learning, it was determined that these subjects were equally poor at PE learning (mean±SEM) incorrect responses of 12 trials: NPE=11.67±0.14, PE=11.25±0.39. "Learners" and "non-learners" did not differ in age (mean±SEM) "learners" =22.12±0.60, "non-learners" =23.50±1.23, t=1.07, n.s.; years of education (mean±SEM) "learners" =14.49±0.22, "non-learners" =14.83±0.47, t=0.71, n.s.; or scores of NS, HA or RD (t values =0.31, 0.58 and 0.49, respectively, all n.s.).

Autonomic and subjective measures identified clear evidence of "bioactivity" for these doses of amphetamine and bromocriptine at the time of LI testing. ANOVAs of difference scores (measures immediately post-LI testing minus pre-drug baseline) revealed that compared with placebo, amphetamine and bromocriptine increased heart rate and systolic blood pressure, amphetamine reduced "drowsiness", and bromocriptine increased ratings of "queasy" and "dizzy".

Discussion

These findings demonstrate LI of learning in a within-subject paradigm in normal adult males. Placebo-group subjects were slower to learn an association with a pre-

exposed symbol than with a NPE symbol. Clearly, the paradigm does not appear to be "optimal" for some purposes: one-quarter of all subjects either failed to learn the association (two consecutive correct responses to the NPE symbol) or met learning criteria only by pressing the space bar at a high rate that suggested indiscriminate responding. Nonetheless, three-quarters of the subjects did learn the association, and, in the placebo group, they demonstrated consistent LI. Our experience suggests that these rates reflect features of this LI paradigm, independent of drug (or pill) administration per se: drug-free studies in progress with this LI paradigm to date demonstrate robust LI in normal men and women, but NPE learning failure rates in men [4 of 18 (22.2%)] and women [3 of 16 (18.8%)] are comparable to those in the present study [12 of 53 (22.6%)]. The present data suggest that NPE "non-learning" is not related to age, years of education or NS, HA or RD personality dimensions. It will be important to pursue systematic studies using this paradigm to assess the effect of specific parametric manipulations (e.g., stimulus and test session features) on non-learning rates.

The effect size for the LI detected by this paradigm was moderate at best (d=0.54 at the point of maximum separation, trial 5). That statistically significant separation could be detected with relatively small samples and a moderate effect size illustrates one advantage of a within-subject LI paradigm. However, the fact that only a moderate effect size was achieved means that detection of between-group interactions with this paradigm, e.g., across patient or drug groups, may be challenging.

There may be ways to optimize the power of this within-subject paradigm via parametric manipulations, but some of our preliminary efforts in this regard have not been fruitful. For example, we have not detected greater group separation using a paradigm that included three graded levels of PE: (targets with 0, 8 and 24 repetitions during PE phase), nor using alternative learning criteria (e.g., number of trials to achieve "x" correct responses).

The present study did not address the sensitivity of this LI paradigm to sex differences or differences based on questionnaire-defined "high schizotypy", both of which have been reported in other LI paradigms (Baruch et al. 1988b; Lubow and de la Casa 2002). Our studies in progress suggest comparable LI in normal men and early follicular phase women using the present paradigm, but the possibility of performance shifts across the menstrual cycle has not yet been evaluated. This paradigm also did not detect changes in response time associated with LI; this likely reflects the fact that RTs were only recorded for correct responses, and no "forced response" was used, as in the one previous report of LI using this measure (Lubow and de la Casa 2002).

While this paradigm detected significant LI in placebo group subjects, it did not do so for subjects who had ingested either amphetamine or bromocriptine. The loss of LI in these subjects did not reflect "non-specific" performance deficits, as assessed by overall learning (total number of correct NPE responses) or RTs. Subjective and autonomic measures verified the bioactivity of these drug doses. The sensitivity of this paradigm to the LI-disruptive effects of DA agonists appears to be generally consistent with current models for the neurobiology of LI (Gray 1998), but a closer inspection of the literature reveals some inconsistencies. For example, Gray et al. (1992a) reported that LI is disrupted by 5 mg but not 10 mg amphetamine in a between-subject paradigm (Gray et al. 1992a). That an even higher dose of amphetamine (20 mg) would disrupt LI in the present study presents a challenge to the notion that the previous results reflect a simple "inverted-U" dose function. Certainly, differential dose sensitivity across these two studies might reflect differences in task demand, design, stimulus modality, subject demographics, and a variety of other factors. Furthermore, a single report of a negative effect of one dose (10 mg) or a positive effect of a second dose (either 5 mg or 20 mg) clearly deserves replication. To our knowledge, there are no published replications of the failure of the 10-mg dose of amphetamine to disrupt LI in normal subjects. Sensitivity to LI disruptive effects of bromocriptine has not been reported previously and suggests the possibility that LI is sensitive to both direct and indirect DA receptor activation. Certainly, larger studies with direct DA agonists would be needed to validate this observation, particularly since – at its simplest cross-species extrapolation – it appears to contrast with the failure of the direct D1/D2 agonist apomorphine to disrupt LI in rats (Weiner et al. 1990).

Perhaps more important will be the application of this new within-subject LI paradigm to clinical populations. The ability to characterize the "amount of LI" and an "LI deficit score" (e.g., relative to a normal population mean) for each individual schizophrenia patient may permit a variety of useful applications of LI as a quantitative "endophenotype". Ultimately, the value of refining the LI paradigm will be judged by its utility in studies ranging from clinical trials to genetic analyses (Braff and Freedman 2002).

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