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Abolition of latent inhibition by a single 5 mg dose of *d*-amphetamine in man

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Abstract. The performance of healthy volunteer subjects on an auditory latent inhibition (LI) paradigm was assessed following administration of a single oral dose of *d*-amphetamine or placebo. It was predicted that a low (5 mg), but not a high (10 mg), dose of *d*-amphetamine would disrupt LI. The prediction was supported with left ear presentation of the preexposed stimulus only. When the preexposed stimulus was presented to the right ear the predicted pattern of findings was not obtained. It is concluded that the dopaminergic system is involved in the mediation of LI in man and it is speculated that the interaction between amphetamine dose and ear of presentation of the preexposed stimulus may reflect normally occurring dopaminergic hemisphere asymmetry.

Key words: Latent inhibition – *d*-Amphetamine – Schizophrenia – Attention – Man – Lateralisation of function

Latent inhibition (LI; Lubow 1973) consists of a retardation or reduction in learning if the to-be-conditioned stimulus (CS) has first been preexposed without consequence. It has been the subject of intense theoretical analysis, most accounts concentrating on the notion that preexposure leads to a loss of the capacity of the CS to engage attention and/or to enter into associations (Lubow 1989). Recently, LI has become the focus of experimental and theoretical work concerned with the neural basis of the cognitive abnormalities, especially the "positive" symptoms, of acute schizophrenia (Gray et al. 1991a, b, and associated peer commentary). This research was initiated by reports that LI is abolished in the rat by the indirect dopamine (DA) agonist, amphetamine (Solomon et al. 1981; Weiner et al. 1981), a drug known to give rise to or exacerbate psychotic symptoms (Ellinwood 1967; Griffiths et al. 1968; Angrist et al. 1974). This result was taken to indicate that enhanced dopaminergic transmission was responsible for a breakdown in normal selective attention, the latter being defined as the screening out of the CS following unreinforced preexposure. Furthermore, since acute schizophrenia has long been regarded as a disorder of selective attention (e.g. Kraepelin 1913; McGhie and Chapman 1961; Hemsley 1977; Frith 1979) and is thought probably to involve abnormally enhanced dopaminergic transmission (Meltzer and Stahl 1976), blockade of LI by amphetamine in the rat was proposed as a plausible animal model of the cognitive abnormalities of acute schizophrenia (Solomon et al. 1981; Weiner et al. 1981).

This proposal received support from the observation that LI is absent in acute schizophrenics, although it can be demonstrated in various other groups: normal human subjects; chronic schizophrenics maintained on DA receptor blocking neuroleptic medication; and agoraphobics (Baruch et al. 1988; Gray 1991). Furthermore, the loss of LI in the acute schizophrenic group took the form of faster learning in the preexposed (PE) condition, as in the amphetamine treated rat, and so could not be attributed to non-specific cognitive deficits. In support of the putative relationship between LI and DA, LI was normalised in the acute schizophrenic group by neuroleptic medication over a period of 6 weeks (Baruch et al. 1988); and the abolition of LI by amphetamine in the rat was found to be reversed by neuroleptics (e.g. Solomon et al. 1981). It should be noted, however, that the actual paradigms used to study LI in the two species are only similar in that they both involve phases of preexposure and associative learning. All other specific details differ. For example: only the human tasks include a masking procedure (cf Ginton et al. 1975); animal procedures employ strong reinforcements (e.g. food, shock), whereas the human subjects are motivated merely by the desire to complete the task successfully (see Solomon et al. 1981; Weiner et al. 1981; Baruch et al. 1988 for details). It must therefore remain an assumption that LI, as studied in rodent and human subjects respectively, truly reflects the same underlying processes in the two cases. The principal aim of the experiment reported here was to put

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this assumption to the test by determining the effects of *d*-amphetamine on LI in normal human subjects using the Baruch et al. (1988) procedure. If human LI and rodent LI are the same then, assuming also similar drug metabolism in the two species, the same pattern of drug effects should be obtained.

The existing data with rats permit a more precise prediction in this regard than simply the abolition of LI by amphetamine. These data show an inverse dose dependence of the amphetamine effect: 1.5 mg/kg *dl*-amphetamine abolishes LI, whereas 6 mg/kg leaves it intact (Weiner et al. 1984, 1987). This pattern of results is consistent with the hypothesis (Solomon and Staton 1982) that abolition of LI occurs by virtue of DA release from the terminals of the mesolimbic projection of nucleus A 10 in the nucleus accumbens, rather than release from terminals of the nigrostriatal dopaminergic projection, since low doses of amphetamine elicit DA release preferentially at the former site, whereas high doses act preferentially at the latter (Hitzemann et al. 1980; Porrino et al. 1984). Thus a similar pattern of inverse dose dependence of the effect of amphetamine on LI in man would not only be evidence that this depends upon the same processes as LI in the rat, but would also provide suggestive evidence for a common neuroanatomical site of action of the drug in the two species.

However, a precise prediction as to the actual doses that would be effective or ineffective in man was not possible, since we are unaware of any data on amphetamine-elicited DA release in the human brain. In addition, the conversion of doses between rat and man is notoriously difficult. Therefore, for our low dose we used the lowest dose which in adult subjects has been demonstrated to have definite behavioural effects (dextroamphetamine, 5 mg PO; British National Formulary 1990, p 172). We made the clear prediction that this dose should attenuate LI, as with the lower doses in the rat. We were constrained by ethical considerations, however, as to the high dose that we were able to use, since 10 mg PO was the highest dose for which ethical permission could be obtained. We made the tentative prediction that this dose should have less effect on LI, as with the higher doses in the rat.

Ethical constraints also required us to use a single administration of amphetamine. In contrast, most of the relevant animal research (Solomon et al. 1981; Weiner et al. 1981, 1987) employed chronic drug administration; indeed, chronic regimes might be considered necessary on the grounds that psychosis has usually been reported in human subjects after amphetamine intoxication only if the drug has been used chronically (Ellinwood 1967; Angrist et al. 1974). However, more recent animal studies have found that two doses of amphetamine, one before preexposure and one before acquisition, are sufficient to abolish LI (Weiner et al. 1988). Thus, the critical requirement appears to be that the subjects are under amphetamine during both preexposure and acquisition. The single dose of amphetamine used in the present experiment fulfilled this requirement.

Materials and methods

Design

The study was double blind. A two-factor independent groups design was used. Factors were: drug level (0 mg, 5 mg, 10 mg) and experimental condition (preexposure, PE; non-preexposure, NPE). The dependent variable was speed of learning the association between a white noise conditioned stimulus (CS), presented via headphones, and incrementation of a number display. Ear of presentation of the white noise stimulus was counterbalanced across subjects. The presentation of the stimulus to the different ears was randomly designated and was achieved by reversing the position of the headphones. Subjects were randomly assigned to LI condition (PE or NPE) and drug condition (0 mg, 5 mg, 10 mg). The study was approved by the Ethical Committee at the Institute of Psychiatry and was performed in the Neurosurgery Department of the Maudsley Hospital, London.

Subjects

Seventy-six normal volunteers took part in the study (39 women and 37 men). All subjects were obtained from an advertisement placed in a local paper. Exclusion criteria included a history of mental illness, drug or alcohol dependency, abnormalities of hearing or vision, lactation or pregnancy, or possibility of pregnancy during the study. Subjects were matched for age, sex, verbal intelli-

Table 1. Means and standard errors of age, weight and verbal intelligence score for each experimental group. *Wgt* = mean weight in kg. *IQ* = mean verbal intelligence score as measured by Set B of the Mill Hill Vocabulary Scale. $N = 12$ per cell. Mean values shown with standard errors in parentheses

Condition	Drug group					
	0 mg		5 mg		10 mg	
Preexposure	Age (yrs)	29.17 (1.0)	Age (yrs)	33.21 (1.3)	Age (yrs)	32.17 (1.3)
	Wgt (kg)	65.3 (1.0)	Wgt (kg)	68.49 (1.0)	Wgt (kg)	75.63 (1.7)
	IQ	112.25 (9.4)	IQ	108.0 (13.3)	IQ	110.85 (10.5)
Non-preexposure	Age (yrs)	29.25 (1.2)	Age (yrs)	31.2 (1.4)	Age (yrs)	25.83 (0.9)
	Wgt (kg)	68.4 (1.5)	Wgt (kg)	69.33 (1.0)	Wgt (kg)	66.89 (1.2)
	IQ	111.42 (9.8)	IQ	111.79 (9.2)	IQ	109.0 (11.1)

gence score, and weight across experimental groups. Table 1 shows the demographic data. Subjects were informed both verbally and in writing about the aims and risks of the trial and about the transient mood-altering effects of amphetamine. Subjects were paid £50.00 each.

Drugs

Dexamphetamine sulphate (Dexedrine; Smith, Kline and Beecham) and placebo formulations were used. The oral administration consisted of 2 × 5 mg tablets which contained 5 mg dexamphetamine or placebo. Each drug dose or placebo was administered under double blind conditions in two opaque capsules, which were identical in colour and size for all subjects. Placebo capsules contained only lactose.

Blood sampling

Venepuncture for amphetamine plasma analysis was made immediately before the task, 90 min after oral administration of drug or placebo. Blood was drawn into heparinized tubes and placed in ice until the end of the testing session. The samples were centrifuged at 3000 *g* for 10 min to separate blood plasma. Plasma samples were frozen at − 20° C until assayed by capillary gas chromatography (amphetamine concentrations expressed in μg/l; detection limit, 1–2 μg/l).

Equipment

The list of nonsense syllables which constituted the masking material (necessary to demonstrate LI in adult human subjects; Ginton et al. 1975) was recorded in a male voice on both tracks of a Sony tape recorder (for binaural presentation). The interval between syllables was 1–2 s. The 30 nonsense syllables were repeated five times successively in a fixed order, for both the preexposure and test phase of the experiment. There was no indication as to the termination or restart of the list.

In the test phase of the experiment the white noise stimulus was superimposed at 25 random time points on track 1 of the recording (monaural presentation) for both groups – PE and NPE – and in the preexposure phase of the experiment for the PE group only. The white noise stimulus had a mean duration of 1.25 s with a (randomly varying) range of 0.5–2.0 s and a randomly varying inter-stimulus interval. The verbal material was set at approximately 73 dB (i.e. within typical speech levels). The intensity of the white noise was set to vary randomly between 50 and 61 dB (mean = 58 dB). The preexposure phase and the test phase lasted approximately 5 min each.

The white noise was produced by a white noise generator (Campden Instruments 530). The "scoreboard" was a grey plastic box measuring 22 × 14 cm and containing two light emitting diode number matrices, 4.5 cm in length. The scoreboard was placed 70 cm in front of the subject in the centre of the visual field.

General procedure

Subjects were screened for contraindications to amphetamine 3 weeks prior to testing. Screening included measures of blood pressure and heart rate to ensure that they were in the normal range. Subjects were also interviewed to ensure that there was no history of thyroid dysfunction, glaucoma, anxiety or stress disorder, heart disease, hypo- or hyper-tension, anorexia, violent or rapid mood swings, or any form of mental illness. A urine sample was collected for a drug screen (cannabis, amphetamine, methylamphetamine, morphine, methadone, benzodiazepines, cocaine and barbituates). Four subjects had a positive urine analysis for one or more of these substances and were excluded from the study.

Testing began at 10.00 a.m. to control for differential amphetamine metabolism at different times of the day. On arrival at the Institute of Psychiatry subjects read and signed a written consent form explaining the nature and aims of the study. The subjects were randomly assigned to drug group and condition. Commencement of the LI task occurred 100 min after drug administration. The highest plasma concentration of amphetamine occurs, on average, 90–100 min after oral administration of amphetamine (Wan et al. 1978). The testing sessions therefore covered the period of maximum drug effect. During the 100 min before task commencement the subjects were weighed and given the synonym-only version (set B) of the Mill Hill Intelligence Scale (Raven 1981) to complete, in order to be able to control for variations in intelligence level between the groups. Blood pressure and heart rate were monitored at 15 min intervals for the duration of the study.

Latent inhibition paradigm

Preexposure. Subjects of both experimental groups (PE and NPE) were asked to listen, via headphones, to a recording of a male voice speaking a list of nonsense syllables. They were told to listen carefully to the recording, to pick just one syllable and to count how many times it was repeated. Monitoring of the syllables served to ensure that the subjects directed their attention to the masking material. At the end of this phase, subjects were asked which nonsense syllable they had chosen and how many times (in fact, 5) it was repeated. Subjects were to be excluded if they reported the number of repetitions to be less than 3 or more than 7. No subjects were excluded on these criteria.

For the non-preexposed group (NPE) the preexposure phase of the paradigm consisted of just the masking material; for the preexposed group (PE) the white noise stimulus was superimposed at 25 random time points on track 1 of the recording, which was randomly assigned to left or right ear presentation.

Test. Subjects were instructed that they were starting a new task. Once again they would listen to a recording of a male voice speaking a list of nonsense syllables. They were told that throughout the recording the experimenter would increase the number displayed on the scoreboard using a small control panel. They were shown the control panel and the experimenter demonstrated how the number would be incremented. The subjects were further told to listen to the recording and to closely watch the scoreboard, that the number on the scoreboard would be incremented according to something that they would hear on the tape, and that their task was to ascertain as quickly as possible what the rule was. As soon as the subject knew the rule, he was to raise his hand and was to continue to raise his hand whenever he expected the experimenter to increment the scoreboard.

The test phase of the paradigm was identical for both groups: the 30 nonsense syllables were presented 5 times in a set order and the white noise stimulus was superimposed at 25 random time points on track 1 of the recording. For the PE group the white noise was always presented to the same ear (randomly assigned) in both preexposure and test; for the NPE group ear of presentation at test was randomly assigned. The number on the scoreboard was manually incremented by the experimenter just prior to the offset of each presentation of white noise. The experiment was terminated when the subject had correctly predicted, by raising his hand after the onset of the white noise but before the number increment, five consecutive number increments with no errors of commission interspersed, or after the termination of the recording (i.e. after 25 presentations of the white noise). The time between the preexposure and test phases of the paradigm varied slightly across subjects, but was typically 2–3 min.

Scoring. The learning score for the task consisted of the number of times the white noise CS had been presented before the subject had reached the learning criterion of correctly predicting five consecutive presentations of the white noise. Thus, the faster the learning,

the lower the obtained score. Subjects who did not reach this criterion were given a score of 30 (i.e. 25 presentations of the white noise stimulus plus 5). Latent inhibition should appear as slower learning in the PE than in the NPE group.

Data analysis

The data obtained from the LI paradigm, as in previous human LI studies, were found to have a bimodal distribution and were therefore submitted to non-parametric analysis. Rank-sum factorial analyses (Meddis 1984, pp 299–344) were performed on the data with drug level (0 mg, 5 mg, 10 mg) and experimental condition (PE, NPE) as factors. Separate analyses were conducted for left and right ear presentation of the white noise CS, as a preliminary visual inspection of the data indicated that the two conditions were quite distinct. Ear of presentation of the white noise CS was not known to be an important variable prior to completion of the study and this factor was not included in a completely balanced design, resulting in unequal numbers of subjects in each cell. The final number of subjects in each cell are shown in Figs. 1 and 2.

Analysis of the placebo data for both ears was conducted to see if there was a significant interaction between LI and the ear in which the CS was presented. This was a post-hoc analysis and can be optimally performed (Meddis 1984; p 298) by carrying out a non-specific factorial analysis. Specific factorial analyses were conducted for data from each ear of CS presentation separately. The specific prediction was tested via a single statistic representing the expected form of the interaction, i.e. a large LI effect in the 0 mg and 10 mg drug groups but a reduced, or absent, LI effect in the 5 mg drug group. If this statistic failed to achieve significance the data were submitted to a non-specific analysis to check for the possibility of any other significant drug by LI interactions.

Table 2. Means and standard errors for plasma amphetamine levels for each experimental condition across drug group. Amphetamine levels measured in μg/l. Mean values shown with standard errors in parentheses

Condition	Drug group	
	5 mg	10 mg
Preexposure	8.23 (0.9) $N=12$	12.69 (1.8) $N=9$
Non-preexposure	9.82 (1.1) $N=11$	13.04 (2.1) $N=12$

Results

Drug plasma concentrations

The mean plasma amphetamine concentrations obtained 100 min after administration of a single oral dose of 5 and 10 mg *d*-amphetamine, for each experimental condition (PE, NPE), are shown in Table 2. As expected, plasma amphetamine concentrations were higher for the 10 mg, as compared to the 5 mg, drug group. All plasma amphetamine concentrations for the placebo group were 0.

Left versus right ear CS presentation – placebo groups only

A 2×2 non-specific factorial analysis of the placebo groups' data was performed with factors of ear (left vs right) and condition (PE versus NPE). This revealed a significant interaction between ear and condition [$H=5.06$, $df=1$; $P<0.025$; H distributed as χ^2]. Inspection of the placebo groups in Figs. 1 and 2 shows that LI was found with left, but not with right, ear presentation of the white noise CS. Indeed, the LI effect appeared to be reversed with right ear presentation. These results demonstrate the need to consider the data for each ear of presentation separately.

Left ear presentation

The data revealed a significant drug by LI interaction in the predicted direction [$Z=2.02$, $P< 0.025$]. That is, LI was present in the 0 mg and 10 mg groups, but not in the

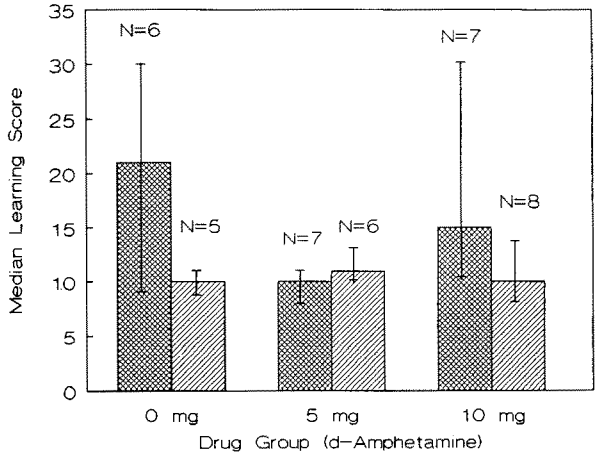

Fig. 1. Median learning scores across experimental condition and drug group for left ear presentation of the white noise conditioned stimulus. Error bars indicate the interquartile range for each condition. *PE*=preexposure (▩); *NPE*=non-preexposure (▨)

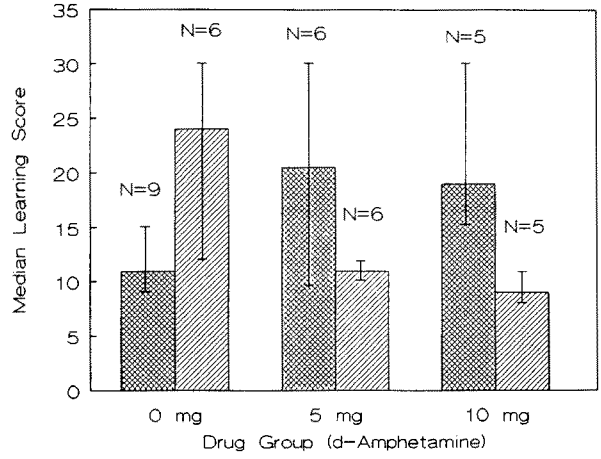

Fig. 2. Median learning scores across experimental condition and drug group for right ear presentation of the white noise conditioned stimulus. Error bars indicate the interquartile range for each condition. *PE*=preexposure (▩); *NPE*=non-preexposure (▨)

5 mg drug group. Figure 1 depicts this interaction. A change in the degree of LI should be reflected in changes in speed of learning the association in the PE group only, with minimal change in the NPE group. Figure 1 indicates that the change in LI is indeed reflected principally in changes in the speed of learning of the PE groups.

Right ear presentation

Unlike the results found for left ear presentation there was no support in the data for the specific prediction tested, i.e., LI absent only in the 5 mg condition [$Z = -0.63$, NS]. In addition to the insignificant value of the statistic its negative sign indicates a poor fit of the data to the prediction. The data were therefore submitted to non-specific factorial analysis. The main effects of preexposure and drug were not found to be significant [$H = 0.0$, $df = 1$, and $H = 0.09$, $df = 2$, respectively]. However, the condition by drug interaction approached significance [$H = 5.71$, $df = 2$, $P = 0.06$; H distributed as χ^2]. Given that non-specific factorial analyses are very insensitive (Meddis 1984, pp 291–298), this trend may reflect a sizeable effect. The degree of LI following right ear presentation of the CS thus appears to be altered by amphetamine, but in a different manner to that found for left ear presentation. Figure 2 depicts the interaction between drug and condition for right ear presentation of the white noise CS.

Discussion

An unexpected finding was that the basic LI effect differed according to the ear of presentation of the white noise CS. In previous experiments using the present paradigm (Baruch et al. 1988), ear of presentation was counter-balanced as here, but not submitted to analysis. In the placebo condition, we found LI only with left ear presentation of the CS; with right ear presentation, in contrast, learning rate appeared to be facilitated by preexposure. This laterality effect is reliable, since we have been able to replicate it in a within-subject LI design (N.S. Gray and M. Peoples, unpublished data). Given the lateralisation of LI in the placebo condition, our major predictions concerning the effects of amphetamine on LI can properly be evaluated only for left ear presentation of the CS. Under these conditions, the obtained pattern of results was the one predicted: LI was abolished by the low (5 mg) dose of *d*-amphetamine, but preserved under the high (10 mg) dose. We may reasonably conclude, therefore, that amphetamine affects LI in human subjects in the same way as in the rat and that, in spite of their considerable differences in detail, the rodent and human LI paradigms tap the same fundamental cognitive and neurochemical processes.

Turning to the effects observed with right ear presentation of the CS, these pose two separate issues: lack of LI in the placebo condition, and the apparent emergence of LI following amphetamine administration. It would be premature, however, to devote too much space to discussion of this latter effect until it has been replicated. There is a great difference in the power of the statistical procedures we used (rank-sum factorial analysis; Meddis 1984) depending on whether or not there is an a priori predicted pattern of results. For left ear presentation of the CS, given that LI was present in the placebo condition, we were armed with such a prediction; for right ear presentation, however, the absence of LI in the placebo condition forces us into the much weaker posture of post hoc testing. Thus the right ear results only approached statistical significance. Nonetheless, some speculation as to their interpretation is warranted.

The most likely explanation for the lack of LI with right ear presentation is that the laterality effects reflect differences in the efficiency of stimulus processing between the cerebral hemispheres. Numerous studies have demonstrated right ear superiority for verbal material and left ear superiority for non-verbal material. These phenomena seem to reflect the different functional specialisation of the two cerebral hemispheres (Kimura 1967). It has been demonstrated in the rat that the degree of LI increases as intensity of the preexposed stimulus is increased (Crowell and Anderson 1972, expt. 1; Schnur and Lubow 1976, expt. 2). Preexposure of the white noise stimulus to the left ear could lead to efficient processing of the white noise CS, which in turn would be expected to lead to large LI. Right ear presentation would lead to less efficient processing of the white noise stimulus and so to decreased, or indeed absent, LI. The need for sufficient processing of the conditioned stimulus in a LI paradigm is well known. For example, if a stimulus is preexposed for only a few trials (e.g. 10) then LI is not found to occur (Lubow 1973, pp 401–402, and 1989, pp 59–63; Weiner and Feldon 1987).

The above explanation is able to account for the lack of LI found in the placebo group for right ear presentation of the white noise CS. However, this hypothesis is not able to account for the apparent emergence of LI following amphetamine administration with right ear presentation. If this finding did not occur by chance and can be replicated, then it suggests lateralisation of LI per se, rather than of auditory processing. This suggestion is plausible, given the findings of lateralised dopaminergic function in both animals (e.g. Glick and Ross 1981) and man (Glick et al. 1982; Tucker and Williamson 1984) and the sensitivity of LI to alterations in dopaminergic activity (Gray et al. 1991a, b, for review; and present results); however, it must clearly remain tentative.

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