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Disruption of the Kamin blocking effect in schizophrenia and in normal subjects following amphetamine

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Abstract

The Kamin blocking effect (KBE) is an established animal learning paradigm measuring selective processing, in which reduced blocking reflects allocation of greater processing resources to non-relevant information. Two KBE tasks are described below. Results from studies using the first (between-subjects) task indicate that KBE is abolished in acute schizophrenics with positive psychotic symptoms. It is also abolished in the relatives of schizophrenic subjects, although interpretation of this finding is hampered by poor performance of subjects in the control condition. The second (within-subjects) task indicated abolition of KBE in schizophrenic patients with positive psychotic symptoms. Administration of acute amphetamine to normal human subjects did not significantly disrupt performance on the first task. Whilst for the second task, although blocking was limited to placebo subjects, overall pre-exposure effects are not sufficiently strong to indicate specific drug effects. © 1997 Elsevier Science B.V.

Keywords: Schizophrenia; Associative learning; Amphetamine; Blocking; Animal models

1. Introduction

A crucial issue in understanding of the nature of schizophrenia is the link (or links) between the biological and clinical features of the disorder. Hemsley [27] among others [45] has suggested that investigations of information processing disturbances in schizophrenia might provide a means by which biological-clinical linkages may be discovered. Certainly there is extensive evidence to support the presence of disturbed information processing performance in schizophrenia [41] but much of this research has been carried out with little reference to biological/neural bases of the disorder.

Broadbent [7] characterised normal information processing as functioning via a limited capacity system which avoids overload, at least in part, through the use of response biases built up on the basis of prior experience, leading to inhibition of processing of redundant information. Other models such as those of Schneider and Shiffrin [54] and Posner [50] support the proposal of inhibition of the awareness of redundant information (effectively a response bias against such information) during automatic (as opposed to controlled) processing of information. This led Hemsley [27] to suggest that some of the clinical features of schizophrenia and in particular the perceptual abnormalities and delusional beliefs characteristic of the disorder, might be linked to weakening of the influence of inhibitory processes involved in attentional processing.

Jones et al. [31] investigated this suggestion using a choice reaction time task in which subjects were presented with either of two letters (e.g. A or B) each requiring a different response. These letters were regularly displayed with two flanking letters (eg. X, Y in the form XAX, YBY) but occasionally interchanged

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(YAY, XBX); response always cued by the central target letter. Normal subjects were slowed on the trials when flankers were changed. Acute schizophrenics however did not show this effect, suggesting that they are less influenced by the regularities of the task which would normally lead to a response conflict on interchange trials. This effect was not disrupted in chronic schizophrenic patients with predominantly negative symptoms. Similarly, whereas normal subjects exhibit increased reaction time when presented with a target which has previously been presented as a distracter (negative priming [59]) schizotypal normal subjects and schizophrenics did not show this effect [48]. The absence of negative priming would also indicate a reduction in the extent to which current attentional processing is influenced by previously presented material.

However, this work leaves unexplored the link between any such information processing abnormality and biological bases of schizophrenia. The work presented below forms part of a larger research programme aimed towards beginning to make such a link, by investigating information processing abnormalities in schizophrenia using associative learning paradigms for which analogous animal learning tasks exist permitting direct investigation of the neural substrates of task performance.

Two experimental paradigms have been used in this work. Namely latent inhibition (LI [37]) and the Kamin blocking effect (KBE [34]). The main focus of this paper will be on the KBE, but as LI is clearly the more extensively research paradigm it is instructive to briefly review relevant findings with respect to this task in animals and man.

In LI, learning of the association between a conditioned stimulus (CS) and an unconditioned stimulus (UCS) is found to be retarded if the UCS is first preexposed for a number of trials without consequence. LI is disrupted by the administration of the indirect dopamine agonist amphetamine (e.g. [57,60]) a disruption which is reversed by neuroleptics. Additionally neuroleptics themselves increase LI effects when presented alone [20]. Thus animals in a hyperdopaminergic state seem to fail to integrate stored memories of regularities of previous input. This is clearly similar to reported observations in schizophrenics of failure to make use of the redundancy and patterning of sensory input to reduce information processing demands and would lead to the prediction of disrupted LI in acute schizophrenia. This predicted finding has been observed [4] and replicated [23]. In addition to such group comparisons LI has been shown to be disrupted in normal subjects who are high scorers on measures of schizotypy [5,25] and also in normal subjects administered low, (5 mg) but not high (10 mg) doses of amphetamine [24]. Enhanced LI [62] have also recently observed in human subjects following adminstration of neuroleptic medication (haloperidol).

The Kamin [34] blocking procedure usually involves a preexposure stage in which the experimental group learns an association between a conditioned stimulus CS1 and an unconditioned stimulus UCS; whilst control subjects learn either no association or a different one at this stage. Both groups are next presented with a series of pairings between a compound of two conditioned stimuli (CS1 + CS2) and the same UCS as before. Finally both groups are tested for what they have learned about the CS2–UCS relationship. KBE is indicated by the decrement in learning exhibited by the subjects exposed to CS1–UCS relationship relative to controls.

Hemsley [27] would argue that the KBE, like LI, reflects the operation of 'contextually elicited inhibitory processes', subjects learn on the basis of prior experience to inhibit processing of the 'redundant' CS2. This would therefore lead again to prediction of disrupted KBE in schizophrenia due to the proposed core cognitive dysfunction of 'weakening of the influence of stored memories of regularities of previous input on current perception' in this disorder. However, whilst both paradigms share this prediction in common, the precise processes which are common to, and differ between LI and KBE require further clarification. Investigation of this would be aided by the development of within-subject versions of both paradigms. Such within-subject paradigms could then potentially be compared within the same subject permitting more detailed analysis of shared and differentiating factors than would be available in group studies.

The paper has therefore two aims. Firstly to review evidence concerning KBE which is relevant to the cognitive model of schizophrenia as described by Hemsley and secondly to illustrate the development of a within-subject KBE task.

KBE has been shown to be disrupted by chronic administration of 4 mg/kg of D-amphetamine, an effect which is reversed by the administration of the neuroleptic drug haloperidol [14]. The same group also found in a later study that the induction of dopamine receptor supersensitivity led to a similar disruption of blocking [15], which would be consistent with a primary involvement of dopaminergic systems. Both of these studies employed a conditioned avoidance response procedure. Ohad et al. [46] investigated the effects of administrating amphetamine separately in preexposure and compound training stages of a conditioned emotional response blocking procedure. They found that amphetamine effects were only observed when administered in preexposure or compound conditioning alone, but not when present in both stages. They therefore argued that amphetamine does not disrupt the ability to learn that a stimulus is irrelevant when (unlike LI) there

is no change in reinforcement contingencies. However, this report does not refute the earlier data as it employs an acute and lower dose regimen of amphetamine and also uses a different type of task. Thus future work should assess more directly whether chronic amphetamine effects are also observable in a conditioned emotional response procedure and also what the effects of single separate drug doses are on conditioned avoidance response blocking tasks.

The focus above has been on the role of dopaminergic systems in LI and KBE, due to the evidence implicating these systems in schizophrenia [8]. However, this does not require that dopaminergic systems are the only ones involved. Thus, Dunne and Hartley [17,18] have reported on blockade of cholinergic systems via scopolamine, and Peters et al. [49] on nicotine receptor activation which both appear to be associated with broadened selective attention, whilst serotonergic systems have also been implicated in the loss of LI [9]. However, Gray et al. [22] have argued that whilst the evidence with respect to LI (and by implication KBE) is not restricted to its relation to dopamine function, the role of dopaminergic activity in nucleus accumbens is seen to be critical. In particular that there is a loss of excitatory drive to the hippocampus (via subiculum) to nucleus accumbens projection which would be consistent with evidence [64] that increased dopamine transmission in the nucleus accumbens is associated with reduced effects of stimulation of the subiculo-accumbens pathway. Furthermore it has been argued [53] that this input to the nucleus accumbens is directly proportional to build of expectancies, a fault in the build up of which could lead to repeated match/mismatch error signals and thus inappropriate attentional allocation.

2. Between-subject Kamin blocking task

As this task was primarily developed for the purpose of testing schizophrenic subjects it was necessary for it to meet particular requirements. It had to be an engaging task which was not overly long and was simple to perform. These requirements were based on the well established problems with sustained attention [41] in schizophrenia which tend to undermine their performance on all experimental tasks. In addition, as all acute patients would be tested as inpatients the task had to be of a form that would be portable. Our initial pilot studies used a version of the computer presented KBE task of Dickinson et al. [16]. This video game task required subjects to watch a series of 'tanks' crossing a 'minefield'. After this series they were then presented with further tanks but on this series in addition to the minefield they were able to fire shells at the tanks. Probability of explosion in both stages was 0.75. Subjects pre-exposed to the contingency of the minefield alone gave lower ratings of the effectiveness of shells than when not so pre-exposed, which was interpreted as a blocking effect. However, whilst this effect has been replicated [56] with further undergraduate subjects, this has not proved possible with normal subjects drawn from a non-undergraduate populations [3,29]. It was therefore necessary to develop a new blocking task which would be reliable in this type of non-undergraduate sample as in terms of intelligence and socio-economic status they would provide a more appropriate comparison group to schizophrenic subjects who rarely have tertiary education.

This procedure has three stages. In Stage 1 the subject learns, in the preexposure condition that a yellow square (the UCS) is predicted by the occurrence of a blue square (CS1); in the control condition a different association is learned. In Stage 2 all subjects experience an association between a compound stimulus (CS1 paired with two white flanker squares (CS2)) and the same UCS. In Stage 3 all subjects experience an association between only the CS2 and the UCS. Preexposed subjects take longer to learn the final association than do controls, thus constituting a blocking effect.

2.1. Between-subject blocking in schizophrenics and their relatives

This task generated a reliable blocking effect in normal subjects [30]. This same procedure was also employed [32] with 29 schizophrenic subjects (14 acute and 15 chronic) diagnosed according to Research Diagnostic Criteria (RDC) [58]. On the basis of the studies of LI and the effects of amphetamine on blocking in animals it was predicted that this effect would be disrupted in acute schizophrenic patients tested within 2 weeks of hospital admission but not in chronic schizophrenics tested whilst on a stable regimen of neuroleptic medication. As predicted normal blocking was observed in chronic patients whilst no significant blocking was found in the acute patients.

This finding indicated that acute schizophrenic patients were failing to employ prior regularities to the extent that they continued to learn about the CS2–UCS association in spite of CS1–UCS preexposure. Further work in this area was carried out by Serra [55], as part of her unpublished doctoral research. She investigated KBE in schizophrenic patients and their families. More specifically she compared an index schizophrenic patient with a schizotypal and non-schizotypal relative. The performance of schizotypal subjects has been a focus of much research into cognitive abnormalities in psychosis. Several workers have argued that the symptoms of schizophrenia exist on a continuum which is distributed throughout the normal population [12]. Schizotypy is usually defined either psychiatrically by means of for instance DSM-IIIR

criteria [1] or by means of self report questionnaire measures [6,13,52]. The results of a number of questionnaire studies of normal subjects self report of schizophrenic-like experiences indicate that such experiences are distributed throughout such populations with the majority having at least some experiences of this type [6,13,52]. If such a continuum is present then abnormalities of task performance observed in schizophrenic subjects would be expected to be apparent in schizotypal subjects. This has been observed for LI, with disruptions in LI being associated with elevated scores on a questionnaire measure of schizotypy in normal subjects [5,25].

The rationale for Serra's study was as follows. Investigation of schioztypal subjects is a useful strategy in itself because such subjects, whilst having many of the features and experiences of the schizophrenic are not in receipt of neuroleptic medication which may of course influence task performance. Furthermore, as has been argued previously [26] the presence of severe psychotic symptoms in the schizophrenic can lead to overcompensation in terms of information processing strategies. Thus chronic schizophrenics may adapt to chronic over-stimulation by a generalised increase in inhibitory processing. However in the schizotypal subject this process might be less likely to occur as the severity of any disturbances would be of a lesser degree.

Reports of the presence of a genetic relationship between schizophrenia and schizotypal personality disorder (SPD) [35,36], indicate that identification of appropriate samples of SPD subjects would be fruitfully sought amongst the first degree relatives of schizophrenic subjects. If disruption of KBE is a specific state effect caused only within acute schizophrenic then normal KBE would be expected in schizotypal groups. However disruptions of KBE in such subjects would suggest a trait explanation consistent with increasing degrees of information processing disturbance from normal to schizotypal to schizophrenic relatives.

The KBE task used by Serra [55] was similar to that reported above. It differed in two respects: (a) vertical non-informative flankers were added to the preexposure stage for both experimental and control subjects; (b) both horizontal and vertical flankers were presented in a grey rather than white hue. This task was employed with a total of 89 subjects: 27 normal controls (no schizophrenic relatives); 19 normal relatives of schizophrenic, 21 schizophrenic subjects and 22 relatives with SPD. Although 22 families were recruited to the study, three normal relatives refused to participate as did one schizophrenic member.

DSM-IIIR [1] criteria for SPD requires presence of at least five of the following symptoms (ideas of reference, excessive social anxiety, odd beliefs/magical thinking, unusual perceptual experiences, odd or eccentric behaviour or appearance, no close friends or confidants, odd speech, inappropriate or constricted affect, suspiciousness or paranoid ideation). A pool of 1063 first degree relatives of psychotic patients was screened with respect to these criteria, 204 of these relatives also completed the SPQ (schizotypal personality questionnaire) [61]. Although DSM-IIIR estimates an incidence rate of 3% for SPD in the normal population this process did not identify sufficient subjects. However when criteria were loosened to allow as SPD subjects those who met four of the DSM-IIIR criteria above and scored at least 14 points on either William's [61] or Raine's [52] SPQ sufficient numbers were obtained. All schizophrenic subjects met research diagnostic criteria [58], whilst normal subjects were defined as such if they did not meet the above criteria for SPD.

Cox regression analysis was used to investigate the effects of group (normal, normal relative, schizophrenic or SPD relative), condition (pre-exposure, control) and group by condition interaction on KBE scores. Significant effects were observed for group membership (main effect = 17.2, df = 3, $P = 0.0006$) for its interaction with condition (interaction = 11.58, df = 3, $P = 0.009$) after allowing for the separate effects of group and condition alone. This indicates that the effect of experimental condition is dependant on group membership. Survival analyses (suitable for the analysis of censored data) were employed for each group to assess the effect of experimental condition. Significant blocking (Fig. 1) was observed for the normal subjects only (Wilcoxon Gehan statistic = 10.66, $P < 0.001$), no effect of condition was observed in SPD subjects ((Wilcoxon Gehan statistic = 0.585, $P > 0.1$), whilst trends towards a reversal of the blocking effect were noted in normal relatives and schizophrenics (Wilcoxon Gehan statistic = 3.29, $P < 0.07$ and Wilcoxon Gehan statistic = 3.05, $P < 0.08$, respectively).

These data indicate that a reliable KBE is absent in schizophrenic, SPD and normal non-schizotypal relatives. Interpretation of this finding is hampered by the poor performance of all three groups in the control condition of the KBE task. This leads to the question of why such subjects should have difficulty with what would normally be the easier of the two task conditions. One speculation which might be relevant in this area is that KBE may share the two factors proposed by Lubow [38] for LI. For LI he suggests that preexposure consists of an initial property extraction phase followed by subsequent stimulus relationship processing, thus suggesting that with small numbers of preexposures facilitated learning would be predicted. Hence an absence of LI might be due to impaired relationship processing or deficient initial property extraction. If the above subjects are impaired in their basic understanding of the task and CS-UCS relationships it might be speculated that the blocking condition improves their performance by providing greater CS-UCS information

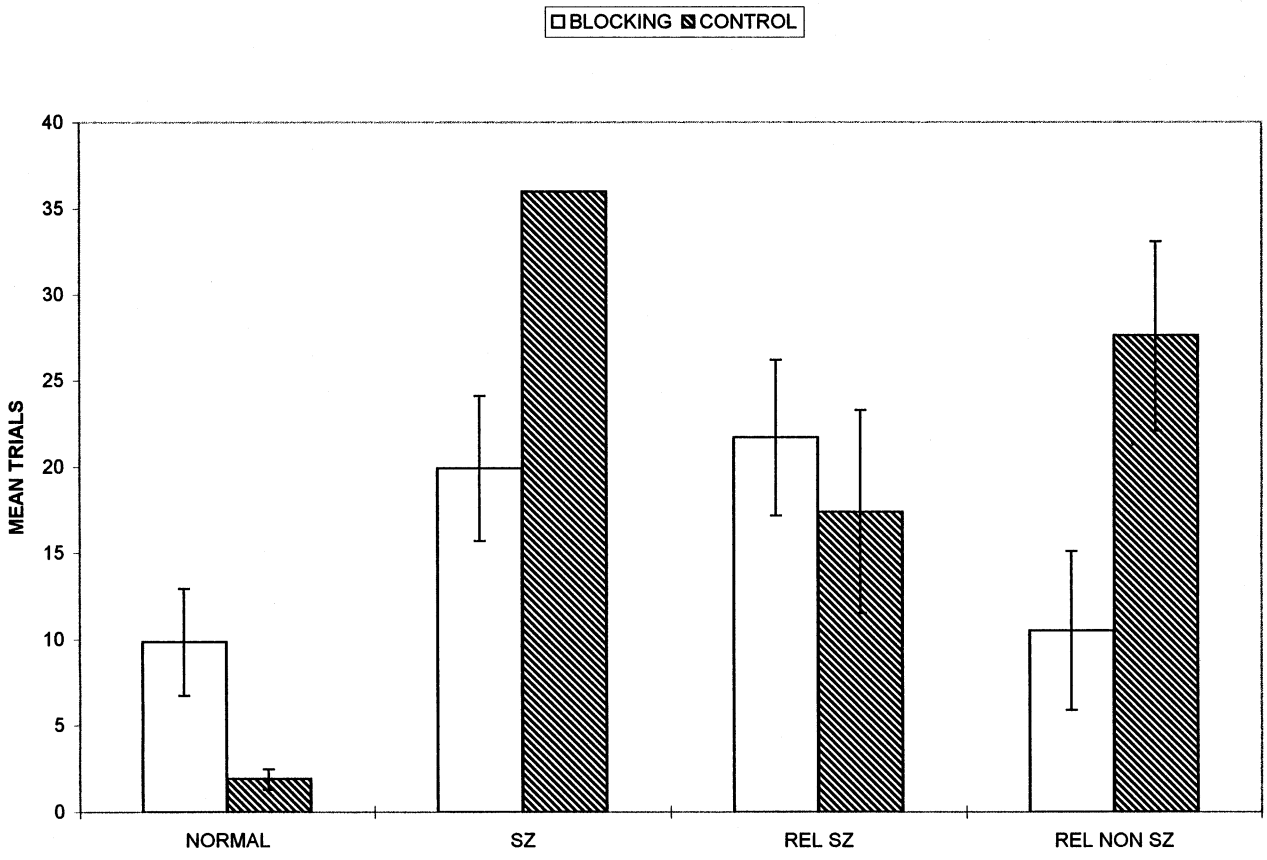

Fig. 1. Between-subjects KBE in schizophrenics, schizotypal and normal relatives and normal controls. Means and S.D. on ranked scores of number of trials taken to learn that CS2 (white flanking squares) predicts UCS (yellow square) in Stage 3 of a between-subjects Kamin blocking task, as a function of experimental condition (blocking versus control) and subject group (normals, schizophrenics, schioztypal relatives and normal relatives). Maximum number of trials available in Stage 3 is 36. Absence of standard deviation bar for schizophrenic subjects in control condition is due to all scoring at ceiling.

in Stage 1, leading to greater opportunities for property extraction with respect to UCS. This might be tested by inspecting the effects of variable CS1-UCS exposures across the relevant groups.

2.2. Between-subjects blocking and amphetamine

As indicated above it was already known that KBE is disrupted by amphetamine in the rat [14] and that acute schizophrenic subjects in a putatively hyperdopaminergic state also show disrupted KBE [32]. Data also indicated that low doses, usually 5 mg of D-amphetamine are sufficient to disrupt LI in human subjects [24].

Serra [55], tested whether similar disruption of performance was obtained in relation to KBE. 84 normal subjects were tested across four groups (no drug, placebo, 5 mg or 10 mg orally administered amphetamine). Fig. 2 summarises these results which appear to show blocking in placebo and non-drug subjects with absence of blocking in both drug groups. However, when subjected to Cox regression analysis to assess the effects of group and condition (blocking, control) the group effect was not significant although condition was ($B = -0.2814$, S.E. $= 0.119$, $P = 0.018$) indicating faster overall learning in the control condition. No significant interaction effects were observed.

Hence it is not at present possible to generalise from the LI findings with respect to amphetamine to the KBE procedure. Given the pattern of results it is possible either that there is no disruption effect to be found, or that the current procedure is insufficiently sensitive to demonstrate it with this sample size.

3. Within-subject Kamin blocking procedure

As indicated above KBE, as a between-subjects procedure, appears to be reliable in normal subjects and to be disrupted in schizophrenics. A major problem with the between-subject task, in terms of assessing clinical populations, is the number of subjects required, a within-subject procedure would therefore be an important advance.

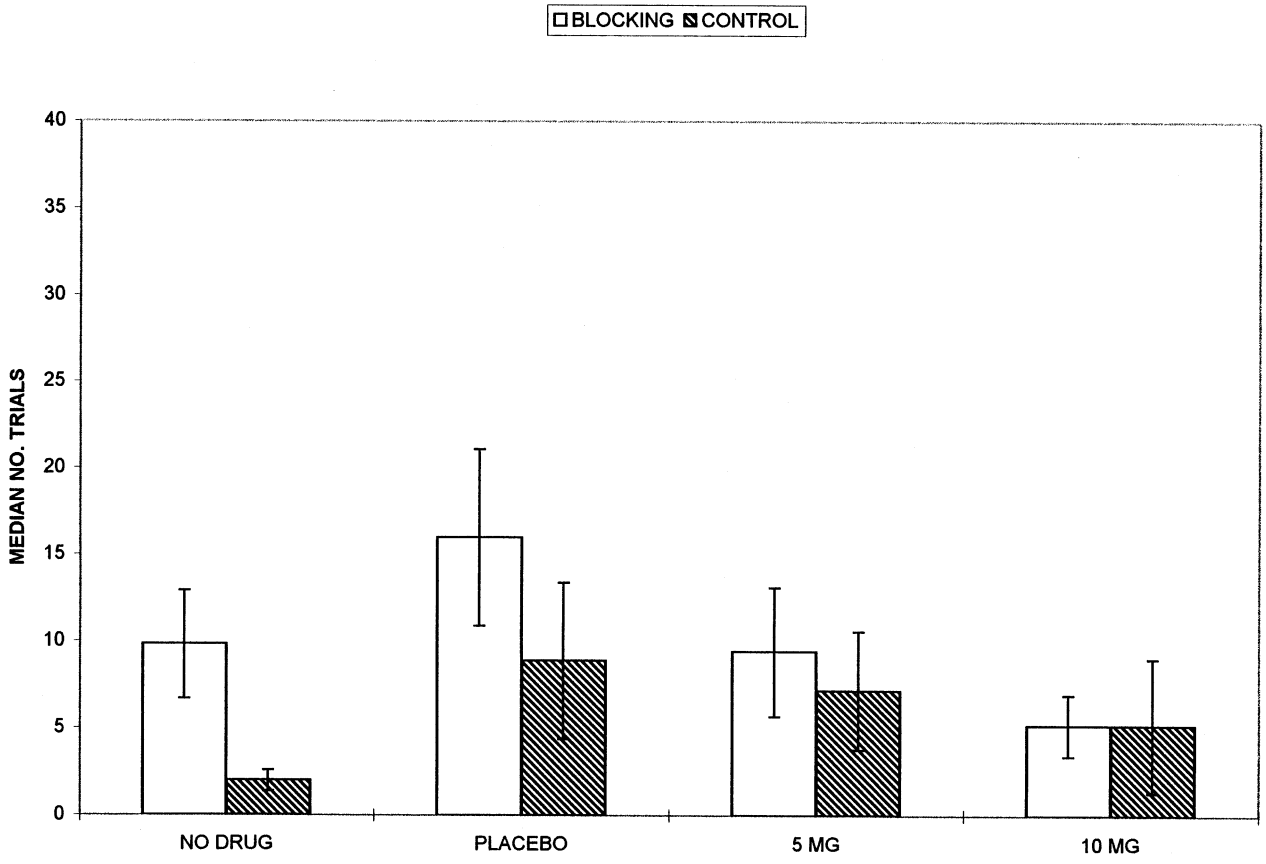

Fig. 2. The effect of amphetamine on the between-subjects KBE in normal subjects. Means and S.D. on ranked scores of number of trials taken to learn that CS2 (white flanking squares) predicts UCS (yellow square) in Stage 3 of a between-subjects Kamin blocking task, as a function of experimental condition (blocking versus control) and subject group (no drug, placebo, 5 mg amphetamine and 10 mg amphetamine) in normal human subjects.

The task discussed below is a within-subject blocking procedure in which subjects make probability estimates. This type of task is different from the simple rule learning procedure above but shares the basic preexposure, compound learning and test phases. Shanks [56] has previously reported successful demonstrations of KBE using a within-subject procedure which required the subject to make contingency ratings on a computer game task. In the current task an adapted contingency judgement procedure was used based on Chapman's [10] work. Chapman [10,11] employed tasks in which subjects made contingency judgements based on trial by trial information regarding individual stocks and stock market fluctuations or symptoms and diseases. It was found that cues (stocks or symptoms) interacted in a manner consistent with a blocking effect. The effects reported were both large and statistically reliable in contrast to the more fragile within-subject blocking effects observed in the psychophysiological experiments of Martin and Levey [39,40].

In the present version of this type of task [33] normal subjects were asked to judge how successful they thought that a number of fictitious 'film stars' were, on the basis of information gained over the course of the experiment. Specifically they were asked to numerically rate how likely it would be that a film (unnamed) would be a hit based on the 'stars' name alone. The task has two stages (Fig. 3)

In both stages subjects rates the likelihood that each of 36 films will be a 'box office hit'. For each 'film' a number is presented (1–72) on the computer screen along with the name or names of the 'film star' appearing in that film and instructions to estimate the likelihood of a 'box office hit' for that film. The subject then enters a rating (0–100) and scrolls to the next screen which indicates whether the film was a 'box office hit' or not. These trial by trial ratings are not used to estimate associative learning effects, but to ensure the subjects concentration on the contingencies presented.

In Stage 1 the subject learns that all films with star CS1-A in are hits, none of star CS1-B's films are hits and none of the films with no 'stars' in are hits.

At the end of this stage subjects are required to rate the 'box office potential' of six fictitious 'stars', including CS1-A and CS1-B. The subjects have no information at that time about these other 'stars' and hence

might be expected to rate them intermediately, as subjects did in Chapman's studies [10,11]. Ratings at this stage indicate whether subjects have learnt to differentiate between 'stars' CS1-A and CS1-B and serves as a check as to whether there is any ratings bias towards the unknown 'stars'.

In the second stage—compound learning—there are three pairs of 'stars' presented. All films with 'stars' are hits, all no star films are misses. The pairings are CS1-A with CS2-A, CS1-B with CS2-B and CS1-C with CS2-C as indicated in Fig. 3.

Subjects again make ratings of the 'film stars' box office potential. The three 'stars' CS2-A, CS2-B and CS2-C have only been presented in the second stage and have all been paired with equal numbers of 'box office hits'. On the basis of this information alone then, ratings for these three 'stars' would be expected to be similar. Differentiation between these 'stars', would therefore have to be based on what had been learnt in the pre-exposure stage about the 'stars' with which they had been paired.

KBE would be indicated by a lower rating of star CS2-A, than of CS2-C. This would indicate that box office potential of CS2-A had been blocked by pairing with CS1-A who had been shown to be previously successful. Superconditioning would be indicated by the finding that ratings of CS2-B were higher than those of

Stage 1	Stage 2
Total 36 trials	Total 36 trials*
BC: CS1-A ---> Hit film (UCS)	CS1-A+CS2-A ---> Hit film (UCS)
12 trials	9 trials
SC: CS1-B ---> No Hit film	CS1-B+CS2-B ---> Hit film (UCS)
12 trials	9 trials
OC: No stars ---> No Hit film	CS1-C+CS2-C ---> Hit film (UCS)
12 trials	9 trials

Key : * includes 9 trials No stars ---> No hit film

BC - blocking condition, SC -superconditioning condition, OC - overshadowing condition

Fig. 3. Within-subject Kamin blocking task. Subjects are presented with 'films' represented by a number (1–72) on a computer screen. All subjects are exposed to all conditions (blocking, superconditioning and overshadowing). Subjects rate the 'box office potential' of each of the six 'film stars' at the end of each of the two stages. After Stage 1 CS1-A is normally rated above CS1-B, whilst all other 'stars' (about whom no information has yet been provided) are rated intermediately. After Stage 2 the ratings are repeated and the comparisons of interest are between CS2-A, CS2-B and CS2-C. Blocking is indicated by lower rating of CS2-A than CS2-C, superconditioning by higher rating of CS2-B than CS2-C.

CS2-C. The box office potential of CS2-B would then have been enhanced by preexposure to CS1-B as not being a star in their own right. CS2-C serves as the overshadowing control condition as he is always paired with CS1-C, both of whom are present only in Stage 2.

An initial group of 34 normal subjects were tested drawn from a general population sample. Data for this within-subject KBE task were approximately normally distributed and therefore analysed paratmetrically by means of mixed repeated measures analysis of variance. Stage 1 ratings were as predicted with CS1-A, CS1-B and CS1-C differing significantly ($F(2,66) = 65.9$, $P < 0.001$) with CS1-A rated above CS1-B which was rated below CS1-C (difference confirmed by post hoc t-tests ($P < 0.05$ in all cases). CS2-A, CS2B and CS2-C did not differ at this stage.

Stage 2 ratings are present in Fig. 4. As can be seen there continued to be differentiation between CS1-A, CS1-B and CS1-C ($F(2,66) = 32.1$, $P < 0.003$). The comparison of interest between CS2-A, CS2-B and CS2-C was consistent with a blocking effect. The three ratings differed significantly ($F(2,66) = 6.37$, $P < 0.003$). Post hoc t-tests confirmed that CS2-A was rated below CS2-B and CS2-C ($P < 0.05$), with a trend towards CS2-C being rated higher than CS2-B ($P < 0.1$). This effect has been replicated in a further group of 30 normal subjects [2].

3.1. Within-subject blocking and schizophrenia

Within-subject blocking has also been employed in two studies of schizophrenic subjects. The first of these [33] involved ten schizophrenics who were all current patients of the Bethlem/Maudsley joint hospitals and were all taking part in a trial of cognitive behaviour therapy for treatment of drug resistant positive psychotic symptoms. All subjects met RDC [58] criteria for schizophrenia. Brief Psychiatric Rating Scale [45,51] scores of these patients indicated primarily positive psychotic symptoms.

Ratings for 'stars' CS1-A, CS1-B and CS1-C differed after both stages of the experiment (Stage 1; $F(2,18) = 10.9$, $P < 0.001$; Stage 2; $F(2,18) = 9.1$, $P < 0.002$) with the same ordering as observed in normal subjects. After stage 1, as with normal subjects, no differentiation was made between CS2-A, CS2-B and CS2-C. However, in contrast to normal subjects the schizophrenic subjects also failed to significantly differentiate between CS2-A, CS2-B and CS2-C after stage 2 (Fig. 5). A second study [2] confirmed this attenuation of within-subject blocking with a further small ($n = 11$) group of schizophrenic subjects, again finding the same pattern of normal performance in all but the ratings of CS2-A, CS2-B and CS2-C after stage 2 ($F(2,20) = 0.26$, $P > 0.1$).

As with between-subjects blocking the effect is abolished in schizophrenia. However unlike the between-

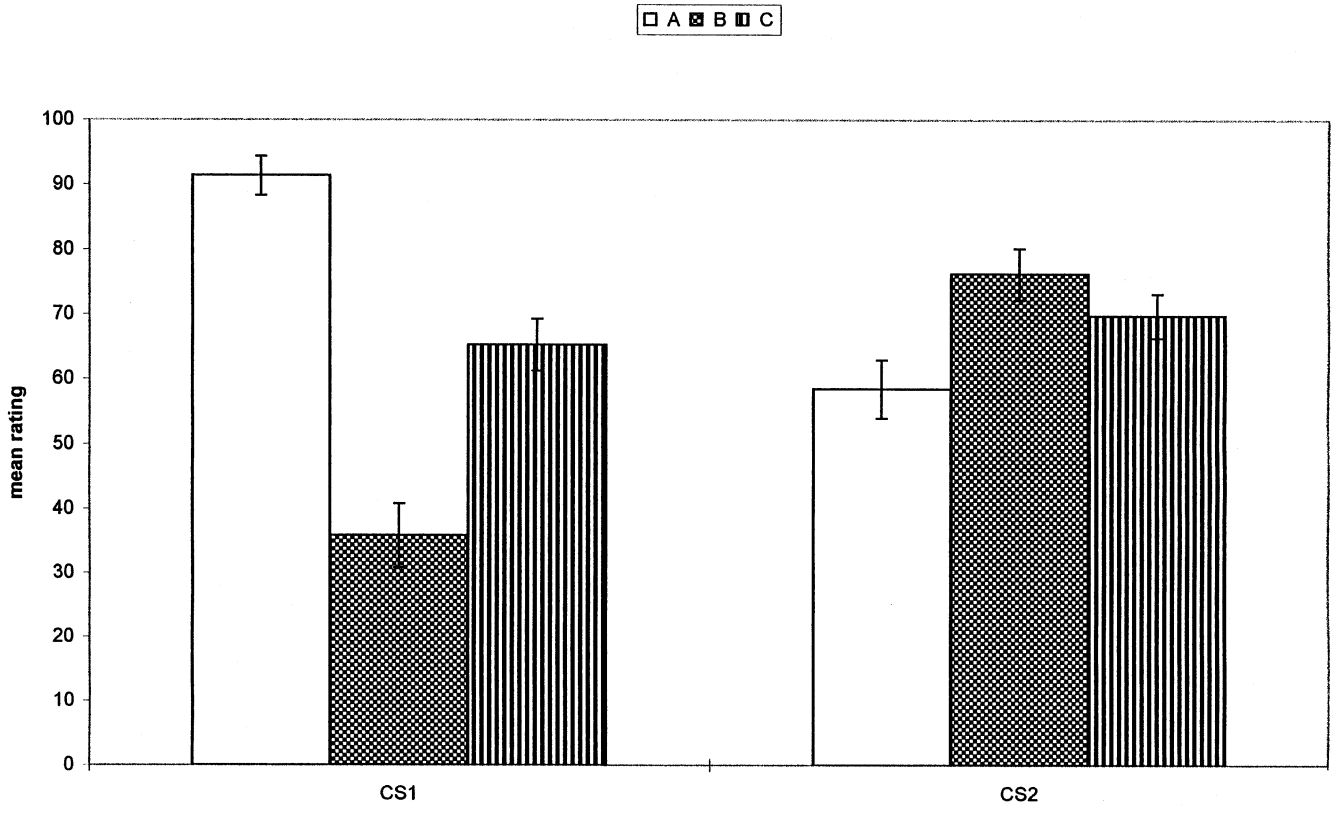

Fig. 4. Within-subject KBE in normal subjects. Means and S.D. of contingency ratings of 'box office potential' of 'film stars' (CS1-A, CS1-B, CS1-C, CS2-A, CS2-B, CS2-C) following Stage 2 of a computerised within-subject blocking procedure in normal subjects. Blocking is indicated by lower rating of CS2-A (blocking condition) than CS2-C (overshadowing condition); superconditioning by higher rating of CS2-B (superconditioning condition) than CS2-C.

subject procedure these subjects have continued with attention abnormalities and positive symptoms in spite of long term treatment with neuroleptic medication. If it is to be argued that this finding is indicative of a persisting dopaminergic abnormality in these subjects a more direct test of this procedure, in terms of sensitivity to a dopamine agonist is required, in this case amphetamine.

3.2. Within-subject blocking and amphetamine

In the amphetamine study [33] 48 normal subjects were randomly allocated to placebo, 5- and 10-mg groups. Ratings for 'stars' CS1-A, CS1-B and CS1-C differed after both stages of the experiment ($F(2,39) = 163$, $P < 0.001$; $F(2,39) = 38.5$, $P < 0.002$, respectively) with the same ordering as observed in normal subjects. Fig. 6. represents CS2 ratings in Stage 2. Over the three groups there was a trend towards differences between the three CS2s, ($F(2,39) = 2.6$, $P < 0.09$) whilst post hoc t-tests indicated that there was a blocking effect in the control subjects ($P < 0.05$) but not in either of the drug groups. However this finding was complicated by there being significant superconditioning ($P < 0.01$) in the 10-mg group only.

We have not yet run an additional group of non placebo normal subjects against these subjects as a reliability comparison. There are therefore a number of possibilities in interpreting these results. One could argue that the fluctuations observed above indicate variations in a weak, unreliable blocking effect; or that it is a reliable effect which is sensitive even to placebo manipulation. As indicated above this effect has been replicated in normal subjects, however further work is necessary to clarify the nature and reliability of the effect observed here.

4. Discussion

As indicated in the introduction the first purpose of this paper was to review recent KBE results relevant to a cognitive model of schizophrenia. The data reported indicate that KBE is absent in schizophrenic subjects suffering from predominantly positive psychotic symptoms, whether they are in the acute or chronic stages of the illness. Furthermore it was not possible to demonstrate blocking in relatives of schizophrenic subjects irrespective of whether they met criteria for SPD. These findings would be most consistent with abolition of

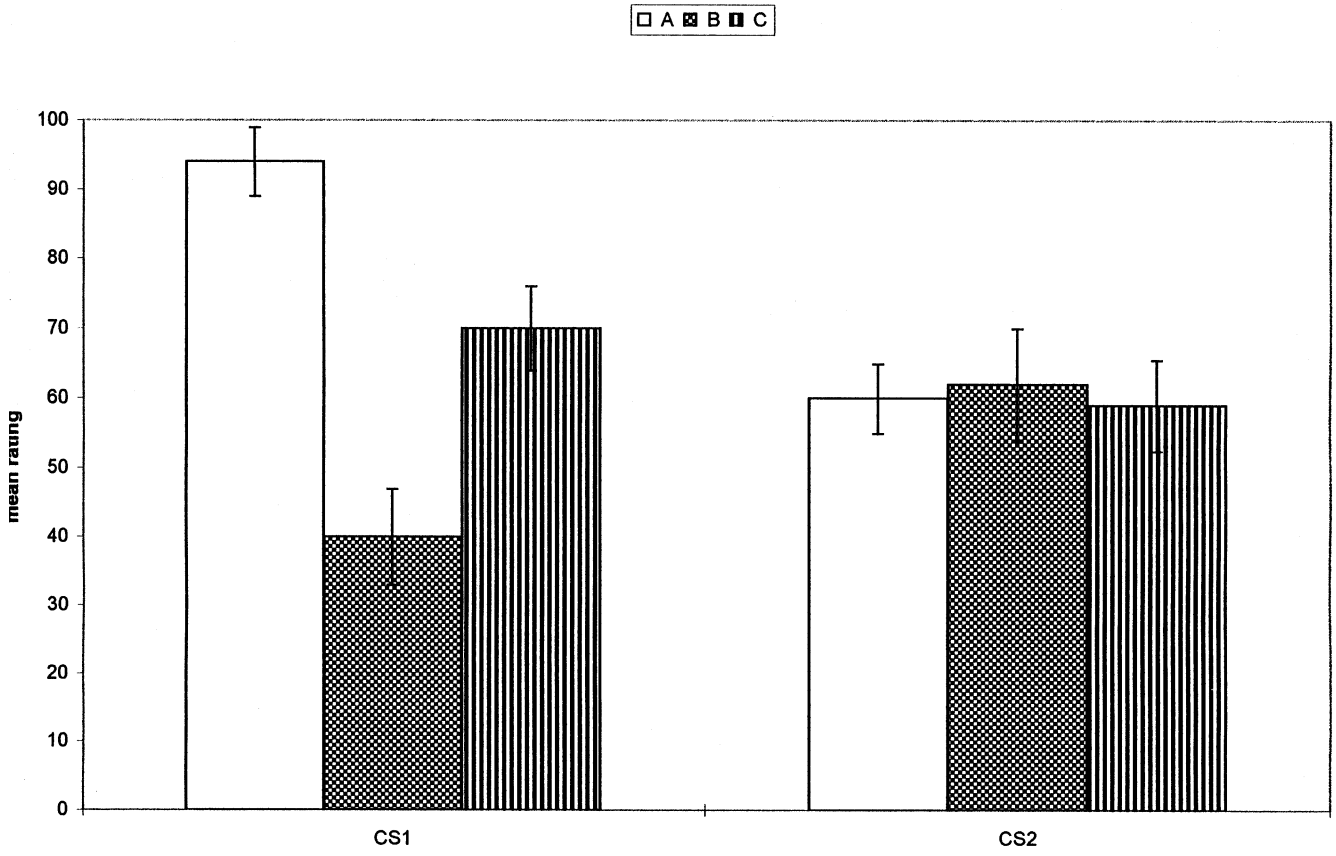

Fig. 5. Absence of within-subject KBE in schizophrenic subjects. Means and S.D. of contingency ratings of 'box office potential' of 'film stars' (CS1-A, CS1-B, CS1-C, CS2-A, CS2-B, CS2-C) following Stage 2 of a computerised within-subject blocking procedure in schizophrenic subjects. Blocking is normally indicated by lower rating of CS2-A (blocking condition) than CS2-C (overshadowing condition); superconditioning by higher rating of CS2-B (superconditioning condition) than CS2-C.

KBE reflecting a trait of 'reduced use of contextually elicited inhibitory processing' present from an early stage in the schizotypal continuum. Two studies of the effects of amphetamine administration on KBE produced inconclusive results. For the between-subject task there was no statistical evidence for a drug effect, whilst an apparent interaction between drug and amphetamine in the within-subject task was present only as a statistical trend.

Oades and co-workers [43–45] are the only other group we are aware of conducting research into blocking in normal and psychiatric subject groups. Oades' task uses a computer game format, with subjects required to direct a 'mouse' to safe areas on a screen indicated by particular colour stimuli, measures of interest being response latencies on particular trials or trial sequences. Control and blocking conditions are performed by the same subjects on two separate occasions (usually a day apart).

Oades [43] reported blocking was attenuated in young (18 year old) non-paranoid psychotic patients, but not in those with significant paranoid symptoms. In addition it was reported that attenuated blocking in the subject group as a whole (including normal and obsessional compulsive controls), was associated with higher levels of dopamine activity as measured in 24 h urine samples. A more recent larger scale study [45] again compared blocking performance of young paranoid and non-paranoid patients with that of normal and obsessional compulsive control subjects. In this case it was reported that blocking was again attenuated in the non-paranoid patients, with a more transient attenuation in paranoid patients. However, patterns of blocking performance in relation to estimates of catecholamine activity were rather different. In normal and OCD subjects higher levels of dopaminergic and noradrenergic activity were associated with normal (rather than attenuated) blocking, whilst in non-paranoid psychotic patients relative increases in noradrenergic activity were associated with attenuated blocking (no such associations being present for paranoid patients).

Direct comparison with our data is not possible because of the differences in task measurement used and the different sub-categories of schizophrenia tested. However, it would clearly be of interest to use these

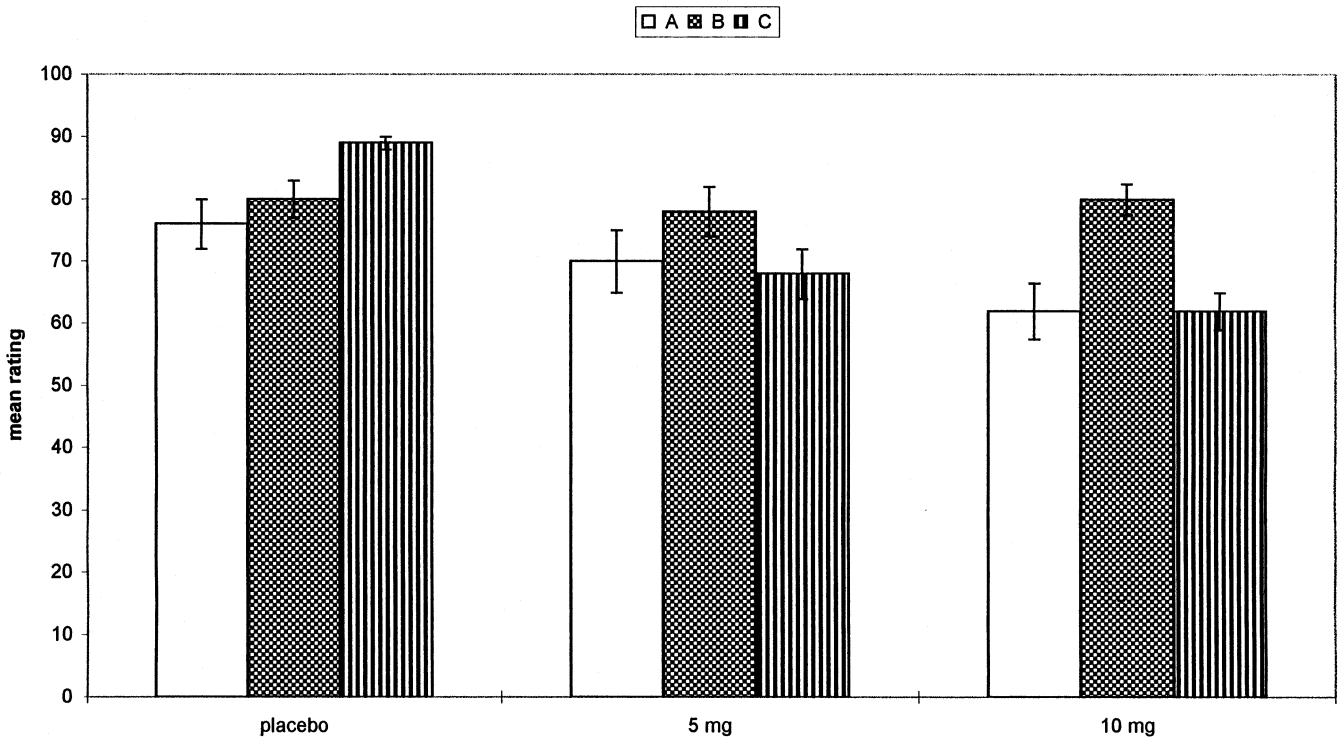

Fig. 6. The effect of amphetamine administration on the within-subject KBE in normal subjects. Means and S.D. of contingency ratings of 'box office potential' of 'film stars' (CS2-A, CS2-B, CS2-C) following Stage 2 of a computerised within-subject blocking procedure in normal subjects as a function of drug condition (placebo, 5 mg amphetamine and 10 mg amphetamine). Blocking is normally indicated by lower rating of CS2-A (blocking condition) than CS2-C (overshadowing condition); superconditioning by higher rating of CS2-B (superconditioning condition) than CS2-C.

two tasks in the same patient groups to directly test the degree to which task effects converge. A relevant issue to address in such a study would be to clarify the extent to which the paranoid/non-paranoid differences observed above are associated with severity of illness, given Nuefeldt's finding [42] of increased symptom severity in non-paranoid patients.

Whilst the data reported are clear in showing disrupted KBE in schizophrenia, it has proved less straightforward to link such disruptions to manipulations of dopaminergic activity in normal subjects. The present results do not provide support for KBE being sensitive to administration of low acute doses of amphetamine, in contrast to the findings for the apparently similar paradigm of LI. Furthermore Oades' findings for the measurement of peripheral catecholamine activity suggested that intact blocking was generally associated with increases in dopamine utilisation [43,45]. Thus simple increases in dopamine turnover are not associated with disrupted blocking. However, if as Gray [22] suggests the critical role of dopaminergic activity (in terms of the underlying cognitive abnormalities of schizophrenia) is limited to nucleus accumbens this may well not be associated with overall elevations in whole brain dopamine activity and indeed the evidence from in vivo studies of schizophrenic subjects would seem to support this [19,28,63]. A further factor in the relationship between amphetamine administration and KBE is that in animal subjects the disrupting effects appear to be limited to chronic higher dose regimes [14,46]. It may therefore be that closer approximations to these regimes may be required in normal human subjects to obtain similar disruptions of KBE.

The absence of blocking in relatives of schizophrenics is, as noted above, most consistent with the cognitive abnormalities associated with schizophrenia being traits. However, interpretation of the performance in the relatives study is hampered by their poor overall performance, in particular in the control condition. If the speculation raised previously concerning the roles of property extraction and associability has merit then altering the blocking task to incrementally increase CS–US exposures in Stages 1 and 2 would be of interest. If subjects' performance in the control condition is improved by these manipulations it would suggest that property extraction is indeed inhibited in such subjects and would permit titration of the appropriate number of exposures required to assess associability effects directly.

The disruption of KBE in schizophrenic subjects indicates that it has value as a task aimed at attempting

to link the cognitive abnormalities of this disorder with its biological basis. The association of this disruption with positive symptoms of schizophrenia would be consistent with Garety and Hemsley's [21] work on the formation of delusional beliefs in particular. They state, with respect to the KBE findings in schizophrenia 'not only is an abnormal view of the relationship between events a prominent feature of delusional thinking but also.... at times this proceeds to the perception and/or attribution of abnormal causal relationships'. This proposal would also be consistent with Oades' finding [45] of a negative relationship between blocking and delusional beliefs in young paranoid psychotic subjects.

As noted in the introduction the impetus for our initial KBE work was in its a similarities with LI in terms of animal data. However, as research has progressed the differences between the results obtained between the two tasks have been noted. LI appears to be disrupted by low doses of amphetamine in an acute regime in man [24], and appears to be less sensitive to symptoms than duration in schizophrenic patients [23], conversely KBE does not seem sensitive to low doses of acute amphetamine but is readily affected in schizophrenic subjects exhibiting positive psychotic symptoms. As noted above a within-subject paradigm has been developed to permit more detailed analysis of shared and differentiating factors in LI and KBE in human subjects. This next stage of analysis will be relevant to further clarification of the fundamental aspects of disrupted inhibitory processing in schizophrenia.

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