Latent Inhibition as a Model of Schizophrenia: from Learning to Psychopathology

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Abstract

In schizophrenia, attentional processes may be altered and become the basis of another symptomatology such as delirium and hallucinations. One of the experimental approaches to the study of attentional processes employs the phenomenon of latent inhibition. Behaviourally, latent inhibition is expressed as a delay or difficulty in learning the relationship between stimuli due to prior experience of the subject with one of the inconsequential stimuli. This learning phenomenon fulfils an adaptive function that enables the organism to release attention from irrelevant stimuli. Schizophrenics do not show this latent inhibition effect due to attentional alterations, that is, they have selective attention difficulties. Clinical data coincide with results obtained from both animals and normal subjects and with data from psychopharmacological studies. Most of the studies show that the dopaminergic system plays an important role in latent inhibition and therefore would support the dopaminergic hypothesis of schizophrenia. Furthermore, latent inhibition is used as a model to evaluate the mechanisms of antipsychotic drug action, as well as for the study of the aetiology of schizophrenia. Finally, latent inhibition opens a line of research in cognitive inhibition processes in schizotypy and the possibility of studying other psychopathological disorders. The model proposed is based on experimental, neurochemical and clinical premises that make it a promising topic of future for research.
Key words: selective attention, schizophrenia, latent inhibition, antipsychotic drugs, latent inhibition model, conditioning, schizotypy.

Resumen

La inhibición latente como modelo de la esquizofrenia: del aprendizaje a la psicopatología
En la esquizofrenia los procesos atencionales pueden encontrarse alterados y estar a la base de otra sintomatología como los delirios y las alucinaciones. Una de las aproximaciones experimentales al estudio de los procesos atencionales utiliza el fenómeno de la inhibición latente. Conductualmente, la inhibición latente se expresa en un retraso o dificultad en el aprendizaje de una relación entre estímulos debido a la experiencia previa del sujeto con uno de los estímulos sin consecuencias. Este fenómeno del aprendizaje cumple una función adaptativa al permitir al organismo dejar de atender a aquello estímulos irrelevantes. Los esquizofrénicos no muestran este efecto de inhibición latente debido a sus alteraciones atencionales, concretamente tendrían dificultades en la atención

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selectiva. Los datos clínicos son convergentes con los resultados obtenidos tanto en animales como en sujetos normales y con los datos provinientes de estudios psicofarmacológicos. La mayor parte de los estudios muestran que el sistema dopaminérgico juega una papel importante en la inhibición latente y, por tanto, apoyaría la hipótesis dopaminérgica de la esquizofrenia. Además, la inhibición latente es utilizada como un modelo para evaluar los mecanismos de acción de las drogas antipsicóticas, así como, para el estudio de la etiología de la esquizofrenia. Finalmente, la inhibición latente abre una línea de investigación de los procesos de inhibición cognitiva en la esquizotipia y la posibilidad de estudiar otros trastornos psicopatológicos. El modelo propuesto esta fundamentado sobre premisas experimentales, neuroquímicas y clínicas que le dotan de un futuro prometedor en la investigación.
Palabras clave: atención selectiva, esquizofrenia, inhibición latente, drogas antipsicóticas, modelo de inhibición latente, condicionamiento, esquizotipia.

It has traditionally been believed that one of the relevant factors in the appearance of the schizophrenic symptomatology is a disturbance in attention process functioning (e.g., Braff, 1993; Gray, 1998). From this perspective, the contributions that have emerged from experimental psychology to explain the normal functioning of this process have become a very useful tool for understanding what mechanisms and what alterations of such mechanisms are found at the core of some schizophrenic symptoms. In this respect, one of the most notable characteristics of the attention process refers to its limitations, since the attentional resources of living beings are limited, so that diverse strategies that allow us to select at every moment what elements in the surroundings must be paid attention to for in-depth processing have developed.

Specifically, in recent decades a growing interest has been drawn to the study of the attention process that determines how irrelevant stimuli come to be ignored. Thus in any situation, as simple as it may seem, hundreds of stimuli may be identified among which the organism must differentiate at every moment which must be paid attention to and which not in order to interact properly with the circumstances. Conduct adapted to any given situation depends on the proper functioning of this process of selection. Experimental psychology has proposed a mechanism that guarantees that the attentional resources do not become engaged with those stimuli which past experience has shown to be irrelevant. This process, which in scientific literature is called Latent Inhibition (hereinafter, LI), in spite of its apparent simplicity, has generated an impressive amount of empirical research and has attracted numerous theoretical debates (see, for recent reviews, Daza, López & Álvarez, 2002; De la Casa, 2002; De la Casa, Ruiz & Sánchez, 2003).

LI is the result of repeatedly presenting a stimulus that becomes irrelevant when it does not have in and of itself attractive or adverse properties and is not followed by consequences that are important to the organism. Thus, for example, we learn not to pay attention to the noise coming in through the window since our previous experience tells us that it is neither important in and of itself nor is it predictive of relevant consequences. As the result of this training in the irrelevance of stimuli, it has been

verified experimentally in numerous situations and with many different species, that the stimulus pre-exposed without consequences loses part of its capacity to establish associative connections with relevant consequences. Research in animals offers numerous examples of how LI may be induced under the strictest conditions of laboratory control: after repeatedly presenting a neutral stimulus (typically a light or a sound) without following it up with relevant consequences, the pre-exposed stimulus is matched to an unconditioned stimulus. The result of this experimental treatment is that acquisition of the association between the pre-exposed stimulus and the unconditioned one is retarded compared to a group for which the neutral stimulus is new.

Numerous theoretical interpretations attempt to explain the process described above (see, for example, Fernández & De la Casa, 1989), although we focus here on a hypothesis that considers that throughout preexposure there would be a gradual descent in attention given the stimulus. (An alternative interpretation of LI, which we will deal with below, alludes to performance more than an attention failure). As a result of this process of *inattention*, the stimulus would be ignored when later, the LI is presented temporarily in combination with the US, making their association with each other difficult. This theoretical perspective, which is called the Conditioned Attention Theory (Lubow, 1989), in addition to receiving the empirical support from a large part of the research carried out in recent years, has become the starting point for a proposal that integrates data coming from research in animals, with humans with no pathologies and with schizophrenic patients.

One of the first results that served to initiate an animal model of schizophrenia in which psychological, biological and psychiatric aspects are combined was the demonstration that LI disappeared when amphetamines are administered prior to pre-exposure and conditioning phases (for example, De la Casa, Ruiz & Lubow, 1993a). Amphetamine, a dopaminergic agonist, has a series of psychological effects among which is an alteration of the attentional process. Specifically, under the effect of the drug, the tendency to pay attention to all the stimulation present would increase, regardless of whether or not the stimulation were informative of the appearance of relevant consequences. Thus, during pre-exposure without consequences of a neutral stimulus, the amphetamine would impede development of *inattention* to it. Thus, when the stimulus in the conditioning phase is paired with the unconditioned stimulus, it would act as if it were functionally new, and would therefore call attention to itself causing unretarded conditioning.

Numerous studies have emphasized the relevance of the alteration of dopaminergic activity in schizophrenic patients. Specifically, the administration of amphetamines in persons with no pathologies produces symptoms similar to the characteristics of paranoid schizophrenic patients and the administration of antipsychotic dopamine agonists cancels out the symptomology induced by the consumption of the amphetamine. In the second place, the amphetamine produces the restoration of the symptomology in schizophrenics in symptom remission phase. Finally, behaviour observed in rats administered amphetamine seemed to reproduce the symptomatology characteristic of schizophrenia in humans. All these data, along with well documented alteration of the attention process in schizophrenics, have served as a basis for the proposal according to which LI can be

employed as an experimental paradigm to analyze the attention process in schizophrenia.

Direct empirical evidence that sustains this model comes from three lines of research: (1) LI does not appear in schizophrenic patients; (2) Administration of amphetamines in humans in absence of pathologies cancels out the effect of LI, and (3) the magnitude of LI is directly proportional to the tendency to psychoticism in individuals without pathologies evaluated on scales designed for the purpose.

In so far as the first of these above-mentioned aspects is concerned, numerous experiments have demonstrated the absence of LI in schizophrenics (e.g., Baruch, Hemsley & Gray, 1988). In this type of research, a procedure generally employed repeatedly presented an inconsequential sound to the preexposure group while they carried out a distractive task consisting of counting the number of times that a syllable was repeated in a list. After preexposure, a learning phase was carried out in which the sound previously pre-exposed became the signal for points to appear on a scoreboard. The task to be solved consisted in discovering what made the score on the scoreboard go up. The result observed in the participants with no pathology is retarded learning of the relationship between the sound and the increase in points on the scoreboard. However, the schizophrenic participants showed superior performance in the learning task, which reveals the attenuation of the LI effect. This result provides research in this sphere with ample validity since, to the contrary of the typical deterioration in performance in the majority of the tasks that is usually observed in schizophrenics, in this case performance improved compared to the participants without pathologies.

Once the absence of LI was established in schizophrenics, to verify the mediation of the dopaminergic system in the processes observed it would be necessary to check whether the same effect described is produced in humans without pathologies to whom the amphetamine is administered. Indeed, this is the result that was obtained in a comparison of performance by two groups of participants in various experiments in which a procedure was employed to generate LI similar to the one used with schizophrenics described above. Specifically, the group for which the preexposure and conditioning phases was carried out after administration of 5 mg amphetamine discovered the relationship between the pre-exposed stimulus and the relevant consequence faster than a control group in which the experimental phases were carried out after administration of a placebo (e.g., Gray, Pickering, Hemsley, Dawling & Gray, 1992).

The third of the experimental demonstrations that sustains the model that relates LI with schizophrenia comes from studies that have analysed the intensity of LI in humans with no pathologies that have been classified by their tendency to psychoticism based on scores obtained in questionnaires designed for the purpose. These results are based on a dimensional concept of psychotic disorder according to which schizophrenia represents the end of a continuum of susceptibility to psychosis that would be applicable to the entire population (Claridge, 1987). From this perspective, we have a normal distribution, at one end of which are those individuals with total absence of psychotic traits, while at the other end there would be schizophrenics. Numerous scales have been developed to quantify the tendency to psychoticism composed by items built up from clinically observed psychotic symptoms. In a typical experiment in which the intensity of LI is analysed based on the tendency to psychoticism, a questionnaire is first given

a large sample, to later select those individuals that have obtained the highest scores and the lowest and form groups with high and low tendency to psychoticism, respectively. After proceeding to the preexposure of the neutral stimulus and later association of it with a relevant consequence typical of the LI experimental design, the learning rate in the groups based on tendency to psychoticism is compared. The result of this comparison is a marked LI effect, that is, retarded acquisition of the association after preexposure in the group with low tendency to psychoticism compared to faster learning in the group with high tendency to psychoticism (for example, De la Casa, Ruiz & Lubow, 1993b).

From the experimental evidence described, Hemsley (1987; see also, Gray, 1998) proposed a model that considers that some of the alterations in cognitive processing that are manifested in schizophrenics are due to the impossibility of integrating the regularity of past experience with recognition, learning and action referring to the current stimulation. The case of LI would illustrate this dysfunction especially clearly: under normal conditions, after repeated presentation of the inconsequential stimulus, its reappearance would produce recognition of its irrelevance and, therefore, lack of attention to it. In the case of schizophrenia, the stimulus previously pre-exposed would not be recognized as such, as the current perception could not be integrated into past experience, so that the stimulus would be treated as if it were functionally new and, therefore, would fully capture the attentional resources available.

Some of the most frequent symptoms of schizophrenics could be explained by the concept proposed by Hemsley. Thus, when some incidental details in the surroundings capture the attention of the individual, it is plausible that a search for the reasons for those stimuli is triggered, which make those stimuli fundamental, and would probably lead to establishment of random associations between the stimuli that might be found at the root of the delirium. On the other hand, faced with an unstructured and ambiguous context such as would be perceived upon not being able to integrate prior experience with the present situation, it would be logical that the information from memory would be confused with real stimulation, producing failures in the differentiation between the two types of sensations. If we consider that this dysfunction could affect not only visual material, but also could extend to other perceptive areas, auditory hallucinations could be included in this perspective. Another aspect approachable from this model refers to alterations in self awareness observed in schizophrenics, since if self awareness is considered the result of regularities stored throughout experience, it is logical that the alteration in the capacity to update such regularities would end up in a breakdown of the *stream of consciousness*, which would go on to be represented as a set of unconnected past and present events.

All these alterations in normal cognitive processing could also be at the root of a series of negative symptoms, such as poverty of speech, social withdrawal or affective insensibility, that might represent adaptive strategies developed by the patients to minimize the social effects of cognitive alterations.

Latent inhibition as an animal model of schizophrenia: the psychopharmacological dimension

Some critics doubt whether an animal model can explain specifically human disorders such as schizophrenia. Animal models offer research an accessible, simplified vision of a much more complex human phenomena. This simplicity is at the same time its main virtue and its weakest point, as it excessively reduces complex phenomena. Schizophrenia is a disorder that affects the most elaborate human cognitive functions. To reproduce in animal models symptoms such as delirium or hallucination, two of the symptoms of schizophrenia that most stand out, is a difficult task.

An animal model should respond to three questions. The first is that it be able to reproduce the factors that induce the disorder (validity of the construct); in the second place, it must be able to reproduce the phenomenology of the disorder (apparent validity) and, in the third place, predict the responses to possible treatment (predictive validity) (Lipska & Weinberger, 2000). Therefore, animal models have focused mainly on discovering aetiological factors in reproducing the symptoms of schizophrenia and predicting pharmacological effects. The LI model seems to comply with these criteria for validity. The most successful animal models are those that focus on the functioning of certain neurotransmitters that could be involved in cognitive or behavioural functions necessary for the organism to adapt properly to its environment.

Once a psychological function model has been elaborated, the neurobiological circuits involved in those tasks can be found using psychopharmacological manipulation or lesioning of the central nervous system.

Relating the neurobiological dimension to the psychological dimension, we can advance in the knowledge of a disorder, avoiding the danger of reductionism. Both psychological/neurobiological dimensions must be explained by bidirectional causality in which there is modulation of both dimensions. In this respect we can understand how, for example, the dopaminergic hypothesis of schizophrenia can contribute to understanding the psychological mechanisms involved in learning and perhaps in schizophrenia. From this perspective, these two interpretations of schizophrenia are not contradictory but complementary. In recent years, research in the neurobiological dimension has grown dizzily due its interest as a model of the effects of antipsychotic drugs in schizophrenia.

Although several neurotransmitters are involved, the most data has been generated about dopaminergic transmission. This is because of the facility with which psychotic symptoms in humans can be reproduced by administering amphetamine, a dopaminergic agonist. This approach has extended the use of dopaminergic antagonists, such as neuroleptic haloperidol, for the treatment of positive schizophrenic symptoms in psychiatry. Most of the research is focused on the dopaminergic system and the structures that supposedly play some role in the physiological pathology of schizophrenia, such as the limbic system (hippocampus, entorhinal cortex and amygdala), frontal cortex and nucleus accumbens, the site where the afferent pathways of the mesolimbic dopaminergic system coming from the above-mentioned structures terminate. Functional and pharmacological convergence in both animals and humans support the LI model as a model of positive

symptoms of schizophrenia.

The logic behind psychopharmacological research in animals shows the advantages and limitations of the model. As we have seen above, there is a preexposure phase and an acquisition phase in all LI studies. One of the first things investigated was what phase the amphetamine and haloperidol exert their action in. Research has demonstrated that these drugs exert their effect when administered during the acquisition phase. These results seem to indicate that these drugs not only affect the capacity to ignore stimuli during the preexposure phase, but also affect the capacity of the stimulus to control behaviour in the acquisition phase. According to this interpretation during LI two contradictory contingencies are acquired, non-event stimulus in the preexposure and reinforcing stimulus in the acquisition phase. These two associations compete to express themselves during conditioning. This perspective is defended by Weiner (1990, 2003). The model proposed by Weiner gives a central role to the nucleus accumbens NAC. This structure is made up of two pharmacologically and functionally different physiological subregions, the shell and the core. He proposes a switching mechanism in the NAC core subregion that would control which of these two contingencies (CS-no US/CS-US) controls behaviour. The core switching mechanism is activated at the moment of conditioning when followed by reinforcement. Under conditions in which LI is produced, the NAC shell inhibits the core switching mechanism, that is, the CS-no US contingency gains control over the expression of behaviour.

From this perspective, one of the most recent contributions of the LI model is permitting the study of new antipsychotic drugs. Antipsychotic drugs are divided into two groups, typical and atypical. The criteria for this distinction is that atypical drugs are more therapeutically efficient, do not cause extrapyramidal side effects and do not induce catalepsy in rodents. Furthermore, their antagonism on DA2 and 5HT2 receptors gives them better antipsychotic efficiency, both in general and in particular in improving negative symptoms.

The mot significant new thing about them is that administration during the preexposure phase eliminates the effect of LI while haloperidol, a typical antipsychotic only exerts its action when it is administered during the acquisition phase. Although the main system related to LI is the dopaminergic system, there other neurotransmitters that may have a role in the expression of LI. In the last decade, the role of the serotoninergic system has been investigated. The most important feature of these compounds is that, contrary to dopaminergic manipulation, they exert their action in the preexposure phase. The serotoninergic system intervenes in the processing of EC-non event association, which is consistent with intervention in attentional processes. The atypical antipsychotics actually antagonize serotonin.

An animal model of schizophrenia also has to be a good model of antipsychotic drug functioning. That is, the model has to be specifically sensitive to treatment with antipsychotics. We know that with amphetamine we can eliminate the effect of LI and that both atypical and typical drugs block the ability of amphetamine to interrupt LI. Furthermore, antipsychotic drugs strengthen the effect of LI under conditions in which it is not produced (either a low number of preexposures or high level of conditioning), which makes the model the test most used to identify substances with antipsychotic

action. When parameters that do not produce LI are used, neither haloperidol or clozapine have any effect when administered in the preexposure phase, while they do have it when they are administered in the conditioning phase. What is new is that when tested under parameters that produce LI, clozapine, but not haloperidol, interrupt LI when administered during preexposure. These results show for the first time that typical and atypical antipsychotics exert their action differently. While ritanserin is able to strengthen LI when administered during conditioning, it interrupts LI when administered during preexposure, supporting the idea that the mechanism explaining the interruption of LI during preexposure by clozapine is due to the antagonism of serotoninergic receptors. The typical effect of the drugs would be founded on the strengthening of LI when applied during conditioning and would dissociate from the atypical drugs because of the disruptive effect of LI when administered during preexposure (Shadach, Gaisler, Schiller & Weiner, 2000).

Returning to schizophrenia in humans, the first clinical data indicate that the interruption of LI is observed in acute phase schizophrenia. Moreover, this absence of LI is related to the positive symptoms and not to negative. Even so, in work by Gray, Hemsley, and Gray (1992), while chronic and medicated groups had similar scores on positive symptoms, LI did not appear in the first although it did in the second. Gray et al. found that there is no LI at the beginning of the disease in subjects that had never been medicated, but that it reappears depending on the chronisity of the disorder. Therefore, it may be concluded that the absence of LI is produced in subjects in acute phase or at the beginning of the disorder so that the animal model of LI serves as a model for acute psychosis.

Nevertheless, some studies have not found the same results. These contradictions may be explained with data obtained in rats. Abnormal LI is not exclusively a manifestation of loss of LI, but may also be one of persistent LI. In fact, only an increase in the dopaminergic function or poor functioning of the entorhinal cortex and the NAC produces an interruption of LI. However, poor functioning of most of the structures implied in schizophrenia, prefrontal cortex, amygdale, hippocampus, NAC core, should not interrupt LI. Therefore, the presence or absence of LI at any time in a schizophrenic is determined by the dopamine level. Pharmacologically, the increase in dopaminergic transmission interrupts the effect of LI, which produces an exacerbation of the psychotic symptoms in humans and increases the positive symptoms in schizophrenia; while blockage of the glutamatergic receptors produces persistence of LI, which causes both positive and negative symptoms in humans and is related to the negative symptoms in schizophrenia. Typical and atypical drugs are consistently effective against the positive symptoms while only the atypical are effective against negative systems also. That is, the interruption induced by amphetamine is reversed both by atypical and typical drugs, while the persistence induced by the glutamatergic antagonist is reversed only by atypical drugs. Interruption of LI would be a valid predictor for positive symptoms of schizophrenia while persistence of LI would be for negative symptoms. The psychopharmacology of LI therefore enables the development of more and more specific drugs with fewer secondary symptoms.

Latent inhibition and Schizotypy: An experimental study

The adaptation of the methodology for the study of the LI effect of animal learning and human conditioning open a very fruitful line of research into the processes of cognitive inhibition in Schizotypy (Cassaday, 1997). In adult humans, operant discrimination tasks are the most commonly used experimental procedure and require the use of a distracting or *masking task* during the preexposure phase. The attribution of irrelevancy and consequent withdrawal of attention to the preexposed stimulus is made possible because attention of the subject is channelled to the masking task which constitutes, according to the instructions, the purpose of the experiment. The preexposure phase thus becomes a laboratory test of selective attention and as a result, in diagnostic tool of indubitable value for the evaluation of the capacity to modulate the assignment of attentional resources. The procedure recently designed by Braunstein-Bercovitz & Lubow (1998a) offers clear advantages over the operant discrimination tasks used in the classical work mentioned above that was based on the Ginton, Urca & Lubow (1975) method of contingency detection. The technical superiority of this task, shown on the computer, permits preexposure and test contexts to be homogenized and the performance of the subject recorded not only in the test phase, but also during preexposure. The procedure comprises the two training phases (preexposure phase and test phase) common in this type of task and the participation of two groups of subjects (preexposed and control). During the preexposure phase, all the subjects do the *masking task*, a "same versus different" reaction time task with four possible combinations of letters (TT, TL, LT, and LL) that appear in the centre of the computer screen. In each test, the experimental subjects also receive a pair of identical geometric figures to the right and the left of the pair of letters. The purpose of the masking task is to channel the attention of the subject toward the reaction time task and indirectly promote the withdrawal of the attention from the figures which are irrelevant to the task and potentially distracting. Immediately after the preexposure phase, all the subjects do the test phase learning task. In it the subject receives different combinations of stimuli, but must press the space bar to obtain a point only in the presence of the *Discriminative Stimulus*: the pair of figures preexposed for the experimental group and new for the control group. The responses in the tests in which these stimuli do not appear are penalized with the loss of a point.

The Latent Inhibition effect (LI) is defined as the *delay* observed in the detection of the *critical stimulus* in the group preexposed compared to the group that received it as a new stimulus in the test phase. In the task designed by Braunstein-Bercovitz & Lubow (1998a), the psychological status of the ED in the test phase is clearly different in both groups. In the experimental group it is a familiar and irrelevant stimulus from the previous phase, while for the control group it is a new stimulus and, therefore, potentially significant. The LI effect in the test phase is the result of selective processing of the relevant and significant stimuli from the masking task in the preexposure phase, compared to those preexposed incidentally, which were ignored as lacking in informative value.

During the last 20 years, a growing interest in analysing the LI effect with regard

to the schizotypal personality has been observed (De la Casa, 2002, for a review). Research on the LI effect with regard to this complex construct rests on a dimensional model. The schizotypy is defined as a non-pathological personality trait proposed as a risk factor predictive of the development of schizophrenia (Claridge, 1999). One of the cognitive alterations characteristic of acute phase schizophrenia is the high distractibility and difficulty in transition of controlled to automatic processing in the face of irrelevant stimulation (e.g., Gray, Feldon, Rawlins, Hemsley & Smith, 1991). The LI effect in humans is precisely the result of an adequate information filtration process during preexposure, in which the masking task must occupy the controlled attentional resources of the subject, at the time that the preexposed stimuli are progressively processed automatically. The study of the LI effect both in schizophrenic patients and in normal subjects with extreme schizotypy scores therefore possesses clear theoretical justification. With very few exceptions, consistent results are observed: the effect of the delay is not observed in acute phase schizophrenic patients and is attenuated significantly in non-clinical samples with extreme schizotypy scores (Lubow & Gewirtz, 1995, for a review). The deficit observed reveals the difficulty in inhibiting attention faced with redundant, irrelevant stimuli during the concurrent performance of a task that requires attentional focus. However, at least in non-clinical samples, studies seem to agree on the idea that this is not a limitation of attentional resources, but an attentional dysfunction, since the LI effect is re-established by modifying certain parameters in the task such as the duration of the preexposure phase or the attentional load of the masking task (Braunstein-Bercovitz & Lubow, 1998b).

Very recently, research has focused on analysis of the possible contribution of the Anxiety factor, often associated with schizoid disorders, in the explanation of the absence of the LI effect in this type of samples (Braunstein-Bercovitz, Rammsayer, Gibbons, & Lubow, 2002, for a review). Braunstein-Bercovitz (2000, Experiment 1) performed a factorial analysis of the nine subscales of the Raine (1991) SPQ (Schizotypal Personality Questionnaire) and the Anxiety Trait Scale of Spielberger, Gorsuch & Lushene (1970). The analysis revealed two clearly differentiated factors. On one hand, the one called *Anxiety*, which was saturated with the SPQ "social anxiety", "affective isolation", constricted affect" and "suspicion" subscales along with the anxiety trait scale. On the other, a Perceptive Disorganization factor was saturated with the SPQ subscales "magic thought", "unusual perceptive experiences", "eccentric behaviour" and "incoherent discourse". Using a non-clinical sample as experimental subjects Braunstein-Bercovitz (2000, Experiment 2) found LI absent exclusively in the subjects with extreme scores in the Anxiety factor or in both, while the subjects who only had extreme cores in the Perceptive Disorganization factor showed a significantly normal LI effect. These results suggest two conclusions (1) The anxiety component of schizotypy, more than the perceptive disorganization which characterizes schizophrenia, seems to be responsible for the attentional dysfunction associated with the schizotypal personality, and (2) since the *Perceptive Disorganization* factor groups the positive symptomatology of schizotypy, compared to the *Anxiety* factor characterized by interpersonal-type deficits associated with negative symptomatology, the attenuation of the LI effect seems to be more related to the negative symptomatology of the schizotypy than the positive.

These conclusions are not backed, however, by prior research in inhibitory cognitive processes in samples of schizotypal subjects with tasks similar to LI, such as negative *priming* procedures (Williams & Beech, 1997, for a review). In such work, the subjects that were not ill that showed high scores in positive schizotypal traits, such as cognitive and perceptive disorganization, showed less capacity for cognitive inhibition than those with high negative trait scores, such as physical and social anhedonia. These results were corroborated in clinical samples of schizophrenics; only the patients that had exacerbated positive symptomatology showed a deficit in selective inhibitory processes, while in patients in whom negative symptomatology predominated, the inhibitory cognitive processes were found intact. The recent work of Rascle, Mazas, Vaiva, Tournant, Raybois, Goudermand, & Thomas (2001), with schizophrenic patients using an LI procedure based on the Ginton *et al.* (1975) task supported these results. These authors found absence of LI in acute patients with low negative symptomatology and a super LI effect in chronic patients with high negative symptomatology.

Along the line of research initiated by Braunstein-Bercovitz (2000), Sánchez Balmaseda, Sánchez-Elvira, Hernández, Amor, & Lasa (in preparation), have analyzed the contribution of the explanatory weight of the positive vs. negative schizotypy symptomatology in attenuating the LI effect in non-clinical samples. Specifically, they analysed LI on the subscale "Unusual Experiences" of positive schizotypy symptoms with an adaptation of the task designed by Braunstein-Bercovitz & Lubow (1998a). The large size of the sample (n= 223) enables the possible modulating role of the Anxiety Trait variable, as a component of the negative schizotypy symptomology, to be analysed.

As measurement instruments they used the subscale "Unusual Experiences" (30 items) from the *Oxford-Liverpool Inventory of Feelings and Experiences* (O-LIFE) by Mason, Claridge & Jackson (1995) and the Spilberger, Gorsuch & Lushene' Anxiety Trait scale (1970). The "Unusual Experiences" scale contains items that allude to aberrant perceptions and beliefs and magical thought, consistent with the positive schizotypy symptoms.

The sample of extreme subjects on the subscale "Unusual Experiences" was defined using the 75th percentile as the cut-off point, while the control sample was made up of a set of subjects with scores under the 50th percentile. The set of subjects with high Schizotypy scores was progressively reduced by taking a higher percentile each time in the Anxiety Trait variable, as shown in Table 1.

Table 1. Number of subjects in the Preexposure and No Preexposure conditions in the different samples defined by the Schizotypy and Anxiety traits.

	Control Sz<P50	**Sz>P75**	**Sz>P75 Anx>P50**	**Sz>P75 Anx>P75**	**Sz>P75 Anx >P77**	**Sz>P75 Anx >P80**
NPE	55	35	23	17	12	11
PE	73	19	10	8	7	5

The procedure employed was an adaptation of the one used by Braunstein-Bercovitz & Lubow (1988a), described above.

As observed in Table 2, the average and low Schizotypy subjects displayed a significant Latent Inhibition effect, showing a significantly higher number of tests to detect the criteria than the control subjects Not Preexposed. To the contrary, in the sample of subjects that scored above the 75th percentile, the retarding effect was not statistically significant, although the tendency of the results indicates a higher number of tests in the Preexposure condition. The covariance analysis performed on this sample of subjects with Anxiety as the covariable and the (PE and NPE) condition as the factor revealed a significant effect of the first [(F 1,53)= 4.34; p<.04)] in explaining the magnitude of the difference in the second. For the total subjects with Sz> 75 an ever stricter criteria was adopted, incrementing the Anxiety variable percentile used as the criteria of selection, which reduced the initial sample more and more. As may be observed in Figure 1, for a constant value of Sz> 75, the number of tests needed to detect the criteria was progressively less in the PE condition with the increase in the Anxiety variable.

The results obtained with the "Unusual Experience" subscale agree with the results of the Braunstein-Bercovitz study (2000), in so much as they seem to indicate that the Anxiety variable exerts a modulating effect on the performance in the test phase of the subjects with high Schizotypy scores. The absence of a significant delay in the PE condition found regardless of the Anxiety variable (Sz> 75, total sample), makes the correlation between the positive schizotypy component and the attenuation of latent inhibition clear, although the speed in detecting the criteria for learning in the test phase is strengthened in parallel with the progressive increase in the Anxiety Trait variable, grouped factorially with the negative component in the work of Braunstein-Bercovitz (2000).

Table 2. Average tests for the criteria in Preexposure and No Preexposure conditions and magnitude of LI in the different samples defined by the *Schizotypy* and *Anxiety* traits.

	Control	**Sz>P75**	**Sz>P75**	**Sz>P75**	**Sz>P75**	**Sz>P75**
	Sz<P50	**Total Sample**	**Anx>P50**	**Anx>P75**	**Anx >P77**	**Anx >P80**
NPE	111	108	86	90	78	83
PE	154	135	101	99	79	65
IL	t (126) = 2.49 p<.01	No IL	No IL	No IL	No IL	No IL

These results indicate that schizotypy is a sufficient factor to abolish the LI effect, but at the same time it highlights the important contribution of the Anxiety Trait as covariable. As pointed out in the discussion of the animal model of schizophrenia based on psychopharmacological research, the abolition of LI seems to be measured by elevated levels of dopaminergic activity. With very high levels of anxiety and stress, an increase in dopaminergic activity is also observed, and studies on negative priming with Stroop procedures indicate that highly anxious individuals show an attentional skew that reveals generalized difficulty in inhibiting attention given irrelevant stimulation whether threatening or not (Braunstein-Bercovitz, Rammsayer, Gibbons & Lubow, 2002).

The results shown are only a sample of the reliability and validity of the LI experimental procedure as a laboratory tool for the evaluation of selective attention processes in the sphere of Personality and Psychopathology. At the *9th International*

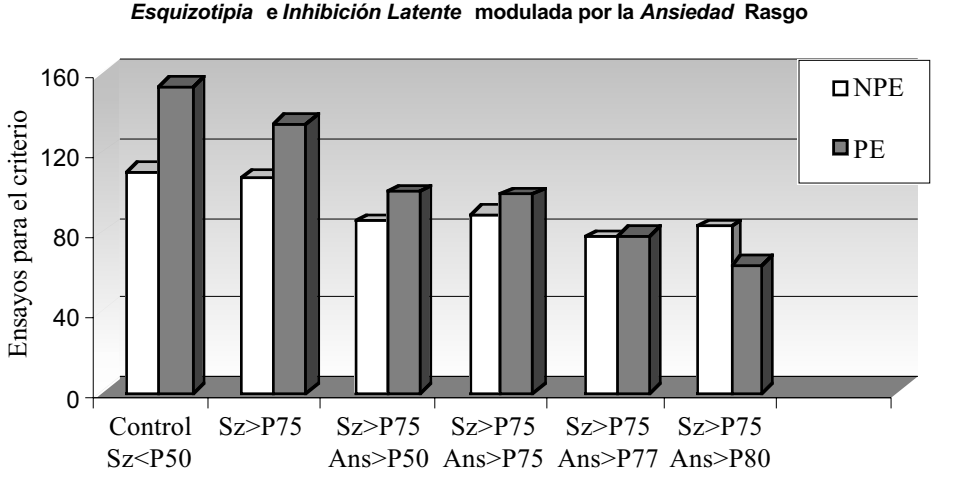

Figure 1. Magnitude of Latent Inhibition as a function of *Schizotypy* trait (Unusual Experiences subscale, Mason, Claridge and Jackson, 1995) and *Anxiety* (scale, Spielberger *et al.*, 1970).

Congress on Schizophrenia Research, held in April 2003 in Colorado, Rascle, Soller, Goudemand & Thomas reported on the relationship between LI and prognosis in schizophrenia. These authors found absence of LI in the sample of patients with recurrent psychotic episodes and a significant LI effect in first-episode patients. In line with the results of Rascle, *et al*. (2001) previously cited, these authors found that first-episode patients showed significantly higher scores in the negative dimension of Schizophrenia Anergia on the positive and negative symptom scale (PANSS). These results establish a link between the negative dimension of schizophrenia and LI. In the opinion of Rascle, Soller, Goudemand & Thomas, the prognostic value of the negative dimension

of schizophrenia suggests that LI could also be an early prognosis factor of the disease.

Conclusions

Future clinical research of LI must develop procedures that enable detection of both absence of LI and its persistence. One very relevant methodological question is the use of intrasubject designs. The groups of schizophrenia classified by some criteria (symptoms, disease phase, etc.) contain individuals that may or may not show LI. Therefore, the statistical groups may mask a differential manifestation of LI and lead to inappropriate conclusions. It would be advisable to have an individual LI score and use it as a continuous measure. Such data can be used to correlate with different symptoms (positive vs. negative), duration of the illness, response to drugs, results in other tests, etc. and thus distinguish different subgroups of patients.

Although laboratory research is more and more complex, its implications the clinical, far from diminishing, are augmented. The LI model can apparently be applied to the clinical and this application is interpreted as a criteria for the validity of the model, however, this animal model must not be judged by its direct application to clinical alone, but by its success in providing an explanation of the cognitive/behavioural deficit, of the neurobiological substrate and by its sensitivity to pharmacological treatments.

It is important to point out that not all the manipulations that affect LI have to be relevant to schizophrenia. LI is paradigm of learning and as such, the drugs and lesions may affect other processes such as learning itself, memory or motor behaviour. It is important to establish a theoretical framework that tells what alterations in LI are relevant for schizophrenia.

One of the most interesting questions that emerges from the pharmacological and lesion studies is the importance of distinguishing the processes that occur in preexposure and conditioning. The serotoninergic compounds are of particular interest since they affect LI during preexposure but also interact with systems (dopaminergic and glutamatergic) that affect LI during conditioning.

It is evident that the model described is highly speculative, although it is firmly established on experimental premises, some of which have been mentioned here, and is accompanied by a proposal of neurochemical and neuroanatomical alterations that have given rise to an integrating theory of schizophrenic symptomatology.

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