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Research report

# Disruption of learned irrelevance in acute schizophrenia in a novel continuous within-subject paradigm suitable for fMRI

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**Abstract**

Learned irrelevance (LIrr) is closely related to latent inhibition (LI). In LI a to-be-conditioned stimulus (CS) is prexposed alone prior to the opportunity to learn an association between the CS and an unconditioned stimulus (UCS). In LIrr preexposure consists of intermixed presentations of both CS and UCS in a random relationship to each other. In both paradigms preexposure leads in normal subjects to reduced or retarded learning of the CS–UCS association. Acute schizophrenics fail to show LI. LI is usually demonstrated as a one-off, between-groups difference in trials to learning, so posing problems for neuroimaging. We have developed a novel, continuous, within-subject paradigm in which normal subjects show robust and repeated LIrr. We show that this paradigm is suitable for functional magnetic resonance imaging (fMRI) and gives rise, in normal subjects, to activation in the hippocampal formation, consistent with data from animal experiments on LI. We also report, consistent with previous studies of LI, loss (indeed, significant reversal) of LIrr in acute (first 2 weeks of current psychotic episode) schizophrenics. Chronic schizophrenics failed to demonstrate learning, precluding measurement in this group of LIrr. These findings establish the likely value of the new paradigm for neuroimaging studies of attentional dysfunction in acute schizophrenia.


*Keywords:* Learned irrelevance; Latent inhibition; fMRI; Acute schizophrenia; Chronic schizophrenia; Hippocampus

## 1. Introduction

Latent inhibition (LI) is the detrimental effect of pre-exposure of a stimulus without consequence on the subsequent ability of that stimulus to enter into a conditioned association [37]. It has been demonstrated in many species, including human subjects [40]. A consequence of LI is that individuals show reduced or slower learning to a familiar (preexposed) stimulus than to a novel (non-preexposed) stimulus. Disruption of LI by indirect dopamine agonists such as amphetamine [50,60] was proposed as an animal model of the attentional deficits that characterize schizophrenia [28]. Subsequently, this proposal, strengthened by evidence that amphetamine disrupts LI also in normal human subjects [25,33,44,54,56], was integrated into two related general models of the neuropsychological basis of the positive symptoms of schizophrenia [19,58]. These have received substantial support from animal experiments, clinical studies and studies of the effects on LI of individual differences in schizotypy (for reviews, see [18,20,22,59,63]). In particular, there is considerable [3,24,26,31,38,43,57] though not universal [53,64] experimental support for disrupted LI (as predicted by these models) in unmedicated schizophrenic patients or in patients during the first two weeks of medication of the current psychotic episode, as well as for restoration of LI after 6 weeks of medication or approximately one year of unmedicated illness. Thus,

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disrupted LI is able to serve as a marker of aberrant cognitive processing during acute exacerbation of schizophrenic illness.

In parallel with this accumulation of clinical evidence, considerable advances have been made in determining in animal experiments the neural and neurochemical bases of LI and its disruption by indirect dopamine agonists (for reviews, see [20,22,40,59,63]). Many of the relevant findings have been incorporated into a detailed neural network model of LI and its basis in brain function [7,45,46,47]. Against this background, LI and its disruption can potentially provide an excellent behavioral paradigm for use with neuroimaging techniques to probe abnormal brain function in acute schizophrenia. However, methods used hitherto to demonstrate LI are difficult to adapt to the needs of neuroimaging. Most of them are between-subject designs, i.e. one group is given pre-exposure to the stimulus subseqently used as a conditioned stimulus, while the other is not. Within-subject designs are inherently more powerful and normally demand less experimental time, an important consideration given the high cost of scanning. Fortunately, it is possible using within-subject designs to demonstrate LI, its dependence upon questionnaire measures of schizotypy [11], and its disruption both in normal subjects administered amphetamine [54] and in patients with schizophrenia [26,57]. But a second difficulty remains. LI is typically measured as a difference in trials to a learning criterion between the pre-exposed and non-pre-exposed conditions. Thus, the critical event occurs just once in each condition for each subject. Such point estimations are incompatible with the requirement in most neuroimaging paradigms for repeated measures. Functional magnetic resonance imaging (fMRI), for example, typically uses either a repeated 'box-car' design or event-related responses averaged over many instances. These designs require the development of a continuous (repeated measure), within-subject paradigm.

In this paper we present such a paradigm and demonstrate its suitability for fMRI and its sensitivity to schizophrenic illness. The paradigm is not, however, one of latent inhibition, but rather the closely related phenomenon of 'learned irrelevance' (LIrr). The two phenomena share the outcome of slowed or reduced learning consequent upon an initial experimental phase of pre-exposure; they differ, however, in the nature of the pre-exposure phase. To set this difference out it is useful to employ the vocabulary of Pavlovian conditioning theory [16], in which a conditioned stimulus (CS) becomes a signal for an unconditioned stimulus (UCS) as the result of repeated associations between the two in which the probability of occurrence of the UCS is elevated relative to baseline for a short period after occurrence of the CS. The pre-exposure phase in LI consists of presentations of the to-be-CS alone. In LIrr [4], in contrast, pre-exposure consists of intermixed presentations of the to-be-CS and the to-be-UCS such that the baseline probability of occurrence of the UCS is unchanged by occurrence of the CS (and *vice versa*). LIrr [1] shares with LI ([59] for review) dependence upon the integrity of the entorhinal cortex, which provides the major neocortical input to the hippocampal formation. It has not to our knowledge previously been studied in relation to schizophrenia.

The strategy we followed was, first, to establish that our LIrr paradigm is suitable for use in an fMRI protocol (Experiment 1), and then to determine whether, like LI [3,24,26,31,38,43,57], LIrr is abolished in acute schizophrenic patients (Experiment 2). Evidence that LIrr is disrupted in schizophrenia in a pattern similar to that observed for LI would at once support the utility of LIrr in studies of this condition and strengthen the case that it shares for this purpose critically relevant features with LI.

## 2. Experiment 1

Animal experiments have shown a key role for limbic structures in mediating LI [20,22,63]. Dopaminergic function in the mesolimbic pathway, terminating in the nucleus accumbens, appears to be critical [30], as does activity in the hippocampal formation and entorhinal cortex [7,27,29,47,65]. Different subcomponents of these systems appear either to enhance LI, e.g. the entorhinal cortex [10,65] and the shell of the nucleus accumbens [61,63], or to interrupt it, e.g. the hippocampus [59], the core of the nucleus accumbens [61,63,66] and the dopaminergic afferents to the shell [30,42]. This differentiation extends even into sub-fields of the hippocampus and dentate gyrus [29,51]. Thus, given the limits of spatial resolution of fMRI with human subjects, one can predict from the animal data that these general regions of the hippocampal and mesoaccumbal systems are likely to be activated in an LI paradigm, but not whether such activity will be relatively greater in the pre-exposed or non-pre-exposed condition. In contrast, LI has been reported to be unaffected by lesions of the frontal cortex [35,36] or amygdala [62]. In broad agreement with the data on LI, it has been reported that lesions to the entorhinal cortex but not the hippocampus disrupt LIrr [1]. The tentative predictions, outlined above, for LI can perhaps therefore be extended to LIrr.

We developed a novel, continuous within-subject LIrr paradigm with visual stimuli (preferred to auditory stimuli because of the intensely noisy scanner environment) for use with fMRI. Subjects are required to learn associations between cue letters (acting as a warning stimulus; see Section 2.1) and a target letter (acting as an imperative stimulus for a speeded manual response). Responses are measured as the reaction time to press a response button when the target letter appears on the screen, and the learning of the cue-target association is indexed by faster responding to cued than non-cued targets. As we report, a differential rate of learning is observed between trials using pre-exposed cue letters compared to trials using non-pre-exposed cue letters; slower responding to targets preceded by pre-exposed relative to non-pre-exposed cues constitutes LI.