Learned Irrelevance and Associative Learning Is Attenuated in Individuals at Risk for Psychosis but not in Asymptomatic First-Degree Relatives of Schizophrenia Patients: Translational State Markers of Psychosis?

Ariane T. Orosz1,2, Joram Feldon1, Andor E. Simon2,3, Leonie M. Hilti4,5, Kerstin Gruber3, Benjamin K. Yee1, and Katja Cattapan-Ludewig2,6

1Laboratory of Behavioural Biology, Swiss Federal Institute of Technology Zürich, Zurich, Switzerland; 2Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, Bern, Switzerland; 3Specialised Outpatient Service for Early Psychosis, Department of Psychiatric Neurophysiology, Bruderholz, Switzerland; 4Institute of Psychology, University of Bern, Bern, Switzerland; 5Neuropsychology Unit, Department of Neurology, University Hospital Zurich, Zurich, Switzerland; 6Sanatorium Kilchberg, Switzerland

*To whom correspondence should be addressed; tel: +41-31-932-83-52, fax: +41-31-930-99-61, e-mail: ariane.orosz@puk.unibe.ch.

Learned irrelevance (LIrr) refers to a form of selective learning that develops as a result of prior noncorrelated exposures of the predicted and predictor stimuli. In learning situations that depend on the associative link between the predicted and predictor stimuli, LIrr is expressed as a retardation of learning. It represents a form of modulation of learning by selective attention. Given the relevance of selective attention impairment to both positive and cognitive schizophrenia symptoms, the question remains whether LIr impairment represents a state (relating to symptom manifestation) or trait (relating to schizophrenia endophenotypes) marker of human psychosis. We examined this by evaluating the expression of LIr in an associative learning paradigm in (1) asymptomatic first-degree relatives of schizophrenia patients (SZ-relatives) and in (2) individuals exhibiting prodromal signs of psychosis ("ultrahigh risk" [UHR] patients) in each case relative to demographically matched healthy control subjects. There was no evidence for aberrant LIr in SZ-relatives, but LIr as well as associative learning were attenuated in UHR patients. It is concluded that LIr deficiency in conjunction with a learning impairment might be a useful state marker predictive of psychotic state but a relatively weak link to a potential schizophrenia endophenotype.

Key words: latent inhibition/prodromal symptoms/selective attention/state marker/endophenotype/associative learning

Introduction

Deficits in selective attention have long been recognized as one of the core features relevant to positive as well as cognitive symptoms of schizophrenia.1,2 The inability to adequately process surrounding stimuli by selectively attending to stimuli relevant to current perception while ignoring irrelevant spurious cues is believed to contribute to the sensory overload characteristic of schizophrenia patients. One form of selective attention is controlled by stimulus history in which subjects learn to ignore specific stimuli with a history of irrelevance. A popular translational paradigm that has been extensively employed to study this form of selective attention is latent inhibition (LI).3 LI refers to the attentional control over learning in which inconsequential experience of a specific stimulus retards subsequent associative learning about that stimulus, eg, its predictiveness over another stimulus. LI can be readily demonstrated in humans and animals and is found to be attenuated in both unmedicated4,5 and medicated6,7 acute schizophrenia patients, although intact LI has also been reported in unmedicated acute schizophrenia patients.8 LI disruption reflects effective learning about the predictor stimulus in spite of the previous experience of its irrelevance as a predictive cue and therefore cannot be merely attributed to a general form of learning failure but rather can be viewed as accelerated learning under such a preexposed condition.

Observations in animals and human volunteers indicate that the expression of LI is highly sensitive to dopaminergic manipulation. For instance, the dopamine-releasing drug amphetamine readily disrupts LI9–11—a finding that is consistent with the hyperdopaminergia hypothesis of schizophrenia, suggesting that acute schizophrenia is associated with heightened mesolimbic dopaminergic neurotransmission.12 Treatment with antipsychotic drugs, which are efficient dopamine receptor antagonists, has been shown to be effective in reinstating LI, and normal LI has been identified in both acute and chronic medicated schizophrenia patients.8,13–16 LI expression in schizophrenia patients also appears to be influenced by the duration of illness, as substantiated by a report showing intact LI in unmedicated symptomatic chronic
schizophrenia patients. Moreover, there are studies demonstrating aberrant LI in both drug-free and medicated chronic schizophrenia patients, suggesting that this form of aberrant LI expression may be related to the negative symptoms that are prevalent in chronic schizophrenia. The apparent inconsistency across LI studies in schizophrenia patients may indicate that changes in LI expression represent a state rather than a trait marker of schizophrenia, linking LI disruption and positive symptoms, and persistent or potentiated LI to negative symptoms. However, demonstration of LI disruption among constantly medicated chronic schizophrenia patients as well as in healthy first-degree relatives of schizophrenia patients challenges this view and suggests instead LI disruption as a trait marker or even an endophenotype of the disease. An endophenotype refers to an internal and intermediate phenotype linking clinical symptoms to the genetic predisposition to the disease. Gottesman and Gould emphasize that endophenotypes are heritable state-independent phenotypes capable of indexing the underlying genetic vulnerability to the disease. In addition, endophenotypes should be associated with the disorder and observed in unaffected family members at a higher frequency than in the general population. Identification of such endophenotypes may offer a better understanding of the complex genetic architecture and related etiological and physiological mechanisms of the disease.

The present study was designed to examine the presence of learned inattention deficits in 2 cohorts of subjects differing in terms of the nature of their susceptibility to developing schizophrenia and their present mental states. One group was asymptomatic first-degree relatives of confirmed cases of schizophrenia (SZ-relatives), who hence had a clear genetic risk but were devoid of any overt signs of psychosis. The other group of subjects were showing prodromal signs of schizophrenia in the form of attenuated positive symptoms, and although some might go on to recover completely, they were considered clinically at ultrahigh risk (UHR) of progressing into schizophrenic psychosis. Hence, both SZ-relatives and UHR subjects were regarded as being along the schizophrenia continuum, the former based solely on a genetic contribution and the latter solely on symptomatological grounds.

In this study, a learned inattention paradigm related to LI—learned irrelevance (LIrr)—was employed. LIrr differs from LI in the critical stimulus preexposure phase in that LIrr involves the explicit exposure to uncorrelated presentations of both the predicted and the future predictive stimuli, whereas in LI, only the latter is preexposed. Theoretical accounts of the 2 phenomena are closely related. Similar to LI, LIrr disruption has been linked to schizophrenia, with reports of LIrr deficiency among both medicated and unmedicated first-episode schizophrenics as well as among medicated acute patients. The 2 existing studies of LIrr expression in chronic schizophrenia patients both demonstrated LIrr impairment (contrasting with some LI studies), although this was attributed to weak associative learning as such rather than to a specific failure in learning to ignore the preexposed stimuli. A within-subject LIrr paradigm was adopted here similar to that which has proven to be sensitive to first-episode schizophrenia.

**Methods**

**Subjects**

The study was conducted at the University Hospital of Psychiatry, Bern, and at the Specialised Outpatient Service for Early Psychosis, Department of Psychiatry, Bruderholz, Switzerland. None of the subjects had previously been assessed for the expression of LI or LIrr. They were first informed with a complete description of the study and the test procedures, whereupon written consent was obtained. Additional informed parental consent was obtained for patients who were under the age of 18 years. The study had been approved by the ethics committees of the cantons of Bern and Basel, Switzerland.

**First-Degree Relatives of Schizophrenia Patients**

Twenty-three (13 females and 10 males) asymptomatic subjects who had one (parents: n = 8, siblings: n = 8, and children: n = 3) or more (n = 4) first-degree relatives with a Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) diagnosis of a schizophrenia-spectrum disorder were recruited from the University Hospital of Psychiatry, Bern, and through support groups by advertisements. All participants were screened for psychiatric disorders according to DSM-IV, using the short check questionnaire of the diagnostic interview Diagnostisches Expertensystem für Psychische Störungen (DIA-X) questionnaire for axis I disorders and the Structured Clinical Interview for DSM Disorders questionnaire for axis II disorders. Subjects with any DSM-IV axis I or axis II disorder or a history of psychiatric conditions (eg, psychosis, depression, anxiety disorder, or substance abuse) were excluded. In addition, all subjects were required to complete the self-report Schizotypal Personality Questionnaire (SPQ).

**UHR Subjects**

Seventeen patients (6 females and 11 males) with prodromal symptoms of schizophrenia were recruited through the Bruderholz Early Psychosis Service, Switzerland. Referrals to this outpatient service were through family physicians and other primary care services, school counseling services, psychiatrists, and psychologists in private practice, as well as family members and by self-referrals. All potential subjects were assessed using the Structured Interview for Prodromal Syndromes (SIPS) and the companion Scale of...
Prodromal Symptoms (SOPS). The SOPS covers 19 items divided into 4 subscales: positive, negative, disorganized, and general symptoms. Symptoms are rated on a 7-point scale from 0 = absent to 6 = severe and psychotic for positive symptoms, extreme for all other symptoms. The SIPS interview also contains a schizotypal rating scale and a relative symptoms, extreme for all other symptoms. The SIPS search version of the Global Assessment of Functioning (GAF).36 Individuals who meet at least one of the following criteria are regarded to be at UHR of developing schizophrenia: (1) brief intermittent psychotic syndrome (SOPS score of 6 on one item of the positive symptom subscale for less than 1 wk), (2) attenuated positive prodromal syndrome (SOPS score of 3–5 on one item of the positive symptom subscale at least once per week over the past month; symptoms having begun or worsened in the last year), and (3) genetic risk and deterioration syndrome (family history of any psychotic disorder in first-degree relatives and/or schizotypal personality disorder in the identified patient and a drop in the GAF score during the last year). All the 17 patients met the UHR criterion of subsyndromal positive symptoms, scoring 3–5 on the positive symptom scale containing unusual thought content (n = 7), suspicion/paranoia (n = 3), grandiosity (n = 1), perceptual anomalies (n = 8), and disorganized communication (n = 1). Two (1 female and 1 male) UHR patients additionally had an identifiable family history of schizophrenia and were excluded from the UHR group. Thus, the UHR and SZ-relative groups were sufficiently distinguishable with respect to (1) positive prodromal syndrome (present in UHR subjects but not in SZ-relatives) and (2) identifiable hereditary (and hence genetic) risk (present in SZ-relatives but not UHR subjects) in a complementary manner.

**Healthy Control Subjects**

Control subjects were recruited through hospital staff and in schools by advertisement and verbal inquiries. Because the SZ-relatives and UHR patients differed substantially in age, 2 separate groups of age-matched healthy control subjects were recruited for the purpose of comparison (see table 1). The mean ± SD age of the healthy control group for the SZ-relative group (n = 33) was 49.4 ± 12.9 years (range = 19–65 y), whereas that of the healthy control group for the UHR patients (n = 17) was 19.1 ± 4.4 years (range = 16–33 y). In addition, gender ratio, education levels, and nicotine consumption were closely matched. The demographic and clinical data of all 4 groups of subjects are detailed in table 1.

All potential control subjects were screened for axis I disorders by the DIA-X questionnaire.32 Control subjects who were matched to the SZ-relatives were additionally asked to complete the SPQ. The SPQ total scores did not differ significantly between groups (t = 0.69, df = 55, not significant [ns]). Subjects with a personal history of a DSM-IV axis I disorder and/or a family history of schizophrenia-spectrum disorders were excluded. Additional exclusion criteria applied to all groups (patients and control subjects) were traumatic brain injury, substance abuse (except nicotine), epilepsy, or other neurological disorder and serious medical conditions that might be suspected to affect information processing or cognitive function.

**The LIRR Test**

The procedure for the demonstration and assessment of the LIRR effect has been fully described before.29,37 It was implemented here using a personal computer running a C++ program. The paradigm was based on a computerized visual target detecting task in which the subjects were instructed to press the space bar of the computer keyboard as soon as the target stimulus (the letter X) appeared on the screen. In addition to the target stimulus, 10 other capital Latin letters were used as non target stimuli: the 5 vowels (A, E, I, O, and U) and a set of 5 consonants (B, D, T, Y, and Z). All stimuli were presented in yellow against a blue background in the center of the screen, one at a time, at a 1-second rate with no interstimulus interval. There were a total of 450 stimulus presentations, from which 75 were targets and the remaining 375 nontargets, with a test session therefore lasting 450 seconds (7.5 min).

The test comprised 15 blocks of stimulus presentation, with successive blocks varying among 3 possible types of test condition: random (R), preexposed (PE), and nonpreexposed (NPE). The blocks were arranged in a predetermined sequence with the restriction that no 2 consecutive blocks belonged to the same condition. Each condition was presented 5 times (ie, 5 blocks) in total.
Regardless of test condition, each block contained a sequence of 30 stimulus presentations: 5 targets (X), 5 potentially predictive nontarget letters by virtue of the fact that they immediately preceded the target, and 20 nonpredictive filler letters taken from the consonants set (B, D, T, Y, and Z). The filler letters (between 1 and 8 in succession, randomized in sequence) served to “fill” the intervals between consecutive predictor-target pairs.

The critical difference between the conditions R, PE, and NPE was the predictability of the target by the pretarget letter. In the R blocks, the 5 pretarget letters varied randomly among the 5 PE letters (ie, B, D, T, Y, and Z), each serving only once as the pretarget letter and hence giving no prediction as to whether the next stimulus would be the target or not (ie, zero contingency). In PE blocks, the pretarget letters also consisted of the consonants (ie, B, D, T, Y, or Z), with the difference to the R blocks that the same consonant was used throughout a block and each of the 5 consonants was used as pretarget letter in one particular PE block. Given that the set of consonants acted as filler letters in all blocks and occasionally as pretarget letters in PE blocks, they were effectively preexposed throughout the test and perceived as poor target-predictor letters. The NPE blocks were essentially configured in the same manner as the PE blocks, except that the pretarget letters were taken from the set of vowels (A, E, I, O, U) each serving as target predictor in one particular NPE block. The vowels were therefore reliable target-predictor letters.

The reaction time (RT) of target detection, defined as the time measured between the target onset and key press, was taken as the key dependent variable (accurate to 1 ms) as a function of test conditions (R vs PE vs NPE). Low RT was expected to reflect good predictability of the target, and the RT was therefore expected to be the lowest in NPE and the highest in R, with the RTs obtained in PE being intermediate. Significantly higher RTs in PE relative to NPE reflect the LIr effect.

In addition to the RTs, the numbers of target misses and false alarms were recorded and separately analyzed.

For the analysis of the LIr effect, only the last 3 target RTs (ie, third, fourth, and fifth) within each block were taken into account on the assumption that the first 2 predictor-target pairings generated an association enabling anticipations of the subsequent target presentations.

Data Analysis

The expression of LIr in the UHR patients and the SZ-relatives was separately examined in comparison with their respective control groups. Preliminary analyses confirmed that the expression of LIr differed significantly between the 2 healthy control groups, and thus, separate analyses were necessary for the effective assessment of LIr in the 2 patient groups.

To better conform to the distributional and homoscedasticity assumptions of parametric analysis of variance (ANOVA), the average RT (in milliseconds) per block calculated for each subject was first subjected to natural logarithmic transformation before being submitted to a 2 \( \times \) 3 \( \times \) 5 (group \( \times \) condition \( \times \) block) split-plot ANOVA. Subsequent significant effects were further examined by pairwise comparisons or restricted ANOVAs whenever appropriate to assist interpretation. The number of target misses and false alarms were analyzed separately by a 2 \( \times \) 3 (group \( \times \) condition) ANOVA.

All statistical analyses were performed using SPSS 15 statistical software. A type 1 error rate of 0.05 or below was accepted as showing statistical significance. The precise \( P \) value as well as the associated effect size as indexed by partial eta-squared (\( \eta^2_p = SS_{\text{treatment}}/(SS_{\text{treatment}} + SS_{\text{error}}) \) of significant effects were reported.

Results

Response Characteristics

SZ-Relatives. Analysis of the number of target misses failed to reveal any significant difference between groups (\( F_{1,54} = 0.09, \text{ns} \)) or across test conditions (\( F_{2,108} = 0.8, \text{ns} \)). The interaction between groups and conditions was also not significant (\( F_{2,108} = 0.39, \text{ns} \)). Similarly, no difference between groups was detected in terms of the number of false alarms (\( F_{1,54} = 0.05, \text{ns} \)), which however did vary across test conditions (\( F_{2,108} = 7.08, P < .005, \eta^2_p = 0.116 \)). This was attributed to a lower false alarm rate in PE (0.46 \( \pm \) 0.09 SEM) compared with R (0.89 \( \pm \) 0.14 SEM) or NPE (1.11 \( \pm \) 0.16 SEM). Importantly, the group-by-condition interaction was not significant (\( F_{2,108} = 0.11, \text{ns} \)), suggesting that this pattern across conditions did not significantly differ between SZ relatives and control subjects.

UHR Patients. The response analysis again failed to reveal any difference between groups (\( F_{1,30} = 1.4, \text{ns} \)), across conditions (\( F_{2,60} = 0.04, \text{ns} \)), or a group-by-condition interaction (\( F_{2,60} = 3.05, \text{ns} \)). A similar pattern of null effects was also obtained in terms of false alarms (group: \( F_{1,30} = 3.9, \text{ns} \); condition: \( F_{2,60} = 1.85, \text{ns} \); group-by-condition interaction: \( F_{2,60} = 1.4, \text{ns} \)). It is concluded that response accuracy was essentially unaffected in the UHR patient group in comparison with its matched control group.

Learned Irrelevance

SZ-Relatives. As expected, the RTs in R were the highest, while NPE yielded the lowest average RTs with PE condition inbetween these 2 extremes. This pattern was observed in both the SZ-relatives and the corresponding control group (see figure 1). However, there was clear evidence that this overall pattern progressively emerged over the course of the 5 blocks of the test, especially with respect to the difference between PE and NPE and especially in the SZ-relatives. In comparison, RTs in R were stably high across blocks. These impressions
were confirmed by a split-plot ANOVA of RT, which yielded a main effect of condition \( (F_{2,108} = 31.8, P < .000001, \eta^2_p = 0.37) \) and a significant condition-by-block interaction \( (F_{8,432} = 3.6, P < .0005, \eta^2_p = 0.06) \). The analysis also did not reveal any significant effect involving group. Pairwise comparisons suggested that overall performance in R significantly differed from NPE \( (P < .0005) \) and PE \( (P < .05) \). Although pairwise comparison between the latter 2 conditions did not yield a significant difference \( (P = .2) \) when performance was collapsed across blocks and groups, the presence of the condition-by-block interaction might indicate also that the expression of LIrr as defined by attenuated performance in the PE condition relative to the NPE condition was dependent on testing blocks. This was evaluated by an additional 3-way ANOVA restricted to the PE and NPE conditions, which provided statistical support to the interpretations that the block-dependent profile of LIrr expression did not differ between groups.

**UHR Patients.** Performance across the 3 conditions again conformed to the expected direction: The highest RTs were observed in R, followed by PE and then NPE. Such a trend was seen in both UHR patients and their matched control subjects (see figure 2). The main effect of condition was highly significant with a similar effect size as in the SZ-relatives \( (F_{2,60} = 13.3, P < .00005, \eta^2_p = 0.31) \). Again, a block-dependent difference among the 3 conditions was evident, which was more pronounced in the control subjects and differed somewhat from the UHR patients. This resulted in the emergence of a group \( \times \) condition \( \times \) block interaction \( (F_{8,240} = 2.3, P < .05, \eta^2_p = 0.07) \). Examination of figure 2 readily suggests that while LIrr was distinctly expressed in block 4 in the healthy control subjects, it was clearly absent in the UHR patients.

Restricted ANOVAs confined to each block revealed a significant group-by-condition interaction only at block 4 \( (F_{2,60} = 4.77, P < .05, \eta^2_p = 0.14) \) but not at any other block. This stemmed primarily from the UHR patients' increase in RT in NPE relative to control subjects \( (P < .05) \). Indeed, the overall ANOVA also yielded a significant effect of group \( (F_{1,30} = 7.01, P < .05, \eta^2_p = 0.19) \), although the group-by-condition interaction failed to attain statistical significance \( (F_{2,60} = 1.71, \text{ns}) \).

The source of the significant group \( \times \) condition \( \times \) block interaction was further examined from 2 a priori perspectives using restricted ANOVAs. On the one hand, learning as such was examined by focusing on the contrast between R and NPE, and on the other, LIrr was investigated by contrasting PE and NPE. The restricted ANOVAs revealed a significant and a close to significant, respectively, 3-way interaction \( \text{PE vs NPE: } F_{4,120} = 3.07, P < .05, \eta^2_p = 0.09; \text{ R vs NPE: } F_{4,120} = 2.34, P = .058, \eta^2_p = 0.07) \), which provides statistical support to the interpretations that the expression of associative learning and LIrr across blocks was impaired in the UHR patients.

**Discussion**

The present study represents the first attempt to examine the expression of LIrr in asymptomatic first-degree
relatives of schizophrenia patients, evaluating its status as a potential endophenotype of information processing deficits in schizophrenia. The parallel study measuring LIrr in UHR patients, who were identified by the overt presence of attenuated positive symptoms, has further enabled us to evaluate if performance deficiency in the present LIrr test might be considered as a state marker of psychosis. The outcome in the SZ-relatives suggests that LIrr was intact in asymptomatic subjects bearing genetic risk to schizophrenia. Although the overall magnitude of LIrr appeared limited, closer examination of the final 3 blocks of the test revealed clear LIrr expression in both SZ-relatives and their matched control subjects (see figure 1) when RTs in PE condition became longer than the NPE condition—satisfying the operational definition of LIrr. Hence, it is unlikely that the failure to detect a deficit in LIrr in SZ-relatives could be solely attributed to the overall weakness of the LIrr effect when the 5 blocks of tests were considered altogether. This outcome contradicts the hypothesis that deficiency in learned inattention as assessed by LIrr and related translational paradigms, such as LI, constitutes a test of an endophenotype of schizophrenia. On the other hand, the study involving the UHR patients provided suggestion of an LIrr deficiency, although this deficit appears to depend critically on blocks (see figure 2). This block dependency suggests that the present test design is prone to the effect of training. As evidenced already in the SZ-relatives, associative learning (as indicated by the shorter RT in the NPE relative to R) was susceptible to a training effect. This may not be attributed to procedural or perceptual training as no such tendency was observed in the R condition. One possibility is that generalization from one NPE target predictor to another might be expected on the basis that they all belonged to the category of vowels. Because the assessment of LIrr depends on the level of learning exhibited in NPE, it comes as little surprise therefore that the LIrr effect also exhibited sensitivity to a training (block) effect. LIrr was absent in both UHR patients and their control subjects in the first block and emerged progressively especially in the control subjects (figure 2). It was against this background that the UHR patients showed a different profile than the control subjects, as indicated by the emergence of a 3-way (group × condition × block) interaction in the absence of a group-by-condition interaction. As it turned out, the most pronounced evidence for a disruption of LIrr in UHR patients was restricted to the fourth block, with a similar but weaker tendency in the second block. We have no explanation as to why the fourth block appeared to be more sensitive to this effect, but it is interesting to note that the UHR patients' performance in PE in this particular block also showed a tendency of shorter RT. This adds to the possibility that this might be linked to some deficiency in inattention to the preexposed stimulus. Nonetheless, it is clear that the contribution of the resulting attenuation of LIrr in the UHR patients was largely accounted for by a deficiency in associative learning (as indexed by a relatively small performance difference between NPE and R). This outcome is not dissimilar to that obtained in first-episode schizophrenia patients and also to that reported by Martins et al in both schizotypal as well as nonschizotypal first-degree relatives of schizophrenia patients. Hence, while the null finding in the SZ-relatives...
here is more directly at variance with the results reported by Martins et al, the present finding of LIrr disruption in UHR patients is still in keeping with their results obtained in schizotypal relatives. Similar to report of Martins et al, the attenuation of LIrr in the UHR patients was severely confounded by a deficit in associative learning as such.

To date, the only studies in LI and LIrr in first-degree relatives are by Martins et al and this present study. However, other techniques sensitive to deficient information processing have been applied, such as prepulse inhibition (PPI) of the acoustic startle reflex and auditory P50-evoked potential. Both PPI and P50 (similar to LI) have been shown to be impaired in healthy first-degree relatives, indicating that deficits in preattentive information processing might serve as an endophenotype of schizophrenia.

In order to be an endophenotype, these deficits must be present along the entire schizophrenia continuum. Indeed, modest impairments in P50 in subjects at risk without an affected family member and profound deficits in at-risk subjects with an affected first-degree relative have consistently been found. Furthermore, a significant PPI deficit has been found in prodromal subjects. In contrast, LIr deficit does not appear to represent a schizophrenia endophenotype but rather a state marker for psychotic symptoms.

In this respect, uniquely state-dependent or symptom-driven translational markers are also valuable. These allow the correlation with pathophysiological mechanisms directly underlying symptom production, and when applied to selective breeding or genetic engineered animals, the identification of inheritable genetic variations that are truly not state-dependent. But a question that arises is what is it that distinguishes LIrr from other related translational paradigms, including LI, PPI, and P50, which seem to be trait sensitive? Although PPI and P50 are more related to early preattentive sensory gating mechanisms, LI is more closely related to LIrr. Indeed, Hall and colleagues assert that LIrr is not dissimilar to LI in the sense that the resulting weaker learning was attributable to reduced salience to the predictive stimulus (conditioned stimulus; CS). The observation that LIrr is typically stronger than LI, and even the sum of LI and the unconditioned stimulus (US)-preexposure effect, was explained by the fact that such stimulus preexposure effects (especially LI) are heavily dependent on contextual consistency. Given that LIrr is conducted with the predicted stimulus (US) being present in both the preexposure and the conditioning stage, this facilitates or promotes the LI effect. Theoretically, Hall’s theoretical account of LIrr is therefore essentially not different from his explanation of LI. In contrast, Mackintosh and colleagues suggest that LIrr involves unique psychological processes that are distinct from and operate in addition to the modulation of attention by preexposed CS and preexposed US alone. Mackintosh and colleagues postulate that the animals learn during the noncorrelative (random) CS/US preexposure the lack of predictive relationship between this particular pair of stimuli, and this as such is responsible at least in part for the measured LIrr effect (in the form of retarded learning). In this sense, the mere sum of the CS preexposure alone and US preexposure is insufficient to capture this element of learning about the specific lack of CS-US relationship. Given that we failed to obtain evidence in support of impaired LIrr in SZ-relatives, who are expected to exhibit LI impairment, is an inconsistency readily accommodated by Mackintosh’s theory but poses some surprise to Hall’s position. The latter should predict that SZ-relatives are similarly affected in LI and LIrr because their emergence essentially involves similar psychological processes. If dysfunction of these processes is responsible for the LI deficit, then a similar outcome ought to be present also when they were evaluated using the LIrr paradigm. Hence, intact LIrr demonstrated in SZ-relatives would appear to support the interpretation by Mackintosh and colleagues. The LIrr paradigm employed might likely capture the particular form of perceptual learning that retards learning of a specific predictor-target association and therefore remained insensitive to SZ-relatives. This hypothesis would need to be directly tested in SZ-relatives by obtaining current indices of LI and LIrr in the same subjects. In addition, novel test paradigms of LIrr would be instrumental for testing if the present LIrr test design might be associated with unique features.

Future studies would profit from the inclusion of the matching schizophrenia patients akin to the SZ-relatives, thereby extending the power of interpretation. Ideally, the recruitment of discordant monozygotic twins would offer a perfect setup to extend the investigation of schizophrenia endophenotypes. Although the findings of LIrr and associative learning impairment in UHR patients are of obvious interest, a follow-up study allowing the distinction between UHR patients that would eventually develop full-blown psychosis or remained symptomatically stable would be tremendously useful. One would then be able to compare if they could be similarly distinguished on the basis of the present dataset. In conclusion, the present study raises critical questions as to whether LI and LIrr are equivalent in terms of their relevance to schizophrenia endophenotypes and suggests the interesting possibility that LIrr deficits may represent a state-dependent marker. Support of this possibility is also derived from a study in healthy subjects showing that LIrr was only disrupted in subjects with high levels of schizotypy, who showed normal LI after the same number of preexposures, while both LIrr and LI were intact in subjects with low schizotypy scores. Taken together, the relative trait and state sensitivities of acquired inattention as...
exemplified by the LIrr and LI paradigms remain to be further evaluated.

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