PATTERN SEPARATION IN CHILDREN AND ADOLESCENTS AT RISK FOR SCHIZOPHRENIA

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ABSTRACT

Aslıhan İmamoğlu: Pattern Separation in Children and Adolescents at Risk for Schizophrenia (Under the direction of Kelly S. Giovanello)

Episodic memory relies critically on the ability to recognize and subsequently organize perceptually similar inputs into distinct, non-overlapping representations, a process termed pattern separation. Prior research has shown that pattern separation arises from the dentate gyrus (DG), a subregion of the hippocampal formation. DG is structurally altered in individuals with schizophrenia who also show related impairments in episodic memory and pattern separation. The current study examined the status of behavioral pattern separation (i.e., mnemonic discrimination) in children and adolescents at high or low familial risk for schizophrenia by utilizing the Mnemonic Similarity Task (MST). High-risk participants demonstrated worse mnemonic discrimination and recognition memory than low-risk (i.e., control) participants. Perceptual discrimination was comparable across both groups. Neither perceptual discrimination nor recognition memory mediated the relationship between risk group and mnemonic discrimination. These results suggest that behavioral pattern separation deficits observed in schizophrenia patients are also present in their high-risk, first-degree relatives.
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<td>CA 1-3</td>
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Introduction

Episodic memory, conceptualized as memory for objects and events that are tied to a specific space and time, is fundamental to adaptive day-to-day functioning (Tulving, 1972). Episodic memory relies critically on the ability to recognize and subsequently organize perceptually similar inputs into distinct, non-overlapping representations (pattern separation), as well as the ability to retrieve a pre-existing representation from a partial and/or degraded cue (pattern completion) (Bakker et al., 2008). The episodic memory system engages in hippocampal pattern separation when an input is similar but not identical to previously learned information and pattern completes when an input is identical to previously learned stimuli and should be recognized or coded as one single representation (Tamminga et al., 2010). For instance, recalling two distinct memories/items that are not perceptually similar (e.g., an oak-wood table vs. a brick) may not require individuals to engage in pattern separation, while pattern separation is crucial in attempting to discern where your vehicle is parked in a garage you use daily due to the level of interference from previously learned parking spots (Yassa & Stark, 2011).

Theoretical models of the function of hippocampal subfields by Rolls and colleagues have postulated that the ability to pattern separate relies critically on the dentate gyrus (DG) subregion of the hippocampal formation (Rolls, 1996; Rolls, 2013; Rolls & Treves, 1994; Treves & Rolls, 1992). The hippocampal formation refers to a collection of medial temporal lobe regions, such as the DG, Cornu Ammonis 1-4 (CA 1-4), and the subiculum (see Figure 1) and functions in conjunction with other medial temporal lobe regions such as the Entorhinal Cortex (EC) to encode and retrieve durable memories (see Figure 2). Although many regions of the
hippocampal formation have been studied in relation to pattern separation, the most prominent theories postulate that mossy fiber projections (originating from DG to CA3) constitute the primary route that establishes new representations of patterns and promotes learning of novel objects by reducing interference in CA3 (Rolls, 1996; Rolls, 2013; Rolls & Treves, 1994; Treves & Rolls, 1992). It has been further suggested that CA3 may be involved in both pattern separation and completion depending on the magnitude of similarity in sensory input (Leal & Yassa, 2018), while pattern completion has been tied to other regions in the medial temporal lobes, namely the EC and CA1. Finally, Rolls and colleagues have postulated that direct perforant path connections from EC to CA3 (i.e., bypassing DG) provide a means for recall during retrieval and subsequently mediate pattern completion (Rolls, 2007; Treves & Rolls, 1992).

Over the past two decades, research conducted in rodents and humans has provided support for this theory of hippocampal function by demonstrating the importance of DG and CA3 in mediating pattern separation. For instance, inactivating mossy fiber synapses that extend from DG to CA3 impairs mice’s ability to learn novel spatial information, while their recall ability remains intact (Lassalle et al., 2000). Likewise, electrophysiological recordings of CA3 and CA1 neurons in rodents exploring rooms of varying similarity have demonstrated that CA3 neurons are more active when rodents encounter rooms with small environmental changes, requiring pattern separation, while CA1 neurons are active irrespective of the change in the environment (Leutgeb et al., 2004). Another study demonstrated that rodents with DG lesions but intact perforant pathway (i.e., input from EC into CA3) are deficient in learning new information (i.e., encoding), while rodents with the opposite lesion placement display deficits in retrieval (Lee & Kesner, 2004). Collectively, these results highlight the importance of mossy fiber input
from DG to CA3 in establishing new patterns, while implicating CA1 and the direct perforant pathway input from EC to CA3 in completing patterns.

Furthermore, there is growing evidence from human studies utilizing structural MRI that CA3 and DG are tied to pattern separation. For instance, Doxey and Kirwan (2015) recruited young and older adults, acquired structural MR images, and behaviorally tested the participants using the Mnemonic Similarity Task (MST), which examines the behavioral correlate of pattern separation (i.e., mnemonic discrimination). The MST included an incidental encoding (i.e., unintentional) task asking participants to make indoor vs. outdoor judgements about images of everyday objects. While these judgements were not of interest, engaging in this decision-making process allowed participants to encode study stimuli (i.e., incidental encoding) without the intention to remember. Next, participants completed a recognition task, during which they were shown either exact repetitions of images presented during the incidental encoding task (i.e., targets), images that were perceptually similar, but not identical to target images (i.e., lures), or entirely novel images (i.e., foils). Participants were asked to make old, similar, and new judgements about these images of objects. Successful performance on the MST relied critically on participants’ ability to respond to lure items that were perceptually similar to the objects shown during the incidental encoding phase. Thus, individuals with intact pattern separation/mnemonic discrimination should be able to encode distinct mnemonic representations of lure objects during study and subsequently recognize lure objects as “similar”, instead of studied. Employing this task, Doxey and Kirwan (2015) found that CA3/DG volume was a significant predictor of performance on the MST, such that lower CA3/DG volume was positively correlated with lower performance on the MST irrespective of age.

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1 Researchers traced CA3/DG as one region rather than two distinct regions due to technological limitations.
Functional neuroimaging studies have also provided valuable insight into the functioning of DG, CA3, CA1, and EC in relation to the processes of pattern separation and pattern completion. One of the earliest studies investigating the neural underpinnings of pattern separation/completion employed high-resolution functional magnetic resonance imaging (fMRI) to measure brain activity during a modified version of the MST incidental encoding phase (Bakker et al., 2008). To this end, participants simply viewed either target, lure, or foil objects to which they were asked to provide indoor vs. outdoor judgements. Bakker et al. (2008) found that neural activity consistent with a strong bias towards pattern separation was exclusively observed in the DG/CA3 region, while activity consistent with a bias towards pattern completion was observed in CA1, the subiculum, and the entorhinal and parahippocampal cortices. More specifically, CA3/DG activity was significantly higher when individuals were viewing similar lures in comparison to repeated images of targets, providing evidence for pattern separation. In comparison, there was not a significant difference between neural activity to lure vs. target images during their first presentation. Findings of Bakker et al. (2008) implicated DG/CA3 in pattern separation further by showing a contrasting case in other regions of the medial temporal lobes, such that activity in response to the presentation of a lure was significantly different than the activity in response to a first presentation, and not significantly different from the repeat presentation.

Extending the findings of Bakker et al. (2008), Lacy et al., (2011) varied the degree of lure similarity to examine the extent to which neural activity in CA1 and CA3/DG fluctuated. They employed lures with four degrees of similarity to the target items, which were then separated into “high” and “low” similarity categories. For high similarity lures, they found activity in the CA3/DG to be significantly higher than the activity in CA1 while there was no
regional difference in activity for low similarity lures or the first presentations. This finding further suggests that CA3/DG are differentially implicated in pattern separation, while CA1 has a broader function related to pattern completion. These findings have also been observed outside the context of participants viewing everyday images of objects. For instance, Kyle et al., (2015) studied pattern separation of similar spatial environments in relation to neural activity in the CA3/DG region. They employed fMRI to study neural activity in individuals viewing four cities, two of which were nearly identical to one another. They found that the neural patterns in the left CA3/DG were uncorrelated for each city, supporting the notion that these regions play a key role in establishing novel representations for stimuli with overlapping contexts (Kyle et al., 2015).

However, a major technical shortcoming of the aforementioned studies is that they were unable to distinguish between CA3 and DG regions of the hippocampal formation.

More recently, Berron et al., (2016) was able distinguish between the DG and CA3 subregions by employing 7T fMRI with a higher functional resolution. Unlike the studies described above, they used two computer generated images that showed similar versions of the same living room. These images were presented in sequences consisting of three to five stimulus presentations and the participants were tasked with identifying the third occurrence of the first stimulus, which tasked them with distinguishing between two perceptually similar stimuli. Berron and colleagues (2016) found that DG showed detectably distinct neural representations for similar stimuli, while no such pattern was observed in other hippocampal subfields. This prominent finding not only extends on previous research highlighting the importance of DG in performing pattern separation, but also isolates DG from CA3, further supporting the notion that it is the neuronal connections extending from the DG to CA3 that is responsible for mediating pattern separation.
The hippocampal formation is compromised both structurally and functionally in individuals with schizophrenia (Shenton et al., 2001), who also report widespread episodic memory impairments (Aleman et al., 1999; Danion et al., 1999; Gold et al., 1992; Keefe et al., 2002). Indeed, reduced hippocampal size is the most prominent (i.e., demonstrating the largest effect size) and widely reported structural finding in patients with schizophrenia, which has been documented by meta-analyses (McCarley et al., 1999; Shenton et al., 2001) and multi-site studies with several varying imaging protocols (Okada et al., 2016; van Erp et al., 2016). Shenton et al., (2001) conducted one of the most comprehensive meta-analyses of this literature, compiling 193 MRI studies looking at structural changes in patients with schizophrenia. The vast majority of these MRI studies (i.e., 74%) reported significant volumetric change in the hippocampus, such that hippocampal volume was smaller in patients with schizophrenia than in controls (Shenton et al., 2001). This consensus regarding the hippocampal volume reductions has also been replicated by other meta-analyses (McCarley et al., 1999; Nelson et al., 1998) and replicates in both first-episode and chronic patients (Shenton et al., 2001). Notably, these structural changes have also been tied to behavioral changes observed in patients with schizophrenia (Antoniades et al., 2018; Nestor et al., 2007), with a substantive amount of evidence implying that these structural changes result in impairments in episodic memory (Antoniades et al., 2018; Exner et al., 2008; Nestor et al., 2007).

Since establishing a clear connection between hippocampal reductions and schizophrenia, a growing body of research has focused on different subregions of the hippocampal formation to examine the extent to which each structure contributed to these overall size reductions. Mathew et al., (2014) demonstrated significant reductions of mean volume in CA1, CA2/3, CA4/DG, presubiculum, and subiculum regions with the most prominent reductions being observed in
CA2/3, subiculum, and CA4/DG. However, this study was unable to distinguish CA2 from CA3 and CA4 from DG and treated these pairs of regions as one, which obscures any interpretations that can be drawn from their findings. Another study partially clarified these findings by demonstrating lower volume in CA1 in patients with schizophrenia (Ota et al., 2017). Nakahara and colleagues (2018) who reviewed the aforementioned studies, as well as 11 other relevant structural imaging publications concluded that CA1, CA2/CA3, DG/C4, and the subiculum were consistently compromised in patients with schizophrenia though they shared similar limitations in being unable to distinguish different regions of the hippocampal formation. Most recently, this was limitation was addressed by Nakahara et al., (2020), who reported that patients with schizophrenia have significantly smaller DG and CA4 than controls, after controlling for mean hippocampal volume, with the DG showing the largest between group difference.

Findings implicating DG in schizophrenia are not limited to neuroimaging studies. Post-mortem studies examining DG in patients with schizophrenia have demonstrated reduced neural stem cell proliferation in patients with schizophrenia, such that their brains had reduced amounts of Ki-67, a marker of cellular proliferation responsible for cell growth, in the DG (Reif et al., 2006). Another study replicated these findings by demonstrating a 60% reduction in Ki-67 in schizophrenia patients compared to controls, further supporting the notion that cell growth is inhibited to a degree in DG (Allen et al., 2016), which can potentially provide insight into volume reductions consistently seen in the DG. Most recently, schizophrenia-associated mutations in a synapse scaffolding protein called SAP97 have been shown to inhibit dentate gyrus functioning and, consequently, impair episodic memory in rodents (Kay et al., 2022). Collectively, these findings demonstrate that patients with schizophrenia have reduced (1) hippocampal volume, (2) DG volume, and (3) neural stem cell proliferation in the DG.
Although the connection between hippocampal reductions and the status of schizophrenia diagnosis has been well-established, models attempting to explain the connection between these impairments and the schizophrenia pathology are relatively novel. Most notably, Tamminga et al., (2010) proposed that patients with schizophrenia exhibit reduced DG neurogenesis and/or signaling onto CA3, which can alter the plasticity of CA3, sensitizing CA3 to input from EC (see Figure 3). As discussed above, the input from EC into CA3 is relatively weaker albeit it is hypothesized to mediate pattern completion, while the stronger input from DG drives pattern separation. If CA3 receives less input from DG, it would lead to increased sensitivity to EC input, which would advantage the formation of inaccurate associations between items, events, and/or contexts. These inaccurate associations would lead to increased false or illogical memories and create a susceptibility to psychosis (Tamminga et al., 2010), which is a hallmark symptom of schizophrenia (Docherty et al., 1978).

Consistently with this model, post-mortem studies investigating CA3 and CA1 regions of the hippocampal formation found that patients have increased concentrations of NMDA (GluN2B-containing) receptors, responsible for short- and long-term potentiation, in CA3 in comparison to controls, which is consistent with the notion that patients with schizophrenia may have increased excitatory signaling in CA3 (Li et al., 2015). Finally, a recent study examining the relationship between mnemonic discrimination performance and hippocampal subfield activation reported that lower DG volume and higher CA3 activation were associated with worse mnemonic discrimination, further supporting this theory (Riphagen et al., 2020).

These structural and cellular changes are not independent of behavioral implications for schizophrenia patients. To date, a small body of research has investigated the behavioral manifestations of these specific impairments in the DG and CA3 by employing the MST. Das et
al., (2014) investigated mnemonic discrimination (i.e., a behavioral correlate of pattern separation) performance in volunteers with schizophrenia and controls. They found that patients with schizophrenia performed worse on the MST, which was mostly driven by their selective inability in correctly identifying lure items as “Similar” rather than old/target. In comparison, schizophrenia patients’ ability to correctly identify old and novel items was comparable to that of control participants’, showing that patients with schizophrenia had intact recognition performance for items that did not require intact mnemonic discrimination.

Another study by Kraguljac et al., (2021) attempted to replicate these findings in first-episode patients with schizophrenia and the schizoaffective disorder (i.e., psychosis group), as well as control participants. They observed that the psychosis group did worse on mnemonic discrimination relative to healthy controls, with patients giving fewer similar responses to lures than controls. They also observed significant differences in recognition memory, with the psychosis group demonstrating worse overall recognition relative to healthy controls. These findings in first-episode patients highlight the possibility that mnemonic discrimination deficits seen in patients may not be independent of recognition deficits. Most notably, this study indicates that schizophrenia-related pattern separation impairments are not merely a result of disease progression. Though, it is crucial to note that Kraguljac et al. (2021) did not assess participants’ visual discrimination ability, which limits the number of conclusions that can be drawn from their results.

To address the shortcomings of the previous studies, Martinelli & Shergill (2015) examined the same relationship between schizophrenia diagnosis and MST performance with the addition of a visual discrimination task. The visual discrimination task was included to determine the extent to which participants’ ability to discriminate between visually similar objects, or the
lack thereof, contributed to their mnemonic discrimination performance (Martinelli & Shergill, 2015). The visual discrimination task assessed the degree to which participants were able to recognize two visually similar objects as distinct, rather than same. Their findings partially replicated that of Das et al. (2014) by showing that patients with schizophrenia exhibited impaired pattern separation in comparison to healthy controls. However, patients also exhibited worse recognition performance than controls. Notably, the relationship between diagnosis and mnemonic discrimination was fully explained by schizophrenia patients’ poor visual discrimination performance and overall impaired recognition performance, suggesting that pattern separation deficits seen in patients is a byproduct of recognition and visual discrimination impairments. This conclusion stands in contrast to previous research demonstrating that schizophrenia patients have intact recognition performance (Mathews & Barch, 2004). In sum, the findings from these three studies are conflicting regarding the extent and nature of pattern separation deficits in people with schizophrenia.

The collection of neuroimaging, molecular, and behavioral findings discussed above demonstrate structural and molecular changes to regions of the hippocampus, as well as behavioral pattern separation deficits in people with schizophrenia. With such changes being observed in first-episode patients, researchers have hypothesized a developmental theory about the nature of these changes. Specifically, it has been postulated that these changes may occur prior to disease onset, thereby creating an underlying vulnerability, which then triggers the clinical symptoms of schizophrenia in conjunction with environmental triggers (see Neurodevelopmental hypothesis; Owen et al., 2011). However, the possibility that these structural and behavioral changes are consequences of the disease process remains plausible
(Copolov, & Crook, 2000). To better address these possibilities, investigators have begun to study asymptomatic relatives of individuals with schizophrenia.

Relatives of patients are in a unique position since they have a genetic predisposition to develop the illness themselves. Specifically, the risk of developing schizophrenia for all first-degree relatives is 18.5 times higher than non-relatives (Gottesman et al., 1987), while the risk for adolescent first-degree relatives varies between 10-16% (Keshavan et al., 2002). A growing body of research examining structural changes in first-degree relatives has demonstrated volumetric changes in the hippocampus in both adult (Francis et al., 2013) and adolescent (for a review, see Ganzola et al., 2014) first-degree relatives of schizophrenia patients. Consistently, changes to episodic memory have also been documented in both adult (Kremen et al., 1998; Toomey et al., 1998; Touloukian et al., 2003) and adolescent (İmamoğlu et al., 2022) relatives, with the largest impairments being documented in recall performance. A portion of these studies also examined the relationship between structural and behavioral changes, demonstrating that lower hippocampal volume is significantly correlated with worse immediate recall in adult first degree relatives (Francis et al., 2013).

Although the merit in studying adult relatives is indisputable, studying adolescent relatives offers a unique opportunity to track the developmental trajectory of schizophrenia-related structural and behavioral changes, as these individuals do not exhibit the clinical symptoms of the disorder yet. These adolescent relatives are therefore referred to as “high-risk” since they are below the typical age of onset for schizophrenia. In the present study, I examined the behavioral correlates of hippocampally-mediated pattern separation by assessing mnemonic discrimination in children and adolescents with (i.e., high-risk) or without (i.e., low-risk) genetic risk for schizophrenia. Specifically, I administered the MST, which is the most frequently used
behavioral task to assess pattern separation, to investigate the extent to which high-risk participants are impaired on mnemonic discrimination. I also assessed each participant’s ability to visually discriminate between objects that are perceptually similar by employing a perceptual discrimination task, which was used to control for the effect of perceptual discrimination on mnemonic discrimination. I hypothesized that participants in the high-risk group would exhibit worse mnemonic discrimination than low-risk participants, while both groups would exhibit comparable overall recognition performance. Finally, I hypothesized that both risk groups would demonstrate comparable perceptual discrimination performance.

Methods

All procedures were approved by the Institutional Review Board of the University of North Carolina at Chapel Hill.

Participants

Participants were 37 children and adolescents (16 female) between the ages of 11 and 17 years. A portion of the participants were recruited from a larger study at the University of North Carolina at Chapel Hill (UNC) entitled, ‘Cognition and Neuroimaging in Teens’ (CogNIT). High-risk participants in the CogNIT pool were recruited from the Outreach and Support Intervention Services, the Schizophrenia Treatment and Evaluation Program, public schools, and community clinics, while low-risk (i.e., control) participants were recruited from the community and nearby schools through flyers and listservs. The high-risk group included 17 children and adolescents with a parent or a sibling (i.e., a first degree relative) with a psychotic disorder diagnosis (i.e., schizophrenia, schizoaffective disorder, bipolar disorder) as these disorders share a common, underlying genetic vulnerability to schizophrenia (Bramon & Sham, 2001; Cardno & Owen, 2014). The low-risk (i.e., control) group included 20 participants with no family history
of psychotic mental illnesses and no current clinical diagnoses. Diagnoses were assessed based on a modified version of the Structured Clinical Interview for DSM-IV Axis I disorders (SCID; First et al., 1995). The exclusionary criteria for both groups included having any DSM-IV psychotic or mood disorders, substance abuse disorder, and/or taking any medications that directly alter cardiovascular function. All participants provided Informed Consent (parent) and Informed Assent (children) prior to their participation. Participants were compensated $10 per half hour of compensation. Participants were age-matched across groups and the mean age did not significantly differ for the groups, F(35) = 0.23, p = .87. Self-reported race/ethnicity represented a sample of 25 Caucasian (67.6%), 9 African American (24.3%), 2 Hispanic (5.4%) and 1 Multiracial (2.7%). While each participant completed all parts of the experiment, partial MST data is included for three participants whose data was corrupted by E-prime. These three participants were still included in the analyses since they had at least one completed MST set including 108 test trials.

**Procedure**

My initial plan was to conduct this experiment remotely by employing E-Prime Go. This plan quickly became unfeasible due to the drastic difference in how E-Prime Go performed on participants computers vs. lab computers. Instead, all reported data were collected in person on a lab computer using E-Prime software (Version 3, Psychology Software Tools).

**Task Design**

The current experiment consisted of three tasks: The Mnemonic Similarity Task, the Psychomotor Vigilance Task (PVT), and the Perceptual Discrimination Task (PDT). These tasks were always administered in a fixed order with the MST being administered first, followed by the PVT and the PDT in respective orders. Details of each task are described below.
Mnemonic Similarity Task

The Mnemonic Similarity Task consisted of three distinct experimental sets with each set containing two phases (Yassa et al., 2011; see Figure 4). In the first phase (i.e., study), participants were presented with pictures of everyday objects and asked to make ‘indoor’ vs. ‘outdoor’ judgements. Specifically, participants were presented with 72 colored pictures of everyday objects on a white background one at a time. Participants were asked to make indoor vs. outdoor judgements for each object presented by pressing buttons. Although these judgements were not relevant to the study, making these indoor vs. outdoor judgements allowed participants to engage in incidental encoding. Each image was present for 2 seconds with a 0.5 second interstimulus interval (ISI).

In the second phase (i.e., test), participants were given a surprise recognition memory test in which they were be shown (1) exact repetitions of images presented in the study phase (i.e., targets), (2) new images that have not been shown before (i.e., foils), and (3) images that are perceptually similar, but not identical, to those seen during the study phase (i.e., lures). For each image presented, participants were asked to make “Old”, “Similar”, or “New” judgments via a button press. Like the study phase, participants had 2 seconds to make these judgements with a 0.5 second ISI. Each of the three test phases consisted of 108 object images containing an equal number of targets (i.e., exact repetitions), lures, and foils. Thus, each participant responded to a total number of 316 critical trials, including 108 targets, 108 lures, and 108 foils. The order in which these stimuli appeared was counterbalanced across participants. The task also included three bins of lure items that varied in the degree of similarity from very highly similar (L1) to moderately similar (L2) to somewhat similar (L3). The rank ordering of these lures was obtained using a large, independent population of young adults (Yassa et al., 2010). There were a total
number of 36 trials per lure similarity bin. Each experimental set contained a different set of stimuli, and the order of experimental sets were counterbalanced across participants. Failure to make recognition judgements before the 2 second deadline resulted in 2.7% missing observations. Notably, there was a significant difference in the percentage of missing observations across risk groups, $F(1, 35) = 8.07, p = .03$ adjusted.

**Psychomotor Vigilance Task**

The Psychomotor Vigilance Task (PVT; Dinges & Powell, 1985) was included to account for the effects of sustained attention on task performance on the MST and the PDT. As a brief task of sustained attention based on repeated reaction time trials (Dorrian et al., 2005), the PVT has been shown to be sensitive to the effects of sleep loss, sustained wakefulness, and/or time of the day on behavioral performance. I administered a 5-minute version of the PVT (Roach et al., 2006) that asked participants to press a response key with their dominant hand as quickly as possible after the appearance of a visual stimulus (i.e., a red dot), which was presented at a variable interval of 2-10 seconds. Participants were not penalized for pressing the response key prior to stimulus presentation. Depending on their quickness and the randomness of the stimuli presentation, participants viewed somewhere between 43 and 55 number of trials.

**Perceptual Discrimination Task**

After the completion of the PVT, participants completed three versions of the PDT with each version containing a different set of object images (see Figure 5). These object images were taken from the MST testing phase, such that participants were shown 108 colored images of objects (i.e., 36 same, 36 similar, 36 different) per PDT set. Pairs appeared in random order and there were 90 total pairs (36 same, 36 similar, and 18 different). Participants were asked to indicate whether these pairs are identical to, different from, or similar to each other. Participants
were given infinite time to make these judgements. Therefore, there were no missing observations as all participants were required to provide a response before advancing to future trials. The three versions of the PDT were administered in a counterbalanced order. This task was used to control for the effect of visual discrimination on the MST performance.

**Data Analysis Plan**

The statistical analyses were conducted via SPSS version 26 (IBM Corp.). The level for significance was set at $\alpha = .05$ for all analyses. In line with Stark et al., (2019), I first calculated a lure discrimination index (LDI) to assess task performance on the MST. The LDI was calculated as the difference between the rate of “Similar” responses given to lure images minus the rate of “Similar” responses given to foil images. This index accounts for the extent a participant may be biased towards providing “Similar” responses in general. Subsequently, the LDI scores were used to assess the extent to which high- and low-risk participants were able to distinguish perceptually similar images (lures) from the target images they saw during encoding, which requires successful encoding of the image and its perceptual details. I also calculated a recognition memory parameter by calculating the difference between the rate of “Old” responses to repeat images (i.e., targets) minus the rate of “Old” responses to foil images (i.e., Hits – False Alarms).

To test between-group hypotheses regarding the LDI, the recognition parameter, and the perceptual discrimination scores, I used one-way ANOVAs to compare high- and low-risk participants on these parameters, respectively. To further examine differences in response accuracy to each of the item types, I conducted multiple comparisons comparing the two groups on their response (‘old’, ‘similar’, ‘new’) probabilities to different item types (‘target’, ‘lure’, and ‘foil’). To examine the influence of the similarity bins on response types per-risk group, I
conducted a three-way repeated measure ANOVA with two within-subject factors [Lure Bin (‘L1’, ‘L2’, ‘L3’) and Response Type (‘old’, ‘similar’, ‘new’)] and Risk Group as the between-subject factor. I corrected the p-values for multiple comparisons by utilizing the Benjamini-Hochberg false discover rate (FDR) p < .05 correction (Benjamini & Hochberg, 1995). For mediation analyses, I used the PROCESS macro Version 3.5 (Hayes, 2017), which utilizes Preacher and Hayes’ (2008) bootstrapping methodology. I based my results on 5000 bootstrap samples with bias correction and 95% CIs. The mediation analysis included Risk Group as the independent variable, Lure Discrimination Index as the dependent variable, and both the Recognition Memory and Perceptual Discrimination Accuracy as mediators (see Figure 9).

Results

Lure Discrimination and Recognition Memory Indexes

Based on earlier studies described in the introduction (Das et al., 2014; Kraguljac et al., 2021; Martinelli & Shergill, 2015), I hypothesized that higher risk for schizophrenia would be associated with a lower lure discrimination index. To test this hypothesis, I collapsed all test trials across three MST sets and computed LDI scores for each participant. A one-way ANOVA on LDI scores detected a significant effect of Risk Group on lure discrimination, such that high-risk participants demonstrated lower lure discrimination (M = .26, SD = .18) than low-risk participants (M = .45, SD = .15), t(35) = 3.34, p < .01 (see Figure 6).

Next, I examined group differences in recognition memory. Prior research reported mixed results about recognition deficits in patients with schizophrenia. One study did not find significant group differences in the recognition parameter (Das et al., 2014), while others reported significant group differences with the schizophrenia group showing impaired overall recognition (Martinelli & Shergill, 2015; Kraguljac et al., 2018). Notably, another study looking
at high-risk youth did not observe significant recognition differences between high- and low-risk children (İmamoğlu et al., 2022). Considering this lack of consensus, I hypothesized that high- and low-risk participants would exhibit comparable recognition performance. When comparing recognition memory, I observed significant differences between high-risk ($M = .67, SD = .18$) and low-risk ($M = .77, SD = .11$) participants, with the former demonstrating lower recognition accuracy, $t(35) = 2.07, p < .05$.

Previously, worse lure discrimination in patients with schizophrenia has been further characterized by lower accuracy in identifying lures as similar (Das et al., 2014; Kraguljac et al., 2021; Martinelli & Shergill, 2015). Therefore, I next examined group differences in responding for each stimulus and response types (see Table 1). Further comparisons showed that high-risk participants provided less similar responses to lures, $t(35) = 3.28, p = .02$ adjusted, which is consistent with the lower lure discrimination index observed in this group. No other significant differences were detected, though high-risk participants provided more old responses to lures than low-risk participants before correcting for multiple comparisons, $t(35) = -2.16, p = .04$. However, the significance of this effect disappeared after correcting for multiple comparisons, $p = .09$. Notably, high-risk participants were more likely to fail to make an observation in the allocated time to both lures, $t(35) = -2.81, p = .03$ adjusted, and targets, $t(35) = -2.96, p = .03$ adjusted.

Finally, to assess overall bias in responding, I compared the two groups in their tendency to respond with a given response type, irrespective of stimulus type (see Table 2). These comparisons demonstrated no group differences in responding with OLD, NEW, or SIMILAR to all item types (all $p$’s $> .05$, adjusted for multiple comparisons) (see Figure 7).

**Lure Similarity Bins**
The lure items varied in the degree of similarity from very similar (L1) to moderately similar (L2) to somewhat similar (L3). To examine the influence of the lure bins on response types, I next examined the percentage of response types (i.e., old, similar, new) to each lure bin (i.e., L1, L2, L3) per risk group (see Table 3). I hypothesized that due to high degree of similarity amongst the object images, L1 would be challenging for both groups of participants, such that I would not observe significant group differences in the rate of old, similar, and new responses to L1. However, I expected to find significant group differences for L2 and L3, with the high-risk group being less likely to recognize these items as similar than the low-risk group.

A three-way repeated measures ANOVA showed no effect of Lure Type \([F(2,70) = .50, p = .61]\), a significant effect of Response Type \([F(2,70) = 78.99, p < .001]\), a significant effect of Group \([F(1, 35) = 8.88, p < .01]\, and a significant Lure Type x Response Type interaction \([F(4, 140) = 41.54, p < .001]\). Finally, there was a significant Response Type x Risk Group interaction \([F(2, 70) = .756, p < .01]\, and no significant Lure Type x Response Type x Risk Group interaction, \([F(4, ) = .218, p = .93]\) (see Figure 8). Post-hoc between-group comparisons showed that high-risk participants were less likely to recognize all three lure bins as SIMILAR, compared to low-risk participants, smallest \(t(35) = 2.68, p = .03\) adjusted for L3. No other group differences were significant after adjusting for multiple comparisons. These results suggest that irrespective of the degree of similarity in lure items, high-risk participants were poorer in recognizing these items as similar than low-risk participants.

**Perceptual Discrimination Performance**

A prior study examining visual discrimination demonstrated that patients with schizophrenia show lower accuracy in responding to similar and identical, but not different pairs of object images (Martinelli & Shergill, 2015). However, I hypothesized that I would not see a difference
between the risk groups in perceptual discrimination. A one-way ANOVA did not detect significant differences in overall perceptual discrimination accuracy, $F(1, 35) = 3.42, p = .07$. To further characterize this relationship, I conducted multiple comparisons, which detected no significant differences in responding to different pairs (i.e., Identical, Similar, Different) across risk groups, largest $t(35) = 1.77, p = .52$ adjusted, for the probability of responding to identical pairs as same.

**Psychomotor Vigilance Task Performance**

Next, I examined group differences in the psychomotor vigilance task by comparing reaction times across risk groups. Since this task was initially included to look at the effects of remote task administration on sustained attention, I did not have a priori hypotheses. A one-way ANOVA did not demonstrate a significant effect of Risk Group on reaction time, $F(1, 34) = 1.18, p = .28$, suggesting that the two risk groups did not differ in their sustained attention.

**Mediation Analysis**

Martinelli and Shergill (2015) conducted a mediation analysis examining the role of recognition deficits on lure discrimination group differences and reported that group no longer had a significant effect on lure discrimination after accounting for recognition deficits. Thus, I wanted to examine whether the group differences in lure discrimination index could be explained by recognition or perceptual discrimination deficits here. Given the exploratory nature of this mediation, I did not have a priori hypothesis.

The mediation analysis revealed that Risk Group did not have a significant effect on perceptual discrimination accuracy (Path $a_1$: $B = -.30, SE = .01, p = .07$) and that perceptual discrimination accuracy did not have a significant effect on the Lure Discrimination Index, (Path $b_1$: $B = .24, SE = .47, p = .16$) (see Figure 10). In contrast, Risk Group had a significant effect on
Recognition Memory (Path a2: $B = -0.33, SE = 0.02, p < 0.05$) and Recognition Memory did not have a significant effect on the Lure Discrimination Index, (Path b2: $B = 0.32, SE = 0.20, p = 0.07$). Finally, Risk Group had a significant effect on the Lure Discrimination Index (Path c: $B = -0.49, SE = 0.03, p < 0.01$), and this effect remained to be significant after controlling for Recognition Memory and Perceptual Discrimination accuracy (Path c': $B = -0.31, SE = 0.03, p = 0.03$). These results suggest that children and adolescents at high-risk for schizophrenia have worse lure discrimination than low-risk children even after accounting for their recognition memory and perceptual discrimination abilities.

**Discussion**

Pattern separation is a crucial component of episodic memory that allows individuals to distinguish between perceptually similar events and stimuli. Prior studies have observed pattern separation deficits in schizophrenia patients (Das et al., 2014; Kraguljac et al., 2021; Martinelli & Shergill, 2015), which were at times accompanied by overall recognition deficits (Kraguljac et al., 2021; Martinelli & Shergill, 2015) that were shown to partially explain the mnemonic discrimination deficits (Martinelli & Shergill, 2015). One theory of hippocampal formation function in schizophrenia has proposed that these pattern separation deficits are tied to volumetric and synaptic reductions in DG and CA3, and that these deficits may underlie the false or illogical memories observed in schizophrenia and, consequently, create a susceptibility to psychosis (Tamminga et al., 2010). While this theory has been partially supported by a number of prior studies detecting behavioral pattern separation deficits in patients with schizophrenia, there has been ambiguity regarding the extent to which these deficits may be attributed to overall recognition deficits. In addition, no study to date examined these behavioral pattern separation deficits in those at high risk for developing the disorder.
To address this gap in the literature, the present study examined schizophrenia-related behavioral pattern separation (i.e., mnemonic discrimination) deficits in children and adolescents with- and without-genetic risk for schizophrenia. I chose children and adolescents aged 11-17 to capture a particular period in development when individuals report elevated vulnerability for psychopathology onset (Kessler et al., 2005). Given the broader episodic memory (Cosway et al., 2000; Hemager et al., 2018; İmamoğlu et al., 2022) and hippocampal (Ganzola et al., 2014) changes observed in this population of at-risk youth, I hypothesized that high-risk first-degree relatives would demonstrate worse mnemonic discrimination than low-risk controls, while both groups would perform comparably on recognition memory and perceptual discrimination.

My findings supported the first part of my hypothesis in showing that on average, the high-risk group performed worse than the low-risk group on the lure discrimination index, which was calculated as the proportion of similar responses to lure items minus the proportion of similar responses to foil items. Further comparisons showed that high-risk participants, in comparison to low-risk participants, were significantly less likely to recognize lure items as similar and instead showed a tendency to provide more old responses ($p > .05$). This difference in responding to lure items likely underlies the risk group differences in the lure discrimination index. This observation is also consistent with prior studies that assessed item and response type interactions in patients with schizophrenia (Das et al., 2014; Martinelli & Shergill, 2015) and first-episode psychosis (Kraguljac et al., 2021). However, unlike prior studies, I did not observe significant differences in responding to target items. This discrepancy could be attributed to qualitative differences between schizophrenia patients and their high-risk relatives. Nevertheless, these findings suggest that pattern separation deficits observed in patients are also present in their high-risk, first-degree relatives that are at heightened risk for the disorder.
Previously, it has been proposed that pattern separation deficits observed in schizophrenia patients may be largely attributed to overall recognition deficits (Martinelli & Shergill, 2015). Yet, prior studies have shown mixed results regarding recognition deficits associated with schizophrenia. Several studies showed no evidence of recognition differences between healthy controls and patients (Das et al., 2014; Mathews & Barch, 2004) nor high-risk first-degree relatives (İmamoğlu et al., 2022). In contrast, others have demonstrated schizophrenia-related impairments in recognition memory (Martinelli & Shergill, 2015) in the form of fewer hits (Heckers et al., 2000; Kraguljac et al., 2021) and more false alarms (Weiss et al., 2004). Given the mixed status of the literature, I did not expect to detect significant differences between high- and low-risk participants in recognition memory. Contrary to this hypothesis, I observed significant group differences in recognition memory, which was calculated as the probability of responding to targets as old (i.e., hits) minus the probability of responding to foils as old (i.e., false alarms). This finding is inconsistent with intact recognition performance previously observed in a largely overlapping sample of first-degree relatives (İmamoğlu et al., 2022).

Notably, the two studies employed different methods to assess recognition memory. For instance, İmamoğlu et al. (2022) administered a two-choice recognition task that asked participants to identify items as either old or new, accompanied by confidence ratings (‘Definitely’, ‘Maybe’, ‘Guess’). In comparison, the current study required participants to respond with one of three choices (i.e., old, similar, new) without providing confidence ratings. İmamoğlu et al. (2022) assessed recognition performance following the approach of detection-theoretic accounts by decomposing performance into sensitivity ($d'$) and response bias ($c$) (Green & Swets, 1966; Macmillan & Creelman, 2005). In the current study, recognition memory was instead assessed by computing a recognition memory parameter that has been widely used for the
mnemonic similarity task. A three-choice recognition task, in comparison to a two-choice recognition task, has its limitations as the latter can be used to assess response bias and sensitivity in accordance with standard signal detection theory accounts (Stanislaw & Todorov, 1999). The presence of a third response choice (i.e., similar) does not meet the signal detection theory assumptions that participants’ responses lie along a simple unidimensional axis on which thresholds can be placed. Prior studies have employed a two-choice approach to the MST (Klippenstein et al., 2020; Loiotile & Courtney, 2015), which was used to compare the recognition memory and lure discrimination parameters to $d'$ in their ability to detect significant group differences (Stark et al., 2015). At least one study showed that the lure discrimination index was comparable to $d'$ scores calculated as the difference between old responses to lures and old responses to foils with both scores being effective in detecting group differences between young and older adults (Stark et al., 2015). The same study observed that neither the recognition memory parameter nor the $d'$ scores, when calculated as the difference between old responses to targets and old responses to foils, were able to detect group differences (Stark et al., 2015).

Nevertheless, future iterations of the current study would ideally administer multiple versions of the MST with at least one two-choice version that could be used to assess sensitivity and response bias. Finally, the absence of significant differences in the prior study examining first-degree relatives could be attributed to difficulty differences between the two tasks (Miller et al. 1995), as the MST included lure items alongside old and new items.

To measure the behavioral response to varying degrees of change in the similarity input, I included lures that varied in their degree of similarity to targets. I then compared the influence of similarity variation on participants’ old, similar, and new responses to lure items. I observed that irrespective of the degree of similarity that was present in lure items, high-risk participants were
less likely to recognize these items as similar in comparison to low-risk participants. This suggests that high-risk participants were insensitive to the change in input, and they were quite rigid in their pattern separation abilities. This observation is consistent with the body of literature that observed representational rigidity in the DG/CA3 subfields in human neuroimaging studies (Yassa et al., 2011). Future iterations of the current study could include less similar lure bins (i.e., L4 and L5) to examine the extent this behavioral rigidity persists with less similar stimuli.

I also examined differences in perceptual discrimination to determine the extent high-risk children are impaired on perceptual discrimination. I observed that high- and low-risk participants were comparable in their perceptual discrimination performance. This is inconsistent with prior research that reported perceptual discrimination deficits in patients with schizophrenia whose methods we replicated (Martinelli & Shergill, 2015). It is possible that young at-risk relatives have more subtle deficits in perceptual discrimination that were not detected here, while the current task might be more sensitive to more profound deficits.

I assessed the effect of risk group on sustained attention by looking at possible group differences in psychomotor vigilance task reaction time. Poor performance on the PVT has been tied to increased fatigue (Loh et al., 2004) and disengagement from a task and related inattention (Drummond et al., 2005). Prior studies examining pattern separation in patients with schizophrenia did not include the PVT. Therefore, I had no a priori hypotheses. I observed that high- and low-risk participants did not significantly differ in their PVT performance, suggesting that the two groups did not significantly differ in their sustained attention during the experimental session. This finding implies that the pattern separation deficits observed between the high- and low-risk participants cannot be accounted for by differences in sustained attention.
Finally, I conducted a mediation analysis to assess the possibility that differences observed in the lure discrimination index could be explained by overall differences in recognition memory and/or perceptual discrimination. This mediation analysis demonstrated that recognition memory and perceptual discrimination did not mediate the relationship between risk group and lure discrimination, such that this relationship continued to be significant after accounting for the two mediators. These results are inconsistent with Martinelli & Shergill (2015), who demonstrated recognition memory to be a significant mediator. The absence of a significant mediation in the current study suggests that while recognition deficits can be observed in high-risk youth, these deficits do not underlie differences in pattern separation.

Altogether, these results suggest that children and adolescents at high-risk for developing schizophrenia have impaired behavioral pattern separation performance in comparison to those without genetic risk. I also demonstrated that while there are significant recognition differences between these two groups, the differences in pattern separation cannot be attributed to overall impairments in recognition or perceptual discrimination. Instead, these differences were mostly tied to high-risk participants inability to recognize lures as similar, irrespective of the degree of lure similarity. The behavioral data presented here highlight the importance of studying pattern separation in not only patients with schizophrenia, but also with their high-risk relatives. Although this is beyond the scope of the current study, characterizing these pattern separation deficits in at-risk youth may provide an effective instrument in predicting future propensity to generate false memories.

In summary, this study is the first to date to examine behavioral pattern separation deficits in first-degree relatives of schizophrenia patients. My main hypothesis was that risk status for developing schizophrenia would be associated with lower pattern separation accuracy.
Consistent with this hypothesis, I found that high-risk children and adolescents demonstrated lower lure discrimination than low-risk children. This is consistent with patterns of mnemonic discrimination deficits previously observed in patients with schizophrenia (Das et al., 2014; Martinelli & Shergill, 2015) and first-episode psychosis (Kraguljac et al., 2021). Future research should investigate the neural underpinnings of pattern separation in individuals at high genetic risk to specify the extent to which DG volume and function are associated with behavioral pattern separation deficits.

**Funding**

This work was supported by the NC TraCS Institute (#2KR1332002) through a CTSA grant from NIH’s National Center for Advancing Translational Sciences (NCATS).
Figure 1. Anatomical Subregions of the Hippocampus.

Note. Figure and note taken from Tamminga et al. (2010).
**Figure 2.** Anatomical Connectivity within the Hippocampus.

Connectivity is characterized by the distinctive one-way excitatory projection from the entorhinal cortex to the dentate gyrus to CA3 to CA1, called the trisynaptic pathway (blue). In addition, the entorhinal cortex also projects to CA3 and CA1 directly and independently. CA3 has a rich recurrent collateral network that strongly connects the CA3 pyramidal neurons with each other and is believed to participate in the memory functions of the hippocampus. Figure adapted from reference 38 by permission of the authors and John Wiley and Sons.

*Note.* Figure and note taken from Tamminga et al. (2010).
**Figure 3.** The Proposed Model of Hippocampal Formation in Schizophrenia.

*Note.* Figure taken from Tamminga et al. (2010).
Figure 4. A visual depiction of the Mnemonic Similarity Task.

Note. Figure adapted from Stark et al. (2019). Color outlines are for illustration purposes only and were not presented during the administration of the task.
Figure 5. A visual depiction of the Perceptual Discrimination Task.

Note. Figure produced by using stimuli by Stark et al. (2019). Color outlines are for illustration purposes only and were not presented during the administration of the task.
**Figure 6.** Average group performance on lure discrimination, recognition, and perceptual discrimination.

*Note.* Lure discrimination scores were calculated as $p("similar"|lure)-p("similar"|foil)$.

Recognition memory parameter scores were calculated as $p("old"|target)-p("old"|foil)$. Perceptual discrimination scores were calculated as the average overall accuracy. Error bars are standard error means.

*$p < .05$. **$p < .001$. 
**Figure 7.** Percent endorsed for the low- and high-risk groups for each stimulus (Targets, Lures, Foils) and response type (Old, Similar, New) on the MST.

*Note.* Error bars are standard error means.

*p < .05.*
Figure 8. Percent endorsed for the low- and high-risk groups for each lure bin and response type on the MST.

Note. Lure Bin 1 had the highest degree of similarity to the repetition items, followed by Lure Bins 2 and 3, respectively. Error bars are standard error means.
Figure 9. Illustration of the general causal model in the mediation analysis.

Note. MV refers to mediator variable, while IV and DV refer to independent and dependent variables, respectively.
Figure 10. Results of the overall mediation model.

Note. Partially standardized model coefficients are shown on relationship lines. Non-dashed lines indicate significant relationships.

*p < .05.
Table 1. Percent endorsed for the low- and high-risk groups for each stimulus and response type on the MST.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Targets</th>
<th>Lures</th>
<th>Foils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Old</td>
<td>New</td>
<td>Similar</td>
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<tr>
<td>Low</td>
<td>.82</td>
<td>.04</td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>(.09)</td>
<td>(.03)</td>
<td>(.08)</td>
</tr>
<tr>
<td>High</td>
<td>.75</td>
<td>.07</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>(.15)</td>
<td>(.08)</td>
<td>(.09)</td>
</tr>
<tr>
<td>Average</td>
<td>.80</td>
<td>.05</td>
<td>.13</td>
</tr>
<tr>
<td></td>
<td>(.13)</td>
<td>(.06)</td>
<td>(.08)</td>
</tr>
</tbody>
</table>

*Note.* Standard deviations are in the brackets.
Table 2. Percent endorsed for the low- and high-risk groups for each response type on the MST.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Old</th>
<th>Similar</th>
<th>New</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>.41 (.05)</td>
<td>.26 (.05)</td>
<td>.32 (.05)</td>
<td>.01 (.00)</td>
</tr>
<tr>
<td>High</td>
<td>.43 (.10)</td>
<td>.22 (.08)</td>
<td>.31 (.05)</td>
<td>.05 (.01)</td>
</tr>
<tr>
<td>Average</td>
<td>.42 (.08)</td>
<td>.24 (.07)</td>
<td>.32 (.05)</td>
<td>.03 (.04)</td>
</tr>
</tbody>
</table>

*Note.* Standard deviations are in the brackets.
Table 3. Percent endorsed for the low- and high-risk groups for each lure bin and response type on the MST.

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Bin 1</th>
<th></th>
<th>Bin 2</th>
<th></th>
<th>Bin 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Old</td>
<td>Similar</td>
<td>New</td>
<td>Missing</td>
<td>Old</td>
<td>Similar</td>
</tr>
<tr>
<td>Low</td>
<td>.48 (.14)</td>
<td>.46 (.15)</td>
<td>.05 (.05)</td>
<td>.01 (.02)</td>
<td>.36 (.14)</td>
<td>.56 (.14)</td>
</tr>
<tr>
<td>High</td>
<td>.57 (.14)</td>
<td>.31 (.15)</td>
<td>.09 (.09)</td>
<td>.04 (.05)</td>
<td>.47 (.18)</td>
<td>.40 (.18)</td>
</tr>
<tr>
<td>Average</td>
<td>.52 (.14)</td>
<td>.39 (.16)</td>
<td>.07 (.07)</td>
<td>.02 (.04)</td>
<td>.41 (.17)</td>
<td>.48 (.18)</td>
</tr>
</tbody>
</table>

Note. Standard deviations in the brackets.
REFERENCES


