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Compensatory Hippocampal Recruitment Supports Preserved Episodic Memory in Autism Spectrum Disorder

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Abstract

Background.—The degree to which individuals with autism spectrum disorder (ASD) evidence impairments in episodic memory relative to their typically developing (TD) counterparts remains unclear. According to a prominent view, ASD is associated with deficits in encoding associations between items and recollecting precise context details. Here, we evaluated behavioral and neural evidence for this *impaired relational binding* hypothesis using a task involving relational encoding and recollection during fMRI.

Methods.—Adolescents and young adults (N_{ASD}=47; N_{TD}=60) performed the Relational and Item-Specific Encoding (RiSE) task during fMRI, including item and associative recognition testing. We modelled functional recruitment within the medial temporal lobes (MTL), and connectivity between MTL and the posterior medial (PM) network thought to underlie relational memory. The *impaired relational binding* model would predict a behavioral deficit driven by aberrant recruitment and connectivity of MTL and the PM network.

Results.—The ASD and TD groups showed indistinguishable item and associative recognition performance. During relational encoding, the ASD group demonstrated *increased* hippocampal recruitment, and *decreased* connectivity between MTL and PM regions relative to TD. Within ASD, hippocampal recruitment and MTL-PM connectivity were inversely correlated.

Conclusions.—The lack of a behavioral deficit in ASD does not support the *impaired relational binding* hypothesis. Instead, the current data suggest that increased recruitment of the hippocampus compensates for decreased MTL-PM connectivity to support preserved episodic

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memory in ASD. These findings suggest a compensatory neurodevelopmental mechanism that may support preserved cognitive domains in ASD: local hyper-recruitment may offset connectivity aberrations in individuals with ASD relative to TD.

Keywords

Autism Spectrum Disorder; Medial temporal lobes; Episodic memory; Relational and item-specific memory; Functional connectivity; Functional magnetic resonance imaging

Background

The ability to encode and retrieve information from experienced events–i.e. episodic memory–is a pivotal component of adaptive cognitive functioning. The degree to which this ability is preserved or impaired in individuals with autism spectrum disorder (ASD) relative to their typically developing (TD) counterparts remains unclear. A prominent view of declarative memory functioning based primarily on behavioral task performance in ASD suggests that semantic memory (i.e. factual knowledge) is spared in ASD, while episodic memory is impaired (1, 2). Conversely, other behavioral studies suggest that episodic memory is broadly intact in those with ASD, and might even be leveraged to promote compensatory treatment of the core socio-affective symptoms of ASD (3, 4). One possible reason for this discrepancy is the degree to which different episodic memory tasks require individuals to ‘bind’ information from multiple items, or between items and their context.

Individuals with ASD often demonstrate difficulties encoding relationships between items and retrieving precise event context information (i.e., relational encoding and recollection, respectively), alongside preserved abilities to encode distinct information about items and retrieve context-independent item information [i.e., item-specific encoding and familiarity, respectively; (5, 6)]. For example, individuals with ASD demonstrate a preserved ability to retrieve individual items from episodic memory, but diminished retrieval of conceptually-related items compared to TD participants [for a review, see (7)]. In contrast, multiple studies have demonstrated similar relational memory functioning across ASD and TD (8–10). One potential source of conflicting behavioral results across studies is the extent to which different tasks support the use of relational processing in ASD [cf., ‘Task Support Hypothesis’; (6, 11)]. Overall, behavioral studies have provided conflicting evidence for *impaired relational binding* in ASD, and further work is needed to determine whether relational encoding and recollection are spared or impaired in ASD.

Functional magnetic resonance imaging (fMRI) provides an ideal opportunity to move beyond inconsistent behavioral findings and test mechanistic models of episodic memory functioning in ASD. Across many task and resting-state fMRI studies, individuals with ASD demonstrate aberrant “functional connectivity” relative to TD (12–19). Functional connectivity refers to statistical dependence between neural time series at distinct brain regions, which is thought to reflect the integration of information in distributed brain networks (20). Of particular importance to the current study, during episodic memory retrieval individuals with ASD demonstrate similar recruitment of local brain regions relative to those with TD, alongside diminished functional connectivity between the

hippocampus (HIPP) and frontoparietal regions (21). These findings fit with an emerging consensus regarding the functional neuroanatomy of ASD: The clinical phenotype in ASD is likely driven by aberrant connectivity, and disrupted information integration across distributed functional brain networks (13, 22–24).

Functional connectivity is pivotal for episodic memory functioning. Relational encoding and recollection are thought to be supported by a functionally connected network comprising the medial temporal lobes (MTL) and several other posterior and medial brain regions [collectively: the posterior medial (PM) network]. The PM network is anchored in posterior MTL (including posterior HIPP and parahippocampal cortex, PHC), and is strongly connected to regions classically associated with the putative 'default network' including posterior cingulate cortex (PCC), ventromedial prefrontal cortex (VMPFC), and inferior parietal lobe [IPL; (25–27)]. A number of human and animal model studies demonstrated recruitment of PM circuits during relational encoding tasks [e.g. PHC (28, 29); lateral parietal regions (30); and medial prefrontal cortex (31)]. A recent set of neurostimulation studies causally implicated MTL-PM network functional connectivity in *both* the formation of relational memories and recollective precision (32–34). Given that atypical MTL structure may represent a hallmark of the neurobiology of ASD (35–37), any disrupted relational memory processing in this group is likely to be driven by aberrant recruitment and connectivity of the MTL. Therefore, investigating MTL and PM network functional recruitment and connectivity during relational encoding could help determine the degree to which relational binding is spared or impaired in ASD, which may have broader implications for our understanding of the functional neuroanatomy of ASD.

Here, we conducted the largest fMRI study to date investigating relational and item-specific episodic memory in ASD (N=107). We recruited adolescents and young adults with ASD (N_{ASD}=47) or TD (N_{TD}=60) to perform an episodic memory task developed and validated by the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia consortium [https://cntracs.ucdavis.edu; Relational and Item-Specific Encoding task, RiSE, Figure 1; (38, 39)]. This paradigm was ideal for the current study given that it was developed for TD participants but is also well-tolerated by clinical groups, has an absence of ceiling or floor effects across healthy and clinical populations, has good reliability across various forms, has strong internal consistency, and is one of the few tasks designed to dissociate relational and item-specific encoding processes [though these processes are correlated between-subjects; (39, 40)]. This enabled us to provide a robust test of the *impaired relational binding* hypothesis, which would be supported by impaired recollection and aberrant recruitment of the MTL and PM network during relational encoding in ASD relative to TD.

Methods and Materials

Participants

Inclusion criteria.—136 participants (N_{ASD}=66; N_{TD}=70) completed the main phases of the RiSE protocol (encoding, ENC; item recognition, IR) and met the inclusion criteria for the current study. All participants were 12–22 years old, had full-scale intelligence quotient (FSIQ)≥70 [estimated via the Wechsler Abbreviated Scale of Intelligence, (41)], were not

taking antipsychotic or antidepressant medications, had no contraindications to MRI, and had no history of substance misuse (also passed a urine screen). Within the ASD group, participants received a community clinical diagnosis of ASD, and a current diagnosis of ASD based on gold standard measures including: i) the Autism Diagnostic Observation Schedule [ADOS-2; (42)], ii) a DSM Criteria Checklist for ASD (43), and iii) a Social Communication Questionnaire [SCQ; (44)] total score ≥15. One ASD participant did not meet criteria on the SCQ (SCQ_{total}=7), and a second participant did not complete the SCQ, however in both cases the decision was made to retain these participants by a licensed clinical psychologist with extensive autism expertise (MS) based on the balance of evidence (i.e. community diagnosis, ADOS-2, and DSM-5 checklist). Within the TD group, participants all failed to meet diagnostic criteria for a current psychiatric disorder based on the Structured Clinical Interview for DSM-5 Disorders [SCID, for participants 18 and over; (45)] or the Kiddie-Sads-Present and Lifetime Version [K-SADS, for participants under 18; (46)]. Five ASD participants in the current study were taking psychostimulants, but consented to a doctor-approved 48-hour washout before their MRI visit (47). Additionally, one participant with ASD was taking topiramate, and a second was taking bupropion, but these participants underwent provider-approved respective 4- and 10-day washouts prior to the study. Lastly, one ASD participant each were taking migraine medication, melatonin, and hypothyroid medication, and two ASD participants were taking allergy medications (Table 1). All procedures were approved by the UC Davis Institutional Review Board.

Exclusion, and final sample.—After data collection and analysis, 19 ASD participants and 10 TD participants were excluded for behavioral and fMRI data quality issues, including: falling 3 standard deviations away from mean performance on the behavioral task (mean and SD defined across groups; ASD: N=5, TD: N=3), having negative d' scores on the IR or associative recognition (AR) tasks (ASD: N=1), or losing >20% of their fMRI data after removing high motion timepoints (ASD: N=13, TD: N=10; 3 high motion TD participants were also excluded for their RiSE performance). High motion was defined as any timepoints where framewise displacement (FD) exceeded 0.9 mm. This cut-off is less conservative than traditional criteria for resting-state fMRI, but is appropriate for fMRI studies involved task-evoked HRF modelling (48). Therefore, the final sample comprised 107 participants, including 47 with ASD and 60 with TD (Table 1). Notably, the RiSE was the second of two fMRI tasks, and several participants were unable to complete the final phase (Associative Recognition, AR) due to fatigue or the termination of their scheduled MRI scan time. As a result, only a subset of the sample (N_{ASD}=25; N_{TD}=39; Table 2) completed the AR task, but their ENC and IR data were retained.

Match between ASD and TD.—Participants with ASD had lower verbal intelligence on the WASI (VIQ; M=101, SD=13.0) than TD (M=106, SD=11.0; p=0.038), but VIQ did not correlate with any performance measures from the RiSE (all r<0.2, p>0.09) and therefore was not an appropriate covariate (49). In the subset of participants who completed the AR, there was a difference in FSIQ (ASD: M=105, SD=13.9; TD: M=112, SD=10.6; p=0.025), and FSIQ was associated with AR performance (r=0.34, p=0.003). Therefore, AR analyses were run both with and without FSIQ as a covariate.

Task Design

The RiSE consisted of three phases: ENC, IR, and AR (Figure 1A). During ENC, participants saw 54 pairs of items, and were asked to make 'yes' or 'no' judgments according to one of two conditions: i) whether one of the items was living or not (item-specific encoding, 27 trials), or ii) whether one item could fit inside the other item (relational encoding, 27 trials). The encoding run was a pseudorandom block design, alternating between item-specific (3 blocks, 9 trials/block) and relational encoding blocks (3 blocks, 9 trials/block) within a single run. During initial task development it was found that blocking was necessary to reduce task-switching demands in order to facilitate performance in clinical samples and avoid floor effects. During IR, all studied items (54 from the item-specific encoding condition, and 54 from the relational encoding condition) were presented one at a time intermixed with 54 unstudied foils, and participants judged whether items were 'old' or 'new'. During AR, all 27 object pairs from the relational encoding condition, and 27 rearranged pairs containing the same items, were presented. Participants made 'yes' or 'no' judgments about whether each pair was intact. During all fMRI task runs (i.e., ENC, IR, and AR), images were presented for 3 seconds, with jittered inter-trial intervals between 1–10 seconds. If participants failed to record a response within the 3 second window, the script moved on to the next trial. Accuracy [d'=z(hit rate)–z(false alarms)] was the primary outcome measure for both the IR (IR-d') and AR (AR-d') retrieval tasks. IR-d' and AR-d' data violated the assumptions of normality and homoscedasticity, and robust inferential statistics were used throughout the behavioral data analyses (50). Notably, whereas IR-d' is thought to index a combination of familiarity and recollection, during the AR task the items from both studied and non-studied pairs are equally *familiar*, and therefore a large difference between hits and false alarms on this task (i.e., high AR-d') is likely to provide a specific index of recollection ability (39).

Functional Magnetic Resonance Imaging (fMRI) Procedures

Image acquisition.—MRI data were acquired on a Siemens TimTrio 3-T scanner with a 32-channel head coil. Sagittal T1-weighted structural images were acquired using an MPRAGE sequence (TR=2530 ms, TE=3.5 ms, slice thickness=1 mm, FOV=256 mm, voxel size=1 mm iso, PAT mode=GRAPPA, PE=2). Functional T2*-weighted images sensitive to BOLD contrast were acquired using an EPI sequence (TR=2000, TE=24, FOV=224, Voxel Size=3.5 mm iso, flip angle=90°, EPI factor=64). All phases of the RiSE task (i.e., ENC, IR, and AR) were performed in the scanner.

Regions-of-interest (ROIs).—Given our *a priori* interest in the brain mechanisms underlying relational encoding and recollection, functional recruitment models were constrained to a recent parcellation of the human MTL including bilateral perirhinal cortex (PRC), bilateral parahippocampal cortex (PHC), and the bilateral head, body, and tail of the hippocampus [HIPP, Figure 2A; (51)]. Additionally, functional connectivity between these nodes of the MTL and the broader PM network were defined using a leading edge parcellation of the human default network [Figure 2B; (52)].

Functional recruitment analysis.—Subject-level fMRI data were preprocessed using a standard FMRIB Software Library [FSL; (53)] pipeline, including: motion correction

(MCFLIRT), distortion correction, spatial smoothing (7 mm FWHM), temporal filtering (high-pass=200), a subject-level GLM, and group-level normalization to MNI 2-mm space. The subject-level GLM was modeled with four task regressors: i) item-specific encoding trials with a response, ii) relational encoding trials with a response, iii) item-specific encoding trials with no response, and iv) relational encoding trials with no response. Because the current study was designed to elucidate relational and item-specific encoding neural activity–*not* the retrieval of veridical concept knowledge (e.g., Is a picked apple living?)–our primary fMRI models included all ENC trials wherein a response was recorded, regardless of correctness (38). Translation and rotation parameters were included in the subject-level models, alongside nuisance regressors to exclude high motion spikes [FD≥0.9mm; (48)]. Group-level recruitment within MTL ROIs was modeled in a 2 (encoding condition: relational vs. item-specific) by 2 (group: ASD vs. TD) model via FSL's Local Analysis of Mixed Effects (FLAME1). Uncorrected maps were corrected for multiple comparisons using nonparametric permutation testing [threshold-free cluster enhancement, TFCE: α=0.05, 5,000 permutations; (54)]. To remain consistent with previous studies [cf., (38)], we also examined MTL functional recruitment for hits relative to misses during IR and AR (Supplementary Figure 1).

Functional connectivity analysis.—Functional connectivity was analyzed using the CONN Toolbox (55). Data input to CONN had been preprocessed at the subject-level in FSL, with two additional steps: 1) tissue segmentation (FSL FAST), and 2) PCA-based removal of noise from white matter and cerebrospinal fluid, which contaminate functional connectivity estimates [*aCompCor*; (56)]. The MTL ROIs (N=8: including bilateral PHC and bilateral head, body, and tail of the HIPP; Figure 2A) were used as seeds in a seed-to-target functional connectivity analysis, including both MTL and the rest of the PM network as targets (N=43 total ROIs; Figure 2A–B). Perirhinal cortex ROIs were not included in the functional connectivity analysis, as PRC is not a part of the PM network [(25); notably, the connectivity results remain unchanged if these ROIs are included in the model]. Functional connectivity was modeled using a regression-based generalized psychophysiological interaction model [gPPI; (57, 58)]. The gPPI involved separate multiple regression models for each target ROI. These models contained the same four task regressors from the functional recruitment model (namely, item response, relational response, item no response, and relational no response), the BOLD timeseries for each of the 8 MTL seed ROIs, and the interaction term between each seed and the task regressors. The group-level functional connectivity model was FDR-corrected for multiple comparisons using nonparametric permutation testing (α=0.05, 10,000 permutations) at the seed-level (q<0.05). Correction at the seed-level is an established approach for seed-to-target gPPI analyses [cf., (59–61)], but to maximize the statistical rigor of our approach, we also report analysis-level (i.e., FDR-correction for all possible seed-target pairs) corrected results. In addition to our hypothesis-driven ROI-based analysis, for exploratory purposes we conducted a seed-to-voxel analysis examining connectivity between MTL and the rest of the brain during encoding. The seed-to-voxel results were FDR-corrected at the whole brain level.

Results

Behavior

Response rates during ENC did not differ between groups (Full sample: ASD=96.3%, TD=97.7%, p=0.261; AR subset: ASD: 95.7%, TD: 97.9%, p=0.169). IR-*d'* was analyzed using a 2 (encoding condition) by 2 (group) robust ANOVA. This analysis revealed a main effect of encoding condition (Q=90.35, p<0.001; Figure 1B), but the effect of group and the interaction term were not significant (ps≥0.894; Figure 1B). Planned comparisons revealed that the main effect of condition was driven by higher IR-*d'* for stimuli encoded in the relational (ASD: M=2.56, SD=0.73; TD: M=2.61, SD=0.680) relative to the item-specific encoding condition across ASD (M=2.23, SD=0.609, t_{yuen}=6.37, p<0.001) and TD (M=2.22, SD=0.570, t_{yuen}=7.12, p<0.001). In fact, there was positive evidence for the null hypothesis: IR-*d'* did not differ between groups after either relational (BF_{01}=4.61, *err*=0.021%) or item-specific (BF_{01}=4.84, *err*=0.019%) encoding (Table 1).

Recollection of pairs from the relational encoding condition was assessed using AR-*d'*. A robust independent samples *t*-test on AR-*d'* revealed no differences between groups (ASD: M=2.00, SD=1.03; TD: M=1.97, SD=0.81; p=0.609; Figure 1C). Again, there was positive evidence for the null hypothesis (BF_{01}=3.80, *err*=0.002%), and this evidence for the null was robust to the inclusion of FSIQ as a covariate (BF_{01}=3.80, *err*=0.002%). Therefore, on tests of both IR–thought to rely on both familiarity and recollection–and AR–thought to rely primarily on recollection–individuals with ASD and TD did not differ in RiSE task performance (Table 2).

Functional Recruitment

It was hypothesized that MTL ROIs would be preferentially recruited during relational relative to item-specific encoding. Additionally, based on the *impaired relational binding* hypothesis, we hypothesized that individuals with ASD would recruit MTL less in this contrast relative to TD participants. Importantly, we ran additional parametric modulation analyses to determine whether brain activity at encoding predicted IR-*d'* and/or AR-*d'* in ASD or TD.

Main contrasts.—TD participants demonstrated increased recruitment of left PHC during relational relative to item-specific encoding (Figure 3A; Table 3). In contrast, the ASD group demonstrated bilateral posterior MTL recruitment of both PHC and HIPP during relational relative to item-specific encoding (Figure 3A; Table 3). Importantly, the two-way interaction revealed that individuals with ASD demonstrated significantly greater right HIPP recruitment relative to those with TD (Figure 3B; Table 3). As in previous studies (38), neither the ASD nor TD groups demonstrated any significant MTL recruitment during item-specific relative to relational encoding. Contrary to the impaired relational binding hypothesis, individuals with ASD did not demonstrate reduced recruitment of any MTL structure during relational relative to item-specific encoding compared to those with TD.

Parametric modulation.—Within the TD group, right HIPP recruitment during relational encoding predicted subsequent recollection performance (AR-*d'*; r=0.49, *95%-CI*=0.20 to

0.70, p=0.002; Figure 3C; Table 4), but MTL recruitment did not predict IR-*d'*. In contrast, recruitment of bilateral HIPP during relational encoding significantly predicted subsequent IR-*d'* for relationally-encoded stimuli in ASD (r=0.30, *95%-CI*=0.02 to 0.54, p=0.039; Figure 3C; Table 4). MTL recruitment did not predict downstream recollection performance (AR-*d'*) in individuals with ASD, and MTL recruitment during item-specific encoding did not predict subsequent IR-*d'* in either group.

Retrieval.—During retrieval, the TD group did not demonstrate any MTL recruitment during hits relative to misses during the IR task, but did demonstrate a trend-level activation within the HIPP head and body during AR hits relative to misses (Supplementary Figure 1A). The ASD group recruited a small cluster of posterior HIPP voxels during IR hits versus misses, specifically for stimuli from the relational encoding condition (Supplementary Figure 1B). However, participants with ASD did not demonstrate any increased MTL recruitment during IR hits for item-specific encoding stimuli, nor did they recruit MTL to a greater extent on AR hits relative to misses.

Functional Connectivity

It was hypothesized that MTL ROIs would demonstrate greater functional connectivity to the rest of the PM network during relational relative to item-specific encoding. Based on the *impaired relational binding* hypothesis, we predicted that individuals with ASD would demonstrate diminished functional connectivity between the MTL and PM ROIs relative to TD participants.

Main contrasts.

MTL-PM network connectivity.: In line with our hypothesis, the TD group demonstrated greater functional connectivity between right PHC and HIPP body, PCC, and IPL during relational relative to item-specific encoding at the seed-level threshold (Figure 4A; Table 5), with only the HIPP-PCC connection remaining significant with FDR thresholding at the analysis-level. In contrast, there were no connections that demonstrated increased functional connectivity during relational relative to item-specific encoding within the ASD group, either at the seed- or analysis-level FDR threshold. Critically, there was a significant two-way interaction, whereby functional connectivity between right PHC and left HIPP, and between right PHC and left PCC was reduced in ASD relative to TD at the seed-level FDR threshold (Figure 4B; Table 5). The two-way interaction was not significant at the more conservative analysis-level FDR threshold. Lastly, neither group demonstrated increased MTL-PM network connectivity during item-specific relative to relational encoding.

MTL-wholebrain connectivity.: We conducted an exploratory MTL-wholebrain seed-to-voxel connectivity analysis on the relational > item-specific encoding contrast. The ASD group did not demonstrate any significant MTL-wholebrain connectivity changes during relational encoding. In contrast, the TD group demonstrated significantly elevated left HIPP Body to left inferior frontal gyrus, and right PHC to left supramarginal gyrus connectivity during relational relative to item-specific encoding (Supplementary Figure 4). There were no significant MTL-wholebrain group differences in functional connectivity that survived FDR

correction, and neither group demonstrated connectivity changes during the item-specific relative to relational encoding.

Parametric modulation.—Within the TD group, there were no MTL-PM network edges demonstrating a significant association between connectivity during item-specific encoding and subsequent IR-*d'*. In contrast, connectivity between right PHC and HIPP head during relational encoding was associated with improved subsequent IR-*d'* (r=0.38, p=0.003; Supplementary Figure 2A), and right HIPP head to PCC connectivity during relational encoding predicted subsequent AR-*d'* in TD (r=0.37, p=0.022; Supplementary Figure 2B). Within the ASD group, right PHC connectivity to lateral temporal (r=0.65, p<0.001; Supplementary Figure 2C) and parietal (r=0.41, p=0.044; Supplementary Figure 2D) regions of the PM network during relational encoding predicted subsequent AR-*d'*, and no MTL-PM network edges demonstrated a significant association between item-specific or relational encoding and subsequent IR-*d'*.

Association Between Functional Recruitment and Functional Connectivity

Given the paradoxical evidence for the *impaired relational binding* hypothesis from our functional recruitment and connectivity data (i.e. increased activation alongside diminished functional connectivity in ASD), we ran exploratory analyses to determine whether there was any relationship between individual differences in *increased* HIPP recruitment and *decreased* MTL-PM connectivity. First, we ran a multivariate analysis contrasting the correlation structure of functional recruitment and connectivity between groups. Correlation matrices were generated separately for each group, comprising mean recruitment within MTL ROIs that were hyper-recruited in ASD, and network edges that were functionally connected during relational encoding in TD. Functional recruitment appeared to be negatively associated with functional connectivity in the ASD group, whereas the TD group did not demonstrate any clear relationship between recruitment and connectivity, and the correlation matrices differed between groups (χ^2=91.90, p<0.001; Figure 4C). This interpretation was confirmed in a bivariate correlation between mean HIPP recruitment and mean PHC-MTL connectivity. The ASD group demonstrated a negative association between mean HIPP recruitment and mean MTL-PM functional connectivity (r=-0.36, *95%-CI*=-0.59 to -0.08, p=0.015; Figure 4D), whereas the TD group did not (r=0.02, *95%-CI*=-0.23 to -0.28, p=0.857; Figure 4D). These bivariate correlations were trending toward a significant difference between groups (z=-1.93, p=0.054).

Discussion

The RiSE task is a well-validated method for dissociating relational and item-specific encoding in clinical populations and TD participants (10, 38, 39). Accordingly, the present study provided an opportunity to test the *impaired relational binding* hypothesis of episodic memory functioning in ASD. Supporting evidence for this hypothesis would entail an associative recognition deficit, alongside aberrant neural recruitment and connectivity during relational encoding. Contrary to this view, the present data provided support for a *relational compensation* interpretation. Specifically, individuals with ASD demonstrated identical item and associative recognition performance relative to TD, but their performance was

accomplished via distinct underlying neural mechanisms supporting relational encoding. This finding supports a recent behavioral finding from our group, where we observed an overreliance on recollection processes thought to be supported by the HIPP and PM network during IR in ASD relative to TD (10).

In the current study, HIPP was hyper-recruited in ASD relative to TD during relational encoding, and this activation was associated with improved item recognition within the ASD group. Conversely, individuals with ASD demonstrated reduced PM network connectivity during encoding relative to TD, and reduced PM connectivity at encoding was associated with diminished recollection across groups. The present data fit with a deep literature documenting aberrant functional connectivity in ASD (22–24), however we also find that aberrant connectivity can be present in the absence of a significant behavioral impairment. Instead, the association between HIPP recruitment and PM network connectivity in ASD suggests a compensatory mechanism which might support preserved episodic memory functioning in ASD. Given that the current study recruited participants within 2 SD of the population mean FSIQ, it is unclear whether this compensatory mechanism would be present in individuals with ASD and intellectual disability. It was recently suggested that the ASD phenotype is the result of adaptive developmental responses triggered by early neurobiological alterations (62). Such developmental adaptations are thought to lead to the emergence of dissociations, whereby *typical* behavioral performance is implemented via *atypical* underlying mechanisms in neurodevelopmental populations (63). From the current imaging results, it is possible that increased local information processing within HIPP reflects a compensatory shift, following diminished integrity of functional connections between hubs of the PM network in ASD. A future longitudinal study of relational and item-specific encoding in ASD starting in childhood will be critical for testing this hypothesis, assuming that diminished PM network connectivity should precede the emergence of local hyper-recruitment of the HIPP in ASD.

The current finding of preserved associative recognition following relational encoding in ASD–which is likely to rely strongly on *recollection*–diverges from prior research [e.g., (21, 64)]. There are at least two potential reasons for a lack of group-level associative recognition impairment in the current study. First, this may be influenced by study-specific differences in retrieval task. Whereas recognition tasks like the IR and AR from the current study provide direct context cues to support retrieval, impairments in ASD might be strongest on tasks involving zero context cues [e.g., free recall (6)]. Further, using a task designed to assess continuous variance in recollection precision–i.e. rather than the presence or absence of recollection as in the AR run of the present study–Cooper and colleagues (2017) recently found evidence for impacted recollection performance in ASD (21). Therefore, whereas the RiSE task is primarily designed to probe relational and item-specific encoding, alternative retrieval paradigms may be better suited to isolating differences in how individuals with ASD reconstruct experienced events at retrieval [cf., (7)]. This notion is directly in line with the ‘Task Support Hypothesis,’ which suggests that relational memory in ASD is not a fixed impairment, but depends on how much support the task provides to facilitate relational processing (6, 11).

In addition to task differences at retrieval, differences at encoding may play a role in driving inconsistencies between the current study and previous work demonstrating impaired relational binding in ASD. Several prior studies on relational encoding utilized verbal rather than nonverbal learning materials [e.g. (6)], and given the fact that verbal IQ is often much lower than nonverbal IQ in ASD samples (Tables 1–2), nonverbal stimuli may make it easier for individuals with ASD to perform at a normative level on relational encoding tasks. Furthermore, meaningful pictorial stimuli like the images used in the RiSE task may provide more task support to facilitate relational encoding than highly complex nonverbal learning materials given the generally recognized visuospatial information processing strengths of those with ASD (65). For example, a study by Bowler, Gaigg, & Gardiner (2014) found that when encoding involves complex abstract stimuli that make relational processing difficult (specifically, 6x6 line-drawing / location grids), associative recognition is impaired in high-functioning adults with ASD (5). At a mechanistic level, increased relational encoding task difficulty might require more diffusely organized functional brain networks than the networks supporting the RiSE relational encoding condition (66, 67), which may be less amenable to the type of neural compensation effects we observed in the current study.

Beyond variation across episodic memory paradigms, the discrepancy between the current study and prior behavioral findings might be influenced by developmental shifts in episodic memory circuitry. The majority of prior studies on episodic memory in ASD have sampled from middle adulthood [30–40 years of age; (6, 64, 68)]. In contrast, few studies have investigated memory in ASD in adolescents and young adults. Hippocampal-cortical circuits demonstrate significant maturation from childhood through young adulthood (69, 70), and continue to change as a function of cognitive aging in adulthood (71). Therefore, it is distinctly possible that impaired relational encoding and recollection precision are most pronounced in adulthood in ASD, when these abilities have reached their highest level of maturity in TD [cf., (10, 72)]. Again, longitudinal studies of episodic memory functioning in ASD from childhood through young adulthood are needed to evaluate this possibility.

An important limitation of the current study is the relatively small sample run through the entire protocol. This resulted in reduced statistical power in the analyses incorporating AR data (including behavioral modeling of AR-*d'*, and parametric modulation of neural recruitment as a function of AR-*d'*; Table 2). Future studies of RiSE task performance in ASD should prioritize collection of all experimental runs to ensure a larger AR dataset. Additionally, it should be noted that the current study recruited a high functioning sample of individuals with ASD (FSIQ>70). Therefore, it is possible that the *impaired relational binding* model would find support within a more cognitively diverse sample of participants with ASD, although this would then make it difficult to distinguish between selective deficits in episodic memory and more generalized cognitive difficulties.

In sum, the current data are compatible both with aberrant connectivity-based models of the functional neuroanatomy of ASD [e.g., (24)], and with the recent hypothesis that ASD is ultimately driven by adaptive neurodevelopmental responses to early, brain-wide differences in synaptic efficiency (62). In particular, we suggest that hyper-recruitment of localized circuits may represents a compensatory mechanism for reduced brain network-wide integration in ASD. A prediction of this view is that analogous neurodevelopmental

mechanisms should be triggered transdiagnostically–i.e. across traditional psychiatric or neurologic patient categories. To test this prediction, future studies should compare PM network development between ASD and individuals who suffered a perinatal lesion to the PM network, hypothesizing that both groups will demonstrate local hyper-recruitment as a compensation for network-level hypo-connectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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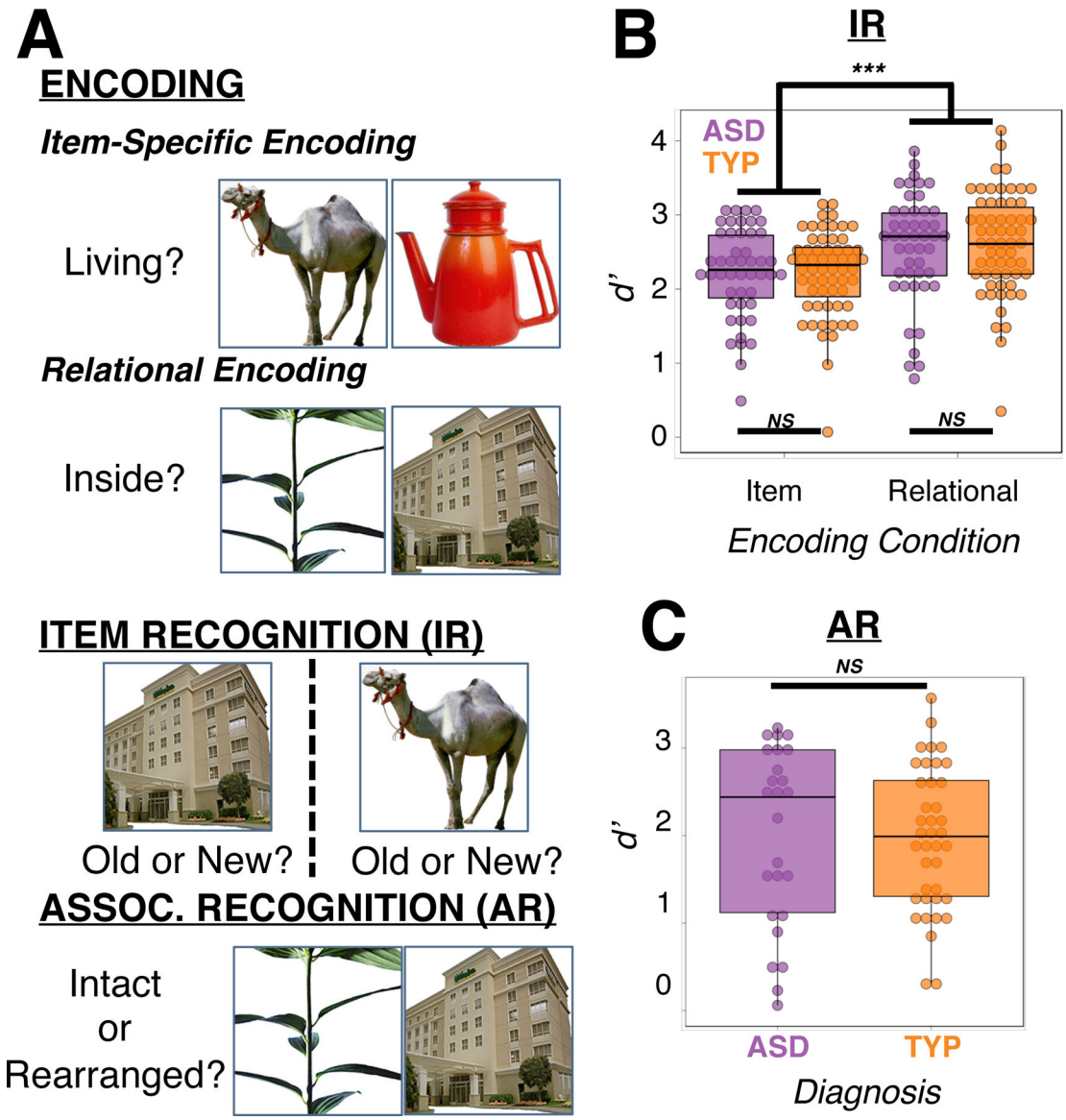

Figure 1.

(A) Schematic of the RiSE task. Participants encoded stimuli by processing either item features ("Living?") or the relationship between items ("Inside?"), and then performed both item recognition (IR) and associative recognition (AR) retrieval tasks. **(B)** Relational encoding led to performance improvements on IR relative to item-specific encoding, but there were no group differences. **(C)** AR accuracy was equivalent between groups. *NS*: $p>0.6$, ***: $p<0.001$.

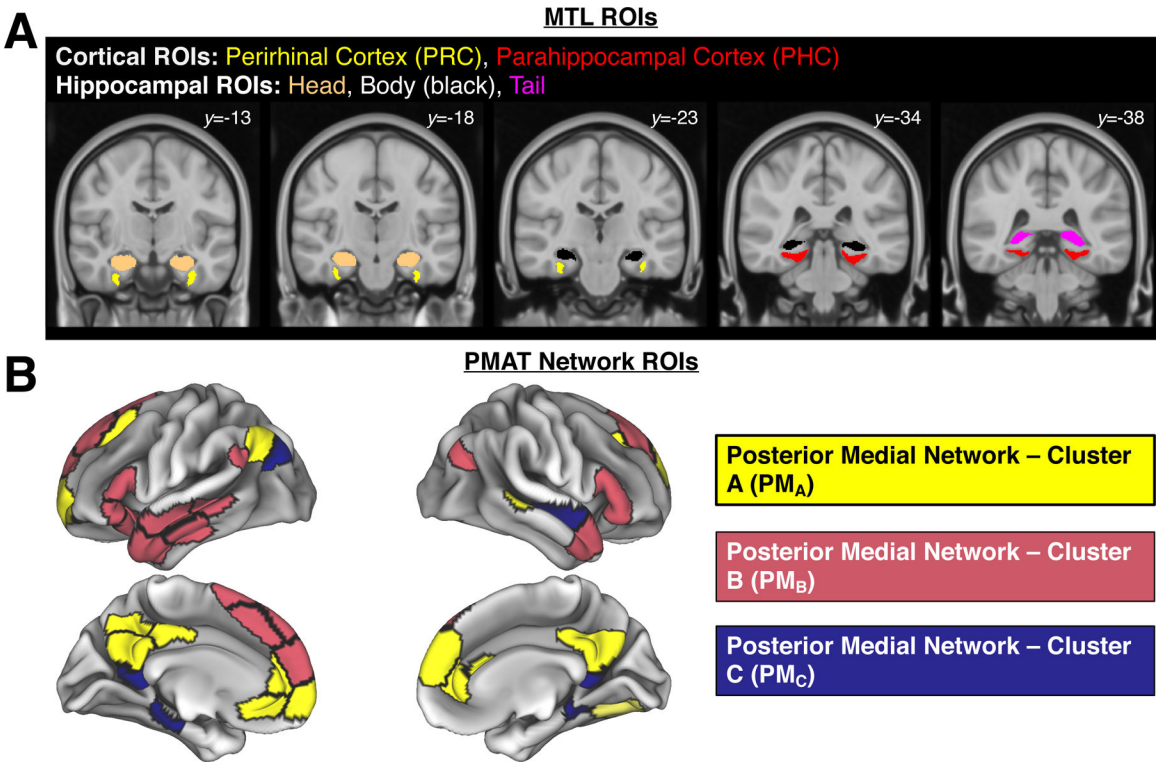

Figure 2.

(A) Human MTL regions adopted from Ritchey et al. (2015). **(B)** Parcellated PM network ROIs via a leading edge parcellation of the human cortex (52). All images in anatomical orientation (i.e., right is right).

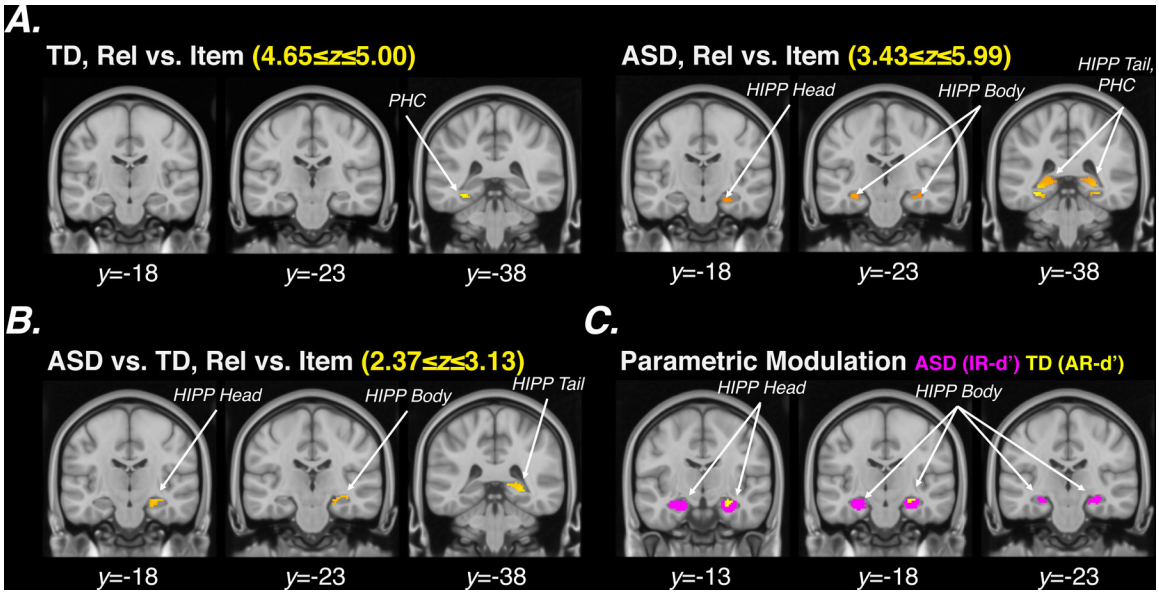

Figure 3.

(A) Functional recruitment within the MTL mask during relational relative to item-specific encoding, confined to left PHC in TD (left), but observed across bilateral HIPP and PHC ROIs in ASD (right). **(B)** ASD group demonstrated hyper-recruitment of right HIPP relative to TD during relational relative to item-specific encoding. **(C)** Recruitment of bilateral HIPP was parametrically modulated as a function of IR-*d'* in ASD (pink), whereas right HIPP recruitment was parametrically modulated as a function of AR-*d'* in TD (yellow). All images thresholded using nonparametric permutation testing (p_{TFCE}<0.05), and displayed in anatomical orientation (i.e., right is right).

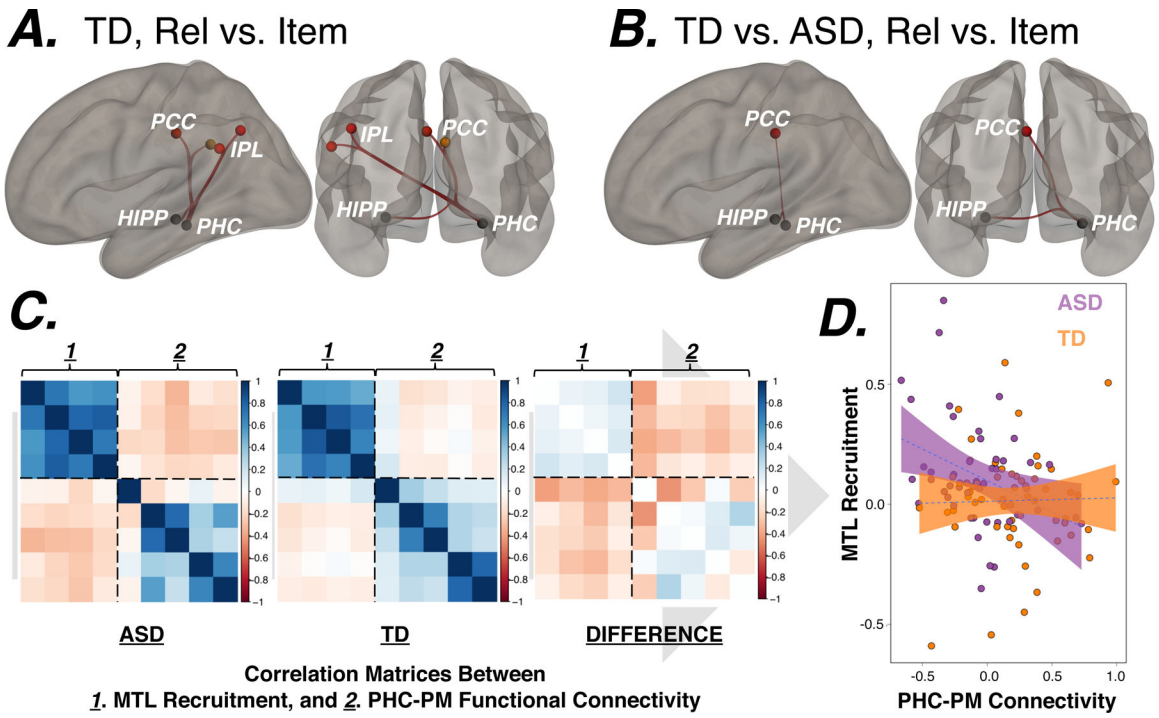

Figure 4.

(A) Functional connectivity (relational – item-specific encoding) between right PHC→HIPP, PHC→inferior parietal lobe (IPL), and PHC→posterior cingulate cortex (PCC) were increased in TD. **(B)** PHC-HIPP and PHC-PCC edges were underconnected in ASD relative to TD. **(C)** There were significantly different multivariate correlations between functional recruitment of the medial temporal lobes (MTL) and PHC-PM network functional connectivity between ASD and TD. **(D)** Averaging across these associations into a single bivariate correlation, there was a negative relationship in ASD that was not present in TD.

Table 1.

Summary of the current study sample.

Variable	ASD (*N*=47)	TD (*N*=60)	Contrast
Demographics & Assessments			
Sex, female/male	12/35	13/47	*OR*=1.24, *p*=0.653
Age	18.4±2.81	17.6±3.14	t_{yuen}=1.21, *p*=0.227
Full-Scale Intelligence (FSIQ)	105±13.4	110±10.2	t_{yuen}=−0.851, *p*=0.401
Nonverbal Intelligence (NVIQ)	108±16.4	111±12.4	t_{welch}=−0.849, *p*=0.398
Verbal Intelligence (VIQ)	101±13.0	106±11.0	t_{welch}=−2.10, *p*=0.039
Autism Diagnostic Observation Schedule (ADOS)	7.53±1.53	N/A	N/A
Social Communication Questionnaire	21.1±5.64	3.08±3.27	t_{yuen}=20.4, *p*<0.001
Prescribed medications?	0	12	N/A
RiSE – IR Task Performance			
IR hits, item-specific encoding	38.49±6.96	38.22±6.80	t_{yuen}=0.0006, *p*=0.999
IR hits, relational encoding	43.64±6.06	43.70±6.27	t_{yuen}=−0.619, *p*=0.538
IR misses, item-specific encoding	14.28±6.96	14.73±6.07	t_{yuen}=−0.484, *p*=0.619
IR misses, relational encoding	9.49±5.62	9.23±5.47	t_{yuen}=0.376, *p*=0.701
IR False Alarms	4.09±3.84	3.85±3.90	t_{yuen}=−0.023, *p*=0.981
IR Correct Rejections	48.70±4.81	48.58±4.81	t_{yuen}=0.570, *p*=0.563
IR *d'*, item-specific encoding	2.23±0.61	2.22±0.57	t_{yuen}=0.160, *p*=0.872
IR *d'*, relational encoding	2.56±0.73	2.61±0.68	t_{yuen}=0.098, *p*=0.920

Notes: t_{yuen}: Yuen's robust *t*-test, t_{welch}: Welch's *t*-test,

*: *p*<0.05

**: *p*<0.01

***: *p*<0.001, blank: *p*≥0.05.

Table 2.

Summary of the sample of participants that completed the AR phase.

Variable	ASD (*N*=25)	TD (*N*=39)	Contrast
Demographics & Assessments			
Sex, female/male	7/18	8/31	*OR*=1.50, *p*=0.553
Age	18.62±2.80	17.51±3.10	t_{yuen}=1.35, *p*=0.176
Full-Scale Intelligence (FSIQ) *	104±13.9	112±10.6	t_{welch}=−2.32, *p*=0.025
Nonverbal Intelligence (NVIQ)	107±16.3	114±12.4	t_{welch}=−1.73, *p*=0.091
Verbal Intelligence (VIQ)	101±13.5	107±11.8	t_{welch}=−1.88, *p*=0.066
Autism Diagnostic Observation Schedule (ADOS)	7.04±1.74	N/A	N/A
Social Communication Questionnaire	21.74±7.14	2.59±3.32	t_{yuen}=10.12, *p*<0.001
RiSE – AR Task Performance			
AR Hits	18.40±6.16	19.33±3.67	t_{yuen}=−0.425, *p*=0.669
AR Misses	7.32±6.26	6.92±3.51	t_{yuen}=−0.450, *p*=0.641
AR False Alarms	3.82±3.40	3.33±2.93	t_{yuen}=−0896, *p*=0.366
AR Correct Rejections	22.52±4.12	22.69±3.66	t_{yuen}=−0.281, *p*=0.782
AR *d'*	2.00±1.03	1.97±0.81	t_{yuen}=0.525, *p*=0.598

Notes: t_{yuen}: Yuen's robust *t*-test, t_{welch}: Welch's *t*-test,

*: *p*<0.05

**: *p*<0.01

***: *p*<0.001, blank: *p*≥0.05.

Table 3.

Local maxima for the relational vs. item-specific encoding contrast contrasts within the MTL mask, within the ASD and TD groups. Coordinates in Montréal Neurological Institute (MNI) space. All results *TFCE*-corrected (p<0.05).

Cluster Index	*t*-stat	MNI Coordinates			*Harvard-Oxford*
		x	*y*	*z*	
TD					
1	5	−30	−40	−12	LH-Parahippocampal Gyrus, posterior division
	4.65	−32	−34	−16	" "
ASD					
2	5.32	34	−34	−16	RH-Temporal Fusiform Cortex, posterior division
	4.66	28	−38	−4	RH-Hippocampus
	3.81	28	−20	−20	" "
	3.43	20	−12	−20	" "
1	5.99	−30	−40	−12	LH-Parahippocampal Gyrus, posterior division
	5.41	−30	−36	−8	LH-Hippocampus
ASD > TD					
1	3.13	22	−30	−10	RH-Hippocampus
	2.92	26	−36	−2	" "
	2.8	14	−38	2	" "
	2.74	28	−10	−20	" "
	2.71	26	−14	−16	" "
	2.37	36	−24	−10	" "

Table 4.

Local maxima for the parametric modulation within the MTL mask as a function of AR-*d'* and IR-*d'*. Coordinates in MNI space. All results *TFCE*-corrected ($p<0.05$).

AR-d' modulation within MTL mask in TD					
Cluster Index	***t*-stat**	**MNI Coordinates**			
		x	***y***	***z***	***Harvard-Oxford***
1	3.68	20	−8	−24	RH-Hippocampus
	3.57	24	−10	−20	" "
	3.54	26	−14	−14	" "
IR-d' modulation within MTL mask in ASD					
Cluster Index	***t*-stat**	**MNI Coordinates**			
		x	***y***	***z***	***Harvard-Oxford***
2	3.47	26	−8	−24	RH-Hippocampus
	3.34	22	−8	−24	" "
	3.32	26	−14	−20	" "
	2.65	32	−28	−10	" "
	2.41	18	−28	−12	RH-Parahippocampal Gyrus, posterior division
1	4.36	−26	−14	−24	LH-Hippocampus

Table 5.

Significant ROI-ROI connectivity results for the relational vs. item-specific encoding contrast, within TYP and between groups. Labels via Schaefer et al. (2017) 200-parcel 17-network atlas, or Ritchey et al. (2015). MNI coordinates are approximate estimates at the centroid of each ROI. Results significant after FDR correction, $q<0.05$.

Relational vs. item-specific encoding connectivity, TD		
Seed Name (MNI)	**Target Name (MNI)**	**Inferential Statistics**
RH_PHC (x=25, y=−32, z=−17)	LH_DefaultA_PCC_2 (x=−8, y=−37, z=36)	T(105)=4.01, p_{FDR}=0.005
	LH_HIPP_BODY (x=−25, y=−29, z=−11)	T(105)=3.51, p_{FDR}=0.014
	LH_DefaultB_IPL_1 (x=−57, y=−56, z=28)	T(105)=3.31, p_{FDR}=0.017
	LH_DefaultA_IPL_1 (x=−48, y=−66, z=37)	T(105)=3.24, p_{FDR}=0.017
	RH_DefaultA_PCC_1 (x=11, y=−45, z=34)	T(105)=2.88, pFDR=0.041
Relational vs. item-specific encoding connectivity, TD > ASD		
Seed Name (MNI)	**Target Name (MNI)**	**Inferential Statistics**
RH_PHC (x=25, y=−32, z=−17)	LH_DefaultA_PCC_2 (x=−8, y=−37, z=36)	T(105)=3.77, p_{FDR}=0.011
	LH_HIPP_BODY (x=−25, y=−29, z=−11)	T(105)=3.39, p_{FDR}=0.021