Report

Current Biology

A distinct route for efficient learning and generalization in autism

Highlights

- Brief memory reactivations induce improvements in ASD visual skill performance
- Learning efficiently generalized to an untrained visual location
- Evidence for a distinct route for efficient visual learning and generalization in ASD

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In brief

Visual learning with multiple stimulus repetitions may be difficult for individuals with autism spectrum disorders (ASDs) and result in poor generalization. Klorfeld-Auslender et al. report that brief memory reactivations induce efficient visual learning in ASD, with learning uniquely generalizing to untrained conditions.

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A distinct route for efficient learning and generalization in autism

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SUMMARY

Visual skill learning is the process of improving responses to surrounding visual stimuli.[1] For individuals with autism spectrum disorders (ASDs), efficient skill learning may be especially valuable due to potential difficulties with sensory processing[2] and challenges in adjusting flexibly to changing environments.[3,4] Standard skill learning protocols require extensive practice with multiple stimulus repetitions,[5–7] which may be difficult for individuals with ASD and create abnormally specific learning with poor ability to generalize.[4] Motivated by findings indicating that brief memory reactivations can facilitate skill learning,[8,9] we hypothesized that reactivation learning with few stimulus repetitions will enable efficient learning in individuals with ASD, similar to their learning with standard extensive practice protocols used in previous studies.[4,10,11] We further hypothesized that in contrast to experience-dependent plasticity often resulting in specificity, reactivation-induced learning would enable generalization patterns in ASD. To test our hypotheses, high-functioning adults with ASD underwent brief reactivations of an encoded visual learning task, consisting of only 5 trials each instead of hundreds. Remarkably, individuals with ASD improved their visual discrimination ability in the task substantially, demonstrating successful learning. Furthermore, individuals with ASD generalized learning to an untrained visual location, indicating a unique benefit of reactivation learning mechanisms for ASD individuals. Finally, an additional experiment showed that without memory reactivations ASD subjects did not demonstrate efficient learning and generalization patterns. Taken together, the results provide proof-of-concept evidence supporting a distinct route for efficient visual learning and generalization in ASD, which may be beneficial for skill learning in other sensory and motor domains.

RESULTS

Learning processes responsible for consistent improvements in visual skill performance have commonly been associated with experience-dependent mechanisms that gradually reorganize the primary visual cortices and their readout pathways.[1,12,13] This experience-dependent plasticity usually requires extensive practice and multiple stimulus repetitions,[13] and often results in over-specificity of learning, thus limiting generalization patterns.[14–16] As such, learning is both exhaustive and restricted to the learned information, such as the target's location and background.[17] Therefore, these learning protocols seem to constrain adaptive behavior that may be necessary for accurately responding to rapidly changing environments.

Autism spectrum disorder (ASD) is a neuro-developmental disorder that is defined by impairments in social communication and the presence of restricted and repetitive behaviors.[18] Many individuals with ASD also have difficulties with processing, integrating, and regulating sensory stimuli.[2] For individuals with ASD, improving skill performance via intensive repetition-based practice is commonly used in learning protocols and treatment approaches;[3,19] however, the efficacy of repetitive learning approaches with respect to perceptual learning is less clear.[20] Interestingly, in terms of generalization in ASD, it was shown that repetition training results in over-specificity of visual learning. Furthermore, it was shown that generalization patterns can be enhanced by reducing sensory adaptation.[4]

Here, we examined whether learning that is based on memory reactivations, i.e., brief task reminders that retrieve visual learning without practice,[8] would enable successful learning and generalization in ASD. Such reactivation-based learning, which consists of several trials each instead of hundreds, may induce plasticity that is not dependent on repetitive experience,

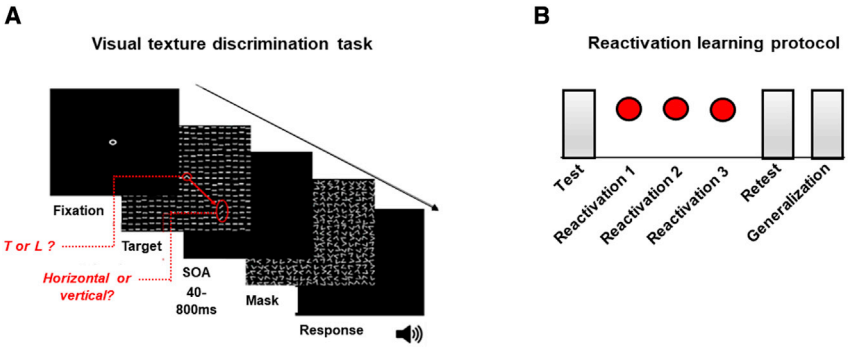

Figure 1. Visual memory-reactivation learning task and protocol of experiment 1

(A) Visual texture discrimination task (TDT): example trial. Subjects maintained fixation while discriminating between horizontal or vertical orientations of a peripheral target consisting of three diagonal bars surrounded by horizontal lines. The target was presented briefly and followed by a patterned mask. The time between target and mask (SOA) was varied within the session to obtain a psychometric curve, from which the SOA discrimination threshold was derived. A letter discrimination task (T/L) was used to enforce fixation.

(B) Visual memory-reactivation learning protocol. Following the initial encoding test session, subjects performed three reactivation sessions, in which five reminder trials were performed using supra-threshold SOA (400 ms) in order to evoke the neural trace of the already consolidated visual memory. On the fifth session, subjects were retested on the visual task and the final visual discrimination thresholds were measured. Finally, to test whether reactivation learning generalized across retinotopic locations, subjects performed the same task at a different location in the visual field. Every two consecutive sessions were separated by 2 days, to stabilize memory processes.

thus offering a rapid form of perceptual learning.[8] We therefore reasoned that brief memory reactivations would successfully induce learning in ASD. Moreover, we hypothesized that reactivation-induced learning would enable generalization of ASD learning across retinal locations.

To test these hypotheses, we had ASD individuals and aged-matched neurotypical (NT) controls perform memory reactivations of a basic visual discrimination task (STAR Methods) that usually requires extensive practice for demonstrating improvement[4,17] (experiment 1). Such reactivations were previously shown to induce learning in NTs.[8] In this task, subjects are required to determine the orientation of a peripheral target embedded within a background, while fixation is enforced by a forced-choice letter discrimination task (Figure 1A). In the initial encoding session, subjects practiced the task and then their individual thresholds were extracted. On each of the following three sessions, subjects came for a short memory reactivation, i.e., only five reminder trials to retrieve the learned task without extensive practice. Then, a full retest session was performed in order to measure post-learning visual thresholds. On the last session, the position of the peripheral target changed, and subjects were required to generalize performance to the new retinotopic location, without additional practice (Figure 1B). This generalization test following reactivation learning was important, since when a similar cohort of age- and gender-matched ASD subjects was tested with the same task but under extensive-learning conditions, generalization failed.[4] An additional experiment was conducted to test whether learning and generalization gains in ASD would emerge without memory reactivations. Thus, in experiment 2, ASD subjects performed the same test, retest, and generalization sessions, but without memory reactivations (STAR Methods).

In order to replicate such experimental designs, customary sample sizes for psychophysical measurements were used (STAR Methods), similar to those employed in the field including in reactivation-induced learning[8,9] and in ASD perceptual learning studies,[4,10,20,21] with each subject yielding large amounts of temporal data for perceptual threshold analyses. Thus, critically, all end point measures (test, retest, and generalization thresholds) were derived from extensive sessions (n = 288 trials each) and not from the reactivation sessions (n = 5 trials each), which were the actual intervention. Therefore, as in previous psychophysical studies, reliable end point measures are derived within each subject, resulting in high power and inferential validity, in accordance with similar statistical approaches.[22]

The common end point measure of perceptual learning was used, as the difference between initial test and final retest thresholds, accounting for the inherent and commonly observed pre-learning test threshold variability.[4,8,12] Memory reactivations induced significant learning in the ASD group, measured as improvements in the individual visual thresholds between test (mean = 140.4 ± 10.2 ms SE) and retest (mean = 106.0 ± 6.3 ms) sessions (Wilcoxon signed-rank test, $p = 0.001$) (Figures 2A and S2A). These results demonstrate that ASD individuals successfully learned with brief reactivations of only 5 trials each.

NT individual thresholds also improved significantly between test (mean = 109.4 ± 9.5 ms) and retest (mean = 82.1 ± 9.0 ms) sessions ($p = 0.005$, Wilcoxon signed-rank test) (Figures 2B and S2A). As expected, performance in the test session showed a trend indicating superior NT performance (Mann-Whitney U tests, $p = 0.063$). Importantly, the magnitude of learning was comparable between groups (mean test-retest improvement of 22.3% ± 3.8% in ASD, 25.8% ± 3.9% in NT, Mann-Whitney U tests, $p = 0.457$) (Figure 2C). Additional analysis on the absolute threshold difference confirmed the comparable learning effects (ASD, 34.4 ± 7.6 ms; NT, 27.3 ± 3.7 ms, $p = 0.951$). The results of comparable magnitude of learning between groups were maintained when initial thresholds were included as a covariate in the analysis (ANCOVA, $p = 0.327$; STAR Methods).

To evaluate whether learning was generalized to the new retinotopic location, we compared the individual thresholds measured at the generalization session to those measured at the test session. Interestingly, reactivation-induced learning facilitated ASD generalization patterns, measured as improved thresholds at the generalization session (mean = 103.1 ± 9.8 ms), compared with the test session ($p = 0.005$, Wilcoxon signed-rank test for paired samples) (Figures 2A and S2A). In line with results obtained by standard visual learning protocols,[12] NT individuals did not show efficient generalization (mean = 103.8 ± 9.7 ms, $p = 0.103$, Wilcoxon signed-rank test), with a highly consistent V-shaped pattern (Figures 2B and

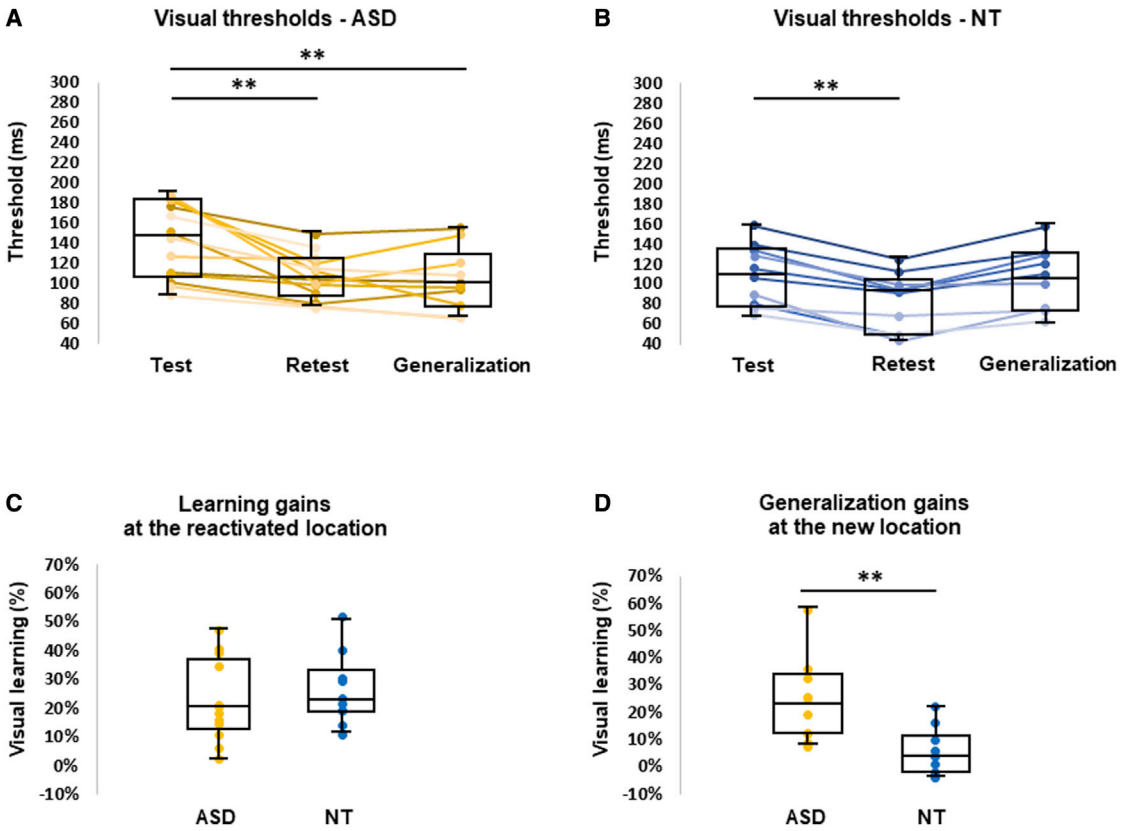

Figure 2. Reactivation learning and generalization

(A) Individual visual thresholds in all sessions for individuals with ASD (test, n = 13; retest, n = 13; generalization, n = 10; STAR Methods). Accordingly, between-session comparisons were conducted independently on test-retest (n = 13) and test-generalization (n = 10) threshold improvements. Each shaded data point represents one subject's performance along the full experiment.

(B) Individual visual thresholds in all sessions (test, retest, and generalization, all n = 10) for neurotypical (NT) individuals.

(C) Individual learning gains at the reactivated location, measured as improvement between test and retest sessions.

(D) Individual generalization gains at the new location, measured as improvement between test and generalization sessions.

In all plots, the squares denote the boxplots. Each box shows the median value (horizontal line inside each box) and the 25th and 75th percentiles (lower and upper limits of each box, respectively). In all boxplots, the whiskers cover the range of the data. See also Figure S2. **p < 0.01.

S2A). Correspondingly, individuals with ASD had significantly greater generalization gains relative to NTs (mean test-generalization improvement of 23.5% ± 4.9% in ASD, 5.2% ± 2.7% in NT, Mann-Whitney U test, p = 0.003) (Figure 2D). Additional analysis on the absolute threshold difference confirmed that ASD subjects obtained significantly greater generalization gains relative to NT subjects (ASD, 34.9 ± 9.6 ms; NT, 5.6 ± 3.1 ms, p = 0.002). These results were maintained when initial thresholds were included as a covariate in the analysis (ANCOVA, with a significant effect of group, p = 0.01).

A complementary repeated-measures mixed-model ANOVA on ranks with session as a within-subject factor and group as a between-subject factor showed a significant interaction ($F_{2,39.255} = 5.036$, p = 0.011). As expected, post hoc comparisons verified significant improvements between test and retest sessions in both groups (ASD, p < 0.001; NT, p < 0.001) and test-generalization improvement in ASD subjects and not in NTs (ASD, p < 0.001; NT, p = 0.266).

To assure that all subjects performed the task as instructed and focused their gaze on the center of the screen, we verified that the average hit rate of the central letter task over all stimulus onset asynchronies (SOAs) maintained a high level of performance across test (ASD, mean hit rate = 90.5% ± 1.1%; NT, 95.0% ± 1.1%), retest (ASD, 92.7% ± 1.3%; NT, 97.2% ± 0.7%), and generalization (ASD, 91.8% ± 2.9%; NT, 96.8% ± 0.8%) sessions. Consistent with the results of the peripheral task, performance in the initial test session was higher for NT relative to ASD subjects (Mann-Whitney U test, p = 0.041). Importantly, the small test-retest improvements (ASD, 2.4% ± 0.9%; NT, 2.4% ± 1.4%, p = 0.324) and test-generalization improvements (ASD, 0.6% ± 2.4%; NT, 1.9% ± 1.4%, p = 0.174) were comparable across groups. In addition, the hit rate for the central letter discrimination task was verified to be above chance level even at the lowest SOAs (Wilcoxon signed-rank test for one sample, p < 0.05 for all tests).

Next, we analyzed the reaction times for each session and group. In accordance with previous findings,[4] ASD subjects demonstrated slower reaction times compared with NT subjects along all experimental sessions. Both groups demonstrated test-retest and test-generalization improvements (Figures S2B and

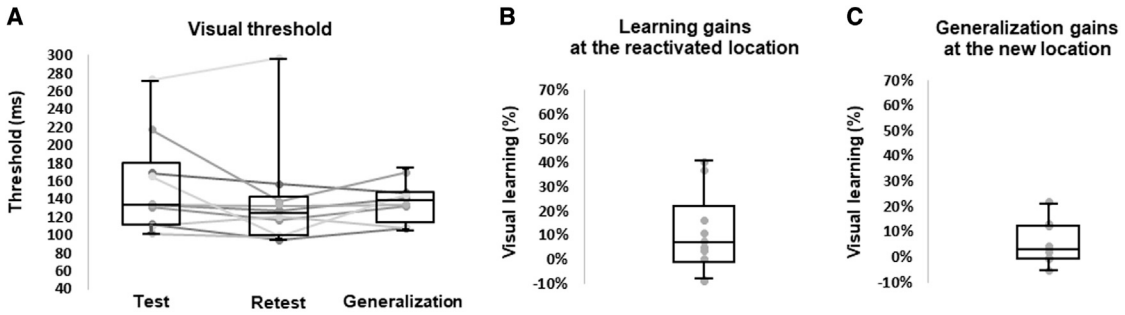

Figure 3. Measuring learning and generalization without memory reactivation

(A) Individual visual thresholds in all sessions (test, n = 10; retest, n = 10; generalization, n = 8; STAR Methods). Accordingly, between-session comparisons were conducted independently on test-retest (n = 10) and test-generalization (n = 8) threshold improvements. Each shaded data point represents one subject's performance along the experiment.

(B) Individual learning gains at the reactivated location, measured as improvement between test and retest sessions.

(C) Individual generalization gains at the new location, measured as improvement between test and generalization sessions.

In all plots, the squares denote the boxplots. Each box shows the median value (horizontal line inside each box) and the 25th and 75th percentiles (lower and upper limits of each box, respectively). In all boxplots, the whiskers cover the range of the data.

See also Figure S3.

S2C), the latter in line with the suggestion that reaction times may reflect general motor and cognitive factors of the task beyond visual learning per se.[23]

Could learning and generalization gains in ASD emerge without memory reactivations? To address this question, we conducted an additional experiment in which a similar age and gender cohort of ASD subjects underwent the same test, retest, and generalization sessions, but without memory reactivations (STAR Methods).

The results showed that without memory reactivations, there was no significant learning between test (mean = 154.6 ± 17.1 ms) and retest (mean = 137.9 ± 18.8 ms) sessions (Wilcoxon signed-rank test, p = 0.114; Figures 3A and S3A; test-retest difference 10.1% ± 5.3%; Figures 3B and S3A). A complementary analysis showed that baseline thresholds of no-reactivation ASD subjects were comparable to those of ASD subjects who underwent reactivations (Mann-Whitney U test, p = 0.620). An additional between-experiments confirmatory analysis showed that ASD learning without reactivations was smaller than learning with reactivations (exp1, 22.3% ± 3.8%; exp2, 10.1% ± 5.3%, Mann-Whitney U test, p = 0.047). This trend was also evident in an additional absolute performance differences analysis (exp1, 34.4 ± 7.6 ms; exp2, 16.6 ± 10.2 ms, p = 0.072).

Without reactivations there was no significant generalization (135.5 ± 7.3 ms, p = 0.161; Figure 3A; test-generalization difference 5.8% ± 3.2%; Figure 3C). An additional analysis revealed that generalization gains were superior following memory reactivations compared to without reactivations (exp1, 23.5% ± 4.9%; exp2, 5.8% ± 3.2%, p = 0.009), which was also evident in an absolute performance differences analysis (exp1, 34.9 ± 9.6 ms; exp2, 10.9 ± 6.3 ms, p = 0.026), further pointing to the beneficial role of memory reactivations in enhancing generalization in ASD.

Subjects in the second experiment performed the task as instructed, focusing their gaze on the letter at the center of the screen, as indicated by the high hit rates across all SOAs (mean hit rate, test = 93.3% ± 1.1%, retest = 93.4% ± 1.4%, generalization = 94.5% ± 1.2%). In addition, the hit rate for the central letter discrimination task was verified to be above chance level even at the lowest SOAs (Wilcoxon signed-rank test for one sample, $p < 0.05$ for all tests). Reaction times again showed general test-retest and test-generalization improvements (Figure S3B).

DISCUSSION

The results indicate that brief memory reactivations induced improvements in ASD visual skill performance. Thus, ASD individuals successfully learned with brief reactivations of only 5 trials each instead of hundreds of trials. Importantly, the magnitude of learning was comparable to NTs, suggesting that offline learning mechanisms operate efficiently in ASD and enable successful learning even without extensive practice, which in itself is highly efficient in ASD.[4] This result is consistent with the notion that "practice makes perfect" is not the only route for skill acquisition, which has received support in previous studies.[8,24,25] In addition, ASD participants efficiently generalized their learning to an untrained visual location. Such generalization fails when a similar cohort of age- and gender-matched ASD subjects perform the same task under extensive practice conditions.[4] Finally, an additional experiment without memory reactivations showed that ASD subjects did not demonstrate efficient learning and generalization patterns.

Our reactivation learning protocol utilizes the framework of memory reactivations as a mechanism for skill modifications.[8] This framework is based on findings showing that following retrieval, memory is susceptible to external and internal alterations, presumably due to the effects of offline neural mechanisms that reconsolidate the memory trace, thus allowing continuous memory updating.[26,27] Accordingly, with each reactivation, the original memory trace may be subsequently strengthened offline,[8,28] providing sufficient conditions for efficient learning without extensive practice. Studies of motor skill learning have also shown that an already consolidated

skill can be modified upon its reactivation.[24,29–32] Based on these commonalities in memory processes, which are shared across skill domains,[5] it would be valuable to test whether reactivation learning may be beneficial for skill learning in other domains[33–36] with potential clinical utility for education and treatment protocols in ASD. Of note, in the current study, we used constant supra-threshold reactivations. However, it is plausible that other reactivation conditions, such as near-threshold reminders, would facilitate learning and generalization in ASD.

Interestingly, individuals with ASD exhibited generalization patterns, potentially pointing to a different reactivation-induced learning mechanism relative to NTs. For example, this may suggest that reactivation-induced learning engages high-order representations that are not restricted to specific low-level retinotopic locations in ASD. Furthermore, a recent study[4] that tested generalization of visual discrimination thresholds found that reducing visual adaptation by inserting non-target trials between stimulus repetitions eliminated over-specificity in ASD. Accordingly, memory reactivations and the absence of extensive training may also prevent adaptation, thus allowing for generalization patterns to emerge in individuals with ASD. In addition, it is conceivable that similar to ''fast learning'' mechanisms that are engaged in initial training,[6,37] memory reactivations may enable ASD participants to learn general aspects of the task, possibly by engaging higher-order regions that communicate with early visual areas that encode the task.[38] In turn, this may facilitate generalization of learning, which is absent in extensive training conditions,[15,39] showing high specificity to trained stimulus features[16,40–45] (but see single condition in Harris et al.[4]). The relation between these mechanisms and reactivation-induced learning in ASD remains to be determined. There are several limitations associated with the current study. First is its focus on a model perceptual learning task. Second, the current study shows both ASD learning and generalization following reactivations, and minimal ASD learning and generalization without reactivations. Insights regarding the conditions of standard extensive ASD perceptual learning and lack of efficient generalization were based on previous experiments with the same task and similar cohort of ASD subjects.[4] Third, the study would have further benefited from additional replications of all groups and conditions. In order to better substantiate and understand reactivation-induced learning in ASD, it would be of interest to replicate and explore in future studies additional visual tasks and learning modalities.

In sum, the results provide proof-of-concept evidence supporting a distinct route for efficient learning and generalization in ASD, which may have further benefits for skill learning in other sensory and motor domains where individuals with ASD exhibit difficulties. These results may, therefore, have important clinical utility in a variety of educational and behavioral intervention contexts.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- QUANTIFICATION AND STATISTICAL ANALYSIS
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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cub.2022.05.059.

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AUTHOR CONTRIBUTIONS

S.K.-A., Y.P., I.D., and N.C. designed the study. S.K.-A., Y.P., and I.S. performed the research. S.K.-A. and Y.P. analyzed the data. S.K.-A., J.R., I.D., and N.C. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
MATLAB	MathWorks	https://www.mathworks.com/
SPSS Statistics 27	IBM	https://www.ibm.com/analytics/us/en/technology/spss

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to and will be fulfilled by the lead contact, Nitzan Censor (censornitzan@tauex.tau.ac.il).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Non-clinical data reported in this paper and any additional information for their analysis will be shared by the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

29 subjects participated in the first experiment, 17 diagnosed with ASD (two females, average age 28.8 years, SD=9.9 years), and 12 aged matched male NT controls (average age 27.0 years, SD=4.0 years). 14 subjects diagnosed with ASD participated in the second experiment (three females, average age 28.2 years, SD=10.4 years). The experiments were approved by the Ben Gurion University and Tel Aviv University Institutional Ethics Committees. All subjects were healthy, did not report any genetic or metabolic disorders and had no history of traumatic brain injury or seizures. All participants had normal or corrected to normal vision, were not video gamers, did not participate in other visual experiments during the current experiment period and reported at least 6 hr of sleep the night before each experimental session.

One ASD subject in exp1 and two in exp2 did not meet the initial practice inclusion criteria (see below). Three ASDs and two NTs in exp1, and two ASDs in exp2, performed repeated mistyping errors and did not maintain fixation, which prevented reliable measurement of their peripheral discrimination thresholds. As for the peripheral target, outlier analysis did not identify extreme values in baseline performance or learning gains. Accordingly, 23 subjects in exp1 (13 ASD) and 10 in exp2 completed all sessions. Three ASDs in exp1 and two in exp2 were not included in the generalization analyses and comparisons to other sessions due to repeated mistyping errors and extreme[46] generalization scores outside the range of 1.5*IQR (inter quartile range).

All participating ASD subjects provided proof of a formal diagnosis of autism that were performed by both a clinical psychologist and a psychiatrist or neurologist according to DSM-IV-TR[47] or DSM-5[18] criteria. All ASD subjects were high-functioning adults with no indications of significant intellectual deviations from the general population and were not required legal guardianship. In addition, ASD symptom severity was assessed with the Autism Quotient (AQ)[48] that measures autistic traits (first experiment: mean ASD score 25.3±2.8, range 15-44; NT 12.3±1.6, range 1-19; groups significantly different (Mann-Whitney U-test, $p<0.001$); second experiment: 32.60±2.38, range 21-43).

METHOD DETAILS

Stimuli and task

All participants performed a modified version of the well-characterized visual discrimination task that was previously used for testing ASD subjects.[4] In each trial, a target frame (40 ms) was followed by a patterned mask (100 ms; Figure 1A). Participants were asked to discriminate whether a target stimulus, consisting of three diagonal bars, was horizontal or vertical. The target stimulus was always presented at the same peripheral location (at the lower right quadrant of the visual field at 5.71°), and embedded in a background of horizontal bars (19 × 19, 0.58° × 0.04° each, spaced 0.82° apart with 0.04° jitter). Fixation was enforced by a forced-choice letter discrimination task ("L" or "T" at the center of the display) with auditory feedback for errors. Display size was 15.6° × 15.1° (viewed from 100 cm away on a 20-inch CRT HP p1230 monitor, refresh rate 100 Hz, mean texture luminance 80.2 cd/m2). The subjects were requested to respond as accurately as they can to both texture and letter discrimination tasks. The intervals between the target and

the mask stimuli (stimulus onset asynchrony [SOA], measured from the onset of the target to the onset of the mask) ranged from 40 to 800 ms (40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 260, 300, 400, 500, 700 and 800 ms). To assure similar exposures to the range of SOAs along the experiment, each session consisted of nine blocks, with two trials per SOA that appeared continuously and in random order within each block (for a total of 288 trials over nine blocks). Each trial was self-initiated by the observer, resulting in ~2-s intertrial interval. To familiarize the subjects with the task, each subject performed three training phases with pre-defined criterions. First, subjects performed blocks of 10 non-masked trials, repeatedly until reaching 100% correct responses for both targets. Afterwards, pretraining blocks of 10 trials at 800 ms SOA were repeated until subjects reached 90% correct responses (a maximum of 10 blocks, after which subjects who did not reach the criterion did not participate in the experiment). Pretraining blocks were followed by a short familiarization block of a single trial per each SOA.

Experimental design

To test whether reactivation learning would facilitate visual skill performance in ASD individuals, we employed a reactivation-learning protocol[8] using a well-established visual discrimination task[12,17] in both neurotypical and ASD individuals (experiment 1, Figure 1B). On the first day, all subjects practiced and then completed a full test session of the modified TDT, to encode the skill and determine the visual threshold. On the following three sessions, subjects came for short memory reactivations (only five reminder trials per session). All reactivation trials were constant at 400 ms SOA, which was much higher than all individual visual thresholds. Then, to test if the reactivation sessions facilitated visual thresholds, all participants performed a full session again (i.e., retest session). Lastly, to test if performance was generalized across retinotopic locations, participants performed a full session at a new peripheral position (i.e., generalization session). Prior to the generalization session, subjects were verbally instructed to perform the same task. Similar to the original reactivation protocol,[8] every two consecutive sessions were separated by two days, to stabilize memory processes. Participants in both ASD and NT groups underwent the same procedure.

In the second experiment, we tested whether learning and generalization effects could emerge without memory reactivations. Subjects underwent the same experimental procedure, with equally spaced test, retest and generalization sessions, but without memory reactivations in between sessions.

QUANTIFICATION AND STATISTICAL ANALYSIS

Data analysis

The perceptual visual threshold of the texture discrimination task (horizontal/vertical) was measured for each session using a standard Weibull fit for a psychometric curve derived from the nine experimental blocks, with slope β and finger error (mistyping) parameter 1 – p, yielding the function:[49]

$$P(t) = p\left\{1 - \frac{1}{2}\exp\left[-\left(\frac{t}{T}\right)^{\beta}\right]\right\} + \frac{1-p}{2} = \frac{1}{2}\left\{1 + p\left[1 - \exp\left[-\left(\frac{t}{T}\right)^{\beta}\right]\right]\right\}$$

where T is the threshold for each curve, defined as the minimal time between the target onset and mask (SOA) for which 81.6% of responses were correct. To estimate the goodness of fit of the Weibull function, R-square was calculated for each individual curve. In the first experiment, R-square values were high for ASD subjects along the test (mean R-square: 0.82±0.04), retest (0.88±0.03) and generalization (0.87±0.03) sessions. Similarly, high R-square values were also observed for NT subjects in the test (0.89±0.02), retest (0.90±0.02) and generalization (0.89±0.02) sessions. In the second experiment, R-square values for ASD subjects were high across test (0.83±0.03), retest (0.81±0.05) and generalization (0.81±0.03) as well (for illustration of group-level psychometric curves and goodness of fit assessments – see Figure S1 in the Supplemental Information). One ASD subject in the second experiment demonstrated unexpected low performance in the four longest SOAs, a difficulty which was also reported by the subject during the experimental session and prevented a reliable estimation of the Weibull fit. Accordingly, the calculation of the baseline test threshold was conducted without the four longest SOAs.

Reliability of baseline visual thresholds: In line with previous studies of the texture discrimination task,[7,8,25,50] the visual thresholds were extracted over all trials within a session. To further investigate potential effects of initial within-session learning, we recalculated the visual thresholds without the first couple of blocks in which subjects might demonstrate poorer performance. This resulted in a Weibull fit based on the last 7-blocks of each session. The results show that the 7-blocks thresholds were highly similar to the original thresholds (Experiment 1: ASD: 136.8±10.7 ms and 140.4±10.2 ms, NT: 110.9±9.5 ms and 109.4±9.5 ms; Experiment 2: 153.4±17.6 ms and mean=154.6±17.1 ms), indicating that the baseline threshold reliably reflected performance in the session.

Statistical analysis

Perceptual thresholds were extracted for each session separately. Non-parametric testes were used to avoid influences of extreme values. Non-parametric Wilcoxon signed-rank tests for paired samples were performed to evaluate within-subject–level changes in performance. To compare the magnitude of learning and generalization percentage between groups, the individual thresholds at each session were normalized to the test baseline session. Additionally, the between-groups analyses were also conducted on the absolute difference in threshold (in ms). Differences between groups were evaluated via non-parametric Mann-Whitney tests. Adjustments for multiple comparisons in each experiment were conducted with Holm-Bonfferoni correction.[51] Between-session

comparisons were performed when data existed across sessions, thus using statistical analyses of paired samples. To control for the effect of baseline test thresholds on the differences in learning and generalization gains between groups, a non-parametric analysis of covariance (ANCOVA on ranks) was conducted with baseline ranks as covariate. A complementary repeated-measures mixed models ANOVA on ranks was conducted to verify the interaction between group (NT/ASD) and session (test/retest/generalization) factors in the first experiment.