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RESEARCH ARTICLE

Arousal-modulated memory encoding and retrieval in adults with autism spectrum disorder

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Abstract

Recently, we have shown that pupil dilation during a recognition memory task can serve as an index of memory retrieval difficulties in autism. At the time of publication, we were unaware of specific data-analysis methods that can be used to shed further light on the origins of such memory related pupil dilation. Specifically, by distinguishing “tonic” from “phasic” changes in pupil dilation and considering their temporal progression, it is possible to draw inferences about the functional integrity of a locus coeruleus—norepinephrine system (LC-NE) that is known to play a key role in regulating memory encoding and retrieval processes. We therefore apply these analyses to our previously published eye-tracking data of adults with ASD ($N = 24$) and neurotypical development (TD, $N = 30$) during the recognition memory task. In this re-analysis, we related pupil dilation during encoding and retrieval to recognition accuracy in a per-trial analysis of linear mixed models. In ASD, we replicated attenuated recognition accuracy, which was accompanied by attenuated pupil dilation during encoding and retrieval. Group differences in pupil dilation during retrieval occurred late during the trial (after 1.75 s) and indicated an altered top-down processing like attenuated attribution of semantic salience in response to previously encoded stimuli. In addition, only in the ASD group were higher pupil dilation during encoding and lower pupil dilation during retrieval associated with decreased recognition accuracy. This supports altered modulation of memory encoding and retrieval in ASD, with LC-NE phasic activity as promising underlying mechanism.

Lay Summary: We investigated the changes of pupil size during memory testing in autism spectrum disorder. Adults with ASD remembered fewer items correctly than neurotypical individuals (TD). This reduced memory was related to increased pupillary responses at study and decreased pupil dilation at test only for adults with ASD indicating a different modulation of memory by the locus coeruleus.

KEYWORDS

ASD, locus coeruleus—norepinephrine system, memory, pupillometry

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INTRODUCTION

Memory is not a record of the past, but rather a sequence of subjectively relevant associations. Atkinson and Shiffrin (1971) distinguished between a short-term memory (STM) with limited and fleeting storage, and a long-term memory (LTM) with unlimited and permanent storage. Memory formation or learning describes the transfer of information from STM to LTM, and is defined by the quality of information encoding (i.e., information processing and consolidation) and retrieval (i.e., access to processed information). Arousal is a physiological state of sensory readiness (Mather & Sutherland, 2011) and has been suggested to modulate memory encoding and retrieval (Sara, 2015), which might explain altered memory performance in autism spectrum disorder (ASD).

In a meta-analysis, Desautay et al. (2020) showed significantly lower memory performance in ASD compared to neurotypical development (TD) on STM tasks with a medium effect size and significant heterogeneity, and on LTM tasks with a small effect size without significant heterogeneity. Lower memory performance was pronounced during recall (i.e., uncued retrieval) compared to cued recall and recognition (i.e., cued retrieval). Others emphasized an impaired recognition ability in ASD to distinguish between previously studied and new items during retrieval (Bowler et al., 2000; Gardiner et al., 2003). However, these previous studies focused on retrieval performance in ASD and thus it remains unclear whether different encoding contributes to lower memory performance.

Eye-tracking captures gazes as overt visual attention, which has been applied to disentangle the effect of encoding and retrieval on memory performance in ASD versus TD. In a recognition task of previously studied versus new static images, explorative gaze behavior during encoding was associated with better recognition accuracy in TD (Cooper et al., 2017). In ASD, a lower recognition accuracy was found and accompanied by a lower similarity of gaze behavior between encoding and retrieval. The lower recognition accuracy has been attributed to a different attention allocation during encoding (Bodner et al., 2019) and may relate to domain-general findings of altered attention function in ASD (Landry & Parker, 2013; Van der Hallen et al., 2015). We proposed that neurophysiological mechanisms underlying arousal might explain this altered attention function (Bast et al., 2018) and provided evidence of altered arousal modulation in ASD (Bast et al., 2021). Arousal might represent a shared neurophysiological mechanism of altered attentional function and lower memory performance in ASD. Arousal is indexed by pupillometry in eye-tracking (Murphy et al., 2011), which can be applied to investigate the implication of arousal in lower memory performance in ASD.

Arousal regulation has been attributed to the locus coeruleus—norepinephrine system (LC-NE) (Nassar

et al., 2012; Sara & Bouret, 2012). The LC-NE releases cortical norepinephrine which emphasizes input-driven sensory processing (McBurney-Lin et al., 2019). The LC-NE displays two concurrent types of activity (Aston-Jones & Cohen, 2005). LC-NE *tonic* activity changes slowly and coincides with transitions in the general arousal level (Murphy et al., 2011). LC-NE *phasic* activity is inversely related to tonic activity (Aston-Jones & Cohen, 2005) and describes transient bursts in activity that are associated with an increased reactivity to salient stimuli (Mather et al., 2016). Thus, LC-NE tonic and phasic activity index interrelated functions of arousal that have been argued to emphasize memory formation (Sara, 2015).

An arousal modulation of memory formation has been explained by an online encoding mechanism, in which (sensory and semantic) stimulus salience is evaluated by anterior insula and amygdala (Uddin, 2015) that leads to increased LC-NE phasic activity in response to salient stimuli (Vazey et al., 2018). The LC-NE phasic activity is expected to emphasize long-term potentiation via LC-hippocampus connectivity in support of encoding (Sara, 2015). This is underlined by an up-regulation of LC-NE activity during memory encoding in neurotypical adults, which was associated with improved memory retrieval and increased activity in the parahippocampal cortex (Clewett et al., 2018). Arousal modulation of memory formation is further achieved by an offline consolidation mechanism related to LC-NE tonic activity, in which NE release in the medial prefrontal cortex (mPFC) supports building up proteins relevant to memory formation (Sara, 2015). This is underlined by gamma band oscillations between LC-NE, hippocampus, and mPFC (Bosman et al., 2014). The arousal modulation of memory formation is characterized by LC-NE phasic activity in memory encoding and LC-NE tonic activity in memory consolidation. Thus, the impact of arousal on impaired memory performance in ASD could be investigated by the assessment of LC-NE tonic and phasic activity during memory tasks.

LC-NE activity as a neurophysiological correlate of arousal is indexed by pupillometry (Joshi et al., 2016; Murphy et al., 2014), where baseline pupil size (BPS) indicates LC-NE tonic activity and stimulus-evoked pupillary response (SEPR) indicates LC-NE phasic activity. Encoding-evoked pupillary response (EEPR) is differentiated from SEPR to dissociate LC-NE phasic activity during encoding versus retrieval. In neurotypical development, EEPR and SEPR distinguished between correctly and falsely remembered items at retrieval (Montefinese et al., 2013; Papesh et al., 2012). In addition, larger EEPR and SEPR have been associated with a higher likelihood of successful retrieval (Kucewicz et al., 2018). Kuipers and Phillips (2020) further reported that a smaller BPS was related to better memory retrieval for word lists, and thus indicated that a relatively lower general arousal during wakefulness might enhance performance

(Gilzenrat et al., 2010). It has also been suggested that early pupillary dilation during retrieval reflects spontaneous recognition associated with stimulus-evoked arousal (“bottom-up”), whereas later pupillary dilation is rather influenced by cognitive demand (“top-down”) (Mill et al., 2016). Pupillometry is a versatile method that can be applied to index various psychological functions and associated brain activities (Peinkhofer et al., 2019) that converge on a modulation of LC-NE activity (Poe et al., 2020). In the context of memory function, pupil size (BPS) and pupillary responses (EEPR, SEPR) can be applied to index LC-NE tonic and phasic activity during different stages of the memory process and thus quantify arousal-modulated memory encoding and retrieval.

Arousal-modulated memory encoding and retrieval in neurotypical development has been characterized by the pupil Old/New effect, which is an increased SEPR during memory retrieval for previously studied (“Old”) compared to new stimuli (Goldinger & Papesh, 2012). This has been shown for different materials (Otero et al., 2011) and can even be replicated in infants (Hellmer et al., 2018). It indicates LC-NE phasic activity in response to previously studied stimuli. The pupil Old/New effect might be explained by an arousal-based salience signal associated with previous encoding (EEPR) (Sara, 2015) that serves as a discriminative cue during retrieval (SEPR). This is supported by previous studies that associated a larger SEPR with more successful retrieval of auditory materials (Papesh et al., 2012), whereas a smaller EEPR has been associated with retrieval performance for visual items (Kafkas & Montaldi, 2011). In contrast, Vö et al. (2008) found no relation between EEPR and later retrieval performance for words. Previous pupillometry studies in memory suggest that LC-NE based modulation of memory performance may explain the pupil Old/New effect.

We conducted the only previous investigation on the pupil Old/New effect in ASD compared to TD (Ring et al., 2020). We replicated the pupil Old/New effect in TD, while pupillary responses did not differ between old and new items in ASD. This was accompanied by a lower recognition rate (hits minus false alarms) in ASD compared to TD. Atypical encoding, which is modulated by LC-NE activity as a neurophysiological mechanism of arousal, may contribute to this altered pupil Old/New effect and impaired retrieval performance in ASD. However, the scope of the initial analysis was limited to pupillary responses during retrieval, while the recent meta-analysis (Desaunay et al., 2020) highlighted the need to differentiate between encoding and retrieval processes.

Thus, the main objective for the present study is to quantify arousal-based modulation of encoding and retrieval and relate it to memory performance. This is an enhanced re-analysis of the previously published data (Ring et al., 2020). Pupillometry is now applied to index

LC-NE tonic (BPS) and phasic (EEPR, SEPR) activity as an underlying mechanism of arousal-modulated memory formation. This is investigated with improved methods by a per-trial analysis to emphasize within trial effects. (1) We hypothesize memory difficulties in ASD during retrieval as attenuated recognition accuracy. In addition, (2) we exploratively investigate EEPR and SEPR as indicators of LC-NE phasic activity between groups to quantify arousal-modulated memory encoding and retrieval, respectively. This is controlled for BPS as indicator of LC-NE tonic activity, given the inverse relationship with LC-NE phasic activity. We further hypothesize (3) that group differences in arousal-modulated memory encoding and/or retrieval will be associated with attenuated recognition accuracy in ASD. This would support that memory retrieval difficulties in ASD are related to arousal-based modulation of memory encoding and retrieval with altered LC-NE phasic activity as an underlying mechanism.

METHODS

Participants

The sample consisted of 24 ASD and 30 TD adults that were matched on gender, $X^2 = 0.66$, $p = 0.42$, chronological age and Intelligence Quotient (IQ) as measured by the third or fourth edition of the Wechsler Adult Intelligence Scale (WAIS-III^{UK} or WAIS-IV^{UK}; see Table 1) (Wechsler, 1999, 2010). The sample was the same as reported in Ring et al. (2020), but three additional participants with ASD were excluded due to insufficient eye-tracking data quality (i.e., less than 40% of valid trials). Participants had (near-)native competence in English and were recruited through a research database of the Autism Research Group at City, University of London. Additional participants were recruited through newspaper advertisements, flyers, and word of mouth. ASD individuals were included when they had received a clinical diagnosis of ASD according to DSM-IV-TR criteria (American Psychiatric Association, 2000) prior study within the UK National Health Service. TD individuals were included if they did not have a personal history of a psychological disorder or a personal or family history of a neurodevelopmental disorder and did not take psychotropic medication, drugs, or drank alcohol excessively. All participants filled in the Autism-Spectrum Quotient (AQ); (Baron-Cohen et al., 2001). All TD individuals were required to score below the AQ cut-off score of 26 (Woodbury-Smith et al., 2005). Further, 21 ASD individuals were available to take part in the Autism Diagnostic Observation Schedule (ADOS-2) (Lord et al., 2012) administered by trained researchers (see Table 1). All participants were reimbursed for their time and travel expenses.

TABLE 1 Descriptive statistics for autism spectrum disorder (ASD) and typically developing (TD) individuals

Measure	ASD (21m, 3f)		TD (23 m, 7f)		<i>t</i> (<i>df</i>)	Cohen's		
	M	<i>SD</i>	M	<i>SD</i>		<i>p</i>	<i>d</i>	CI
Age (years)	41.8	11.5	43.9	12.7	0.41 (52)	0.52	0.18	−0.36, 0.72
VIQ/VCI ^a	110	14.3	113	14.0	0.64 (52)	0.42	0.22	−0.32, 0.76
PIQ/PRI ^b	106	15.2	106	13.8	0.01 (52)	0.94	0.02	−0.55, 0.52
FIQ ^c	110	14.7	110	13.4	0.00 (50)	0.99	0.00	−0.54, 0.55
AQ ^d	36.0	6.3	15.0	6.6	140 (52)	0.00	3.32	2.22, 4.38
BPS ^e encoding	2.85	0.37	2.76	0.33	0.79 (49)	0.37	0.26	−0.82, 0.31
BPS ^e retrieval	3.07	0.38	2.99	0.36	0.55 (52)	0.46	0.21	−0.74, 0.34
ADOS-C ^f	2.6 (0–5)	1.3						
ADOS-RSI ^g	6.06 (3–13)	2.8						
ADOS-Total ^h	8.67 (5–17)	3.5						
ADOS-Im ⁱ	1.06 (0–2)	0.6						
ADOS-SB ^j	1.33 (0–5)	1.4						

^aVIQ—Verbal IQ (WAIS-III^{UK}) or VCI—Verbal Comprehension Index (WAIS-IV^{UK}).

^bPIQ—Performance IQ (WAIS-III^{UK}) or PRI—Perceptual Reasoning Index (WAIS-IV^{UK}).

^cFull-scale IQ (WAIS-III^{UK} or WAIS-IV^{UK}) was available for 26 ASD and 29 TD individuals.

^dAQ—Autism-Spectrum Quotient.

^eBPS = baseline pupil size (participant aggregated means).

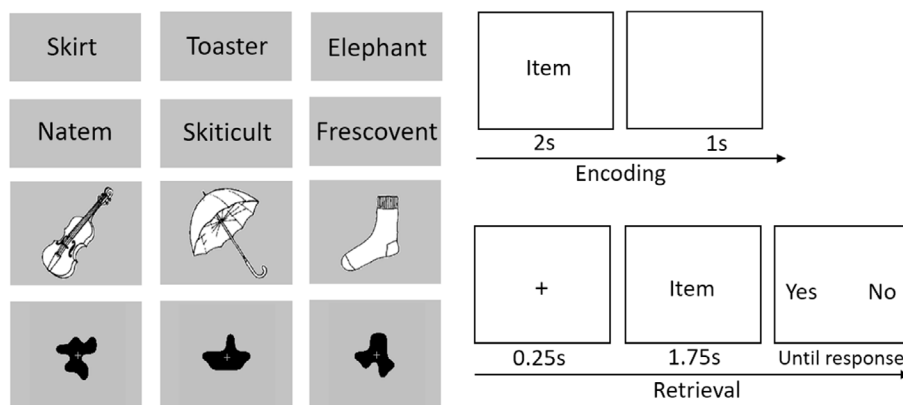
^f(f–j) ADOS scores are from a subset of 21 out of the 27 ASD individuals; ADOS—Communication subscale;

^gADOS—Reciprocal Social Interaction subscale;

^hADOS Total score—Communication + Reciprocal Social Interaction;

ⁱADOS—Imagination/Creativity subscale;

^jADOS—Stereotyped Behaviors and Restricted Interests subscale. ADOS scores are presented with range in brackets.

**FIGURE 1** Left: Examples of materials, from top to bottom: words, non-words, pictures, shapes. Right: procedures for encoding (top) and retrieval (bottom)

Materials

The materials used are described in detail in Ring et al. (2020); also see Figure 1. In brief, pictures and words as their labels were selected from Snodgrass and Vanderwart (1980), abstract shape images were provided by Haenschel et al. (2007) and non-words were selected from Gathercole et al. (1991). Material was selected based on pilot studies ensuring an appropriate difficulty level, avoiding ceiling and floor effects for remembering all items, and naming the shapes and pictures. The final set of materials included 80 items, 20 of each category (words, non-words, pictures, shapes). Images were black and white, words were typed in black font

and all materials were presented in the center of the screen on the same gray background on a 23-inch screen with a 16:9 aspect ratio. At the participant's viewing distance of approximately 60 cm the shapes were 2.85×2.86 degrees, pictures were 4.77×3.82 degrees, and words and non-words were 5.72×1.91 degrees of visual angle. Two lists of each category were created to serve as study ("old") or lure items ("new") respectively. The presentation of all items was counter-balanced across participants so that each item was presented equally often as old and new item. The presentation order of the four material categories was kept the same for study and test phase but was counter-balanced across participants.

Procedure

The procedure was carried out in a dedicated eye-tracking lab without any windows, closed doors and constant ambient lighting across participants. The recognition memory task was preceded by a five-point calibration procedure. Pupil diameter was recorded throughout the task by a Tobii TX300 eye-tracker (Stockholm, Sweden) with a sampling rate of 120 Hz. The task consisted of an encoding and a retrieval phase (see Figure 1 right). Participants were instructed before the encoding phase to memorize 40 items grouped into the four categories (words, pictures, shapes, non-words) for a subsequent memory test. At encoding, items were presented for 2 s interspaced by the presentation of a blank screen for 1 s. The retrieval phase immediately followed the encoding phase. Participants were presented with 80 items, half of which were presented during encoding (“old”). Every retrieval trial started with a fixation cross for 0.25 s, followed by the item presentation for 1.75 s. Subsequently, participants had to indicate on a “Yes” versus “No” slide whether they had seen the item previously during encoding. “Yes” responses were followed by a differentiation on episodic or semantic memory, which was not analyzed in the present study. Recognition accuracy was defined by correct “Yes” versus “No” decisions. All stimuli including the blank screen during encoding and the fixation cross during retrieval were presented on the same gray background to ensure similar luminance within and across conditions. We analyzed 40 trials per participant at encoding and 80 trials at retrieval. Each trial consisted of 240 pupil dilation (PD) samples based on a sampling rate of 120 Hz.

Pupil data pre-processing

We assessed 54 raw datasets with 40 encoding and 80 retrieval trials each and dropped trials with less than 50% valid data, which excluded in total 27.3% of all trials (ASD: 28.9%, TD: 25.9%). The number of valid trials did not differ between groups (ASD: $M = 62.6$, $SD = 14.3$; TD: $M = 61.7$, $SD = 14.4$; $t < 1$). We analyzed the pupil dilation (PD) data for the stimulus presentation phase in encoding trials and for the fixation cross plus stimulus presentation phase in retrieval trials, which resulted in 2 seconds of analyzed data for encoding and retrieval trials. We preprocessed raw PD data according to recent recommendations (Kret & Sjak-Shie, 2018). This included the omission of PD data outside plausible ranges (2–8 mm), the filtering of PD speed outliers with more than 3 times median absolute deviation in a two-pass approach, and median smoothing and linear interpolation within running 150 ms time frames. PD was calculated as the mean of both eyes. When tracking was unsuccessful for one eye, only data from the successful

eye were selected, while considering offsets between eyes. Relative PD as the standardized dependent variable was calculated for each PD sample by subtracting the mean PD during of the first 250 ms of each trial (see Figure 2 left).

We further controlled for fixation behavior. Relative PD was only considered for analysis if corresponding fixations were within 2 standard deviations from the screen center, which translates to the central 54% of the display area (see Figure 2 right).

Three PD measures were calculated on a per-trial level. Baseline pupil size (BPS) was estimated as mean relative PD during the first 250 ms of each encoding and retrieval trial (Mathôt et al., 2018). This timespan ensures that the measured PD is not influenced by the presented stimulus in the corresponding trial (Joshi et al., 2016) and, thus, can be considered as an indicator of LC-NE tonic activity (Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011). Encoding-evoked pupillary response (EEPR) was estimated accordingly as mean relative PD during the encoding stimulus phase (0–2000 ms) minus respective BPS for each encoding trial. This trial-specific baseline correction ensures that resulting response measures (EEPR, SEPR) are comparable across trials as BPS declines across trials due to fatigue or habituation (Dragone et al., 2018). Stimulus-evoked pupillary response (SEPR) was estimated as mean relative PD during 1750–2000 ms minus respective BPS for each retrieval phase trial (Blaser et al., 2014; Isabella et al., 2019). This timespan was chosen based on visual inspection of the pupil dilation progression across trials and participants (see Figure 4). EEPR and SEPR can be considered as an indicator of LC-NE phasic activity during the encoding and retrieval phase, respectively (Gilzenrat et al., 2010; Murphy et al., 2014).

Statistical analysis

All analyzes were done in R statistics 3.5.1 (R Core Team, 2014) with additional packages (Aust & Barth, 2018; Bates et al., 2014; Kuznetsova et al., 2017; Lenth, 2016; Wickham, 2016; Zeileis & Grothendieck, 2005). We investigated the hypotheses by generalized linear mixed models to correct for the interdependency of measurements in a per-trial analysis. We calculated three models with the dependent variables (recognition accuracy, EEPR, or SEPR), participant and stimulus category (word, non-word, picture, shape) as random intercepts, and group as fixed effect (ASD versus TD) to investigate group differences in recognition accuracy (hypothesis 1) and arousal-modulated memory encoding (EEPR) and arousal-modulated memory retrieval (SEPR; hypothesis 2). The model with recognition accuracy (i.e., incorrect trial = 0, retrieved trial = 1) as dependent variable was a generalized logistic regression. In a next step, we added EEPR and SEPR as fixed

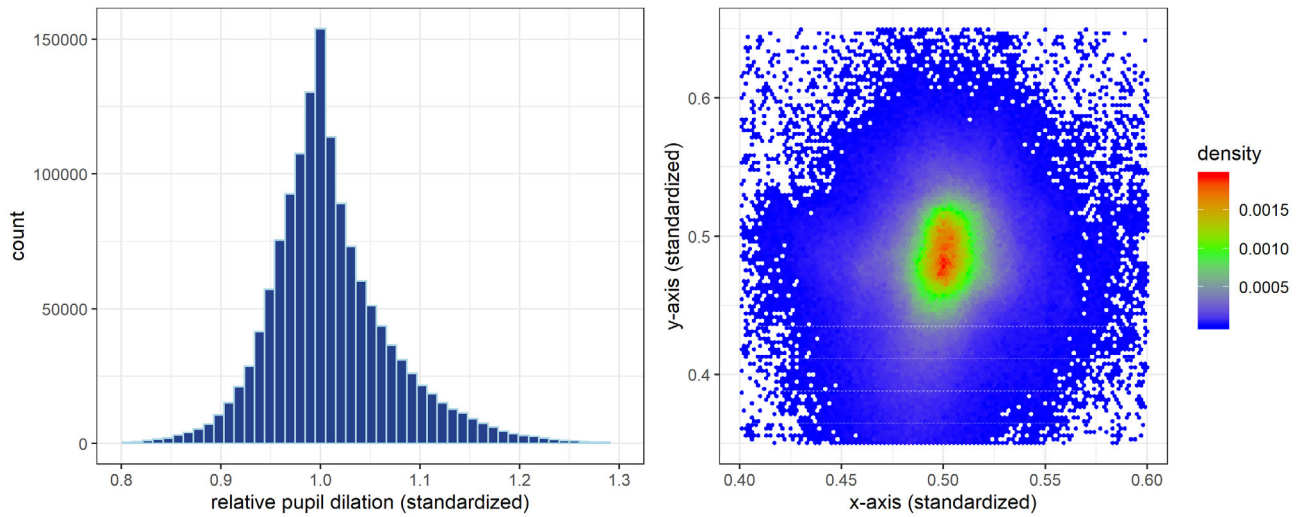


FIGURE 2 Distribution of preprocessed data. Left: histogram of preprocessed and standardized pupil dilation estimates. Right: heatmap of corresponding gazes included in the analysis. X- and Y-axis represent the stimulus presentation screen

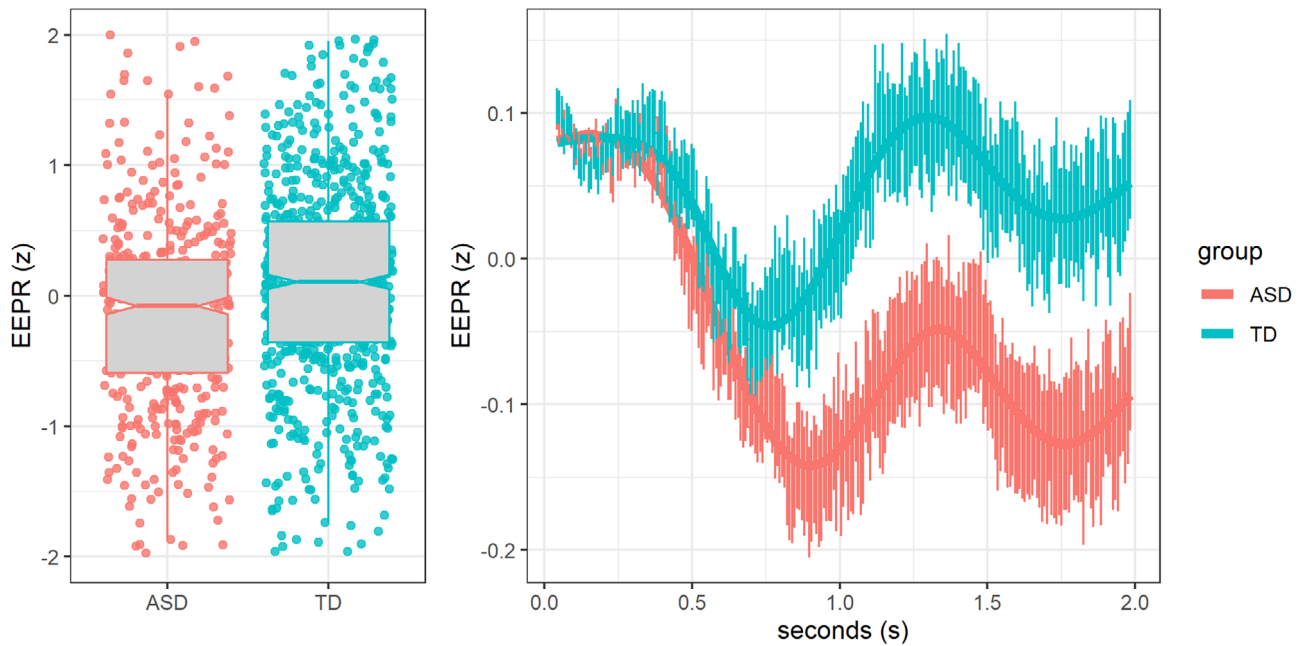


FIGURE 3 Encoding-evoked pupillary response (EEPR) during the encoding phase. Left = boxplot of per-trial EEPR between groups. Right = temporal profile of EEPR across encoding trials between groups

effects to this model and estimated all interactions ($EEPR \times SEPR$, $EEPR \times group$, $SEPR \times group$, $EEPR \times SEPR \times group$) to investigate differential effects between groups of arousal-modulated memory formation on recognition accuracy (hypothesis 3). We report significant effects as standardized coefficients (β) that are the logarithm of the odds ratio (log-odds) for logistic regression coefficients and can be interpreted as effect size estimates. Contrasts of estimated marginal means were calculated with corresponding 95% confidence intervals (CI-95) to post-hoc contrast main and

interaction effects (ΔM , $\Delta\beta$). Thus, a significant difference is indexed by a CI-95 that does not include zero.

RESULTS

Recognition accuracy between groups (hypothesis 1)

Recognition accuracy was descriptively different between groups on the aggregated participant level (ASD:

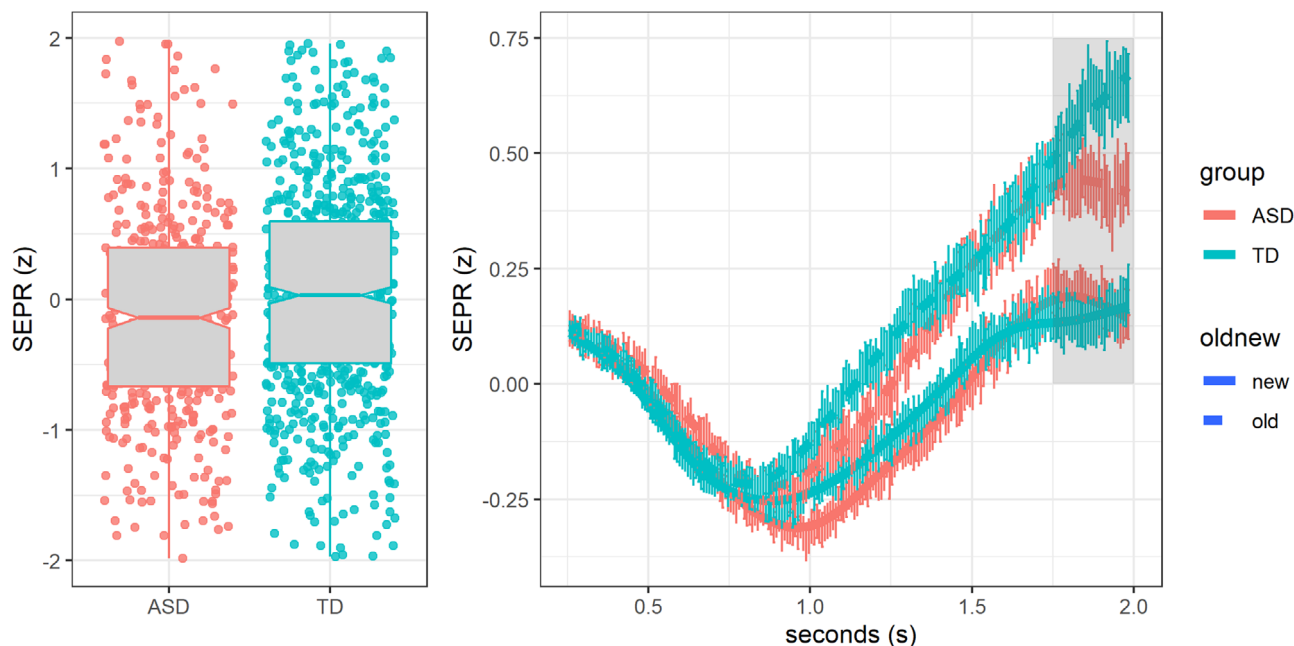


FIGURE 4 Stimulus-evoked pupillary response (SEPR) during the retrieval phase. Left = boxplot of per-trial SEPR between groups. Right = temporal profile of SEPR across retrieval trials between groups. Oldnew = stimulus condition. Solid lines indicate new stimuli that were not presented before. “Old” stimuli indicate stimuli that were presented before during encoding trials. Shaded areas represent standard errors. Gray rectangle highlights the attenuated SEPR in ASD for old stimuli

$M = 0.74$, $SD = 0.16$; TD: $M = 0.85$, $SD = 0.12$). Accordingly, we observed a significant effect of group on recognition accuracy in a generalized logistic regression on the per-trial level ($z = 2.80$, $p = 0.005$), which is explained by higher recognition accuracy in TD compared to ASD ($\Delta M = 0.66$, CI-95 [0.19–1.12]).

Encoding-evoked pupillary responses (EEPR) between groups (hypothesis 2)

During the encoding phase, EEPR was different between groups ($F[1,43] = 4.13$, $p = 0.048$) with a significantly lower EEPR in ASD compared to TD ($\Delta M = -0.21$, CI-95 [-0.42 to -0.01]; see Figure 3). This effect is not explained by differences in baseline pupil size (BPS) during encoding that did not differ on a per-trial basis between groups ($F < 1$).

Stimulus-evoked pupillary responses (SEPR) between groups (hypothesis 2)

During the retrieval phase, SEPR was different between stimulus conditions ($F[12600] = 61.54$, $p < 0.001$) with significantly higher SEPR for old compared to new stimuli ($\Delta M = 0.20$, CI-95 [0.10–0.31]). This effect was different between groups, as indicated by a significant interaction of condition and group ($F[12595] = 4.96$, $p < 0.026$), which indicated an altered Pupil Old/New effect between groups. Post-hoc comparisons showed an

attenuated Pupil Old/New effect in ASD ($\Delta M = 0.12$, CI-95 [0.09–0.31]) compared to TD ($\Delta M = 0.36$, CI-95 [0.27–0.46], see Figure 5). The temporal profile illustrates that this difference in Pupil Old/New effect between groups is driven by a difference in phasic PD response that occurs late (1750–2000 ms) during retrieval trials (see Figure 4). This effect is not explained by differences in baseline pupil size during retrieval that did not differ on a per-trial basis between groups ($F < 1$).

SEPR and EEPR effects on recognition accuracy (hypothesis 3)

We analyzed the effects of SEPR and EEPR on recognition accuracy (see Table 2). The effects interacted and were different between groups as indicated by a significant three-way interaction ($z = 2.36$, $p = 0.018$). Post-hoc analyzes revealed that different EEPR during encoding in ASD altered the effect of SEPR during retrieval on recognition accuracy (see Figure 5). In ASD, below average EEPR levels during encoding were associated with an increased effect of SEPR on accuracy (EEPR–2 SD : $\beta = 1.20$, CI-95 [0.38, 2.02], EEPR–1 SD : $\beta = 0.76$, CI-95 [0.24, 1.27]). In contrast, in TD, SEPR was not associated with higher accuracy at all EEPR levels.

As a secondary analysis, we estimated the effects of EEPR and SEPR on recognition accuracy separately for each group (see Tables S3 and S4). For ASD, we found a significantly positive effect of SEPR on accuracy ($\beta = 0.40$, CI-95 [0.11, 0.71]), that is, if SEPR increases

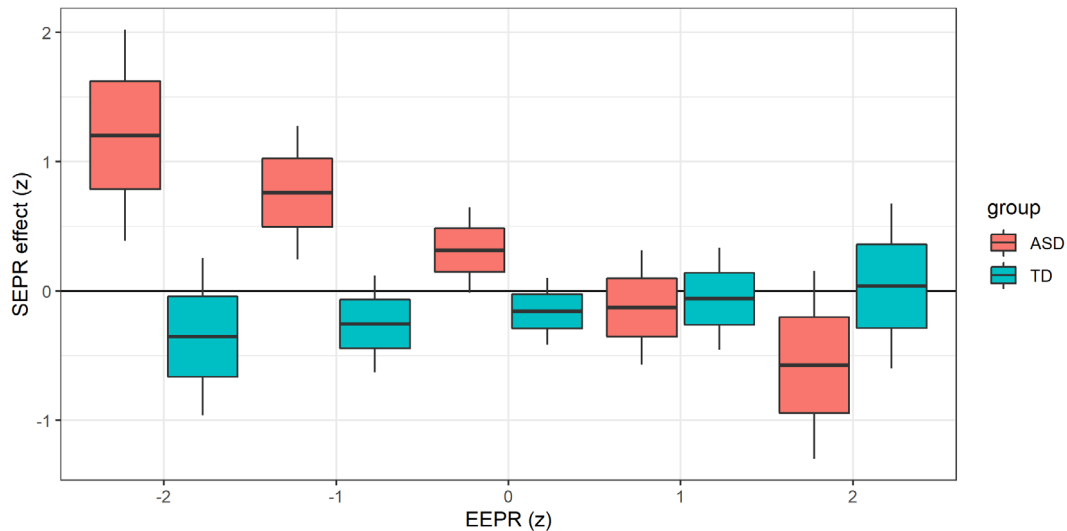


FIGURE 5 Three-way interaction in the effect of encoding-evoked pupillary response (EEPR), stimulus-evoked pupillary response (SEPR), and group on accuracy: Effects of SEPR for different levels of average EEPR between groups

TABLE 2 Logistic regression: EEPR and SEPR effect on recognition accuracy

	Estimate	Std error	z-value	p-value
Intercept	1.295	0.252	5.144	0.000
EEPR (z)	-0.394	0.152	-2.598	0.009
SEPR (z)	0.316	0.169	1.871	0.061
Group (TD)	0.616	0.278	2.215	0.027
EEPR × SEPR	-0.444	0.178	-2.492	0.013
EEPR × group	0.524	0.207	2.524	0.012
SEPR × group	-0.474	0.215	-2.204	0.028
EEPR × SEPR × group	0.542	0.229	2.366	0.018

Abbreviations: EEPR, encoding-evoked pupillary response; SEPR, stimulus-evoked pupillary response.

by one standard unit, the likelihood of an accurate response will increase by 49% (OR = 1.49, CI-95 [1.13, 2.04]). In addition, we found a significantly negative effect of EEPR on accuracy ($\beta = -0.35$, CI-95 [-0.65, -0.08]) in ASD, that is, an accuracy likelihood decrease by 30% (OR = 0.70, CI-95 [0.52, 0.93]). For TD, the effects of EEPR ($\beta = 0.15$, CI-95 [-0.10, 0.42]) and SEPR ($\beta = -0.13$, CI-95 [-0.39, 0.13]) were not significant.

DISCUSSION

The current study explored arousal as a modulator of the encoding and retrieval of memories in ASD compared to TD individuals. This extended our analysis of Ring et al. (2020) with the following aims: (1) to investigate potential encoding differences in pupil size between ASD and TD groups, (2) to explain the absence of the pupil size Old/New effect in the ASD group, that is, retrieval differences in pupil size, and (3) to analyze how pupil size

during encoding and retrieval interacted with recognition accuracy. This allowed us to dissect the overall objective, whether altered memory performance in ASD is due to different arousal-modulated memory encoding or retrieval, or both. It was implemented by analyzing pupillary responses on a per-trial level (Bast et al., 2019), which has a higher sensitivity to detect group differences compared to aggregated mean analysis.

Regarding Aim 1, the encoding evoked pupillary response (EEPR) was significantly lower for the ASD compared to the TD group independent of the baseline pupil size (BPS). As this is the first study to investigate pupil size during memory encoding in ASD, this leaves room for interpretation. We controlled the pupil data for fixation behavior, which is an indicator of overt visual attention (Groner & Groner, 1989) and, thus, lower EEPR is unlikely to be caused by attenuated attentional engagement in ASD. We further conceptualized EEPR as an indicator of arousal during the encoding of memories with LC-NE phasic activity as underlying mechanism. Thus, lower EEPR suggests attenuated LC-NE

phasic activity in ASD during arousal-modulated encoding of memories. In contrast, pupil dilation is also considered as a proportional indicator of cognitive demand (Goldinger & Papesch, 2012). A decrease in dilation as observed in ASD relative to TD may result from cognitive overload due to the task demands during encoding (Piquado et al., 2010; Porter et al., 2007). In other participant groups such as patients with mild cognitive impairment, a reduced pupillary response which increases with cognitive load has been linked to LC dysfunction (Elman et al., 2017), which further attenuated EEPR as indicator of altered LC-NE activity. In ASD, we thus propose relatively lower responses of LC-NE phasic activity during the encoding of memories that may suggest attenuated salience attribution (Vazey et al., 2018).

Regarding Aim 2, temporal profiles suggested that group differences in PD during retrieval were driven by a stimulus-evoked pupillary response (SEPR) difference, which occurs late during each trial (i.e., the last 250 ms). This indicates that the underlying cause of this PD difference rather reflects a top-down compared to a bottom-up process (Bast et al., 2019; Mill et al., 2016). This top-down process could represent an evaluation of semantic content compared to sensory processing (Chambers et al., 2004). Such a semantic evaluation relates to a goal-oriented interpretation of salience that is functionally represented by top-down projections of the anterior insula to the LC (Kucyi & Parvizi, 2020). In ASD, we propose that a decreased SEPR during retrieval indicates an attenuated attribution of semantic salience in response to previously encoded stimuli.

Regarding Aim 3, the effects of pupillary response during encoding (EEPR) and retrieval (SEPR) on recognition accuracy differed between groups. In the TD group, no relation between pupillary response and accuracy was found. Previous studies in TD individuals reported conflicting results that varied by stimulus material. Whereas Vö et al. (2008) found no relation between encoding pupil size and retrieval performance for words, Papesch et al. (2012) reported larger pupils at encoding as predictor of successful retrieval for auditory materials. In contrast, a small encoding pupil size has been associated with later recollected visual stimuli, whereas a large encoding pupil size has been associated with later forgotten visual stimuli (Kafkas & Montaldi, 2011). Similarly, Kuipers and Phillips (2020) found smaller a pupil size before item presentation at encoding being related to better memory at retrieval. These previous studies suggested that smaller pupil sizes during the encoding of visual stimuli could be associated with increased recognition accuracy. This contrasts with our null findings in TD, which might be explained by ceiling effects in recognition accuracy.

In contrast, pupillary responses had specific effects on recognition accuracy in ASD, where a lower pupillary reaction during encoding (EEPR) and a higher pupillary reaction during retrieval (SEPR) were associated with

increased recognition accuracy. This is in line with previous research in TD that associated smaller pupil sizes during encoding (Kafkas & Montaldi, 2011) and larger pupil sizes during retrieval (Kucewicz et al., 2018) with improved recognition accuracy for visual stimuli. We provide the first empirical evidence that arousal-modulated memory formation during encoding and retrieval might be altered and relates to decreased recognition accuracy in ASD.

These differential relations of pupillary reactions (EEPR, SEPR) and recognition accuracy between groups indicate that the physiological processes underlying arousal-modulated memory formation might differ between ASD and TD (Gaigg & Bowler, 2008). One possibility is that individuals with ASD learn better during relative relaxation which might be indicated by a lower EEPR being related to better recognition accuracy. This emphasizes a clinical implication that arousal regulation strategies during learning might enhance memory performance in individuals with ASD. In addition, Individuals with ASD are often affected by comorbid anxiety disorders and elevated stress levels (Croen et al., 2015; Simonoff et al., 2008) that are associated with impaired learning. Thus, the association of lower pupillary reaction during encoding and better recognition accuracy could be driven by ASD individuals without comorbid anxiety symptoms and/or relatively lower stress levels.

Another explanation is that memory formation per se is altered in ASD. This is indicated by a lower recognition accuracy in ASD compared to TD (Desaunay et al., 2020). In addition, we observed attenuated EEPR and SEPR in ASD compared to TD, which suggests attenuated LC-NE phasic activity during encoding and retrieval phases. This is corroborated by previous findings that suggested attenuated ability in ASD to adapt LC-NE phasic activity during task performance (Bast et al., 2021). LC-NE phasic activity has been suggested to modulate memory formation by the (1.) online encoding mechanism as increased reactivity to salience and the (2.) offline consolidation mechanism as norepinephrine-supported memory protein synthesis (Sara, 2015). This modulation of memory formation is supported in the ASD group by a positive association of SEPR and recognition accuracy. Thus, we conclude that attenuated memory formation in ASD might be explained by altered LC-NE phasic activity during encoding and retrieval.

However, in ASD, we also found a negative association of EEPR and recognition accuracy, which corresponds to previous findings in neurotypical controls (Kafkas & Montaldi, 2011). This effect even emphasized the positive effect of SEPR on recognition accuracy in ASD (see Figure 5), which contrast with current conceptualizations of LC-NE modulated memory formation (Sara, 2015). This increased LC-NE phasic activity could be a mechanism to compensate for lower recognition accuracy specific to ASD. Alternatively, when considering pupillary response as an indicator of cognitive

demand (Goldinger & Papesh, 2012), lower encoding cognitive demand with lower EEPR might be compensated by higher retrieval cognitive demand with higher SEPR. These explanations remain speculative and, thus, future studies need to further investigate conditional effects on the association of LC-NE modulated memory encoding and recognition performance.

Our findings are limited. We did not have enough trials to separately consider each of type of material. We previously found better memory for visual stimuli and meaningful material in both groups (Ring et al., 2020), which is in line with the picture superiority effect (Shepard, 1967). Another limitation is that we were not able to dissociate online encoding and offline consolidation mechanisms related to LC-NE memory formation. Future studies might be able to experimentally manipulate arousal during memory formation by an application of varying degrees of valence-loaded stimuli. In addition, the specificity of our findings to ASD remains unknown. Altered LC-NE functioning has been discussed as a domain general mechanism in altered neurodevelopment (Poe et al., 2020) and, thus, future studies might compare additional neurodevelopmental conditions concerning LC-NE functioning in memory performance. Our findings highlight that the interaction between arousal and cognition during learning in autism merits closer attention in the future.

We reported an association of pupillary responses as proxy of LC-NE phasic activity and memory performance in a recognition task. In ASD compared to neurotypical controls, we observed attenuated pupillary responses during encoding and retrieval, as well as attenuated recognition accuracy. These findings indicate altered LC-NE modulated memory formation as underlying mechanism of attenuated recognition accuracy in ASD. Interestingly, we also observed a negative association of pupillary reactivity during encoding and performance that is not predicted by theories on LC-NE functioning but corresponds to previous observations in neurotypical development. Pupillary responses during recognition tasks might be a promising paradigm to further understand LC-NE modulated memory encoding in neurodiversity.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the local ethics committee (PSYETH [UPTD] 13/14 53) and adhered to the ethical guidelines set out by the British Psychological Society and was in accordance with the provisions of the World Medical Association Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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