# Early Intervention Increases Reactive Joint Attention in Autistic Preschoolers with Arousal Regulation as Mediator

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## Abstract:

Introduction: Reactive joint attention (RJA) describes an early ability of shared attention on a target that was cued by a human. This key ability of socio-cognitive development is altered in autistic compared to non-autistic preschoolers, and often trained in early interventions. We evaluated the development of RJA in autistic preschoolers in a randomized controlled trial of a naturalistic developmental behavioral intervention (NDBI; intervention versus treatment-as-usual, TAU); and compared to non-autistic preschoolers.

Methods: We applied a screen-based eye-tracking paradigm to assess RJA at baseline, after 6 months, after 12 months (end of intervention), and after 36 months (follow-up). Pupil size changes were assessed to investigate arousal regulation as a mediator in RJA group differences. Generalized linear mixed models were applied to estimate the likelihood to show RJA in response to videos of a human cueing on-screen targets.

Results: At end of intervention, the intervention group - but not the TAU group - showed a RJA likelihood increase compared to baseline. Across groups, a quantitative increase in RJA likelihood with intervention predicted improved social responsiveness at follow-up. At follow-up, a higher RJA likelihood was found in the intervention versus TAU group. A higher baseline pupil size within trials was associated with a lower RJA likelihood and mediated the group difference on RJA likelihood in causal mediation analysis.

Conclusion: The NDBI early intervention increased reactive joint attention in autistic preschoolers up to two years after end of intervention, which likely cascades on improved socio-cognitive development. Arousal regulation in response to social stimuli is outlined as a promising mediating mechanism.

## Introduction

Joint attention is a shared attention between two individuals on a stimulus that develops within the first year of life (Scaife & Bruner, 1975). It is considered a key ability of non-verbal communication (Mundy, 2018) that is ubiquitous in the development of language (Morales et al., 2000) and social cognition (Brooks & Meltzoff, 2015). Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by different social communication and restricted and repetitive behaviors. Attenuated joint attention has been described as an early risk marker for autism (Nyström et al., 2019) that likely cascades to a different development of language and social cognition (Happé & Frith, 2014).

Joint attention combines orienting attention to persons (Hirai et al., 2020), identification of their communicative signals (Senju & Csibra, 2008), and utilizing re-orienting cues to a target (Falck-Ytter et al., 2022). In early development, joint attention encourages inferences on human intentions and facilitates social learning (Mundy & Newell, 2007). In preschoolers, countless practice of joint attention likely shapes a theory of mind (Frith & Frith, 2008; Klin et al., 2003). Joint attention has been differentiated into reactive joint attention (RJA) as responding to human re-orienting cues, and initiating joint attention (IJA) as active induction by the child (Mundy et al., 2007). RJA precedes IJA development within the first year of life (Mundy, 2018). RJA is often used synonymously to gaze following (Falck-Ytter et al., 2022; Gredebäck et al., 2010) but gestures as re-orienting cues should also be considered specifically pointing (Charman, 2003). In longitudinal studies, gaze following in infancy predicted utilization of mental-state words as toddlers that predicted social cognition as preschoolers (Brooks & Meltzoff, 2015). This represents a developmental cascade that might differ in autism (Bradshaw et al., 2022).

Attenuated joint attention has been established in autistic preschoolers (Falck-Ytter et al., 2022; Guillon et al., 2014). A first longitudinal study in autistic children associated IJA at 20 months-of-age with better language ability and lower symptom severity at 42 months-of-age (Charman, 2003). Recently, RJA in autistic preschoolers has also been shown to predict the growth rate of expressive language over a course of 9 months (Frost et al., 2024). Meta analytic findings supported a cross-sectional association of joint attention with receptive and expressive language ability (Bottema-Beutel, 2016). This association was most consistent for RJA versus IJA and significantly higher in autistic versus non-autistic individuals. Another meta-analysis on cross-sectional findings reported a moderate effect size on the association of RJA with measures of social functioning (Bottema-Beutel et al., 2019). However, a prospective effect of RJA on socio-cognitive development has only been shown in non-autistic children (Brandone & Stout, 2023; Charman et al., 2000; Lasch et al., 2023). Thus, we will assess the prospective effects of RJA on socio-cognitive development in autistic preschoolers.

Joint attention including RJA are often trained in early interventions in autism. These are interventions that are applied in the preschool age. A meta-analysis on early interventions training joint attention explicitly reported a moderate joint attention increase after the end of treatment (Murza et al., 2016). Naturalistic, Developmental, Behavioral Interventions (NDBI) represent a type of early interventions that utilize natural contingencies in reinforcement learning to teach developmentally appropriate skills like joint attention in a naturalistic learning environment (Schreibman et al., 2015). A recent systematic review on randomized-controlled trials showed that NDBI are the only type of early intervention that has been associated with a reduction in autism core symptoms when controlling for studies’ risk of bias (Sandbank et al., 2023). The Frankfurt Early Intervention Program for Autism Spectrum Disorder (A-FFIP) is a manualized NDBI of low intensity that can be easily scaled in local health care systems (Kitzerow et al., 2020). A randomized controlled trial on A-FFIP showed [main effect reported in manuscript]. The current study investigates the effect of A-FFIP on RJA in autistic preschoolers and its cascading effect on socio-cognitive development.

Joint attention usually is assessed by evaluating observations of children’s social interactions (Murza et al., 2016). For example, the Early Social Communication Scales (ESCS) utilize videotaped observations of structured social interactions to assess RJA and IJA (Mundy et al., 2003). This process is time and labor intensive. Alternatively, RJA can be measured in eye-tracking paradigms that provide a more standardized assessment (Navab et al., 2012), which is imperative in repeated-measure designs like longitudinal studies. However, eye-tracking paradigms on gaze following as RJA measure were not able to show differences between autistic and non-autistic preschoolers (Falck-Ytter et al., 2022) compared to paradigms that utilize less standardizable live social interactions (Stallworthy et al., 2022). This null finding in eye-tracking studies is based on an established RJA paradigm (Senju & Csibra, 2008) that has been analyzed with an aggregated difference measure in fixed effect models (Bedford et al., 2012; Falck-Ytter et al., 2015; Parsons et al., 2019). Given the interindividual heterogeneity in autism, an aggregated difference measure likely reduced the statistical power to capture between group differences (Bell & Jones, 2015). The power to detect group differences in RJA might be improved by the application of linear mixed models that consider interindividual variability and are able to utilize RJA assessments on a per trial basis (Moscatelli et al., 2012).

In addition, the neurophysiological mechanisms of different RJA in autistic preschoolers remain elusive. The recent model proposed atypical early-stage processing as a mediator in the effect of genotypic on phenotypic autism markers (Johnson et al., 2021). This early-stage processing can be assessed by pupillometry in video-based eye tracking (Laeng et al., 2012). Pupillometry provides a baseline pupil size (BPS) as an index of neurophysiological arousal and a stimulus-evoked pupillary response (SEPR) as an index of stimulus-specific processing (Nassar et al., 2012). The Locus Coeruleus – Norepinephrine (LC-NE) System is the underlying mechanism of pupillary responses (BPS and SEPR), which has been discussed as a modulator of alerting (Peterson & Posner, 2012) and orienting attention (Sara & Bouret, 2012). We showed pupillometric markers of LC-NE activity as a predictor of attentional performance (Boxhoorn et al., 2020), which differentiated between autistic and non-autistic children (Bast et al., 2023). Thus, we propose that pupillometric measures of LC-NE activity mediate a putative between-group difference in RJA.

The current study investigates the effect of an early intervention in autistic preschoolers (A-FFIP) within a randomized-controlled trial on the development of RJA. In an intervention group and a treatment-as-usual (TAU) group, we assess RJA longitudinally with an eye-tracking paradigm at baseline, after 6 months, after 12 months (end of intervention), and after 36 months (follow-up). This was compared to the RJA of non-autistic preschoolers at baseline and after 36 months. Generalized linear mixed models are applied to assess a likelihood to show RJA within a trial, which is modelled between measurement timepoints and groups. We expect to showed lower RJA likelihood at baseline in autistic versus non-autistic preschoolers. We hypothesize that A-FFIP compared to TAU improves RJA likelihood in autistic preschoolers at end-of-intervention and follow-up. As a developmental cascade, we further hypothesize a positive prospective effect of RJA change at end-of-intervention on socio-cognitive functioning at follow-up. Lastly, we hypothesize pupillometric measures of arousal (BPS) and stimulus-specific processing (SEPR) to mediate putative group differences in joint attention. This would support LC-NE activity as an underlying mechanism of a different RJA development in autism.

## Material & Methods

### Sample

The final sample (n = 112) consisted of n = 32 autistic preschoolers in the A-FFIP intervention, n = 28 autistic preschoolers in the treatment-as-usual (TAU) group, and n = 52 non-autistic preschoolers (see table 1). Trained psychologists confirmed an autism spectrum disorder (ASD) diagnosis according to DSM-5 diagnostic criteria using the German versions of the Autism Diagnostic Observation Schedule 2 (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R). Autistic preschoolers were recruited within a randomized controlled trial on the A-FFIP program by contacting families that were on the wait list for therapy at the Frankfurt Autism Intervention and Research Center of Excellence (Kitzerow et al., 2020). In a study addon, non-autistic preschoolers were recruited by local advertisement in kindergartens, social media and health system institutions. Detailed inclusion and exclusion criteria have been described previously (Polzer et al., 2024).

[table 1]

Autistic groups (A-FFIP versus TAU) were matched at baseline concerning age, gender distribution, non-verbal IQ, autism symptom severity, comorbid psychopathology, and eye-tracking data quality. We assessed non-autistic preschoolers that were on average 12-months younger than the autistic children to achieve more comparable groups concerning developmental age. However, the non-autistic group compared is characterized by a younger age, higher nonverbal IQ, and higher proportion of biological girls.

### Procedure

Caretakers of the participants provided written informed consent for study participation (local ethic approval: autistic preschoolers [10/18], non-autistic preschoolers [361/18]).

Eye-tracking assessments were done in a child-friendly lab with constant artificial lighting. The eye tracker was a Tobii TX300 eye-tracker at 300 Hz sampling rate that allowed free head movement within 50–80 cm of screen distance. Participants either sat on a highchair or on the caregiver's lap in front of the presentation screen. Participants were instructed to attend to the screen. A child-friendly five-point calibration was performed. The joint attention paradigm took 3 min to complete and was part of a larger eye-tracking battery (25 min) coded in Psychtoolbox-3 for MATLAB (see [github](https://github.com/nicobast/BOSCA_battery)). Cross-sectional data of this eye-tracking battery on different paradigms with partially overlapping samples has been published previously (Polzer et al., 2022; Polzer et al., 2024).

All preschoolers were repeatedly assessed with the eye-tracking battery at different timepoints. The non-autistic group was assessed at baseline and after 36 months (follow-up). The autistic groups (A-FFIP, TAU) were assessed at baseline, after 6 months, after 12 months (end of intervention), and after 36 months (follow-up). This allowed (a.) to assess the development of joint attention in autistic and non-autistic preschoolers over 36 months and (b.) to evaluate the change of joint attention in response to treatment (table 2).

[table 2]

Autistic preschoolers participated in additional assessments within the A-FFIP study protocol (Kitzerow et al., 2020). In non-autistic preschoolers, we accordingly assessed cognitive ability (Bayley-IIII, WPPSI-III), autism symptoms (SRS), and comorbid psychopathology (CBCL-1.5-5).

### Stimuli

The joint attention paradigm was presented on a 24-inch monitor with a resolution of 1920 x 1080 pixels. It measures reactive joint attention (RJA) based on a well-established paradigm that focuses on gaze following (Senju & Csibra, 2008) but is extended here by a varying intensity of facial expressions (neutral, mild, intense) and including pointing as reorienting cue (Franchini et al., 2017). The paradigm consists of 16 trials that are presented in a pseudorandom order, in two blocks. Each trial had a duration of 11 seconds. Each trial had different phases (see figure 1): An initial attention grabber directing gazes to the location where a human face will appear (1s), intro direct gaze: a human looks directly into the camera and two stimuli are presented (2s), target cueing: the human initiates a reorienting cue to one target stimulus as a gaze on the target and a facial expression (6s), outro direct gaze: the human stops the reorienting cue and looks into the camera again maintaining the facial expression (2s).

Trials differ by the social agent’s reorienting cue (neutral gaze, mild facial expression, intense facial expression, neutral gaze + pointing) and the presented stimuli (rabbit, truck, ball, flower). The position of the target stimulus (left, right) was counterbalanced between trials.

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Figure 1. Stimulus Material and main measures. A.) Different phases of each trial. The initial attention grabber phase (1s) is displayed as insert. Left picture also shows the area-of-interest (AOIs) definition across phases. B.) Heatmap of gaze fixation data between trial phases. Online supplement X shows an animation of the gaze fixation within trials C.) Reactive joint attention (RJA) likelihood within trials as density plot between groups and timepoints. Solid vertical line indicates the end of the attention grabber phase and start of the video. Dashed lines show the onset and offset of the target cueing phase. D.) Pupil size change within trials between groups. Initial increase and decrease is likely associated with dilation and constriction due to the onset and offset of the dark attention grabber stimulus. The second dilation is utilized to calculate the SEPR and might be evoked by observed target cueing.

### Data Preprocessing

Raw eye-tracking data were preprocessed with R statistics (4.3) according to peer-reviewed guidelines for gaze (Nyström & Holmqvist, 2010) and pupillometry data (Kret & Sjak-Shie, 2018). The data preprocessing script is available online (see github). All data were segmented per trial. An eye blink correction excluded blinks between 75 and 250 ms and 25 ms before and after the blink. Trials with less than 50% of data were dropped.

#### Reactive joint attention (RJA)

Gaze data points beyond biologically plausible values were dropped (velocity > 1000 degrees of visual angle per second [°/s], acceleration > 10000 °/s). Gaze data were smoothed with a Savitzky-Golay filter with a length of 70 ms. Saccades were identified by a velocity-based algorithm with data-driven thresholds that considers intra- and interindividual differences in data noise (Nyström & Holmqvist, 2010). Fixations were identified by the absence of saccades and a gaze position change smaller than 1 °/s for at least 100 ms. Figure 1B shows a heatmap of the preprocessed fixation gaze data within trials.

RJA was defined based on previous literature of the paradigm (Franchini et al., 2017) when (1.) a fixation on the head of the presented human occurred in the last 500 ms and (2.) was followed by a fixation on the target object in the target cueing phase or after. Area-of-interest definition across the trial phases is shown in figure 1A (left). We deviated from the original definition as we did not consider a distinct hand area-of-interest for the pointing condition to retain comparable RJA definitions across trial conditions. For each trial, RJA likelihood was defined as the occurrence of any RJA within a trial (true versus false). Figure 1C shows the occurrences of RJA within trials between group and timepoints.

#### Pupillometry (BPS, SEPR)

Data points outside a biologically plausible range were dropped (< 2 mm, > 8 mm). Pupillometry data were smoothed by a linear filter (< 3 times median absolute deviation) with missing interpolation (150 ms window) (Bast et al., 2023). The estimated pupil size was based on the mean of both eyes (r = .97). A baseline pupil size (BPS) was calculated as a mean pupil size during the first 500 ms of each trial, which overlaps with the attention grabber phase. Pupil size estimates were normalized by subtracting the respective BPS (Mathôt et al., 2018). For each trial, we estimated a stimulus-evoked pupillary response (SEPR) to the reorienting cue as mean normalized pupil size between 4500 and 5500ms after stimulus onset, which indicates a pupil size change from the first 500ms to the 4500-5500 ms window. Figure 1D shows the normalized pupil size changes within trials.

### Statistical Analysis

Analyses were done with R statistics (4.3) and the script is available online (see github). Preprocessing of the eye-tracking data provided RJA, BPS, and SEPR that were investigated as dependent variables in distinct models on a per-trial level. We applied generalized linear mixed models with a binomial link function to estimate group differences in RJA likelihood. Group (autistic A-FFIP, autistic TAU, non-autistic) and measurement timepoint (baseline, +6 months, +12 months [end-of-treatment], +36months [follow-up]) and their interaction were included as a fixed effect. In an intervention model, autistic groups (A-FFIP versus TAU) were compared at baseline and end-of-treatment. In a development model, autistic and non-autistic groups (A-FFIP versus TAU versus non-autistic) were compared at baseline and follow-up (see figure 1C). Participant and trial number were included as random intercepts to control for interindividual variability. In linear mixed models, the same fixed and random effect structure was applied to investigate intervention and developmental effects on BPS and SEPR between groups. There were no effects of task conditions including cueing condition (neutral, mild, intense, neutral+pointing), stimulus (rabbit, truck, ball, flower), or target position (left, right) on RJA likelihood (all *F*s<1). Thus, these variables were not considered for reasons of parsimony.

Model fits were estimated with the marginalized (*mR*²) and conditional (*cR²*) coefficient of determination (Nakagawa & Schielzeth, 2013). In generalized linear mixed models, planned contrasts of RJA likelihood between groups and timepoints were investigated with marginalized means and 95% bootstrapped confidence intervals ([2.5%, 97.5%]) that can be interpreted as odds ratio (OR). In linear mixed models, planned contrasts of BPS or SEPR between groups and timepoints were investigated with marginalized means and 95% bootstrapped confidence intervals ([2.5%, 97.5%]) that can be interpreted as effect size (Δβ).

In causal mediation analysis (Imai et al., 2010; Robins & Greenland, 1992), we tested whether observed group differences in RJA likelihood between A-FFIP and TAU at end-of-treatment or follow-up are mediated by pupillometry (BPS, SEPR). This approach utilizes simulations (k = 1000) to estimate an average causal mediation effect (ACME) that represents the expected difference in RJA likelihood between autistic groups, when pupillometry values across groups would change from TAU to A-FFIP means. In addition, the average direct effect (ADE) represents the expected difference when the pupillometry measure as mediator is held constant. ADE and ACME add up to the total effect of group on RJA likelihood, which are controlled for the moderated mediation effect of timepoint (baseline, follow-up). Quasi-Bayesian Monte Carlo simulations are applied to estimate 95% confidence intervals.

In linear models, we tested cascade effects as whether changes in key variables (RJA likelihood, BPS, SEPR) from baseline to end-of-treatment influenced changes in socio-cognitive development from baseline to follow-up. Socio-cognitive development was investigated by changes in parent-reports of social responsiveness (SRS-16 sum score) (Sturm et al., 2017), restricted and repetitive behavior (RBSR sum score) (Kästel et al., 2021), and non-verbal IQ (Bayley III or WPPSI-IV).

Eye-tracking assessments were optional within the study protocol of the A-FFIP randomized-controlled trial (Kitzerow et al., 2020). Potential group differences in autistic groups could thus be associated with systematic dropouts. This was investigated in the autistic groups by two-way ANOVA models at baseline. We included group (A-FFIP versus TAU) and retention status (at end-of-treatment: True versus False; or at follow-up: True versus False) as two-level factors. Dependent variables were RJA likelihood, autism symptom severity, comorbid psychopathology, or eye-tracking data quality. Dropout analyses models achieved a power = 0.82 to detect a moderate effect size or interaction (η² = 0.12) with the given sample.

**Results**

### RJA Likelihood

In the intervention model (supplements, *mR*² = 0.05, *cR²* = 0.37), RJA likelihood significantly increased from baseline (BL) to end-of-treatment (ET) in the autistic A-FFIP group (OR = 1.52 [1.07, 2.18], z = 2.31, p = .021), but not in the autistic TAU group (OR = 1.49 [0.96, 2.31], z = 1.78, p = .075). At baseline and end-of-treatment, RJA likelihood was higher in autistic A-FFIP compared to autistic TAU (OR|BL = 2.47 [0.94, 6.51], z = -2.40, p = .032; OR|ET: 2.53 [0.93, 6.87], z = -2.38, p = .034).

In the development model (supplements, *mR*² = 0.18, *cR²* = 0.52), the RJA likelihood increased significantly from baseline (BL) to follow-up (FU) in the non-autistic group (OR = 2.37 [1.72, 3.26], z = 5.26, p < .001) and the autistic A-FFIP group (OR = 2.38 [1.41, 4.04], z = 3.21, p = .001), whereas RJA likelihood did not increase in the autistic TAU group (OR = 1.40 [0.77, 2.52], z = 1.10, p = .269). At follow-up, RJA likelihood was higher in autistic A-FFIP compared to autistic TAU (OR = 4.40 [1.07, 18.11], z = 2.98, p = .003).

In supporting sensitivity analysis across groups, RJA likelihood at baseline as predictor did not influence RJA likelihood at end-of-treatment (odds = 1.38 [0.81, 2.35]) or follow-up (odds = 1.28 [0.73, 2.23]). In an intervention model (*mR*² = 0.05, *cR²* = 0.37), this effect did not differ between autistic groups (OR|A-FFIP = 1.29 [0.68, 2.44]; OR|TAU = 1.49 [0.65, 3.42]). In a developmental model (*mR*² = 0.09, *cR²* = 0.88), RJA likelihood at baseline predicted RJA likelihood at follow-up only in the non-autistic group (OR = 1.84 [1.04, 3.25]) and not in the autistic A-FFIP (OR = 0.50 [0.19, 1.32]) or autistic TAU group (OR = 2.26 [0.65, 7.84]). Thus, the higher RJA likelihood increase in the autistic A-FFIP compared to autistic TAU group at end-of-treatment and follow-up is unlikely to be explained by the different RJA likelihood at baseline.

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Figure 2. RJA likelihood, baseline pupil size (BPS), and stimulus-evoked pupillary response (SEPR) between groups and measurement timepoints. Violin plots show the density of the measure, while boxplots indicate central tendency as mean and dispersion as interquartile range.

### Baseline Pupil Size (BPS)

Lower BPS (pupil size during the first 500ms of a trial) predicted higher RJA likelihood (β = 0.32 [0.19, 0.46], z = 4.79, p < .001). In an intervention model (*mR*² = 0.01, *cR²* = 0.63), BPS decreased from baseline to end-of-treatment in the autistic TAU group (Δβ = -0.17 [-0.29, -0.05]) but not in the autistic A-FFIP group (Δβ = -0.01 [-0.12, 0.10]). However, at end-of-treatment, BPS did not differ between the autistic groups (Δβ = 0.05 [-0.36, 0.47], *t* < 1). In a developmental model (*mR*² = 0.04, *cR²* = 0.64), BPS decreased from baseline to follow-up in the non-autistic group (Δβ = -0.16 [-0.25, -0.07], t(1846) = -3.37, p < .001) and the autistic A-FFIP group (Δβ = -0.28 [-0.43, -0.12], t(1886) = -3.45, p < .001), but increased in the autistic TAU group (Δβ = 0.18 [0.02, 0.36], t(1898) = 2.14, p = .032). At baseline, BPS did not differ between group (*t*s < 1.84, *p*s > .162). At follow-up, BPS was lower in the non-autistic group (Δβ = -0.68 [-1.14, -0.22], t(152) = -3.51, p = .001) and the autistic A-FFIP group (Δβ = -0.66 [-1.17, -0.14], t(166) = -3.04, p = .008) compared to the autistic TAU group.

### Stimulus-evoked Pupillary Response (SEPR)

Higher SPER (pupil size change coinciding with target cueing) predicted a higher RJA likelihood (β = 0.13 [0.00, 0.26], z = 2.01, p = .044). In addition, higher SEPR was strongly associated with lower BPS (β = -0.88 [-0.93, -0.84], t(1864) = -44.17, p < .001). In an intervention model (*mR*² < 0.01, *cR²* = 0.12), SEPR did not change significantly from baseline to end-of-treatment in the autistic groups (A-FFIP: Δβ = 0.09 [-0.08, 0.25], t(968) = 1.02, p = .306; TAU: Δβ = 0.00 [-0.19, 0.18], t(1005) = -0.02, p = .982). In a developmental model (*mR*² = 0.01, *cR²* = 0.14), SEPR decreased from baseline to follow-up in the autistic TAU group (Δβ = -0.18 [-0.29, -0.08], t(1123) = -3.34, p < .001), and did not change significantly in the autistic A-FFIP (Δβ = -0.02 [-0.11, 0.07], t < 1) or non-autistic group (Δβ = 0.02 [-0.04, 0.07], t < 1).

### Mediation Model

In causal mediation analysis of the developmental model with BPS as mediator, a significant total effect of d = 0.26 [0.08, 0.44] (p = .008) was observed as the standardized difference in RJA likelihood between A-FFIP and TAU at follow-up. This total effect consisted of a significant mediating effect of BPS (ACME = 0.08 [0.03, 0.15], p < .001) that rendered the direct effect of group to be insignificant (ADE = 0.17 [-0.01, 0.36], p = .056). The proportion of mediation by BPS of the total effect was estimated as 0.32 [0.11, 0.98] (p = .008). In causal mediation analysis of the developmental model with SEPR as mediator, a significant total effect of d = 0.23 [0.20, 0.26] was observed as the standardized difference in RJA likelihood between A-FFIP and TAU at follow-up. This total effect consisted of a significant mediating effect of SEPR (ACME = -0.03 [-0.05, 0.00], p = .034) and a significant direct effect of group (ADE = 0.25 [0.24, 0.27], p < .001). The proportion of mediation by SEPR of the total effect was estimated as -0.11 [-0.23, -0.01] (p = .034), i.e., the consideration of SEPR as mediator increased the total effect. Causal mediation analysis with BPS or SEPR in the intervention model did not show a significant mediating effect (BPS: ACME = 0.00 [-0.03, 0.04], p = .874; SEPR: ACME = 0.00 [-0.01, 0.01], p = .500).

### Cascade Effects

In a subsample with available data at all timepoints, cascading effects were investigated in linear models. Increases in RJA likelihood from baseline to end-of-treatment were associated with an improvement of social responsiveness (i.e. lower SRS-16 total scores) from baseline to follow-up (β = -1.00 [-1.89, -0.11], t(12) = -2.46, p = .029). Accordingly, higher RJA likelihood at end-of-treatment also predicted higher social responsiveness (i.e. lower scores) at follow-up (β = -0.53 [-1.04, -0.01], t(12) = -2.26, p = .045) when considering RJA likelihood at baseline as a covariate (see figure 3).

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Figure 3. Cascade effects of changes in reactive joint attention (RJA) likelihood or baseline pupil size (BPS) from baseline (BL) to end-of-treatment on changes in socia-cognitive development from BL to follow-up (FU). Social responsiveness is measured by SRS-16 sum score. Repetitive behavior is measured by RBSR sum score. Nonverbal IQ is measured by Bayley III development quotient or WPPSI-IV nonverbal IQ.

### Dropout Analysis

The retention rate for eye-tracking assessments in autistic preschoolers from baseline to end of treatment was 87.5% in the A-FFIP group and 71% in the TAU group, while the retention rate from baseline to follow-up was 34% in the A-FFIP group and 50% in the TAU group. In dropout analyses, no significant fixed effects of or interactions with retention status were found at baseline for the dependent variables of RJA likelihood, autism symptom severity, comorbid psychopathology, or eye-tracking data quality (see supplement X). Thus, autistic preschoolers with longitudinal eye-tracking assessments compared to dropout children likely did not differ on core measures at baseline. Dropout analysis indicate that joint attention differences in response to intervention are unlikely to be attributed to systematic dropouts within and between autistic groups.

* Discussion:
  + Limitation: assumption of causal mediation analysis cannot be tested
  + Limitation: small sample size for socio-cognitive development at follow up

**Outcome Measure**

* **First fixation**
* **Dwell time on target – RJA duration**
* **Social attention 🡪 face orienting**
* **Correct – incorrect trials difference 🡪 Senju & Csibra**

## Data preprocessing

* Key measures
  + Outcome measures
    - Joint attention duration
    - Joint attention likelihood
    - Social attention – orienting to Face attention

**Key resources**

* Social attention – Falck-Ytter 2023
  + Focuses on early predictive markers of ASD
  + General definition: attention to social stimuli
    - Hyp1: specific process
    - Hyp2: general attention process
  + Phenotypes of joint attention
    - Gaze cueing – faster orienting to cued objects
    - Gaze following – rather reactive joint attention (RJA)
    - Initiating joint attention – different brain network than RJA
* Joint attention - Nyström 2019
  + Live action joint attention in infancy
  + No difference in face preferences
  + RJA outcome measure was *difference score*: correct – incorrect trials
    - Difference score produced high variance
    - “RJA distinguished infants based on familial ASD risk, albeit not ASD diagnosis” – differed between high and low risk
  + No difference in RJA (low power?), but differences in IJA in
    - high risk children that later developed ASD
* JA and autism
  + Joint attention is trained is early intervention programs, see Jasper
    - Mureza 2016
  + Some have suggested a higher prognostic relevance of IJA compared to RJA in autistic development – Stallworthy 2022, JAACAP; Nyström et al., 2019; Falck-Ytter 2022
  + Underlying processes unclear 🡪 arousal regulation

## References

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