# Early Intervention Increases Reactive Joint Attention in Autistic Preschoolers and Cascades on Improved Socio-Cognitive Development

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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 social agent. This key ability of socio-cognitive development is altered in autistic compared to non-autistic preschoolers. Thus, RJA is 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; treatment 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). Pupillometry was 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 an experimenter cueing on-screen targets.

Results: At end of intervention, the treatment group - but not the TAU group - showed a higher RJA likelihood compared to baseline. The increase in RJA likelihood with intervention predicted higher 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 predicted a lower RJA likelihood and mediated the group difference on RJA in causal mediation analysis.

Conclusion: The early intervention increased reactive joint attention in autistic preschoolers up to two years after end of intervention, which likely initiated a developmental cascade of socio-cognitive development. Improved 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 social agents (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 the social agent’s 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 others’ 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 synonymous to gaze following (Falck-Ytter et al., 2022; Gredebäck et al., 2010) but gestures as re-orienting cues specifically pointing should also be considered (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 have been associated with a reduction in autism core symptoms when controlling for a study’s 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). The null findings in eye-tracking studies are 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).

The underlying 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 neurophysiological mechanism of pupillary responses (BPS and SEPR) and 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 are associated with joint attention and mediate a putative between-group difference in reactive joint attention (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 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 measure of LC-NE activity as an index of arousal (BPS) and stimulus-specific processing (SEPR) to mediate putative group differences in joint attention. This would support 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 to the autistic groups 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. The study was approved by the local ethics committee (autistic preschoolers [10/18], non-autistic preschoolers [361/18]) and in accordance with the Declaration of Helsinki.

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 children to freely move their head within 50–80 cm 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 standard 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). The battery was 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 by 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 social agent’s face location (1s), face attention: a social agent looks directly into the camera and two stimuli are presented (2s), joint attention: the social agent initiates a reorienting cue to one target stimulus after both stimuli started to shake (6s), re-establish face attention: the social agent stops the reorienting cue and looks into the camera again (2s).

[figure of phases with heatmaps + RJA + pupillometry]

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

### 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 for all preprocessing. 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.

#### Gaze

Data points beyond biologically plausible values for velocity and acceleration 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 no gaze change larger than 1 °/s for at least 100 ms. Figure 1 shows a heatmap of the preprocessed fixation gaze data within trials.

#### Reactive joint attention (RJA)

The definition was based on previous literature of the paradigm (Franchini et al., 2017). RJA was defined when a fixation on the head of the social agent occurred in the last 500 ms, followed by a fixation on the target object during the joint attention phase. Supplements provide a definition of the head and object area-of-interest (see supplements). We deviated from the original definition as we did not consider a distinct hand area-of-interest for pointing trial to retain comparable trails across conditions. Figure 1 shows the occurrences of RJA within trials.

#### 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). 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. Pupil size estimates were normalized by subtracting the BPS (Mathôt et al., 2018). For each trial, we estimated stimulus-evoked pupillary responses (SEPR) to reorienting cues as mean normalized pupil size between 4.5 and 5.5 s after stimulus onset. [other rpd measures relevant?]. Figure 1 shows the normalized pupil size within trials.

### Statistical Analysis

Statistical analyses were done with R statistics (4.3) and the analysis script is available online (see github). Preprocessed eye-tracking data including RJA, BPS, and SEPR were aggregated per trial and matched to demographic and questionnaire data. RJA likelihood was defined as the occurrences of any RJA within a trial (true versus false) and investigated as a dependent variable. 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]) were included as a fixed effect. The comparison of autistic versus non-autistic groups was limited to the timepoints baseline versus follow-up based on the assessment plan. Participant and trial number were included as random intercepts to control for interindividual variability and reflect the multilevel data structure. [extend when results are complete]

Casual Mediation model

### 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 drop-out analyses in autistic preschoolers, we applied two-way ANOVA models. We included group (A-FFIP versus TAU) and reassessment status (at end-of-treatment: True versus False; or at follow-up: True versus False) as two-level factors. These models achieved a power = 0.82 to detect a moderate effect size or interaction (η² = 0.12) with the given sample. No significant fixed effects or interactions were found for RJA likelihood, autism symptom severity, comorbid psychopathology, or eye-tracking data quality (see supplement X). Autistic preschoolers with eye-tracking reassessments compared to drop-out children likely did not differ on core measures at baseline. Dropout analysis indicate that joint attention differences in response to treatment are unlikely to be attributed to systematic dropouts within and between autistic groups.

**Results**

* **RJA likelihood**
* **Pupillometry data**
  + **BPS**
  + **SEPR**
  + **Causal mediation analysis**

**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

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