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# Developmental sequelae and neurophysiologic substrates of sensory seeking in infant siblings of children with autism spectrum disorder

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ABSTRACT

It has been proposed that early differences in sensory responsiveness arise from atypical neural function and produce cascading effects on development across domains. This longitudinal study prospectively followed infants at heightened risk for autism spectrum disorder (ASD) based on their status as younger siblings of children diagnosed with ASD (Sibs-ASD) and infants at relatively lower risk for ASD (siblings of typically developing children; Sibs-TD) to examine the developmental sequelae and possible neurophysiological substrates of a specific sensory response pattern: unusually intense interest in nonsocial sensory stimuli or "sensory seeking." At 18 months, sensory seeking and social orienting were measured with the Sensory Processing Assessment, and a potential neural signature for sensory seeking (i.e., frontal alpha asymmetry) was measured via resting state electroencephalography. At 36 months, infants' social symptomatology was assessed in a comprehensive diagnostic evaluation. Sibs-ASD showed elevated sensory seeking relative to Sibs-TD, and increased sensory seeking was concurrently associated with reduced social orienting across groups and resting frontal asymmetry in Sibs-ASD. Sensory seeking also predicted later social symptomatology. Findings suggest that sensory seeking may produce cascading effects on social development in infants at risk for ASD and that atypical frontal asymmetry may underlie this atypical pattern of sensory responsiveness.

## 1. Introduction

Autism spectrum disorder (ASD) is characterized by social and communication deficits accompanied by a pattern of repetitive behaviors, restricted interests, and unusual responses to sensory stimuli. Atypical sensory responsiveness has been observed or reported in many individuals with ASD from infancy to adulthood (Baranek et al., 2006; Crane et al., 2009; Dawson and Watling, 2000). Previous research indicates that atypical sensory responsiveness emerges early in life (i.e., as early as 2–6 months of age; Bryson et al., 2007; Dawson et al., 2000), possibly *before* some of the social and communicative impairments typically associated with ASD (Baranek, 1999a,b; Dawson et al., 2000; Mulligan and White, 2012). This evidence is consistent with the developmental primacy of basic sensory neural pathways, many of which are in place prenatally (Anderson and Thomason, 2013). Recent work also suggests that sensory responsiveness is related to other core symptoms of ASD (Foss-Feig et al., 2012; Gabriels et al., 2008; Kern et al., 2007; Stevenson et al., 2015). Together, this evidence suggests that atypical sensory behaviors may serve as early markers of ASD risk. Furthermore, since the early sensory environment likely influences the

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development of social and communicative skills associated with ASD, a better understanding of the cascading effects of basic sensory disturbances may elucidate the developmental trajectory of later-developing social and communication deficits in ASD. However, to better understand this process, prospective longitudinal studies are needed to examine the predictive value of sensory behaviors on social and communicative development (Cascio et al., 2016).

Given the early development of atypical sensory responsiveness, it is possible that behavioral response patterns to sensory stimuli may serve as an early biomarker or endophenotype of ASD. An endophenotype is a heritable intermediate phenotype that is expressed in both affected and non-affected family members. The identification of endophenotypes provides clues into the biological underpinnings of a disorder (Gottesman and Gould, 2003), and may ultimately help to discriminate between inherited behavioral features of the disorder and features that are secondary or epiphenomenal. Infant siblings of individuals with ASD are an ideal population in which to study candidate endophenotypes. This line of research compares infant siblings of children diagnosed with ASD (Sibs-ASD) to infant siblings of typically developing children (Sibs-TD), in order to better understand the characteristics associated with a genetic risk for ASD. Sibs-ASD are at heightened risk for ASD and, even when they are not later diagnosed with ASD, often show subclinical symptoms associated with the disorder (Georgiades et al., 2013; Messinger et al., 2013; Ozonoff et al., 2014; Stone et al., 2007). Despite some preliminary studies suggesting that atypical sensory responsiveness may be an early characteristic of the broader ASD phenotype (Brian et al., 2008; Loh et al., 2007; Ozonoff et al., 2008), the developmental trajectory of atypical sensory responsiveness in Sibs-ASD and the neural mechanisms driving these atypicalities remain poorly understood.

Previous research suggests that atypical sensory responsiveness in ASD can be characterized as three separate empirically-derived constructs: hyper-responsivity, hypo-responsivity, and sensory seeking (Ben-Sasson et al., 2008; Boyd et al., 2010). Most previous research has focused on hypo- or hyper-responsivity (i.e., reduced or exaggerated behavioral responses to sensory stimuli, respectively) in ASD. There is little research focusing specifically on sensory seeking (Ben-Sasson et al., 2009), defined here as behaviors with the goal of enhancing or prolonging a nonsocial sensory experience (e.g., visual examination, repetitive touching, banging, or licking an object). In understanding the developmental trajectory of ASD symptoms, sensory seeking is particularly of interest because these behaviors are likely to divert attention away from social learning opportunities. In addition, though sensory seeking may be directed towards other individuals (e.g., hair stroking), the odd nature of these behaviors may actually obstruct the development of typical social relationships. Supporting this, sensory seeking has been linked to increased severity of concurrent social and communication deficits in children with ASD (Hilton et al., 2007; Liss et al., 2006; Watson et al., 2011).

The extent to which early sensory seeking behaviors and early sensory experiences more broadly relate to later ASD symptomatology remains unclear, however. In addition, because sensory atypicalities are present so early in infancy and emerge before many of the social and communicative impairments associated with ASD, the neural networks that support these atypical sensory behaviors may also be critically involved in the emergence of the core diagnostic features of ASD. Yet, very little is currently known about the neural correlates of sensory responsiveness in typically developing infants, and virtually nothing is known about these processes in Sibs-ASD. To address these questions, the present study examines sensory seeking behaviors in Sibs-ASD and the neural mechanisms that may be driving these behaviors. The present study also investigates the extent to which sensory seeking behaviors might be related to later ASD symptomatology, and thus their potential utility as early markers or endophenotypes for ASD.

As a potential neural basis for sensory seeking in infants at risk for ASD, the current study measured asymmetry in resting state alpha band oscillations (approximately 6–9 Hz in infants) at frontal electrode sites using EEG. Frontal asymmetry as measured by resting state EEG (i.e., the relative difference in power between hemispheres in the alpha band) is a reliable and stable measure that has been used to index risk for psychopathology across the lifespan (Coan and Allen, 2004). Frontal asymmetry is believed to reflect individual differences in the lateralization of brain activity which may be attributable to differences in thalamic inhibition of cortical processing across hemispheres (Jensen and Mazaheri, 2010). It is partly heritable (Anokhin et al., 2006) and has been studied as a potential endophenotype in other clinical conditions, such as depression (Allen and Cohen, 2010). Frontal asymmetry may also serve as a marker of cortical development, as hemispheric differences in alpha power tend to change over the course of the first two years of life, and may contribute to changes in exploratory behavior over this developmental period (Fox et al., 1994; Fox et al., 2001).

Patterns of resting frontal asymmetry may be particularly useful for understanding sensory seeking in Sibs-ASD, as frontal asymmetry has already been correlated with ASD symptomatology. More specifically, more severe ASD symptoms and social inhibition have been observed in children with ASD with relatively greater right frontal asymmetry (Burnette et al., 2011; Sutton et al., 2005), whereas fewer parent-reported social deficits have been observed in children with relatively greater left frontal asymmetry. Most relevant to the present study, by the age of 18 months Sibs-ASD on average demonstrate relatively greater right frontal asymmetry, whereas Sibs-TD on average display relatively greater left frontal asymmetry (Gabard-Durnam et al., 2015).

Frontal asymmetry has also been associated with sensory responsiveness in Sibs-ASD. Specifically, the atypical pattern of greater right frontal asymmetry has already been observed to co-occur with higher sensory hyporesponsivity in this high risk group (Simon et al., under review). This finding is of interest because hyporesponsivity has been theoretically and empirically linked to sensory seeking. Dunn's (1997) Model of Sensory Processing postulates that sensory seeking and hyporesponsivity are both associated with a high neurological threshold, but represent different behavioral response patterns (i.e., active versus passive). Consistent with this theoretical framework, past studies have demonstrated behavioral associations between hyporesponsivity and sensory seeking in children diagnosed with ASD (Ausderau et al., 2014; Dunn, 1997; Freuler et al., 2012). Together, these results suggest that frontal asymmetry may reflect differences in neural organization and processing that relate to sensory atypicalities in a population at risk for ASD.

The specific aims of the present study are as follows: (a) to determine whether high-risk Sibs-ASD differ from low-risk Sibs-TD in sensory seeking behaviors at 18 months, (b) to evaluate whether resting frontal asymmetry may reflect a potential neural mechanism underlying sensory seeking differences, and (c) to examine whether early sensory seeking is related to concurrent social orienting and later social deficits associated with ASD at 36 months. We hypothesized that increased sensory seeking at 18 months diverts attention from important social cues and thus reduces social orienting, which ultimately has cascading effects on social development and results in more social deficits at 36 months. We also anticipated that Sibs-ASD would exhibit more atypical frontal asymmetry patterns (i.e., greater right frontal asymmetry) as previously observed in Sibs-ASD at 18 months (Gabard-Durnam et al., 2015). Further, we predicted that right frontal asymmetry would serve as a potential neural correlate of increased sensory seeking, as right frontal asymmetry has been linked with ASD symptomatology in children who are diagnosed with or at risk for ASD (Burnette et al., 2011; Simon et al., 2017; Sutton et al., 2005).

## 2. Materials and methods

### 2.1. Overview of study design

To test our hypotheses, we drew upon data from a multisite,

longitudinal study of Sibs-ASD and Sibs-TD (Edmunds et al., 2016; Key et al., 2015). For a subset of participants in the aforementioned study, sensory seeking and social orienting behavior were measured when infants were 18 months old. Frontal asymmetry was measured via resting state EEG at this same time point. Social symptomatology was measured when participants were 36 months old, in the context of a comprehensive diagnostic assessment.

### 2.2. Participants

The current sample included 20 Sibs-ASD and 20 Sibs-TD from the larger longitudinal study for whom sensory seeking, social orienting, and/or resting frontal asymmetry was measured at 18 months (+/−30 days) and for whom diagnostic outcomes were ascertained. Infants were excluded from participation in the study if they had (a) severe motor, hearing or vision impairment according to parent report, (b) identified metabolic, genetic or progressive neurological disorders, (c) birth weight under 2500 g, and/or (d) a gestational age of less than 37 weeks. Sibs-TD were also required to have no history or present concern of developmental delay and no family history of ASD in first-degree relatives. Proband diagnoses for older siblings of Sibs-ASD and 36 month outcome diagnoses for Sibs-ASD and Sibs-TD were confirmed by the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), Autism Diagnostic Interview-Revised (Lord et al., 1994) and clinical judgment of a licensed psychologist according to criteria from the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV; American Psychiatric Association, 2000). The Mullen Scales of Early Learning (Mullen, 1995) was administered at 12 months to characterize the sample. Table A1 further details participant characteristics.

### 2.3. Measurement of early sensory seeking

Infants' sensory seeking was measured using the Sensory Processing Assessment (SPA; Baranek, 1999a), a behavioral sampling procedure developed to assess patterns of sensory responsiveness in young children (with chronological ages approximately 9 months – 6 years). During this 15- to 20-min observational sample, children are presented with a series of novel toys (e.g., musical dome, bubble blower, vibrating toy) that afford sensory experiences across a number of modalities (e.g., visual, auditory, tactile). For each novel toy, two aspects of sensory seeking were coded from video records of SPA administrations (Kirby et al., 2015). An overall rating of sensory seeking behavior from 0 to 2, wherein 0 = no unusual sensory seeking behavior, 1 = occasional clearly unusual and/or intense seeking interests, and 2 = frequent, intense and/or unusual sensory seeking, was assigned. Additionally, the presence or absence (Y/N) of discrete sensory seeking behaviors in 12 categories (flap, posture, lick, bite, smell, sight, touch, proprioceptive, spin, auditory, other repetitive, other) was recorded. From these codes, we derived two variables for sensory seeking. Seeking intensity was quantified as the sum of overall ratings of sensory seeking behavior (0–2) across all novel toys. Seeking inventory was quantified as the total number of discrete sensory seeking behaviors endorsed for the 12 aforementioned categories across the SPA sample. The z-scores for these two component variables were averaged to create one aggregate variable that reflected both the intensity and inventory of sensory seeking behavior. We aggregated these two component variables because they were conceptually linked and empirically related, and because doing so increases the stability and thus the potential validity, of the predictor (Rushton et al., 1983). Evidence of the empirical relation amongst component variables will be presented in the Preliminary Analyses section of the Results.

### 2.4. Measurement of concurrent social orienting and future social symptomatology

Within the context of the SPA, infants are also presented with a number of "presses" for social orienting. When the infant is engaged with a novel toy, social stimuli (e.g., name call, shoulder tap, wave) are presented until the child shows a definite behavioral orienting response or for a maximum of three trials, whichever comes first. No prompting or scaffolding, aside from the prescribed repetitions (max of three per bid), is provided in response to a failure of the infant to orient. The infant is simply permitted to continue his or her ongoing activity. Infants' responses are assigned a score from 1 to 4, wherein 1 = child orients on the 1st trial, 2 = child does not orient until the 2nd trial, 3 = child does not orient until the 3rd trial, or 4 = child does not orient across the three trials for that stimulus. Social orienting was operationalized as the sum of scores (1–4) assigned across all social orienting items. Thus, a higher score for social orienting reflects reduced orienting/the need for increased cueing in order to elicit an orienting response.

The ADOS Module 2 (Lord et al., 2000) was utilized to measure social symptomatology at 36 months. This assessment was administered as part of comprehensive diagnostic evaluation by a licensed psychologist who was research-reliable in ADOS administration and experienced in evaluating young children with ASD. The Social Interaction domain score was utilized as the metric of social symptomatology in analyses.

### 2.5. Measurement of resting frontal asymmetry

Eyes open resting EEG was recorded while infants sat quietly on their parents' laps in a sound- and light-attenuated psychophysiology laboratory. Parents were instructed to help their child sit as still as possible and watch a muted video that involved simple moving shapes ('Baby Einstein', Kids II, Inc.). EEG data were collected from 124 (four eye channels excluded) or 128 electrodes using a NetAmp 200 or 400 amplifier and Geodesic Sensor Net (Electrical Geodesics Inc.). Data were acquired at a sampling rate of 250 or 500 Hz, referenced to the vertex (Cz), and online filtered from 0.1 to 100 Hz. Data were then exported and further processed using EEGLAB (Delorme and Makeig, 2004), down sampled to 250 Hz and band-pass filtered with a zero phase finite impulse response filter between 1 and 50 Hz.

Epochs 2 s long with 50% overlap were extracted, baseline corrected to the mean, and rigorously visually inspected for artifacts and bad channels. We manually inspected all channels for EOG, EMG, and movement artifacts and rejected epochs and channels containing artifacts. Residual artifacts were corrected with independent component analysis. Data were then re-referenced to the average, and removed channels were interpolated. Peripheral electrodes (26 total) were excluded from all analyses due to high levels of artifact contamination and interpolation. A total of 602 ( ± 118) seconds of data were recorded per subject (range 232–803 s) and 279 ( ± 106) epochs were retained per subject (range 85–475). An average of 9.46 ( ± 3.23) channels were interpolated per subject, and an average of 2.96 ( ± 1.06) artifact related independent components were removed.

EEG epochs were transformed using a zero padded fast Fourier transform (0.061 Hz resolution) after application of a Hann window. We selected two electrode groupings (six electrodes each) centered on the F3/F4 selections used in previous studies of frontal alpha power in children diagnosed with and infants at risk for ASD (Gabard-Durnam et al., 2015; Sutton et al., 2005). The left frontal grouping consisted of electrode 25 (F3) and its five neighbors (20, 21, 24, 28, and 29). The right frontal grouping consisted of electrode 124 (F4) and its five neighbors (3, 4, 118, 119, and 123). Amplitude values were averaged across these electrodes, squared to power, and natural log transformed. Frontal asymmetry was calculated by subtracting log left power from log right power (log R – log L). The alpha band was defined as 6–9 Hz

based on previous literature in children this age and confirmed by a notable peak in this range in the average power spectrum.

### 2.6. Analytic plan

An independent-samples *t*-test was utilized to test between-group differences in sensory seeking and resting frontal asymmetry at 18 months. A series of multiple regression analyses was then utilized to test (a) whether early sensory seeking was related to concurrent social orienting and future social symptomatology and (b) whether early sensory seeking was related to resting frontal asymmetry. For each of these models, variables were added in step-wise fashion. The predictor of interest (sensory seeking or frontal asymmetry, respectively) was entered first to examine whether it accounted for a significant amount of variance in the dependent variable of interest (social indices and sensory seeking, respectively) across groups. Risk group (Sibs-ASD versus Sibs-TD) and the relevant product (risk group × predictor of interest) terms were then added to determine if risk group moderated the effects of the predictor of interest on the dependent variable. Throughout regression analyses, Cook's D was used to determine whether any individual data points were unduly influencing regression coefficients (Cook's D greater than 1 was the criterion value applied for determining undue influence on the regression line across all analyses).

### 2.7. Preparation of data for analysis

The chosen analysis method assumed multivariate normality, and multivariate normality is more likely when univariate distributions do not grossly depart from the normal distribution (Tabachnick and Fidell, 2001). Thus, all variables were evaluated for normality. Variables showing univariate skewness > |1.0| or kurtosis > |3.0| were transformed prior to imputation and analysis. Missing data points (ranging from 5 to 32.5% across variables) were then imputed using stochastic regression imputation, which generates plausible values for missing scores according to the association of variables with missing data to variables with observed scores. This method is preferable to traditional methods for dealing with missing data (e.g., listwise deletion, mean imputation, last observation carried forward) in longitudinal data sets because it prevents loss of information related to missing data, reduces bias, improves parameter estimates, and preserves statistical power to detect effects of interest (Enders, 2010). This is particularly true when auxiliary variables (which are not utilized in the primary analyses but provide extra information about missing values) are considered in the imputation process (Enders, 2010), as was afforded by the rich dataset from the multisite, longitudinal study of Sibs-ASD and Sibs-TD on which we drew (Edmunds et al., 2016; Key et al., 2015). The data used in the present imputation model included all variables involved in primary analyses as well as auxiliary variables from the aforementioned larger dataset (e.g., Vineland Socialization scores) that were theoretically and empirically (*r* values > .40 per Enders, 2010) related to, and thus possible of informing the imputation of, one or more of the variables involved in primary analyses. Note that all analyses reported in the results, by virtue of the stochastic regression imputation, are based on the complete sample of 20 Sibs-ASD and 20 Sibs-TD, unless otherwise indicated (i.e., with the exception of instances wherein undue influence was detected). Further information regarding missing data, as well as effect sizes in observed versus imputed data for group differences and associations contributing to the results we report here, are provided in accompanying Supplemental material (Tables S1–S3).

## 3. Results

### 3.1. Preliminary analyses

#### 3.1.1. Interobserver reliability for coded variables

Interobserver reliability of the sensory seeking component variables, and the social orienting variable from the SPA, was estimated for a randomly selected 20% of samples using absolute agreement intraclass correlation coefficients (ICCs). The ICCs for seeking inventory and intensity were 0.78 and 0.80, respectively. The ICC for social orienting was 0.99. Thus, inter-rater reliability was good-excellent for coded variables.

#### 3.1.2. Justification for aggregation of sensory seeking component variables

The intercorrelation among the sensory seeking inventory and intensity component variables exceeded our criterion ($r \geq 0.4$) for aggregation ($r = 0.86$, $p < 0.001$).

#### 3.1.3. Transformation of variables

ADOS Social Interaction domain scores at 36 months were positively skewed, but were corrected with a square-root transformation.

### 3.2. Primary analyses

#### 3.2.1. Group differences in sensory seeking and frontal asymmetry

Analyses confirmed that Sibs-ASD and Sibs-TD groups significantly differed in early sensory seeking, $t_{(38)} = -2.26$, $p = 0.029$. Sibs-ASD ($M = 0.24$, $SD = 1.09$) showed significantly higher seeking relative to Sibs-TD ($M = -0.44$, $SD = 0.79$). This effect was moderate in magnitude ($d = 0.72$). Fig. A1 illustrates this result. Sibs-ASD also differed from Sibs-TD in frontal asymmetry at 18 months, $t_{(38)} = 2.311$, $p = 0.026$. Sibs-ASD ($M = -0.19$, $SD = 0.31$) showed significantly greater right asymmetry relative to Sibs-TD ($M = 0.13$, $SD = 0.53$). This effect was also moderate in magnitude ($d = 0.73$). Fig. A2 depicts this result. Levene's tests indicated Sibs-ASD and Sibs-TD were non-significantly different in variance for early sensory seeking and/or resting frontal asymmetry, and thus that the assumption of equal variance inherent to the *t*-test was not violated in either of the aforementioned analyses.

#### 3.2.2. Associations between frontal asymmetry and sensory seeking

The relation between frontal asymmetry and sensory seeking at 18 months varied according to risk group (*p* value for the frontal asymmetry x risk group product term in the moderation model < 0.001). One participant unduly influenced the regression line within the Sibs-TD group (Cook's D = 4.43). Even with this participant removed from analyses, however, this moderated effect remained significant (*p* value for the frontal asymmetry x risk group product term in the moderation model = 0.002). The frontal asymmetry score was negatively correlated with sensory seeking (zero-order correlation = −0.528, $p = 0.017$) within the Sibs-ASD group, but positively correlated with sensory seeking (zero-order correlation = 0.486, $p = 0.035$) within the Sibs-TD group. Thus, increased sensory seeking was associated with relatively greater right asymmetry (reflected by more negative scores for frontal asymmetry) in Sibs-ASD. Conversely, sensory seeking was associated with relatively greater left asymmetry (reflected by more positive scores for frontal asymmetry) in Sibs-TD. See Table A2 for the results of regression analyses and Fig. A3 for a depiction of this result. Note that the relation between frontal asymmetry and social orienting at 18 months also varied according to risk group. Further information on this moderated relation is provided in accompanying Supplemental material (Result S1).

*3.2.3. Associations between sensory seeking and concurrent social orienting and later social symptomatology*

Sensory seeking at 18 months was related to concurrent social orienting across groups ($p$ value for the effect of seeking on social orienting, not controlling for any additional factors < 0.001), and this effect did not significantly vary according to risk group ($p$ value for the sensory seeking x risk group product term in the moderation model = 0.24). One infant was found to unduly influence the regression line within the Sibs-TD group (Cook's D = 1.76). Yet, even with this participant removed from the analyses, this association remained significant ($p$ value for the effect of seeking on social orienting, not controlling for any additional factors < 0.001), and the moderated effect did not reach statistical significance ($p$ value for the sensory seeking x risk group product term in the moderation model = 0.11). Within group analyses excluding this participant, however, suggested that this effect was driven by the Sibs-ASD group, who showed an extended range of seeking relative to the Sibs-TD group (magnitude of the relation between sensory seeking and concurrent social orienting, excluding the statistical outlier within the Sibs-TD group = 0.76 and 0.10 for Sibs-ASD and Sibs-TD, respectively). Thus, increased sensory seeking was associated with reduced social orienting (as a higher social orienting score reflects delayed or absent social orienting), but this effect is largely limited to Sibs-ASD. See Table A3 for the results of regression analyses and Fig. A4 for a depiction of this result.

Early sensory seeking additionally predicted future social symptomatology across groups ($p$ value for the effect of seeking on future social symptomatology, not controlling for other factors = 0.008), but this effect significantly varied according to risk group ($p$ value for the sensory seeking x risk group product term in the moderation model = 0.008). Sensory seeking was positively correlated with later social symptomatology in Sibs-ASD ($r = 0.54$, $p = 0.014$). Thus, higher seeking at 18 months predicted increased social symptoms of ASD (i.e., reduced reciprocal social interaction) at 36 months in Sibs-ASD. The relationship between sensory seeking and social impairment trended in the opposite direction in Sibs-TD, but did not reach statistical significance ($r = -0.34$, $p = 0.15$). There was no evidence of undue influence within or across groups in these analyses. See Table A4 for the results of regression analyses and Fig. A5 for a depiction of this result.

Early sensory seeking additionally predicted future social symptomatology across groups ($p$ value for the effect of seeking on future social symptomatology, not controlling for other factors = 0.008), but this effect significantly varied according to risk group ($p$ value for the sensory seeking x risk group product term in the moderation model = 0.008). Sensory seeking was positively correlated with later social symptomatology in Sibs-ASD ($r = 0.54$, $p = 0.014$). Thus, higher seeking at 18 months predicted increased social symptoms of ASD (i.e., reduced reciprocal social interaction) at 36 months in Sibs-ASD. The relationship between sensory seeking and social impairment trended in the opposite direction in Sibs-TD, but did not reach statistical significance ($r = -0.34$, $p = 0.15$). There was no evidence of undue influence within or across groups in these analyses. See Table A4 for the results of regression analyses and Fig. A5 for a depiction of this result.

*3.3. Exploratory analyses*

Based on prior work, we anticipated that early social orienting would also be predictive of future social symptomatology, at least in high risk infants (e.g., Baranek, 1999a,b; Dawson et al., 2004; Zwaigenbaum et al., 2005). Social orienting at 18 months did predict future social symptomatology across risk groups (zero-order correlation for the effect of orienting on future social symptomatology, not controlling for other factors = 0.38, $p$ value = 0.017), but this effect significantly varied according to risk group ($p$ value for the social orienting x risk group product term in the moderation model predicting future social symptomatology = 0.015). Social orienting was positively correlated with later social symptomatology in Sibs-ASD ($r = 0.68$, $p = 0.001$), but not in Sibs-TD ($r = -0.05$, $p = 0.84$).

We subsequently examined whether the relation between early sensory seeking and later social symptomatology could be explained, at least in part, by social orienting (i.e., whether early sensory seeking *indirectly* impacted later reciprocal social interaction by reducing social orienting in infancy). This possibility can be statistically tested using modern mediation analyses that test the *indirect effect* of early sensory seeking on future social symptomatology through social orienting (Hayes, 2009; See Fig. A6A). Two pathways comprise this indirect effect. The first pathway, referred to as the "a path," represents the relation between early sensory seeking and social orienting. The second pathway, referred to as the "b path," represents the relation between social orienting and future social symptomatology, controlling for early sensory seeking. An indirect effect is statistically significant when the confidence interval for the product of the unstandardized coefficients for these two paths does not include zero. Because the relations for early sensory seeking with social orienting and future social symptomatology were only significant for Sibs-ASD in the analyses reported above, we suspected that this indirect effect would only apply to the infants at heightened risk for ASD. That is, we thought that this indirect effect would be *conditional* on risk group status. We therefore further evaluated whether risk group moderated the mediation relation of interest.

The moderated mediation analysis depicted in Fig. A6A was tested using the PROCESS macro in SPSS (Hayes, 2013). Bias-corrected confidence intervals for effects of interest were generated using 1000 bootstrap samples with the confidence level set at 95%. Results indicated that this proposed mediation relation was moderated by risk group, 95% CI for the conditional indirect effect [.0001, 0.9148]. The indirect effect (a x b) was significant for the Sibs-ASD group, 95% CI [.05, 0.84], but was not significant for the Sibs-TD group, 95% CI [−0.10, 0.30]. The significant indirect effect within the Sibs-ASD group confirms that social orienting mediates the relation between early sensory seeking and later social symptomatology for the high-risk group. This mediation is considered complete because the *direct effect* of early sensory seeking on future social symptomatology, called the "c' path," becomes non-significant when controlling for social orienting in Sibs-ASD, 95% CI [−0.38, 0.45]. The indirect effect for the Sibs-ASD group is depicted in Fig. A6B.

As sensory seeking and social orienting were measured concurrently, it is logical that one may question whether the observed mediation relation would hold if the present predictor (i.e., sensory seeking) and mediator (i.e., social orienting) were interchanged in the model. The indirect effect of social orienting on future social symptomatology through sensory seeking was not statistically significant, however, for either Sibs-ASD, 95% CI [−0.33, 0.38] or Sibs-TD, 95% CI [−0.23, 0.33]. Thus, although this alternative explanation was an intriguing possibility, sensory seeking does not appear to mediate the relation between social orienting and future social symptomatology in either group.

In post hoc analyses, we additionally examined whether sensory seeking varied not only according to risk group, but also between the following outcome groups: (a) Sibs-TD, all of whom had non-ASD outcomes (n = 20), (b) Sibs-ASD who did not receive a diagnosis (Sibs-ASD-No ASD; n = 14), and (c) Sibs-ASD who did receive a diagnosis of ASD (Sibs-ASD-Dx ASD; n = 6). To explore this possibility, we carried out a one-way ANOVA with Least Significant Difference (LSD) comparisons. Results confirmed that outcome groups did differ in early sensory seeking, $F_{(2,37)} = 4.87$, $p = 0.013$ (Fig. A7). Post hoc comparisons revealed that Sibs-ASD-Dx ASD showed increased sensory seeking

relative to both Sibs-ASD-No ASD ($p = 0.048$) and Sibs-TD ($p = 0.003$). The between-group difference for Sibs-ASD-No ASD and Sibs-TD did not reach statistical significance ($p = 0.21$).

## 4. Discussion

The present study examined the developmental sequelae and neurophysiological substrates of an understudied pattern of atypical sensory responsiveness – sensory seeking – in a group of infants who were at high risk for ASD based on their status as infant siblings of children who are diagnosed with ASD relative to a control group of infants at relatively lower risk for ASD. The overarching aim of this work was to investigate sensory seeking as a potential early marker for ASD risk, or endophenotype, as well as the mechanisms by which sensory seeking might impact later social development. Towards this aim, we examined how sensory seeking relates to concurrent social orienting at 18 months, as well as social symptomatology at 36 months, in Sibs-ASD versus Sibs-TD. We also explored a potential neural signature for sensory seeking – resting frontal asymmetry.

### *4.1. Sensory seeking is elevated and related to later social symptomatology in sibs-ASD*

Past research has linked high levels of sensory seeking to social impairment in children and adults who are diagnosed with ASD (Hilton et al., 2007; Liss et al., 2006; Watson et al., 2011). We extend the aforementioned work to show that sensory seeking is elevated at 18 months and predictive of later social symptomatology in infants at high-risk for ASD, providing further evidence that early differences in sensory function may produce cascading effects on development across other domains, such as social skill (Cascio et al., 2016). Seeking appears to be highest for those infant siblings who will go on to receive a diagnosis of ASD. These findings suggest that sensory seeking behaviors at 18 months may serve as an endophenotype of ASD or an early marker for social deficits in this high-risk population.

### *4.2. Social orienting mediates the relation between sensory seeking and social deficits*

Our findings indicate that high sensory seeking may impact social development via its association with reduced social orienting. In our sample of Sibs-ASD, reduced social orienting accounts for the significant association between sensory seeking and future social symptomatology. This result suggests that infants at risk for ASD who engage in sensory seeking behaviors may be too distracted or preoccupied with enhancing sensory experiences to attend to social cues in their environment. By failing to orient to these social cues, these “high seekers” are likely missing out on essential social learning opportunities, which may translate to social deficits at 36 months. This finding has implications for clinical practice, as it suggests that sensory seeking may be an important target of early intervention. Although, to our knowledge, no treatment studies to date have attempted to target sensory seeking in infants at risk for ASD, the current results suggest that social development might be facilitated by interventions that aim to reduce the frequency of sensory seeking behaviors and/or to increase social orienting in Sibs-ASD who are seeking out enhanced or prolonged non-social sensory experiences.

### *4.3. Atypical resting frontal asymmetry may underlie sensory seeking behavior*

As a potential neural marker for sensory seeking in this high-risk population, the present study also examined whether frontal asymmetry, as indexed by the relative distribution of frontal alpha oscillations, was (a) different in Sibs-ASD versus Sibs-TD and (b) associated with sensory seeking. Alpha oscillations are believed to tap localized cortical inhibition from both cortical and subcortical inputs, and this transient inhibition is believed to play a crucial role in the gating of cortical processing (Jensen and Mazaheri, 2010). Although further research is warranted in order to better understand the psychological constructs associated with frontal asymmetry, differences in the relative balance of these inhibitory oscillations are believed to influence the degree to which individual hemispheres contribute to top down regulatory functions critical for both ‘bottom up’ processing of sensory inputs and regulation of complex behaviors such as attentional orienting (e.g., Mazaheri et al., 2009).

Typically, infants gradually shift in the laterality of frontal asymmetry between 6 and 18 months of age, exhibiting relative left frontal asymmetry (i.e., relatively reduced alpha power in the left versus right hemisphere) by 14–18 months of age (Fox et al., 1994; Fox et al., 2001; Gabard-Durnam et al., 2015). Because alpha oscillations are inversely related to cortical activation, this pattern can be interpreted as reflecting greater left hemisphere activation at rest in typically developing infants by around 18 months. Recent research suggests that Sibs-ASD show the opposite developmental trajectory, progressing from a frontal asymmetry pattern suggestive of relative left hemisphere activation to relative right hemisphere activation over the same 6–18 month window (Gabard-Durnam et al., 2015). This atypical pattern of frontal asymmetry has additionally been documented, and linked with characteristics of ASD, in older children who are diagnosed with autism (Burnette et al., 2011; Sutton et al., 2005), further supporting the notion that a disruption in rhythmic neural processes is related to ASD symptomatology.

As hypothesized, the Sibs-ASD group showed greater right frontal asymmetry when compared to the Sibs-TD group at 18 months. This result is consistent with previous research (Gabard-Durnam et al., 2015). In addition, within the Sibs-ASD group, increased sensory seeking was associated with this atypical pattern of greater right frontal asymmetry (i.e., relatively reduced alpha power in the right versus left hemisphere) at 18 months of age. This finding suggests that increased sensory seeking in Sibs-ASD may be associated with atypical organization and maturation of oscillatory processes. It is also possible that greater right frontal asymmetry may develop as a compensatory neural function due to reduced left cortical activity in this population, as some previous research suggests that differences in the lateralization of brain function may occur over development when one hemisphere compensates for reduced functioning in the other hemisphere (Dehaene-Lambertz et al., 2004). Further research is needed along these lines.

Interestingly, Sibs-TD demonstrated the opposite pattern, with relatively greater left frontal asymmetry being associated with increased sensory seeking. This result is somewhat difficult to interpret. We note, however, that there was a fairly limited range of sensory seeking behavior observed across Sibs-TD. The moderated results that we obtained indicate that increased seeking, to the extent that it was observed within the TD group, not only tended to co-occur with a more left lateralized or “typical” resting brain state, but also did not predict future social deficits. On the whole, these results may suggest that some degree of sensory seeking behavior may be adaptive. Thus, there is a need for future research to determine at what point, and in what populations, sensory seeking has implications for social development.

Past work linking frontal asymmetry to hyporesponsiveness in Sibs-ASD (Simon et al., under review) and to other symptoms of ASD within children who are diagnosed (Burnette et al., 2011; Sutton et al., 2005), suggests that atypical frontal asymmetry is not specific to sensory

seeking, but is associated with sensory responsiveness and ASD symptomatology more broadly. As such, further work is also warranted to elucidate how these early-emerging oscillatory patterns contribute to atypical development in ASD.

### 4.4. Limitations and future directions

The results of the present study have important implications for understanding the developmental course of social deficits associated with ASD and the broader autism phenotype, but are limited. Findings are subject, of course, to the limitations of the longitudinal correlational design. We cannot rule out alternative explanations for any of the associations we have observed or conclude that any of the links that we have observed are causal in nature. Along these lines, one possibility is that an unmeasured variable has contributed to one or more of the relations of interest in this report. For example, it is possible that anxiety in the Sibs-ASD group contributed to both reduced social orienting and increased sensory seeking during the sensory assessment. Anxiety is of particular interest because it has previously been linked to ASD symptomatology, including atypical responses to sensory stimuli (e.g., Mazurek et al., 2013). In addition, anxiety has been associated with greater right frontal asymmetry (Davidson et al., 2000; Wiedemann et al., 1999). Future studies should examine the potential role of anxiety in the relations among sensory seeking, social orienting, and frontal asymmetry.

Additionally, measurement of sensory seeking and social orienting at a single time point precludes us from establishing temporal precedence for sensory seeking. The same is true for the concurrent measurement of frontal asymmetry and seeking behavior. Future studies, with measurement at additional time points, planned a priori to establish the presence of atypical frontal asymmetry prior to the emergence of sensory seeking, and to ascertain the presence of sensory seeking prior to diminished social orienting, would increase our confidence in the direction of effects suggested here. Further research is also needed to determine whether these results generalize to other groups at risk for autism spectrum disorder (e.g., premature infants, infants who are showing red flags but have no family history of ASD), or whether the present pattern of results is specific to infants who are genetically predisposed to ASD. Finally, subsequent work should seek to determine how we might best intervene upon atypical sensory responsiveness in Sibs-ASD, and whether effects of treatment on sensory responses translate to more optimal developmental outcomes in children who are diagnosed with, or at high risk for, ASD. Large-scale studies that evaluate which of the variables of interest here (frontal alpha asymmetry, sensory seeking, social orienting), in combination with other brain and behavioral factors previously observed to covary with social symptoms, show incremental validity or have “added-value” in predicting future social symptomatology in Sibs-ASD would be helpful for focusing our efforts at early identification and intervention in infants at heightened risk for ASD.

## 5. Conclusions

The present study found that sensory seeking behaviors may serve as an early marker for social deficits, or an endophenotype, in ASD. Infant siblings of children with ASD demonstrate increased sensory seeking at 18 months, and sensory seeking is related to later social symptomatology at 36 months. In addition, results provide insight into the mechanisms by which sensory seeking might impact later social development by showing that the predictive relationship between sensory seeking and social deficits at 36 months is mediated by social orienting. Finally, findings suggest that resting frontal asymmetry is a potential neural marker of atypical sensory seeking in this high-risk population. Further research is needed to increase our confidence in the associations suggested here, to determine whether findings generalize to other populations at high-risk for ASD, and to guide clinical practice with infants who present with atypical patterns of sensory responsiveness.

## Conflict of Interest

None.

## Acknowledgments

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## Appendix A

**Table A1**
Sample Characteristics at Time 1.

| Characteristic | Sibs-ASD | Sibs-TD |
|---|---|---|
| Chronological Age In Months | 18.24 (0.42) | 18.34 (0.29) |
| Sex (Male:Female) | 8:12 | 10:10 |
| Mullen Early Learning Composite[†] | 103.05 (12.69) | 110.42 (7.46)[*] |
| Mullen Receptive Language[†] | 43.40 (6.76) | 47.11 (4.76) |
| Mullen Expressive Language[†] | 50.50 (8.69) | 54.58 (7.62) |

*Note.* [*] $p < 0.05$. Mullen = Mullen Scales of Early Learning (Mullen, 1995). Early Learning Composite is a standard score. Receptive and Expressive language scores are T-scores. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-TD = Infant siblings of children with typical developmental histories.

[†] Mullen Scales of Early Learning were collected when infants were 12 months old as part of the larger study of social-emotional development.

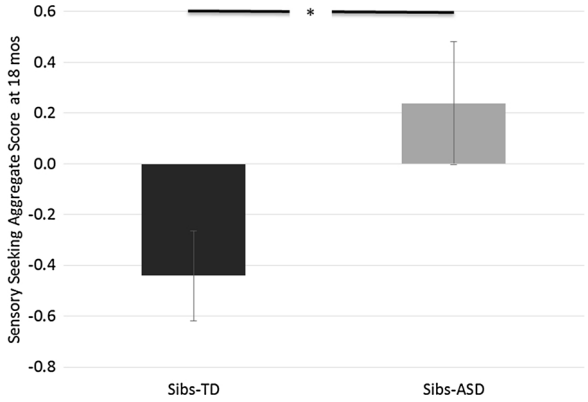


**Fig. A1.** Risk group differences in early sensory seeking. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-TD = Infant siblings of typically developing children. Sensory seeking aggregate = average of z-scores for seeking intensity (sum of seeking ratings across eight novel toys) and seeking inventory (sum of discrete seeking behaviors across 12 categories) component variables derived from the Sensory Processing Assessment (Baranek, 1999a). Error bars represent standard error of the mean. * $p < 0.05$.

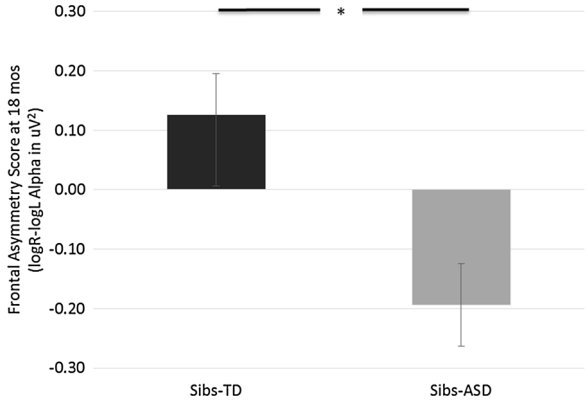


**Fig. A2.** Risk group differences in resting frontal asymmetry. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-TD = Infant siblings of typically developing children. Frontal asymmetry = log right alpha power – log left alpha power (log R – log L). Note that negative scores for frontal asymmetry reflect relatively greater right hemisphere activation (i.e., a more atypical pattern at this chronological age), whereas positive scores reflect relatively greater left hemisphere activation (i.e., a more typical pattern at this chronological age). Error bars represent standard error of the mean. * $p < 0.05$.

**Table A2**
Results of Regression Analyses for Effect of Frontal Asymmetry on Sensory Seeking by Risk Group.

| Model | | Unstandardized Coefficients | | Standardized | | |
|---|---|---|---|---|---|---|
| | | B | SE | Beta | t | Significance |
| 1 | Constant | −0.231 | 0.147 | | −1.563 | 0.126 |
| | Seeking | −0.811 | 0.414 | −0.307 | −1.959 | 0.058 |
| 2 | Constant | −0.610 | 0.170 | | −3.585 | 0.001 |
| | Seeking | 0.610 | 0.482 | 0.230 | 1.266 | 0.214 |
| | Risk Group | 0.490 | 0.259 | 0.267 | 1.891 | 0.067 |
| | Seeking x Risk Group | −2.458 | 0.727 | −0.636 | −3.380 | 0.002* |

*Note.* *$p$ value for effect of interest < 0.05. Models exclude Sib-TD infant who unduly influenced analyses.

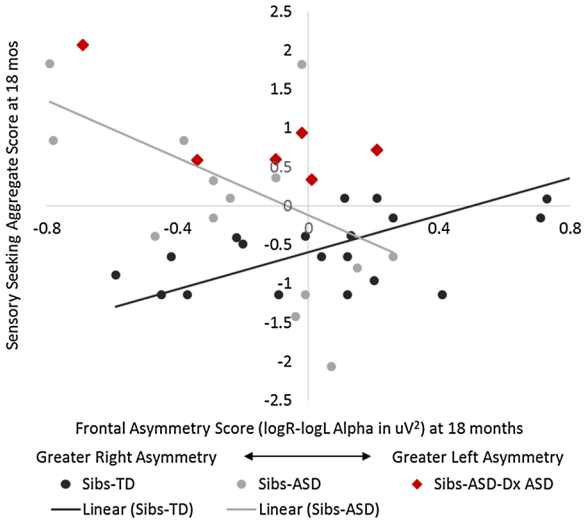


**Fig. A3.** Relation between resting frontal asymmetry and early sensory seeking. Sibs-TD = Infant siblings of typically developing children. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-ASD-Dx ASD = Infant siblings of children diagnosed with autism spectrum disorder who are diagnosed with autism spectrum disorder at 36 months. Sensory seeking aggregate = average of z-scores for seeking intensity (sum of seeking ratings across eight novel toys) and seeking inventory (sum of discrete seeking behaviors across 12 categories) component variables derived from the Sensory Processing Assessment (Baranek, 1999a). Note that negative scores for frontal asymmetry reflect relatively greater right hemisphere activation (i.e., a more atypical pattern at this chronological age), whereas positive scores reflect relatively greater left hemisphere activation (i.e., a more typical pattern at this chronological age).

**Table A3**
Results of Regression Analyses for the Effect of Sensory Seeking on Social Orienting by Risk Group.

| Model | | Unstandardized Coefficients | | Standardized | | |
|---|---|---|---|---|---|---|
| | | B | SE | Beta | t | Significance |
| 1 | Constant | 2.279 | 0.119 | | 19.089 | 0.000 |
| | Seeking | 0.570 | 0.128 | 0.590 | 4.448 | 0.000* |
| 2 | Constant | 2.219 | 0.265 | | 8.366 | 0.000 |
| | Seeking | 0.136 | 0.361 | 0.140 | 0.376 | 0.709 |
| | Risk Group | −0.175 | 0.309 | −0.099 | −0.566 | 0.575 |
| | Seeking x Risk Group | 0.642 | 0.389 | 0.557 | 1.649 | 0.108 |

*Note.* *$p$ value for effect of interest < 0.05. Models exclude Sib-TD infant who unduly influenced analyses.

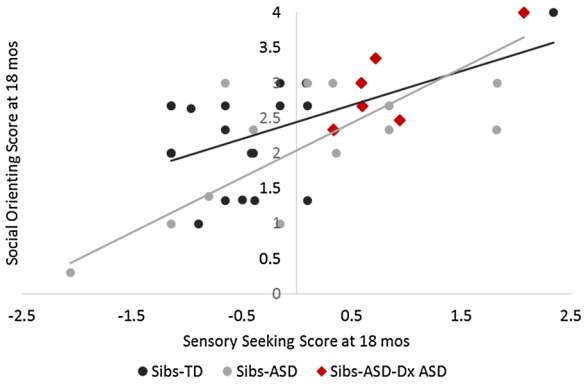


**Fig. A4.** Relation between early sensory seeking and social orienting. Sibs-TD = Infant siblings of typically developing children. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-ASD-Dx ASD = Infant siblings of children diagnosed with autism spectrum disorder who are diagnosed with autism spectrum disorder at 36 months. Sensory seeking aggregate = average of z-scores for seeking intensity (sum of seeking ratings across eight novel toys) and seeking inventory (sum of discrete seeking behaviors across 12 categories) component variables derived from the Sensory Processing Assessment (Baranek, 1999a).

**Table A4**
Results of Regression Analyses for the Effect of Sensory Seeking on Social Symptomatology by Risk Group.

| Model | | Unstandardized Coefficients | | Standardized | | |
|---|---|---|---|---|---|---|
| | | B | SE | Beta | t | Significance |
| 1 | Constant | 2.020 | 0.134 | | 15.032 | 0.000 |
| | Seeking | 0.376 | 0.136 | 0.411 | 2.777 | 0.008* |
| 2 | Constant | 1.337 | 0.171 | | 7.824 | 0.000 |
| | Seeking | −0.229 | 0.193 | −0.249 | −1.186 | 0.243 |
| | Risk Group | 1.083 | 0.229 | 0.599 | 4.734 | 0.000 |
| | Seeking x Risk Group | 0.672 | 0.238 | 0.564 | 2.822 | 0.008* |

*Note.* *$p$ value for effect of interest < 0.05. There was no evidence of undue influence on analyses.

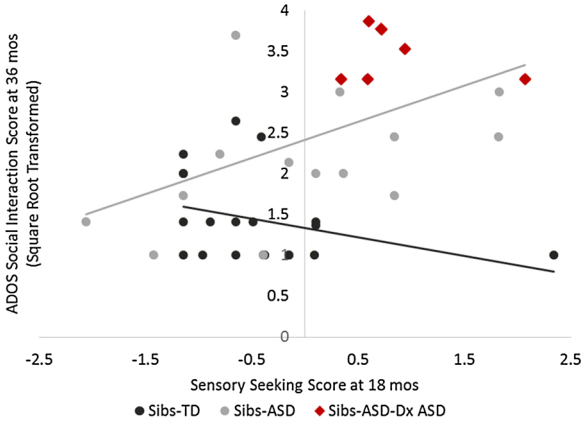


**Fig. A5.** Relation between early sensory seeking and future social symptomatology. Sibs-TD = Infant siblings of typically developing children. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-ASD-Dx ASD = Infant siblings of children diagnosed with autism spectrum disorder who are diagnosed with autism spectrum disorder at 36 months. Sensory seeking aggregate = average of z-scores for seeking intensity (sum of seeking ratings across eight novel toys) and seeking inventory (sum of discrete seeking behaviors across 12 categories) component variables derived from the Sensory Processing Assessment (Baranek, 1999a).

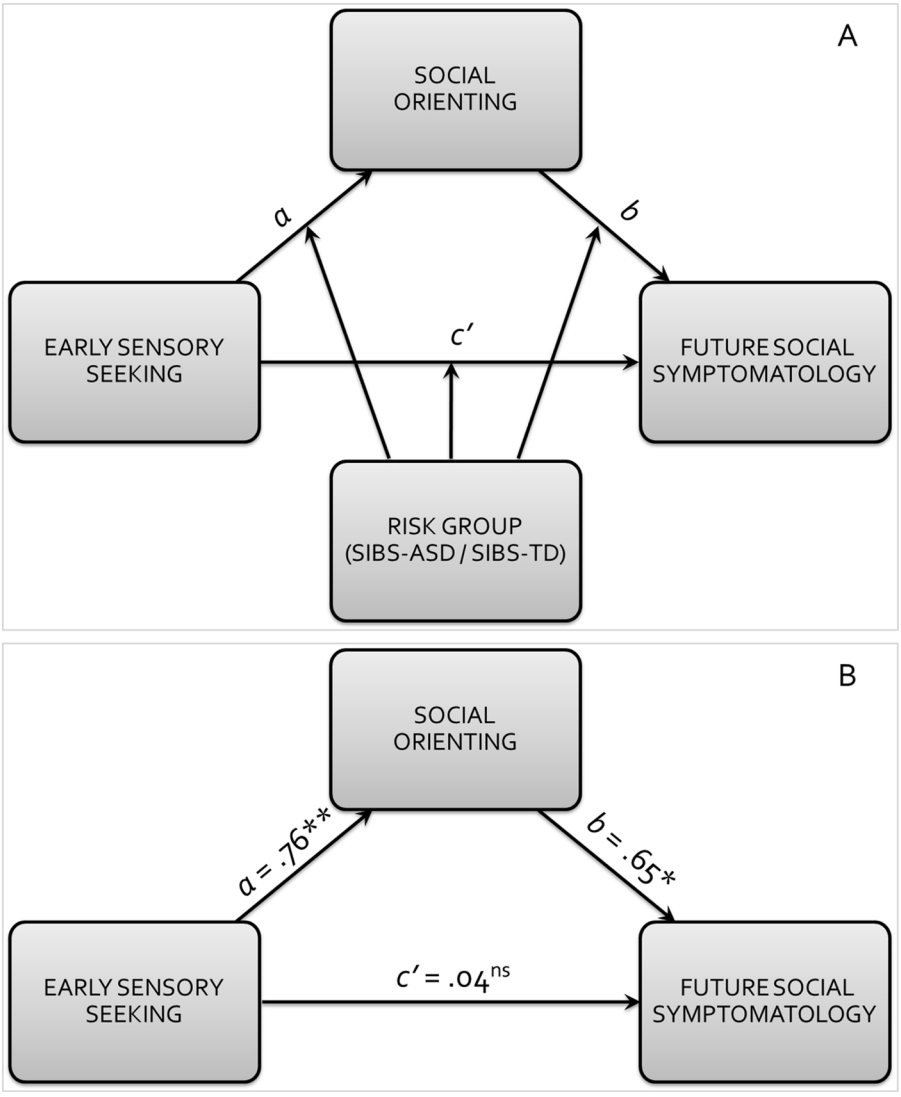


**Fig. A6.** Conditional indirect effect between early sensory seeking and future social symptomatology through social orienting, according to risk group. Figure A depicts the conceptual model for the moderated mediation relation. Figure B represents the significant mediation relation within the Sibs-ASD group, product of a * b paths reflecting the indirect effect = 0.41; 95% CI [.05, 0.84]. Note that both the a path, representing the association between sensory seeking and social orienting, and the b path, representing the association between social orienting and future social symptomatology when controlling for sensory seeking, are statistically significant. The c' path, representing the association between sensory seeking and future social symptomatology when controlling for social orienting, is non-significant. Thus, reduced social orienting accounts for the observed association between sensory seeking and future social symptomatology in Sibs-ASD. Sibs-ASD = Infant siblings of children diagnosed with autism spectrum disorder. Sibs-TD = Infant siblings of typically developing children. Values in Figure B are standardized coefficients. * $p < 0.05$. ** $p < 0.001$. *ns* = non-significant result.

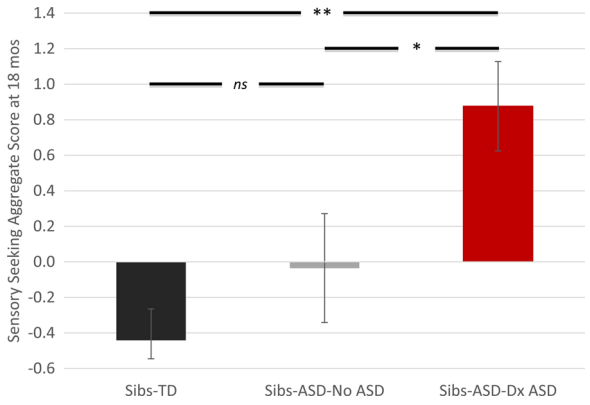


**Fig. A7.** Outcome group differences in early sensory seeking. Sibs-TD = Infant siblings of typically developing children. Sibs-ASD-No ASD = Infant siblings of children diagnosed with autism spectrum disorder who do not receive a diagnosis of ASD. Sibs-ASD-Dx ASD = Infant siblings of children diagnosed with autism spectrum disorder who do receive a diagnosis of ASD at 36 months. Sensory seeking aggregate = average of z-scores for seeking intensity (sum of seeking ratings across eight novel toys) and seeking inventory (sum of discrete seeking behaviors across 12 categories) component variables derived from the Sensory Processing Assessment (Baranek, 1999a). * $p < 0.05$. ** $p < 0.005$. *ns* = non-significant result. Error bars represent standard error of the mean.

## Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2017.08.005.

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