The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 58:12 (2017), pp 1351–1359 doi:10.1111/jcpp.12746

Brainstem as a developmental gateway to social attention

Ronny Geva,[1,2] Ayelet Dital,[2] Dan Ramon,[3] Jessica Yarmolovsky,[1,2] Maor Gidron,[1,2] and Jacob Kuint[4,5]

[1]Department of Psychology, Bar Ilan University, Ramat Gan; [2]The Gonda Multidisciplinary Brain Research Center Bar Ilan University, Ramat Gan; [3]Psychology Department, Ashkelon College, Ashkelon; [4]Neonatology Department, Sheba Medical Center, Ramat Gan; [5]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Background: Evolution preserves social attention due to its key role in supporting survival. Humans are attracted to social cues from infancy, but the neurobiological mechanisms for the development of social attention are unknown. An evolutionary-based, vertical-hierarchical theoretical model of self-regulation suggests that neonatal brainstem inputs are key for the development of well-regulated social attention. **Methods:** Neonates born preterm ($N = 44$, GA 34 w.) were recruited and diagnosed at birth as a function of their auditory brainstem evoked responses (ABR). Participants enrolled in a prospective 8-year-long, double-blind, follow-up study comparing participants with brainstem dysfunctions and well-matched controls. Groups had comparable fetal, neonatal, and familial characteristics. Methods incorporated EEG power analysis and gaze tracking during the Attention Network Test (ANT, four cue types, and two targets) and a Triadic Gaze Engagement task (TGE, three social cue levels). **Results:** Results showed that neonatal brainstem compromise is related to long-term changes in Alpha- and Theta-band power asymmetries ($p < .034$, $p < .016$, respectively), suggesting suppressed bottom-up input needed to alert social attention. Gaze tracking indicated dysregulated arousal-modulated attention ($p < .004$) and difficulty in gaze engagement to socially neutral compared to nonsocial cues ($p < .012$). **Conclusions:** Integrating models of Autism and cross-species data with current long-term follow-up of infants with discrete neonatal brainstem dysfunction suggests neonatal brainstem input as a gateway for bottom-up regulation of social attention. **Keywords:** Brainstem; development; social attention; attention.

Introduction

Attention regulation and social behaviors are thought to involve late maturing prefrontal cortical neural networks (Elliott, 2003; Niendam et al., 2012; Schore, 1996). Maturational spurts characterize these trajectories in childhood, trends that taper off well into the third decade of life (De Luca et al., 2003). This development has been related to changes in synaptic density and prolonged axonal myelination (Giedd et al., 1999).

Little, however, is known about the neurobiological infrastructure that drives the development of cortically mediated social attention. Theoretical models suggest that subcortical neural networks (Schore, 1996; Tucker, Derryberry, & Luu, 2000), some known to mature prebirth (Geva & Feldman, 2008), set a platform for these later-emerging networks. No empirical support has shown this developmental trajectory.

Anatomical differences were seen in response to early social experience and learning (Zatorre, Fields, & Johansen-Berg, 2012). Researchers noted myelination changes in the medial prefrontal cortex (Makinodan, Rosen, Ito, & Corfas, 2012); amygdala-limbic network, frontoparietal systems (Amodio & Frith, 2006), and medial dorsal thalamus (Bolhuis, Okanoya, & Scharff, 2010). Still, these later maturing distributed cortical systems do not mature in the neonatal phase. More distal brainstem-level loci, which mature neonatally at a key developmentally sensitive time window for social attention regulation, are understudied.

Indeed, higher level cognitive functions that involve cortical activity, such as social attention (Tucker et al., 2000) and recent work with working memory (Breeden, Siegle, Norr, Gordon, & Vaidya, 2016; Shine et al., 2016), were noted to involve brainstem-, midbrain-, and limbic-level functioning in adults. These neural networks possibly play an integral role in these 'higher level' capacities, through bidirectional top–down, bottom–up feedback loops (Panksepp, 1998; Shine et al., 2016). Still, it is not yet known how early emerging bottom-up paths affect the development of the evolving neural activity through the first decade of life.

The developmental research proposes that vertical-hierarchical maturational processes are enabling neural development to play a central role in attention regulation and social development (Porges, 2003b). Models, including our own, have suggested that brainstem neural networks that mature prebirth set a platform for later emerging, higher order, arousal regulation and social networks (Geva & Feldman, 2008). Brainstem input mediates early social behavior. This is evident by its effects on gaze engagement (Geva et al., 2011), affective responses (Shinya, Kawai, Niwa, & Myowa-Yamakoshi, 2014),

Conflict of interest statement: No conflicts declared.

vagal tone regulation (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1998), and initiation of social responses at infancy (Geva, Schreiber, Segal-Caspi, & Markus-Shiffman, 2014).

Finding a human model to examine the aftermath of brainstem pathology is quite challenging, as gross structural brainstem aberrations are under-represented in human live birth cohorts due to their fatal implications (Smith, Levine, Barnes, & Robertson, 2005). Milder alterations, such as a whole brainstem volume reduction, was reported as a distinguishing marker for extremely low birth weight neonates (Padilla, Alexandrou, Blennow, Lagercrantz, & Ådén, 2014) and adolescents who were born very preterm (Nosarti et al., 2008). These are possibly due to low, delayed, and altered synaptic density neural wiring (Kostovic & Judas, 2010; Volpe, 2009). These alterations may be evidenced by early brainstem neural conductance changes (Geva et al., 2011; Jiang, Brosi, Wu, & Wilkinson, 2009).

Electrophysiological research of brainstem neural conductance shows sensitivity to physiological regulation, homeostasis (Batterham et al., 2007), and alerting of attention, in the neonatal phase (Gardner, Karmel, & Flory, 2003). This sensitivity has been postulated to influence later maturational changes in collicular–basal ganglia functions and the development of the posterior attention systems (Posner, Petersen, Fox, & Raichle, 1988), as well as connectivity to the thalamus and the limbic system (Tucker, Luu, & Derryberry, 2005).

Brainstem connectivity to the limbic circuit supports emotional signaling and affect sharing (Porges, 2003a; Prechtl, 1992; Tucker et al., 2000), social gaze engagement (Geva et al., 2011), and initiation of social regulation strategies (Geva et al., 2014). These relations suggest a potential role for brainstem-related pathways, which mature at late term age, in setting a time-sensitive window for later maturing limbic-cortical neural networks that enable social attention (Doesburg et al., 2011; Geva & Feldman, 2008). Given these neuropsychological, neurobiological, and psychological findings, we postulate that early maturing brainstem pathways gate social attention throughout development and expect that as children mature through the first decade of life, remnants of neonatal brainstem functioning would still be traceable, affecting social neural networks electrophysiologically and behaviorally.

Spontaneous oscillatory electrophysiological activity at resting state has been considered a hallmark representation of brain homeostasis, reflecting development and experience (Berkes, Orbán, Lengyel, & Fiser, 2011). Middle-frequency range bands (theta and alpha; 4–12 Hz) are suggested to indicate a bottom-up-directed interaction (von Stein, Chiang, & Konig, 2000).

Studies with typical populations using EEG suggest a posterior–anterior developmental progression (Rodríguez Martinez et al., 2012). At the same time, children's social attention has been shown to be coupled with suppression of the power over the precentral scalp regions and posterior theta power increases (Orekhova, Stroganova, Posikera, & Elam, 2006).

Research with children at risk for social attention deficits points to both electrophysiological changes and specific gaze-regulation characteristics alternations. Specifically, social attention issues are evident by EEG power decreases in left frontal alpha (Davidson, 2004) and theta posterior–anterior difference (Cristofori et al., 2013). Behavior social attention characteristics are particularly evident by gaze-regulation changes in response to alerting cues (Johnson et al., 2008) and socially ambiguous events (Andrade et al., 2012). Thus, these dependent measures were selected for testing the notion that neonatal brainstem functions set the groundwork for social attention.

Earlier works with children with brainstem dysfunction conducted at younger ages have shown effects of brainstem functioning on social interaction and arousal. At 4 months, children with compromised brainstem function are more prone to avert their gaze when facing a social agent (Geva et al., 2011). Also, at 12 months, brainstem dysfunction increased the risk for behavioral inhibition, characterized by shyness and passivity (Geva et al., 2014). We anticipated traces of this phenotype at 8 years of age, expecting social gaze aversion in a triadic gaze engagement task (TGE), alerting deficits in the attention network task (ANT), lack of frontal alpha asymmetry, and theta power differences on EEG in children with neonatal brainstem dysfunctions.

Methods

The research paradigm was a prospective double-blind longitudinal design testing neonatal auditory brainstem-evoked responses (ABR). Follow-up procedures explored EEG baseline at resting state; along with gaze-tracked responses reflecting social attention 8 years after the neonatal brainstem compromise.

Participants

A subsample of 44 children (52% females) were followed from birth through 7–9 years of age (mean = 8.6 ± .76 years). Participants were recruited from the Level III Neonatal Intensive Care Unit at Sheba Medical Center and screened during the neonatal period for brainstem function using ABR [gestation age (GA) = 33.4 ± 1.4 weeks, Birth weight (BW) = 1,741 ± 307, postconception age (PCA) = 35.31 ± 1.62]. Maternal inclusion criteria at birth were age>21 years, living with the child's father, reporting no use of psychoactive drugs or psychiatric medication during pregnancy or after birth, and middle-class status ratings according to Israeli standards (Abramson, Gofin, Habib, Pridan, & Gofin, 1982).

The normality of brainstem functions for the infant's gestational age was used to divide the sample into two groups: compromised brainstem function (CBSF, $N = 19$), and normal brainstem function (NBSF, $N = 25$). The rate of abnormality was comparable to that in earlier follow-up reports (Geva et al., 2011, 2014). Demographic analysis indicated that groups were

Table 1 Demographic characteristics of the participating groups

	CBSF	NBSF	Sig. *p*
Infant			
Gender (% female)	52%	52%	.90 NS
Gestation age (weeks)	32.47 ± 0.29	33.20 ± 0.26	.07 NS
Post conceptual age (weeks)	35.08 ± 1.31	35.49 ± 1.83	.41 NS
Birth weight (g)	1,669.57 ± 72.82	1,829.84 ± 63.48	.10 NS
Familial			
Maternal inattention score[a]	1.45 ± 0.70	1.55 ± 0.52	.91 NS
Paternal inattention score[a]	2.36 ± 0.80	1.62 ± 0.66	.48 NS
Maternal hyperactivity impulsivity score[a]	1.18 ± 0.62	1.30 ± 0.46	.88 NS
Paternal hyperactivity impulsivity score[a]	2.54 ± 0.55	2.06 ± 0.46	.51 NS
Maternal age (years)	32.41 ± 1.13	33.47 ± 0.97	.47 NS
Paternal age (years)	33.61 ± 0.94	34.77 ± 0.85	.36 NS
Maternal education (years)	15.46 ± 0.76	16.20 ± 0.86	.52 NS
Paternal education (years)	16.00 ± 0.57	14.83 ± 0.66	.20 NS

CBSF, compromised brainstem function; NBSF, normal brainstem function.
[a]Score based on the DSM-IV ADHD questionnaire.

well-matched on prenatal, neonatal, and familial variables (Table 1), including on parental attention and hyperactivity scores, known to be related to changes in alpha and theta power measures. Furthermore, GA and the PCA of ABR test were similar across groups and had narrow distributions (ABR was typically conducted within 1 week to 10 days of birth), enabling us to hone in on the pathology rather than on maturational differences among participants.

Procedure

The study was approved by the Institutional Review Boards at Sheba Medical Center and by Bar Ilan University. Parents signed an informed consent before each experimental phase, and in the second phase, children expressed verbal consent.

An ABR procedure was conducted according to Geva et al. (2011). The criterion for CBSF was determined by latencies of waves III & V, as compared with latency norms for GA (Karmel, Gardner, Zappulla, Magnano, & Brown, 1988). Delays >1.5 standard deviations from the mean for GA were classified as CBSF, while scores within 1.5 standard deviations of the mean were considered as NBSF (Geva et al., 2011). The ABR function first emerges around 30–33 weeks' gestation (Jiang et al., 2009), a period at which many premature births occur. This period is critical for major developmental changes in the equilibrium and the auditory pathways in the brainstem (Jiang et al., 2009; Krumholz, Felix, Goldstein, & McKenzie, 1985; Moore, Perazzo, & Braun, 1995). ABR emergence at this time offers a potential window to evaluate the functional efficacy of emerging brainstem projections in vivo in neonates born prematurely using surface electrodes (Jiang et al., 2009). Neonatal ABR, even when abnormal at first, resolve rapidly in the absence of a sensory/neural hearing impairment (Geva, Zivan, Warsha, & Olchik, 2013) or autism (Miron et al., 2016). Recovery of ABR transmission times occurred as expected in all participants.

The second phase of the study was launched at the Developmental Neuropsychology Lab at Bar Ilan University, employing a complete double-blind paradigm protocol. Children first underwent a baseline EEG recording at resting state, followed by computerized tasks presented on a high-speed remote eye-tracking system.

Materials

EEG recording. The EEG alpha and theta wave frequencies were recorded using Net station software by EGI's Geodesic 64-channel EEG System. EEG data collection was conducted for a duration of 3 min while the child sat in a reclined resting condition with his/her eyes closed, using an electrode cap designed to facilitate electrode placement, with Cz (vertex of the head) electrodeposition as the recording reference on the child's head.

EEG analysis. ASA ANT 4.8.1 (ANT neuro, Enschede, the Netherlands) software enabled the removal of all artifacts from the EEG data, and to quantify signals with a discrete Fourier transformation using a Hamming window 1s wide with 50% overlaps. Before applied computation, the mean voltage was subtracted from each data point to eliminate any influence of DC offset. Power (in units of microvolts-Ohms) was computed for 1-Hz frequency bins for frequencies between 4 and 30 Hz. Power density (in mV^2/Hz) was extracted for analysis purposes in the theta (4–7 Hz) and the Alpha (8–13 Hz) bands. These data were log-transformed to normalize their distribution because power values are positively skewed (Davidson, 1988; Davidson, Jackson, & Kalin, 2000). Alpha and theta were calculated per brain quadrant (i.e., Right, Left, Posterior, and Anterior), guided by the central sulcus and the medial longitudinal fissure (Figure 1); and averaged for each participant.

Gaze tracking. A two-computer setup was employed, integrating E-prime experiment building software with a Tobii-TX300 binocular eye-tracking system that uses near infrared diodes to generate reflection on the corneas of the user' eyes. The system tracks both eyes to a rated accuracy of 0.5° and samples at 300 Hz. Participants underwent a successful 5-point calibration before beginning each task. Gaze tracking was recorded for two tasks: the ANT (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) and the TGE, specifically designed for the current study.

The ANT is a highly established computerized task that measures attention to visual stimuli in adults (Fan, McCandliss, Sommer, Raz, & Posner, 2002) and children (Rothbart & Rueda, 2005; Yaakoby-Rotem & Geva, 2014). Children were presented with three arrows and were instructed to press either the left or right mouse key in response to the corresponding direction of a central arrow. An ANT session consisted of three experimental blocks with 144 Alerting, Orienting and Executive Control network trials (detailed procedure in Yaakoby-Rotem & Geva, 2014). Participants' gaze toward the target stimuli was recorded.

The TGE is a passive observation task that evaluates gaze regulation in social interaction. The task introduces emotional verbal and nonverbal content and examines the participant's nonverbal interaction using gaze direction (Pfeiffer et al., 2012). Participants in the TGE engaged in triadic interactions

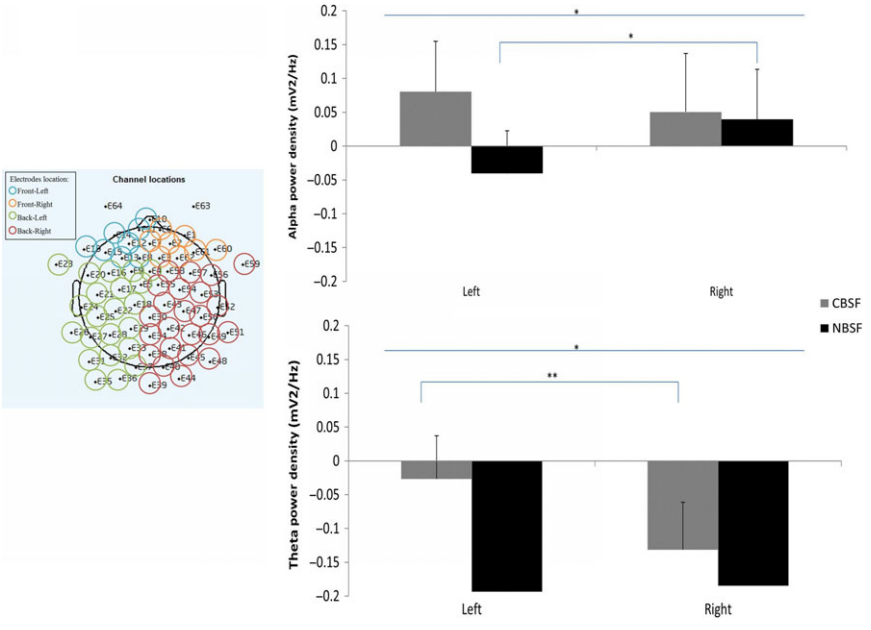

Figure 1 Posterior–anterior power gaps in the left and the right hemispheres in Alpha and Theta bands as a function of neonatal brainstem integrity at 8 years of age. Configuration on the left depicts the electroencephalogram electrode distribution map and the four cerebral quadrant loci. Panel A depicts alpha power and Panel B depicts theta rhythm power. *$p < .05$; **$p < .01$

involving unfamiliar human agents and nonhuman stimuli. During the social blocks, participants observed two social video clips, each with two interacting agents who take turns expressing one of four affective narratives (neutral/angry/happy/sad) while alternating their gaze spontaneously between the other agent and the participant. To control for the saliency of motion evident more in the speaking agent as compared with the listening agent, a nonsocial block was added. The nonsocial block included an interchanging still and motion clip windows depicting a flock of birds flying (Figure 3). Each video was about 1-minute long, and all blocks were presented in random counterbalanced order. Testing was conducted in a quiet room. Total fixation duration (TFD) was calculated for each of the two areas of interest (AOI), splitting the screen to active (i.e., speaking agent and moving nonsocial stimuli) and passive panels (i.e., a listening agent and still nonsocial stimuli). To control for presentation time differences, TFDs to each AOI were computed as a function of total gaze durations to both AOIs and transformed to Z-scores to enable intercondition comparisons.

Results

Power asymmetry as a function of ABR

A repeated measures analysis was run comparing posterior–anterior gaps in the two hemispheres (e.g., back minus front differences in the left hemisphere compared with back minus front differences in the right hemisphere) as a function of ABR for the alpha and theta bands. Results showed no main effect for alpha anterior–posterior gaps, but rather an alpha asymmetry X ABR interaction effect ($F = 4.915$, $p < .034$, $\eta^2 = .120$; Figure 1A),

Bonferroni corrected post hoc analysis indicated that NBSF group shows a lateralization effect: a positive left hemisphere gap suggesting greater anterior suppression, and a negative right hemisphere gap, indicating greater posterior alpha suppression ($F = 6.170$, $p < .018$; Figure 1A); while the CBSF group had a homogeneous anterior–posterior gap pattern in both hemispheres ($F = 0.633$, $p = .432$; Figure 1A).

Furthermore, a theta-lateralized asymmetry was found ($F = 4.477$, $p < .042$, $\eta^2 = .111$; Figure 1B) such that the anterior advantage was noted mostly in the right hemisphere. The main effect was complimented by a lateralized asymmetry X ABR interaction effect ($F = 6.331$, $p < .016$, $\eta^2 = .150$; Figure 1B). Bonferroni corrected post hoc comparisons showed that the main effect of theta-lateralized asymmetry difference was mostly due to the CBSF group who show the anterior–posterior gap only in the right hemisphere ($F = 9.265$, $p < .005$; Figure 1B), while the NBSF group showed the anterior–posterior gap in both hemispheres ($F = 0.95$, $p = .760$; Figure 1B). Integrating these results suggests a diminished power lateralization difference upon the maturational transition from back to front activity, evident less on the right hemisphere, in the CBSF group as compared with controls.

Attention alerting as a function of ABR

A repeated-measures analysis of gaze latencies to ANT networks (alerting, orienting and executive attention) as a function of ABR group indicated a network X ABR interaction ($F = 3.392$, $p < .044$, $\eta^2 = .151$). Post hoc analysis showed a difference in the alerting network ($F = 9.538$, $p < .004$, $\eta^2 = .197$; Figure 2), such that while the NBSF group regulated

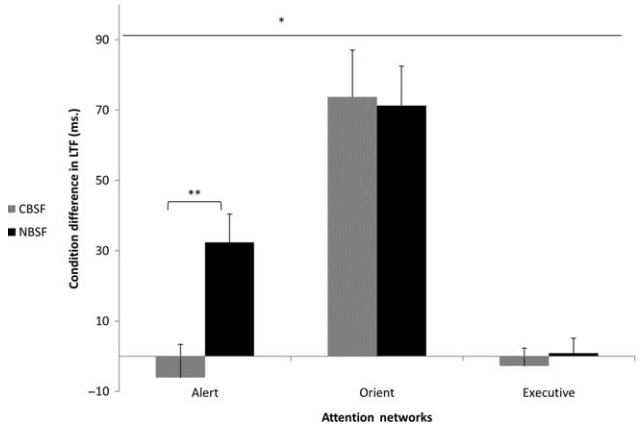

Figure 2 Gaze latencies in the attention network task as a function neonatal brainstem integrity.*$p < .05$; **$p < .01$; LTF (on the *y*-axis) = Latency to Fixate

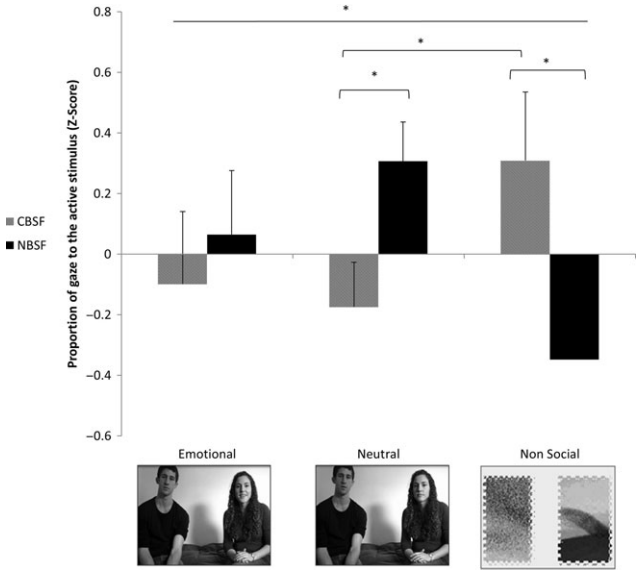

Figure 3 Triadic gaze engagement differences in total fixation durations as a function of social content and neonatal brainstem integrity. The proportion of total fixation duration towards the active stimulus relative to the total socioemotional scene gaze length (e.g., total fixation duration to Active/Active+passive represents), *$p < .05$

their latency to fixate (LTF) according to available preceding cues, the CBSF group did not. This finding suggests malfunctioning of the alerting attention network in the CBSF group.

Social attention as a function of ABR

A repeated-measures analysis of the TGE was conducted comparing TFD *z*-scores toward social and nonsocial stimulus types [three levels: *social-emotional* (comprising of happy, sad, and angry scenes with human agents), *social-neutral*, and *nonsocial* (comprising of bird scenes)] as a function of ABR (CBSF, NBSF). Results showed a stimulus typeXABR interaction effect ($F = 4.988$, $p < .012$, $\eta^2 = .208$; Figure 3). Post hoc analysis with Bonferroni adjustment for multiple comparisons showed while the proportion of gaze at the active agent was symmetrical in the affective scenes it was preferential in the socially neutral and in the nonsocial blocks ($F = 3.735$, $p < .033$, $\eta^2 = .164$): While NBSF children were less interested in moving nonsocial events, CBSF children did ($F = 5.977$, $p < .019$, $\eta^2 = .133$); NBSF children showed higher interest in the social–neutral interaction compared with nonsocial events ($F = 3.735$, $p < .033$, $\eta^2 = .164$). While NBSF children showed preferred the active agent in the neutral social interaction, CBSF children preferred the passive agent ($F = 4.714$, $p < .036$, $\eta^2 = .108$). Significance was preserved when BW ($F = 4.611$, $p < .016$, $\eta^2 = .200$), PCA ($F = 5.292$, $p < .01$, $\eta^2 = .222$), frontal alpha asymmetry ($F = 5.616$, $p < .008$, $\eta^2 = .266$), and LTF Alert ($F = 3.681$, $p < .035$, $\eta^2 = .174$) were included as covariates. This finding suggests that sensitivity to social content is not due to either immaturity or by arousal difficulties; but rather is sensitive to neonatal brainstem integrity.

Relations among dependent measures

Correlations between EEG, TGE, and ANT measures indicated unique associations as a function of neonatal brainstem integrity (Figure 4). Importantly, moderately strong relations were noted only in children with CBSF and not in the NBSF group. The CBSF had relations between electrophysiological measures and social attention; Specifically, between non-Social TFD and frontal alpha asymmetry, $r = .704$, $p < .004$; and with posterior theta asymmetry $r = .573$, $p < .026$, and between left posterior alpha and Social TFD ($r = .519$, $p < .05$). Additionally, CBSF showed relations between electrophysiological measures and alerting of attention. Specific relations were found between anterior right and left alpha power and front left and overall front theta power and LTF at the ANT double cues ($r = -.728$, $p < .003$; $r = -.584$, $p < .03$; $r = -.665$, $p < .01$, $r = -.646$, $p < .01$, respectively). Finally, in the CBSF group, inter-relations between alerting of attention and social attention were found between ANT alert and social-TFD ($r = .502$, $p < .04$). Such relations were typically not evident in the NBSF group, except for the expected relationship between socioemotional TFD and frontal alpha asymmetry $r = .575$, $p < .008$, a relationship which was not seen in CBSF; and relations between the posterior left alpha and LTF at the ANT double cue ($r = -493$, $p < .02$), which was seen in frontal loci in the CBSF group ($r = -.728$, $p < .003$). The unique correlations seen in each group support a brainstem-dependent double dissociation.

Discussion

This study examined the postulation that brainstem input at late preterm gestational ages, present a sensitive window for shaping later developing social attention skills. Using EEG and gaze tracking in a

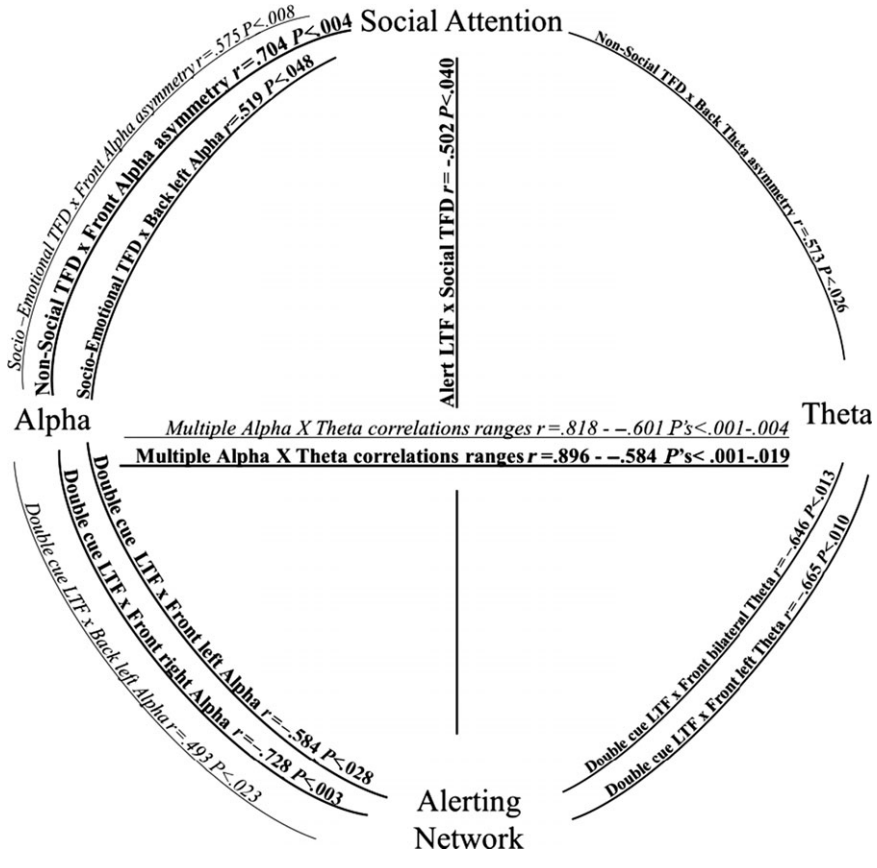

Figure 4 Relations between electrophysiological changes and social attention as a function of neonatal brainstem dysfunction. Electrophysiological changes: alpha and theta power density in cerebral loci and power distribution asymmetry; Attention alerting: LTF – latency to fixate following a double alerting cue, and alerting network LTF differences; Social attention: TFD – total fixation durations on social and nonsocial stimuli; Bold – significant relationships evident in CBSF; Italic – significant relationships evident in NBSF

prospective 8-year-long follow-up study of children with brainstem dysfunction provided support for this notion for the first time.

Since ABR tests were conducted soon after birth (typically within 1 week to 10 days postbirth) results may reflect brainstem integrity rather than the effects of recovery or maturation. Earlier findings with infants with brainstem compromise suggested an increased risk for social gaze disengagement (Geva et al., 2011), and behavioral inhibition at infancy (Geva et al., 2014). To further characterize the long-term neurobehavioral phenotype, we explored whether it relates to changes in gaze behavior, power asymmetry changes on EEG in bands known to be involved in regulating social attention, and social avoidance.

Gaze tracking showed that brainstem integrity at birth is related to social attention. Findings from the TGE task at 8 years of age revealed that, unlike the NBSF group who preferred active social agent over active nonsocial events, CBSF preferences were the opposite. This finding supports the proposed notion in showing that the neonatal brainstem input sets the stage for gaze engagement toward social content while suppressing orienting toward nonsocial cues later in life.

Baseline EEG findings corroborated this gaze behavior pattern. The emergence of left anterior alpha advantage seen in the NBSF group is a pattern typical of people with social approach motivation (for a review Harmon-Jones, Gable, & Peterson, 2010). Children with CBSF did not show this trend suggesting that they are less prone to exhibit prosocial initiation tendencies in novel contexts than controls.

Developmental trajectories of resting-EEG power in infants at risk for ASD suggest lowered frontal power during the first decade of life (Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012), particularly among autistic children who are passive (Dawson, Klinger, Panagiotides, Lewy, & Castelloe, 1995). Similar trends now seen in the CBSF group may suggest that it is a sensitive marker for milder forms of social hyperarousal, characterizing children who do not necessarily have autism, yet showing passivity and behavioral inhibition. This behavioral inhibition pattern was seen previously in CBSF at infancy (Geva et al., 2014).

As for theta power, here controls had greater posterior–anterior differences than the CBSF group in both hemispheres. This is compatible with the known developmental trajectory occurring during childhood, whereby neural network progresses from posterior loci to anterior ones. Little is known about electrophysiological maturation and what should be considered as typical childhood posterior–anterior

gaps in power EEG in general, as neuro-maturation data with typically developing low-risk children is under-reported (Marosi et al., 1992). Early work with normally developing children at various ages showed that low-frequency activity patterns are positively correlated with each other but negatively correlated with alpha band activity (Eeg-Olofsson, Petersen, & Sellden, 1971; Gasser, Verleger, Bächer, & Sroka, 1988). This opposing trend may resonate with the trends seen in the current study in the control group of children born preterm with no neurological dysfunction. They showed opposing lateralization and posterior–anterior asymmetry trends in alpha band range as compared with theta band range. Further work in light of current findings may complement the earlier work, by looking at power gaps in earlier maturing posterior loci as compared with frontal ones which are assumed to mature later. Given suggested interplay between resting-state alpha and theta band activity as a function of age (Eeg-Olofsson et al., 1971; Gasser et al., 1988); of particular interest for future research may be interband power relation changes in different loci as a function of maturation.

As for the aftermath of CBSF, the lack of anterior alpha advantage and the diminished left anterior advantage in theta power seen in CBSF possibly indicates a compromise of the prefrontal attention neural network (Ardid et al., 2015). Importantly, the current study indicates that the deficit in the anterior attention network emerged as a result of incoherent neonatal brainstem input. Neonatal CBSF seems to have resulted in decreased bottom-up input needed to suppress cortical activity at 8 years (Chatila, Milleret, Buser, & Rougeul, 1992; von Stein et al., 2000). This notion fits with the vertical hierarchical model theory for neonatal brainstem dysfunction role in self-regulation (Geva & Feldman, 2008).

To further support the model, we explored the behavioral expressions of these neural alterations, using ANT data. Results show a difference in the alerting network. Children with CBSF were unable to regulate gaze as a function of alerting cues preceding the target. This pattern suggests that neonatal brainstem function serves a supporting role in preparing to engage with arousing stimuli (Schatzberg & Geva, submitted) by preactivating the autonomic nervous system centers in the brainstem in response to salient stimuli (Geva et al., 2013). Arousal-modulated attention has been shown to be mediated by neonatal brainstem pathway activation even in the absence of corollary damage (Gardner et al., 2003). Current results extend this notion by showing such effects 8 years after the initial neonatal deficit, thereby suggesting a persistent fetal programming effect.

Integrating the gaze tracking and electrophysiological data, points to brainstem input in coding social cues as salient, thereby guiding attention and enabling gaze fixations toward conspecific organisms. This behavior is possibly evolutionary based. Cross-species studies with zebrafish, Argentine ants, and sticklebacks, as well as Bayesian estimation models, demonstrate that reliance on early ancestral neural networks enables the use of social information to counteract the ambiguity of sensory data through gazing at each other (Arganda, Pérez-Escudero, & de Polavieja, 2012). Current data extend the cross-species notion by showing that in humans too brainstem pathways serve this task by enabling coding of social cues to afford alerting and adaptation, particularly effective in processing neutral and ambiguous social cues.

Indeed, the TGE data uncovered CBSF-related difficulty in processing socially ambiguous (or neutral) content (Birtles, Braddick, Wattam-Bell, Wilkinson, & Atkinson, 2007). This difficulty was apparent by a diminished preference of gaze to active, information-conveying speaking social agent than to an active nonsocial agent seen in children with CBSF, unlike controls. This characteristic fits with a deficit suppressing attention to nonrelevant information. A similar difficulty exists in children diagnosed with Autism (Klin, 2000). Indeed, ABR susceptibility and attention-modulated arousal deficits were shown in infants later diagnosed with autism (Cohen et al., 2013; Miron et al., 2016). Current data extend this finding to participants who showed transient brainstem pathology without autism, still exhibiting a social orienting deficit. These findings support the notion of a social attention spectrum, offering neonatal brainstem input as a mechanism for gating social attention.

Conclusions

Findings unveil the importance of neonatal brainstem development for social attention and underscore its vulnerable nature. Following an evolutionarily based vertical-hierarchical model, current 8-year-long prospective data highlight a sensitive window for setting the trajectory of social attention. Specifically, the integrity of brainstem pathways during late gestation paves the way for social-neural network and engagement in childhood.

Acknowledgements

This research was funded by the Infrastructure Development Grant of the National Office of Science, Technology and Space, 3-10842; and the Israel Science Foundation, 1510/16 awarded to Prof. Ronny Geva. We thank the participating families, the medical team at the Sheba Medical Center Department of Neonatology and the Developmental Neuropsychology team at the Gonda Brain Research Center. The authors have declared that they have no competing or potential conflicts of interest.

Correspondence

Ronny Geva, Department of Psychology, The Gonda Multidisciplinary Brain Research Center, Bar Ilan University, 5290002 Ramat Gan, Israel; Email: Ronny.Geva@biu.ac.il

Key points

- Neonatal brainstem integrity is key for the development of social attention in childhood.
- The late-term gestation period is a sensitive developmental window for setting the trajectory of social attention.
- Neonatal brainstem input relates to the emergence of EEG frontal alpha asymmetry- and theta-band posterior–anterior power difference at childhood.
- Neonatal brainstem functions seem to play a role in cortically mediated social engagement behaviors.
- Current empirical data provides an 8-year-long support for the vertical hierarchical model of self-regulation.

References

Abramson, J.H., Gofin, R., Habib, J., Pridan, H., & Gofin, J. (1982). Indicators of social class: A comparative appraisal of measures for use in epidemiological studies. *Social Science and Medicine*, *16*, 1739–1746.

Amodio, D.M., & Frith, C.D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience*, *7*, 268–277.

Andrade, B.F., Waschbusch, D.A., Doucet, A., King, S., MacKinnon, M., McGrath, P.J., … & Corkum, P. (2012). Social information processing of positive and negative hypothetical events in children with ADHD and conduct problems and controls. *Journal of Attention Disorders*, *16*, 491–504.

Ardid, S., Vinck, M., Kaping, D., Marquez, S., Everling, S., & Womelsdorf, T. (2015). Mapping of functionally characterized cell classes onto canonical circuit operations in primate prefrontal cortex. *Journal of Neuroscience*, *35*, 2975–2991.

Arganda, S., Pérez-Escudero, A., & de Polavieja, G.G. (2012). A common rule for decision making in animal collectives across species. *Proceedings of the National Academy of Sciences*, *109*, 20508–20513.

Batterham, R.L., Ffytche, D.H., Rosenthal, J.M., Zelaya, F.O., Barker, G.J., Withers, D.J., & Williams, S.C. (2007). PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature*, *1*, 106–109.

Berkes, P., Orbán, G., Lengyel, M., & Fiser, J. (2011). Spontaneous cortical activity reveals hallmarks of an optimal internal model of the environment. *Science*, *331*, 83–87.

Birtles, D.B., Braddick, O.J., Wattam-Bell, J., Wilkinson, A.R., & Atkinson, J. (2007). Orientation and motion-specific visual cortex responses in infants born preterm. *NeuroReport*, *18*, 1975–1979.

Bolhuis, J.J., Okanoya, K., & Scharff, C. (2010). Twitter evolution: Converging mechanisms in birdsong and human speech. *Nature Reviews Neuroscience*, *11*, 747–759.

Breeden, A.L., Siegle, G.J., Norr, M.E., Gordon, E.M., & Vaidya, C.J. (2016). Coupling between spontaneous pupillary fluctuations and brain activity relates to inattentiveness. *European Journal of Neuroscience*, *45*, 1–7.

Chatila, M., Milleret, C., Buser, P., & Rougeul, A. (1992). A 10 Hz "alpha-like" rhythm in the visual cortex of the waking cat. *Electroencephalogry and Clinical Neurophysiology*, *83*, 217–222.

Cohen, I.L., Gardner, J.M., Karmel, B.Z., Phan, H.T., Kittler, P., Gomez, T.R., … & Barone, A. (2013). Neonatal brainstem function and 4-month arousal-modulated attention are jointly associated with autism. *Autism Research*, *6*, 11–22.

Cristofori, I., Moretti, L., Harquel, S., Posada, A., Deiana, G., Isnard, J., … & Sirigu, A. (2013). Theta signal as the neural signature of social exclusion. *Cerebral Cortex*, *23*, 2437–2447.

Davidson, R.J. (1988). EEG measures of cerebral asymmetry: Conceptual and methodological issues. *International Journal of Neuroscience*, *39*, 71–89.

Davidson, R.J. (2004). What does the prefrontal cortex "do" in affect: Perspectives on frontal EEG asymmetry research. *Biological Psychology*, *67*, 219–234.

Davidson, R.J., Jackson, D.C., & Kalin, N.H. (2000). Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychological Bulletin*, *126*, 890–909.

Dawson, G., Klinger, L.G., Panagiotides, H., Lewy, A., & Castelloe, P. (1995). Subgroups of autistic children based on social behavior display distinct patterns of brain activity. *Journal of Abnormal Child Psychology*, *23*, 569–583.

De Luca, C.R., Wood, S.J., Anderson, V., Buchanan, J.-A., Proffitt, T.M., Mahony, K., & Pantelis, C. (2003). Normative data from the CANTAB. I: Development of executive function over the lifespan. *Journal of Clinical and Experimental Neuropsychology*, *25*, 242–254.

Doesburg, S.M., Ribary, U., Herdman, A.T., Miller, S.P., Poskitt, K.J., Moiseev, A., … & Grunau, R.E. (2011). Altered long-range alpha-band synchronization during visual short-term memory retention in children born very preterm. *NeuroImage*, *54*, 2330–2339.

Eeg-Olofsson, O., Petersen, I., & Sellden, U. (1971). The development of the electroencephalogram in normal children from the age of 1 through 15 years. *Paroxysmal activity. Neuropadiatrie*, *2*, 375–404.

Elliott, R. (2003). Executive functions and their disorders: Imaging in clinical neuroscience. *British Medical Bulletin*, *65*, 49–59.

Fan, J., McCandliss, B.D., Fossella, J., Flombaum, J.I., & Posner, M.I. (2005). The activation of attentional networks. *NeuroImage*, *26*, 193–222.

Fan, J., McCandliss, B.D., Sommer, T., Raz, A., & Posner, M.I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*, 340–347.

Gardner, J.M., Karmel, B.Z., & Flory, M.J. (2003). Arousal modulation of neonatal visual attention: Implications for development. In S. Saroci & K.M. Sacori (Eds.), *Perspectives on fundamental processes in intellectual functioning*, Vol. *2*. Visual information processing and individual differences (pp. 125–154). Westpost, CT: Praeger.

Gasser, T., Verleger, R., Bächer, P., & Sroka, L. (1988). Development of the EEG of school-age children and adolescents. I. Analysis of band power. *Electroencephalography and Clinical Neurophysiology*, *69*, 91–99.

Geva, R., & Feldman, R. (2008). A neurobiological model for the effects of early brainstem functioning on the development of behavior and emotion regulation in infants: Implications for prenatal and perinatal risk. *Journal of Child Psychology and Psychiatry*, *49*, 1031–1041.

Geva, R., Schreiber, J., Segal-Caspi, L., & Markus-Shiffman, M. (2014). Neonatal brainstem dysfunction after preterm birth predicts behavioral inhibition. *Journal of Child Psychology and Psychiatry*, *55*, 802–810.

Geva, R., Sopher, K., Kurtzman, L., Galili, G., Feldman, R., & Kuint, J. (2011). Neonatal brainstem dysfunction risks infant social engagement. *Social Cognitive and Affective Neuroscience*, *8*, 158–164.

Geva, R., Zivan, M., Warsha, A., & Olchik, D. (2013). Alerting, orienting or executive attention networks: Differential patterns of pupil dilations. *Frontiers in Behavioral Neuroscience*, *7*, 145.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., … & Rapoport, J.L. (1999). Brain

development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*, 861–863.
Harmon-Jones, E., Gable, P.A., & Peterson, C.K. (2010). The role of asymmetric frontal cortical activity in emotion-related phenomena: A review and update. *Biological Psychology*, *84*, 451–462.
Jiang, Z.D., Brosi, D.M., Wu, Y.Y., & Wilkinson, A.R. (2009). Relative maturation of peripheral and central regions of the human brainstem from preterm to term and the influence of preterm birth. *Pediatric Research*, *65*, 657–662.
Johnson, K.A., Robertson, I.H., Barry, E., Mulligan, A., Dáibhis, A., Daly, M., … & Bellgrove, M.A. (2008). Impaired conflict resolution and alerting in children with ADHD: Evidence from the Attention Network Task (ANT). *Journal of Child Psychology and Psychiatry*, *49*, 1339–1347.
Karmel, B.Z., Gardner, J.M., Zappulla, R.A., Magnano, C.L., & Brown, E.G. (1988). Brainstem auditory evoked responses as indicators of early brain insult. *Electroencephalography and Clinical Neurophysiology*, *71*, 429–442.
Klin, A. (2000). Attributing social meaning to ambiguous visual stimuli in higher-functioning autism and Asperger syndrome: The Social Attribution Task. *Journal of Child Psychology and Psychiatry*, *41*, 831–846.
Kostovic, I., & Judas, M. (2010). The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatrica*, *99*, 1119–1127.
Krumholz, A., Felix, J.K., Goldstein, P.J., & McKenzie, E. (1985). Maturation of the brain stem auditory evoked potential in premature infants. *Electroencephalography and Clinical Neurophysiology*, *62*, 124–134.
Makinodan, M., Rosen, K.M., Ito, S., & Corfas, G. (2012). A critical period for social experience-dependent oligodendrocyte maturation and myelination. *Science*, *337*, 1357–1360.
Marosi, E., Harmony, T., Sánchez, L., Becker, J., Bernal, J., Reyes, A., … & Fernández, T. (1992). Maturation of the coherence of EEG activity in normal and learning-disabled children. *Electroencephalography and Clinical Neurophysiology*, *83*, 350–357.
Miron, O., Ari-Even Roth, D., Gabis, L.V., Henkin, Y., Shefer, S., Dinstein, I., & Geva, R. (2016). Prolonged auditory brainstem responses in infants with autism. *Autism Research*, *9*, 689–695.
Moore, J.K., Perazzo, L.M., & Braun, A. (1995). Time course of axonal myelination in the human brainstem auditory pathway. *Hearing Research*, *91*, 208–209.
Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., & Carter, C.S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective, and Behavioral Neuroscience*, *12*, 241–268.
Nosarti, C., Giouroukou, E., Healy, E., Rifkin, L., Walshe, M., Reichenberg, A., … & Murray, R. (2008). Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain*, *131*, 205–217.
Orekhova, E.V., Stroganova, T.A., Posikera, I.N., & Elam, M. (2006). EEG theta rhythm in infants and preschool children. *Clinical Neurophysiology*, *117*, 1047–1062.
Padilla, N., Alexandrou, G., Blennow, M., Lagercrantz, H., & Ådén, U. (2014). Brain growth gains and losses in extremely preterm infants at term. *Cerebral Cortex*, *25*, 1897–1905.
Panksepp, J. (1998). The preconscious substrates of consciousness: Affective states and the evolutionary origins of the self. *Journal of Consciousness Studies*, *5*, 566–582.
Pfeiffer, U.J., Schilbach, L., Jording, M., Timmermans, B., Bente, G., & Vogeley, K. (2012). Eyes on the mind: Investigating the influence of gaze dynamics on the perception of others in real-time social interaction. *Frontiers in Psychology*, *3*, 537.
Porges, S.W. (2003a). The polyvagal theory: Phylogenetic contributions to social behavior. *Physiology and Behavior*, *79*, 503–513.
Porges, S.W. (2003b). Social engagement and attachment: A phylogenetic perspective. Roots of mental illness in children. In J.A. King, C.F. Ferris & I.I. Lederhendler (Eds.), *Annals of the New York Academy of Sciences* (Vol. *1008*, pp. ix–316). New York: New York Academy of Sciences.
Porges, S.W., Doussard-Roosevelt, J.A., Portales, A.L., & Greenspan, S.I. (1998). Infant regulation of the vagal brake predicts child behavior problems: A psychobiological model of social behavior. *Developmental Psychobiology*, *29*, 697–712.
Posner, M.I., Petersen, S.E., Fox, P.T., & Raichle, M.E. (1988). Localization of cognitive operations in the human brain. *Science*, *217*, 1627–1631.
Prechtl, H.F.R. (1992). The organization of behavioral states and their dysfunction. *Seminars in Perinatology*, *16*, 258–263.
Rodríguez Martinez, E.I., Barriga-Paulino, C.I., Zapata, M.I., Chinchilla, C., López-Jiménez, A.M., & Gómez, C.M. (2012). Narrow band quantitative and multivariate electroencephalogram analysis of peri-adolescent period. *BMC Neuroscience*, *13*, 104.
Rothbart, M.K., & Rueda, M.R. (2005). The development of effortful control. In U. Mayr, E. Awh, & S.W. Keele (Eds.), *Developing individuality in the human brain: A tribute to Michael I. Posner* (pp. 167–188). Washington DC: American Psychological Association.
Schore, A.N. (1996). The experience-dependent maturation of a regulatory system in the orbital prefrontal cortex and the origin of developmental psychopathology. *Development and Psychopathology*, *8*, 59–87.
Shine, J.M., Bissett, P.G., Bell, P.T., Koyejo, O., Balsters, J.H., Gorgolewski, K.J., … & Poldrack, R.A. (2016). The dynamics of functional brain networks: Integrated network states during cognitive task performance. *Neuron*, *92*, 544–554.
Shinya, Y., Kawai, M., Niwa, F., & Myowa-Yamakoshi, M. (2014). Preterm birth is associated with an increased fundamental frequency of spontaneous crying in human infants at term-equivalent age. *Biology Letters*, *10*, 20140350.
Smith, A.S., Levine, D., Barnes, P.D., & Robertson, R.L. (2005). MRI of the kinked fetal brainstem: A sign of severe dysgenesis. *Journal of Ultrasound in Medicine*, *24*, 1697–1709.
von Stein, A., Chiang, C., & Konig, P. (2000). Top-down processing mediated by interareal synchronization. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 14748–14753.
Tierney, A.L., Gabard-Durnam, L., Vogel-Farley, V., Tager-Flusberg, H., & Nelson, C.A. (2012). Developmental trajectories of resting EEG power: An endophenotype of autism spectrum disorder. *PLoS ONE*, *7*, e39127.
Tucker, D.M., Derryberry, D., & Luu, P. (2000). Anatomy and physiology of human emotion: Vertical integration of brain stem, limbic and cortical systems. In J.C. Brood (Ed.), *The neuropsychology of emotion: Series in affective science* (pp. 56–79). New York: Oxford University Press.
Tucker, D.M., Luu, P., & Derryberry, D. (2005). Love hurts: The evolution of empathic concern through the encephalization of nociceptive capacity. *Development and Psychopathology*, *17*, 699–713.
Volpe, J.J. (2009). Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. *Lancet Neurology*, *8*, 110–124.
Yaakoby-Rotem, S., & Geva, R. (2014). Asymmetric attention networks: The case of children. *Journal of the International Neuropsychology Society*, *20*, 434–443.
Zatorre, R.J., Fields, R.D., & Johansen-Berg, H. (2012). Plasticity in gray and white: Neuroimaging changes in brain structure during learning. *Nature Neuroscience*, *15*, 528–536.

Accepted for publication: 24 February 2017
First published online: 15 May 2017