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SCIENTIFIC FORUM: COMMENTARY

The motivation for very early intervention for infants at high risk for autism spectrum disorders

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Abstract
The first Autism Research Matrix (IACC, 2003) listed the identification of behavioural and biological markers of risk for autism as a top priority. This emphasis was based on the hypothesis that intervention with infants at-risk, at an early age when the brain is developing and before core autism symptoms have emerged, could significantly alter the developmental trajectory of children at risk for the disorder and impact long-range outcome. Research has provided support for specific models of early autism intervention (e.g., Early Start Denver Model) for improving outcomes in young children with autism, based on both behavioural and brain activity measures. Although great strides have been made in ability to identify risk markers for autism in younger infant/toddler samples, how and when to intervene during the prodromal state remains a critical question. Emerging evidence suggests that abnormal brain circuitry in autism precedes altered social behaviours; thus, an intervention designed to promote early social engagement and reciprocity potentially could steer brain development back toward the normal trajectory and remit or reduce the expression of symptoms.

Keywords: *Autism spectrum disorders, ASD, communication, speech, language, intervention.*

Introduction

In "Early Identification and Early Intervention in Autism Spectrum Disorders: Accurate and Effective?", Camarata (2014) highlights the difficulty with early identification, specifically in differential diagnosis between conditions such as autism spectrum disorders (ASD) and communication disorders, which often have overlapping risk markers and early presentation. Communication concerns are often a primary cause of referral to early intervention. While these communication concerns do not necessary result in an ASD diagnosis (e.g., Turygin, Matson, Konst, & Williams, 2013), many children who do develop autism have early language delays or atypicalities (e.g., Mitchell, Brian, Zwaigenbaum, Roberts, Szatmari, Smith, et al., 2006; Webb, & Jones, 2009; Zwaigenbaum, Bryson, Lord, Rogers, Carter, Carver, et al., 2009). We propose that very early intervention, when conducted with toddlers who have received a multi-disciplinary clinical evaluation for autism, is effective in moving young children toward better outcomes, that the first 2 years represent an important period in which foundational social-communication skills develop for positive language, social, and cognitive outcomes, and that a stepped diagnostic and treatment approach should be implemented to provide children with an individualized level of clinical care and intervention.

Motivation for very early intervention

Over the past few years, support for very early intervention (below age 3 years) has begun to emerge in the literature. Two studies have reported positive effects of even brief interventions during this time period (Landa & Kalb, 2012; Rogers, Estes, Lord, Vismara, Winter, Fitzpatrick, et al., 2012). Only one study to date has examined the impact of a comprehensive and intensive intervention. This study was a randomized clinical trial for young toddlers with autism (18–30 months) based on the Early Start Denver Model (ESDM), a developmental model that integrated play-based relationship-focused strategies with applied behaviour analysis. Children who received ESDM for 2 years exhibited significantly greater gains in IQ, language, and adaptive and social behaviour compared to children who received standard treatment in the community (Dawson, Rogers, Munson, Smith, Winter, Greenson, et al., 2010). At outcome, the ESDM group also demonstrated more neurotypical patterns of cortical activation (decreased

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alpha power and increased theta power) and increased neural response (faster Nc latency) to social stimuli. In fact, the responses in the ESDM group did not differ from age-matched neurotypical controls. In contrast, the control group of children with ASD who received community-based interventions showed the opposite pattern (increased cortical activation and faster processing of objects compared to faces). In the ESDM group, normalized patterns of viewing social information were also associated with improved social behaviour (Dawson, Jones, Merkle, Venema, Lowy, Faja, et al., 2012). Longitudinal follow-up is still in progress, but it is hypothesized that children who received ESDM will have foundational skills that will allow them to be better integrated into schools and communities, with less support cost and greater social and adaptive opportunities.

It is noteworthy that, although greater improvements in cognitive, social, and language skills and normalization of some aspects of brain activity were apparent in the children who received the ESDM intervention, children in the comparison group who received community-based intervention also showed improvements in brain activity. Specifically, after early identification and access to 2 years of intervention, both ASD groups (ESDM and Community Intervention) showed a typical pattern of early stage processing of facial information (e.g., faster and more negative N170 amplitude to faces than objects). These findings represent an improvement from neural responses to faces found at the entrance to the study (Webb, Jones, Merkle, Venema, Greenson, Murias, et al., 2011). These results, suggest that both groups demonstrated improvement of basic neural social processes (compared to Webb, Dawson, Bernier & Panagiotides, 2006; Burner, Jones, Venema, Murias et al., 2013). We suggest that, due to the dynamic and plastic nature of early brain development in ASD, both specific and general early interventions may alter the course of brain and behavioural development in young children.

How might early interventions that focus on social engagement improve outcomes, including brain responses to social stimuli, in young children with ASD? The s*ocial motivation hypothesis* (Dawson, Webb, & McPartland, 2005) posits that autism is related to core impairment in social motivation—the affective tagging of socially relevant stimuli (e.g., Dawson et al., 2005; Grelotti, Guathier, & Schultz, 2002; Waterhouse, Fein, & Modahl, 1996). The emergence of core symptoms may be related to dysfunction or delay in the development of the neural circuits involved in forming representations of the reward value of social stimuli, such as the orbitofrontal cortex-amygdala pathway (Schoenbaum, Setlow, Saddoris, & Gallagher 2003). This system is involved in the formation of stimulus-reward learning. Tasks that involve the temporal lobe-orbitofrontal circuit such as the delayed non-match to sample and object discrimination reversal are impaired in young children with autism (Dawson, Carver, Meltzoff, Panagiotides, McPartland, & Webb, 2002; Jones, Webb, Estes, & Dawson, 2013), and are related to the severity of the joint attention impairment in autism (Dawson, Munson, Estes, Osterling, McPartland, Toth, et al. 2003).

As children become more motivated to attend to and engage with other people, their experience with faces and voices, which occurs in the context of social interactions, increases. This facilitates cortical specialization for faces and linguistic stimuli and the fine-tuning of perceptual systems for social and linguistic processing (Johnson, Griffin, Csibra, Halit, Farroni, De Haan, et al., 2005). These areas become specialized for the processing of social information, and become increasingly integrated with regions involved in reward circuitry as well as regions involved in attention and actions (cerebellum, prefrontal/cingulate cortex). As a result, a more complex social brain circuitry emerges, supporting more complex behaviours, such as disengagement of attention, joint attention, intentional communication, imitation and language.

Early core symptoms of autism may represent the failure of these brain systems to develop and become specialized and functionally integrated (Johnson et al., 2005). Both general and specific neural pathways within the social-brain system circuitry could be affected by early intervention during a period of (potential) maximal plasticity. Models of intervention such as ESDM, which is a comprehensive approach focused on interpersonal exchanges and shared engagement, may provide the necessary supplementary stimulation to promote brain circuitry that integrates motivation and attention, thereby facilitating learning and continued brain and behavioural development.

Why the first 2 years matter

Summarized by Zwaigenbaum, Bryson, and Garon (2013), a number of behavioural risk markers of autism can be identified at 12 months in infants who go on to develop ASD. These behavioural markers have been documented in both prospective high-risk samples as well as using retrospective reports and home videotapes. These markers reflect decreased social–communicative behaviours such as failure to orient to social stimuli (e.g., responding to name), reduced eye contact, reduced positive affect, and fewer communicative gestures. While differentiation of ASD from general developmental delay during the 12 and 24 months remains difficult; by 2 years, reduced social-communicative initiations and responses in the context of social information begins to differentiate groups. Social communicative gestures (such as gaze and pointing) between 12–24 months are critical to the formation and maintenance of shared awareness of an event or object

and are predictive of level of later language development (e.g., Carpenter, Pennington, & Rogers, 2002; Charman, Baron-Cohen, Swettenham, Baird, Drew, & Cox, 2003; Mundy, Sigman, & Kasari, 1990; Stone & Yoder, 2001; Toth, Munson, Meltzoff, & Dawson, 2006) above and beyond early language ability (Morales, Mundy, Crowson, Neal, & Delgado, 2005). These behaviours are also predictive of later social cognitive skills (e.g., Charman et al., 2003; De Schuymer, De Groote, Desoete, & Roeyers, 2012; Mundy et al., 1990; Sigman & McGovern, 2005) as well as inhibitory and self-regulation behaviours (Morales et al., 2005; Vaughan Van Hecke, Mundy, Block, Delgado, Parlade, Pomares, et al., 2012). Thus, interventions that improve social and communication skills during infancy have the potential for pervasive effects on later development.

Intervening in the first year

The first Autism Research Matrix (IACC, 2004) listed the identification of behavioural and biological markers of risk for autism as a top priority. This emphasis was based on the hypothesis that, by identifying infants at-risk at an early age when the brain is developing and before core autism symptoms have emerged, it might be possible to alter the developmental trajectory of children and have a significant impact on long-range outcome. It is known that susceptibility genes interact with the social environment, thereby influencing gene expression (e.g., Fox, Nichols, Henderson, Rubin, Schmidt, Hamer, et al., 2005). There may exist a "pre-symptomatic period" in autism during which intervention may have more potent effects on gene expression and symptom emergence (e.g., Lewis, 2004). If intervention, initiated during infancy and before the full onset of core symptoms, can influence the development of social and language brain circuitry, it may be possible to reduce the manifestation of core or secondary symptoms, and steer development back toward a more normative pathway (Dawson, 2008).

The recurrence rate for ASD in younger siblings of children with autism is close to 20% (Ozonoff, Young, Carter, Messinger, Yirmiya, Zwaigenbaum, et al., 2011), and many siblings without autism exhibit impairments in receptive and expressive language skills (Landa & Garrett-Mayer, 2006; Zwaigenbaum et al., 2005). Infants who show a pattern of declining or slowing in rate of skills acquisition from the first to the third year are at higher risk for developing ASD (Bryson, Zwaigenbaum, Brian, Roberts, Szatmari, Rombough, et al., 2007; Landa, Gross, Stuart, & Faherty, 2013). Within the Autism Speaks Baby Sibs Research Consortium, research to identify risk markers is rapidly progressing: in 2012 alone, 29 studies were published from the consortium identifying behaviours or neural patterns related to the onset of autism by 2 or 3 years (Autism Speaks, 2012). Since our ability to identify infants at risk for autism is rapidly improving, how to and if to intervene during the prodromal state is an increasingly critical question.

Based on the hypothesis that abnormal social brain circuitry in autism emerges in the context of altered social interaction, in the University of Washington Autism Center of Excellence study Early Connections, the efficacy of an intervention designed to enhance social motivation and promote early social engagement and reciprocity for improving both behavioural outcomes and indices of brain activity is being evaluated (also see Green, Wan, Guiraud, Holsgrove, McNally, Slonims, et al., 2013). Promoting First Relationships (PFR) (http://pfrprogram.org), which was specifically designed to facilitate parent–infant interaction in at-risk infant populations, promotes infant contingent responding, positive affect, self-regulation, and parental sensitivity to the infant's communicative cues. Facilitating parent–infant interaction prior to 12 months of age, including the infant's ability to attend to and respond to his or her social partner, is important as early patterns of parent–child interaction may be disrupted by early autism behaviours (Grzadzinski, Luyster, Gunn Spencer, & Lord, 2012; Hoppes & Harris, 1990; Seskin, Feliciano, Tippy, Yedloutschnig, Sossin, & Yasik, 2010; Wan, Green, Elsabbagh, Johnson, Charman, & Plummer, 2012). When interacting with their mothers, young children with autism as well as infant siblings of children with autism show less frequent contingent responses as well as reduced joint attention, affective sharing, and responsive social smiles (e.g., Dawson, Hill, Spencer, Galpert, & Watson, 1990; Dousard-Roosevelt, Joe, Bazhenova, & Porges 2003; Kasari, Sigman, Mundy, & Yirmiya 1988; Yirmiya, Gamliel, Pilowsky, Feldman, Baron-Cohen, & Sigman, 2006). Upon reunion after separation, 2–3-year-olds with ASD (with mental age <24 months) are less likely to go to their parents and show pleasure or be soothed upon their parent's return (Grzadzinski et al., 2012). Higher levels of parental synchronization and contingent responses during interaction has been found to be associated with improved child communication skills over periods of 1, 10, and 16 years (Siller & Sigman, 2002). Other studies have found that the relation between early deficits in social attention and later child's language ability is mediated by the child's ability to share attention with others (e.g., Toth et al., 2006).

Promoting first relationships

Promoting First Relationships is based on the assumption that relationships are transactional; the infant exerts an effect on the parent and influences the sensitivity and quality of the parent response. PFR focuses on promoting positive characteristics in the parent–child interaction and strengthening families rather than targeting specific domains of impairment. Parents find it more difficult to respond

sensitively to infants who have regulatory difficulties and who have less reciprocal interaction styles (Kelly, Day, & Streissguth 2000; O'Connor, Sigman, & Brill 1987; Tronick & Field, 1986; Yehuda, Engel, Brand, Seckl, Marcus, & Berkowitz, 2005). Interventions, such as PFR, that help parents regulate infants' negative affect, appear to both increase caregiver sensitivity to infant cues and promote communicative development (van Den Boom 1994, 1995). Such interventions are designed to take into account the individual characteristics of both members of the dyad, and they are sensitive to the "dance" that the dyad performs together (Poehlmann & Fiese, 2001). Evidence suggests that brief, relationship-focused interventions, such as PFR, can be quite effective when the specific target outcome is parental sensitivity and infant contingent responding. Bakermans-Kranenburg, van Ijzendoorn, and Juffer (2003) conducted a meta-analysis of 81 studies promoting mother–infant interaction and found that interventions focusing on promoting maternal sensitivity were more effective than the combination of all other types of interventions. The most effective interventions for enhancing maternal sensitivity involved fewer than 16 sessions, used video feedback, and were utilized with populations in which child characteristics, rather than parent characteristics, were risk factors. PFR has resulted in improved quality of the mother–child interaction, as reflected in more maternal contingent responses and greater overall responsiveness and sensitivity to the child (Kelly, Buelhman, & Caldwell, 2000). Importantly for children at-risk for autism, the children also became significantly more responsive and contingent with their mothers (Kelly, Zuckerman, & Rosenblatt, 2008).

Given the likelihood that many high risk infant siblings of children with autism will be showing only mild or even no impairments in the first year, and the fact that many families will be under stress (e.g., Estes, Munson, Dawson, Koehler, Zhou, & Abbott, 2009), positive family focused interventions are highly appropriate and potentially beneficial for all families. Families of children with disabilities experience many types of stressors, including lack of available medical resources, financial burden, distress related to concerns of a second child at genetic risk, perceived personal distress, and the challenge of child behaviour problems (Baker, Blacher, Crnic, & Edelbrock, 2002). Early interventions should provide appropriate "anticipatory guidance" regarding strategies for enhancing parent–infant interactions that can be utilized later when problems begin to arise (Nelson, Wissow, & Cheng, 2003). Moreover, as autism symptoms may emerge after the first year, or change in severity and presentation, parent coaching in autism-specific interventions may help to offset stress increases (e.g., Estes, Vismara, Mercado, Fitzpatrick, Elder, Greenson, et al., 2013: McConachie & Diggle, 2007).

Models of early intervention: Primary and stepped care

One promising approach is to address early intervention using a stepped care method, in which treatments are provided sequentially according to need (Davison, 2000; Fairburn, Agras, & Wilson 1992; Garner & Needleman 1997). Also referred to as "multi-level" or "tiered", such approaches have been used to treat other child-onset disorders (e.g., Fairburn et al., 1992; Garner & Needleman 1997; Sanders, Turner, & Markie-Dadds, 2002; Wilson, Vitousek, & Loeb, 2000). For both symptomatic and non-symptomatic high-risk infants, PFR is an appropriate low-intensity and low-cost intervention focused on enhancing the ability of the parent to respond adaptively to infant cues, which is expected to have positive benefits for infant–parent dyads in light of the well-documented high levels of stress that families with children with autism experience (Abbeduto, Seltzer, Shattuck, Krauss, Orsmond, & Murphy, 2004; Blacher & McIntyre, 2006; Eisenhower, Baker, & Blacher, 2005; Estes et al. 2009; Gallagher & Bristol 1989; Kasari & Sigman, 1997). Following a stepped care model, as symptoms emerge, a more targeted ASD-specific intervention (e.g., such as parent-mediated ESDM; Rogers et al., 2012) could be provided. Such interventions would involve autism-specific training delivered by the parent within the toddler's home environment. Then, if symptoms persist or worsen, transition to an increased intensity/therapist delivered intervention would be appropriate. Intervention models such as PFR and ESDM reflect theoretical continuity, as both interventions view the child's social motivation and ability to engage in social relationships as a critical foundation and final common pathway responsible for promoting and maintaining many aspects of development. Both interventions utilize strategies that make social relationships more rewarding for the child, thereby improving the child's social motivation.

Conclusion

We agree with Camarata (2014) that additional empirical evidence is critically needed to evaluate ASD treatment models, including timing, intensity, and delivery in young children with ASD, and should be a research priority. The Interagency Autism Coordinating Committee continues to highlight this need, focusing on "Which treatments and interventions will help?" as a primary domain of the Strategic Plan for autism spectrum disorder research (IACC, 2012). This is a field that is rapidly moving forward, with recent investigations documenting treatment success in the use of medications for both primary and secondary symptoms, the role of targeted joint attention training, and improvement in peer relations and core symptoms through social skills training among a

number of other critical discoveries (see IACC, 2013 for review).

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