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SCIENTIFIC FORUM: COMMENTARY

Moving beyond behaviour-only assessment: Incorporating biomarkers to improve the early detection and diagnosis of autism spectrum disorders

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Abstract
This paper presents a response to the Camarata (2014) lead article regarding the accuracy and effectiveness of early identification and early intervention for young children with autism spectrum disorders (ASD). While Caramata focused heavily on the challenges of behavioural screening for ASD, we believe that he has overlooked the potential that the identification of ASD biomarkers may have for the early detection of the disorder. We propose that the discovery of biomarkers, particularly those that may be used in conjunction with behavioural screening, may provide an important next step in reliably detecting and accurately diagnosing ASD in the early years. This would have important clinical implications in terms of providing early intervention, which may alter the developmental path for the child.

Keywords: *Autism spectrum disorders, early identification, biomarkers*

Introduction

Camarata (2014) presents an insightful and interesting discussion of the theoretical and practical challenges associated with early identification and early intervention for children with autism spectrum disorders (ASD). It is integral that we work towards improving the early identification of ASD, so that children can access early intervention from as young as possible. In addition, it is important to ensure that there is adequate empirical support for early intervention, so that young children and families are able to access effective therapies. Accurate identification of ASD and the provision of effective early intervention are fundamental to maximize the developmental outcomes for children with ASD.

Camarata (2014) provided a framework for examining the issues of early identification and early intervention for ASD. While he examined the literature regarding the behavioural screening and detection of ASD, Camarata did not address the global trend towards identifying biomarkers for the condition. Therefore, in our response, we will review some of the evidence for ASD biomarkers and consider future directions in terms of identifying biomarkers for ASD, which, when used in conjunction with the early behavioural signs of the disorder, may serve as more reliable and accurate indicators of ASD in the very early years.

Early identification of ASD and the discovery of biomarkers

The identification of biomarkers may overcome some of the limitations of early behavioural screening raised by Camarata, such as the difficulty in reliably detecting ASD in young children. For example, early biological screening may enable the identification of children with mild ASD symptoms that may not otherwise be recognized in the early years. In addition, improving the specificity of ASD biomarkers may assist with the differential diagnosis of ASD and other developmental disorders, and help to distinguish typical from atypical development which, as Camarata indicated, are key challenges in the early identification of ASD. Here, we outline evidence for biological markers that may have predictive power for later ASD diagnoses.

Incorporating biomarkers into ASD diagnostic protocols may be helpful both to provide a reliable screening tool to determine risk for developing the disorder, and to improve the reliability of clinical diagnoses (Yerys & Pennington, 2011). One

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promising method for identifying predictive biomarkers for ASD has been large-scale, longitudinal prospective studies that investigate high-risk infant siblings of children already diagnosed with ASD (see Elsabbagh & Johnson, 2010; Zwaigenbaum, 2010; Zwaigenbaum, Bryson, Lord, Rogers, Carter, Carver, et al., 2009). This population is at increased genetic risk of developing ASD, and prospective studies of infant development allow the collection of parent-report, biological, environmental, and behavioural data that may signal risk for later developing ASD (Newschaffer, Croen, Fallin, Herz-Picciotto, Nguyen, Lee, et al., 2012). In particular, several studies have investigated aspects of brain function and structure in infant siblings of children with ASD and mapped these early biological signs of ASD onto later behavioural features of the disorder. For example, in a study that used event-related potentials (ERPs), McCleery, Ackshoomoff, Dobkins, and Carver (2009) found that, in contrast to low-risk infants, those at high-risk of developing ASD had relatively faster neural responses when shown pictures of objects (e.g., familiar and unfamiliar toys), compared to pictures of faces (e.g., mother's face and unfamiliar woman's face). McCleery et al. (2009) also reported a lack of hemispheric asymmetry for the high- relative to the low-risk infants across the responses to pictures of the face and the objects. Collapsed across all responses, the low-risk but not the high-risk infants showed greater left than right hemisphere responses for the P100 and P400 components, and greater right than left hemisphere responses for the N290 component[1]. While McCleery et al. (2009) did not follow-up these infants to determine whether those with atypical neural responses later received clinical diagnoses of ASD, these findings do suggest that there may be a neurological signature of social information processing, and that qualitative differences in these markers may be present from as early as 10 months in infants at heightened risk for developing ASD.

Two other studies have employed Event Related Potentials (ERPs) to examine the neural underpinnings of eye gaze processing for high-risk infant siblings of children with ASD (Elsabbagh, Mercure, Hudry, Chandler, Pasco, Charman, et al., 2012; Elsabbagh, Volein, Csibra, Holmboe, Garwood, Tucker, et al., 2009). In these studies, the infants viewed static images and dynamic videos of female faces. In the static images, the eye gaze was either directed to, or averted from the infant, and, in the videos, the gaze of the females shifted either towards, or away from the infant. Elsabbagh et al. (2009) found longer neural latencies to respond to direct eye gaze for the high- compared to the low-risk infants. The longer latencies were observed on the P400 component, thought to be sensitive to face processing in infants. In a follow-up to this study, Elsabbagh et al. (2012) conducted a longitudinal analysis that examined whether early differences in response to eye gaze were associated with later ASD diagnoses. Indeed, these authors reported that, while the typically-developing and high-risk infant siblings who were not diagnosed with ASD had higher P400 amplitudes for gaze shifts away than towards the observer, the ASD group did not discriminate the two gaze directions. Therefore, the neural response to eye gaze in infancy was associated with a later clinical diagnosis of ASD. These findings are also consistent with Camarata's claim that non-verbal social engagement may be a useful marker of ASD in the early years, particularly in terms of distinguishing ASD from other developmental language disorders. However, the use of ERP measures has come under some criticism due to a possible lack of reliability and replicability (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). The methodological limitations of these studies emphasize the necessity of including both behavioural and biological measures in the early identification of ASD. When used in conjunction with behavioural measures of social engagement, biological markers of social impairment may be a significant indicator of ASD from early infancy.

Several recent studies have used prospective longitudinal designs to investigate brain structure in infants at high familial risk of developing ASD (Elison, Paterson, Wolff, Reznick, Sasson, Gu, et al., 2013; Shen, Nordahl, Young, Wootton-Gorges, Lee, Liston, et al., 2013; Wolff, Hongbin, Guido, Elison, Styner, Gouttard, et al., 2012). Using diffusion tensor imaging, Wolff et al. (2012) identified significant qualitative differences in white matter development between high-risk infants who were diagnosed with ASD by 24 months, compared to those who did not receive an ASD diagnosis. Adopting a similar neuroimaging technique, Elison et al. (2013) reported associations between the white matter structure of the splenium and visual orienting for typically-developing infants but not for high-risk infants who went on to show behavioural features of ASD. Shen et al. (2013) presented consistent results from a study that used magnetic resonance imaging. These authors found that infants diagnosed with ASD at 24 months had significantly greater extra-axial fluids at 6–9 months and larger brain volumes at 12–24 months, compared to infants who did not have a clinical diagnosis of ASD. While in need of replication, these studies provide evidence for the existence of early neurological signs that may represent risk for later developing ASD. These results also highlight the potential for promising biomarkers to be used to supplement behavioural screening in infants at high risk of developing the condition.

[1]An ERP component represents the neural activation that is associated with certain behavioural or cognitive processes. ERPs are characterized by polarity (negative or positive), latency, and location. For example, a P100 component is a positive waveform that occurs 100 milliseconds after stimulus onset and is related to processing visual stimuli.

In recent years, several large-scale longitudinal pregnancy studies, including the Early Autism Risk Longitudinal Investigation (EARLI; Newschaffer et al., 2012) and our Pregnancy Investigation of Siblings and Mothers of Children with Autism (PRISM), have also emerged. These studies provide additional advantages over studies of high-risk infant siblings, as they enable the examination of the pre-, peri-, and post-natal development of infant siblings of children already diagnosed with ASD. In particular, the PRISM study is investigating possible ASD biomarkers such as levels of testosterone *in-utero* and in umbilical cord blood, as well as the trajectory of head growth pre- and post-natally. It is already established that some children with ASD may have a period of rapid brain development, and the results of one preliminary study also suggest that a small number of children later diagnosed with ASD had disproportionately large head circumferences at 18 weeks gestation (Whitehouse, Hickey, Stanley, Newnham, & Pennell, 2011). While these results are promising, the brain overgrowth hypothesis of ASD has recently come under criticism (Raznahan, Wallace, Antezana, Greenstein, Lenroot, Thurm, et al., 2013). Following a systematic review and analysis of early brain overgrowth data, Raznahan et al. (2013) reported that patterns of early brain overgrowth in ASD reflect selection biases in the comparison groups, and, when compared to community-based population norms, findings of overgrowth in ASD are inconsistent. Nonetheless, while the link between pre-natal brain growth and later ASD diagnosis has not yet been determined, these results indicate that there could be atypical biological processes that are associated with increased ASD risk, apparent even in the pre-natal period.

While the results of these studies are encouraging in terms of describing possible biological indicators for ASD, more longitudinal studies are needed to examine relationships between biomarkers and later clinical diagnoses of ASD. In addition, there is currently limited evidence to suggest that these biomarkers are specific to ASD, which is important if the marker is to be used as part of a suite of screening measures. The current evidence regarding biomarkers is promising and, when incorporated with behavioural measures, will have important implications for the early detection and more accurate diagnosis of ASD. However, studies investigating the early biological signature of ASD are only now emerging, and the knowledge of biomarkers is not yet at a stage where it can be utilized clinically.

Clinical applications of biomarkers: Potential for tracking developmental change and measuring outcomes

Camarata (2014) referred to the need for plausible outcome measures that are directly relevant to autistic symptomatology to be included in intervention trials. Biomarkers present an opportunity to both predict developmental outcomes and measure the effects of early intervention. When integrated into intervention trials, biomarkers may help to provide evidence of the effectiveness of different therapeutic approaches.

Camarata (2014) argued that "classic autism" may be diagnosed more reliably than less severe ASDs. The results of a recent study that used ERPs of word processing in 2-year-olds with ASD to predict developmental outcomes at age 6 years (Kuhl, Coffey-Corina, Padden, Munson, Estes, & Dawson, 2013) are consistent with this claim. Kuhl et al. (2013) found that children with more severe symptoms of ASD at 2 years old had atypical neural responses when hearing known and unknown words. The results of a longitudinal follow-up of these children showed that the ERP measure taken at age 2 was a strong predictor of behavioural outcomes, including language, cognition, and adaptive behaviour. Recent results reported by Shen et al. (2013) also indicated that the amount of extra-axial fluid detected at 6 months predicted the severity of ASD symptoms in infants who received a clinical classification at outcome (24–36 months). These results provide evidence to suggest that early measures of neurological function may be useful in terms of determining the severity of ASD and predicting later developmental outcomes.

The inclusion of ASD-specific biological outcome measures in intervention trials could also assist in tracking developmental change. One study in particular has investigated neural responses (ERPs) to objects and faces for young children with ASD and young typically-developing children (Dawson, Jones, Merkle, Venema, Lowy, Faja, et al., 2012). This research was conducted as part of a larger randomized controlled trial that compared the outcomes of the Early Start Denver Model (ESDM) of early intervention to those of a community-based intervention program. Relative to the children with ASD in the community intervention condition, the children who received the ESDM intervention had faster neural responses to pictures of faces than to pictures of objects. In addition, the neural responses of children in the ESDM condition were similar to those of the typically-developing children, which led to the conclusion that brain responses for the ASD group were "normalized" following early intervention. While these findings provide preliminary evidence supporting the utility of including biological outcome measures in research studies, the lack of difference in ERPs for the ESDM and TD groups reported by Dawson et al. (2012) needs to be interpreted with caution. In addition, the methodological limitations of neuroimaging studies emphasize the necessity of including both behavioural and biological outcome measures in intervention trials, which may provide more reliable evidence for the effectiveness of early intervention for ASD.

Conclusions

The delivery of targeted intervention for ASD is predicated on the accurate identification of the disorder. Camarata (2014) discussed some of the challenges that are associated with detecting ASD in the early years, particularly the lack of sensitivity of current behavioural measures and the difficulty discriminating between ASD and other developmental disorders in infancy and toddlerhood. We propose that future research in ASD will benefit from identifying biomarkers that are indicators for increased risk of developing the disorder. In addition, research focused on improving the sensitivity and specificity of behavioural and biological markers of ASD independently and when applied together, will help to improve diagnostic accuracy. Future studies that involve investigations of possible predictive markers for the disorder have the potential to shift what is primarily a behaviourally-based diagnostic process into one that integrates both biological and behavioural measures of the characteristics of ASD.

Camarata (2014) noted the challenge of the behavioural heterogeneity of ASD and the difficulty drawing clear boundaries between sub-types of ASD. Indeed, current difficulties in the diagnosis and treatment of ASD are closely linked to the variability of the behavioural features of the disorder. The heterogeneity of the ASD profile will continue to present a challenge to the pursuit of biomarkers, as it is unlikely that every child with ASD will share underlying biological processes. Furthermore, there is growing recognition that ASD is not a unitary condition, but represents a collection of related disorders that have certain behavioural features (Whitehouse & Stanley, 2013). However, if we can begin to unite sub-groups in terms of aetiology and map biological processes onto behavioural features of the disorder, we can move towards a diagnostic scheme that relies on biology as well as behaviour. From there, we can develop interventions—whether behavioural or biological—that are targeted towards the specific aetiology of each sub-group of disorder. The ultimate purpose of the pursuit of biomarkers for ASD is to identify infants and toddlers who are at increased risk of developing the disorder and monitor these children closely, with the possibility of commencing early intervention at a younger age than is currently practical. By matching children at the earliest age with the most efficacious intervention, we can realistically hope to promote the best outcomes for children with ASD and their families.

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