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Can the N170 Be Used as an Electrophysiological Biomarker Indexing Face Processing Difficulties in Autism Spectrum Disorder?

To the Editor:

Difficulties in understanding facial signals of social communication, including facial identity and emotional expressions, have been hypothesized for many years in autism spectrum disorder (ASD). These difficulties are thought to impede social communication and interaction, which, in combination with a pattern of restricted and repetitive behavior and interests, constitute the core symptoms of ASD (1). Many behavioral studies have investigated face processing impairments in ASD, and recent reviews conclude that there are both quantitative and qualitative differences compared with neurotypical individuals (2,3). Quantitatively, individuals with ASD score worse than neurotypical individuals in the categorization of facial identity and expressions (2–4). Qualitative differences are assessed by markers of typical face processing, such as the inversion effect (5–8). However, there is inconsistency between studies, even while using the same tasks [e.g., (4,6–12)]. This might be due to the large heterogeneity in ASD but also to the explicit character of behavioral testing, which allows other factors, such as attention, motivation, task understanding, and compensatory strategies, to affect performance.

Partly to overcome the impact of these general processes, researchers have turned to scalp electroencephalography, which allows for the measurement of face processing without explicit tasks and verbal instructions. The majority of electroencephalography studies in children and adults with ASD focused on the N170, a negative event-related potential (ERP) peaking at about 170 ms over occipitotemporal sites after the sudden onset of a face stimulus [for review see (13,14); for "M170" in magnetoencephalography see (15)]. These studies failed to provide consistent evidence of abnormal N170 amplitude, latency, or scalp topography in response to face stimuli (7,16–24). Despite acknowledging this inconsistency, a recent meta-analysis by Kang *et al.* (25) in *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* identified a small but significant delay in N170 latency in ASD compared with neurotypical individuals. The authors use this observation to support the use of N170 as a biomarker of face processing abnormality in ASD. Here, while acknowledging the valuable effort of the authors and the importance of such meta-analyses, we question the validity of their conclusion.

Many familiar visual stimuli elicit an N170 response. This component reliably differentiates only between faces and other stimuli in terms of its face-specific increased amplitude (13,26), its sensitivity to face inversion [i.e., amplitude and latency increase (26)] and, to a lesser extent, its face-specific right hemispheric lateralization (27). Hence, a delay in absolute N170 latency to face stimuli in ASD may merely reflect the generally slower processing of visual stimuli, as illustrated in the meta-analysis by the medium effect size for nonsocial stimuli (25). In fact, the N170 delay in response to faces may even be present in earlier visual components, such as the P1, reflecting basic sensory processes [as hinted at by Kang *et al.* (25) but only investigated in a minority of studies]. For these reasons, the authors' statement that "the N170 is a plausible biomarker indexing neural mechanisms of face processing in ASD and may help to refine theoretical models" (25) appears unfounded.

Despite these limitations in interpretation, systematic N170 latency delays in ASD may still yield potential clinical diagnostic value. Unfortunately, contrary to the authors' claim, the N170 measure does not provide a "reliable, objective, and rapid assessment of treatment outcome and changes over development" (25). This is because the absolute parameters of the N170 evoked by a face stimulus cannot be directly used to index processes subtending social communication, such as the categorization of faces in terms of identity, expression, or eye gaze. Particularly, there is no evidence that the N170 latency relates to the relative speed of performing these categorizations. Moreover, providing a valid biomarker of impaired processes in neuropsychiatry goes beyond identifying mere statistical group differences (28–30). A clinically valuable biomarker needs to capture a reliable measure of an individual's status and its development over time, should be practically applicable to all individuals, and should be able to stratify them into relevant clinical groups. Furthermore, it needs to show discriminant validity, i.e., measure a specific impairment related to a specific clinical profile. Considering these criteria, the N170 (latency) does not provide a valid biomarker of ASD for several reasons. First, a small effect size of g = 0.36 implies that 64% of individuals with ASD score below the mean of the control group and that 86% of the two groups overlap, which is clearly inadequate to categorize individuals. Second, a delayed N170 latency to face stimuli has been observed in many psychiatric and neurological disorders, regardless of diagnosis (31), and therefore lacks specificity to ASD. Third, even though there is no significant group difference in N170 latency for nonface stimuli in the meta-analysis (owing to the small number of studies presenting nonfaces), the effect size for nonfaces is even larger than that for faces (i.e., g = 0.51 vs. g = 0.36, respectively), which leads us to question the specificity of the effect to face stimuli (24). Fourth, although the N170 latency is reliable within typical individuals (32,33), it varies substantially across individuals [i.e., 130–200 ms (14)], making the detection of an abnormal delay in a given individual virtually impossible. Fifth, despite no obvious change in face selectivity, the N170 latency decreases over typical development (34), thereby further complicating the identification of an abnormal N170 delay in children with ASD. Sixth, the morphology of ERP components can vary dramatically across individuals and across age groups [e.g., (34,35)], complicating the objective determination of latency and amplitude indices in individuals. Finally, given the low

https://doi.org/10.1016/j.bpsc.2018.07.015
ISSN: 2451-9022 Biological Psychiatry: Cognitive Neuroscience and Neuroimaging March 2019; 4:321–323 www.sobp.org/BPCNNI

signal-to-noise ratio of the standard ERP approach—requiring tens of trials to obtain clear components such as the N170 (36) —a rapid assessment, which is important for clinical populations, is only a vain hope.

In conclusion, contrary to Kang *et al.* (25), the face-evoked N170 does not provide a reliable, objective, and rapid biomarker indexing neural mechanisms of face processing in ASD. Rather, this review of 15 years of research suggests that this component cannot be used to support diagnosis and monitor treatment outcomes in ASD, and that it is time for researchers and clinicians to turn toward alternative neurofunctional measures.

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Acknowledgments and Disclosures

This work was supported by an "Excellence of Science (EOS)" FNRS/FWO grant (HUMVISCAT) Grant No. 30991544 (to BR and BB), a MM Delacroix foundation fellowship (to SV), and a Research Foundation Flanders Research grant (Grant No. G0C7816N [to BB and BR]).

The authors report no biomedical financial interests or potential conflicts of interest.

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See also associated correspondence: https://doi.org/10.1016/j.bpsc.2018.09.004.

Received Jun 29, 2018; accepted Sep 18, 2018.

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