

Biomarkers of Face Perception in Autism Spectrum Disorder: Time to Shift to Fast Periodic Visual Stimulation With Electroencephalography?

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Back when I was a postdoctoral researcher in 2001, I collaborated with researchers at the Yale Child Study Center to measure the N170 event-related potential (ERP) evoked by faces and objects in a population of children with autism spectrum disorder (ASD). Based on my previous experience measuring this component with neurotypical observers, we applied a series of simple visual stimulations (e.g., faces vs. objects; upright vs. inverted faces) while participants performed an orthogonal task to ensure that they paid attention to each visual stimulus (1). Despite our promising initial observations, after months of recordings and analysis we concluded in an internal research meeting that there was no evidence of substantial and reliable abnormalities in the amplitude and latency parameters of the N170 of children with ASD. This research was considered as leading to a null result, which was difficult to reconcile with the early evidence obtained by my colleagues at the time that face-selective responses in the fusiform gyrus of children with ASD were reduced. Therefore, the ERP data were never published. A few years later, in 2004, the first report of atypical N170 characteristics in ASD appeared in the literature (2). Given my experience, I have remained skeptical about the validity of these observations.

As Key and Corbett (3) report in the introduction of their article in this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, the positive report from 2004 has been followed by at least 165 publications of (mainly) empirical studies and opinion papers on the N170 response serving as a biomarker of social information processing in ASD, with the majority of these papers having been published in the past 10 years. Despite this flurry of research (with undoubtedly a selection bias for reporting positive results), there is no consistent evidence of abnormal N170 amplitude, latency, or scalp topography in response to face stimuli in ASD, as acknowledged by a recent meta-analysis that was also published in *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (4). Kang *et al.* (4) nevertheless emphasized a small effect size delay in the N170 latency as a possible biomarker of social information processing in ASD and highlighted the need for further research along these lines. For various reasons related to a lack of specificity, objectivity, sensitivity, and reliability of the N170 measurement, my colleagues and I recently criticized this conclusion (5), yet the issue remains contentious.

In this context, Key and Corbett (3) provide further original evidence that the N170 does not fit the definition of a biomarker of social deficits in ASD. Their study is original in its

large sample size and because rather than focusing on a usual comparison between ASD and neurotypical children it relies on the variability of the ASD population to test for correlations between electrophysiological and behavioral measures. Specifically, the authors recorded a larger N170 response to faces and houses in 77 children with ASD 7 to 16 years of age both before and after a social skills intervention. These responses were measured 3 months apart. Contrary to the authors' hypothesis, the N170 amplitude and latency in response to faces were only modestly correlated with behavioral measures of social functioning, including, importantly, caregiver reports and observational measures of naturalistic social interactions. Moreover, the associations were not consistently present across the two assessment time points, and none of the face-evoked N170 parameters were sensitive to the positive behavioral effects of a social skills intervention. In particular, the observations on N170 latency offered no support whatsoever to the view that this index could be used as a biomarker of social information processing in ASD (3). In fact, if anything, behavioral measures were more correlated with the N170 evoked by the house stimuli, although for both these stimuli and for faces, the test-retest reliability of the N170 in the population tested was weak, possibly because of difficulties in extracting unambiguous peak latency values in individual participants.

Key and Corbett (3) take the (absence of) results against the view that social difficulties in ASD may be due (only) to perceptual processes, and recommend the use of other ERP measures, such as a parietal "old/new" response elicited within 250 to 500 ms after stimulus onset, indexing stimulus repetition (6). In their most recent work, they appear to have obtained evidence of face specificity, sensitivity to ASD, and correlation with behavioral measures of social functioning and treatment effects of this electrophysiological index (6). However, standard ERP techniques remain seriously limited in objectively defining components or window of interest in the time domain, and quantification of these responses of interest across individuals (5). Moreover, the low signal-to-noise ratio of the approach often requires relatively long recording times. Hence, alternative options should be seriously considered for developing biomarkers of social functioning in ASD and neuropsychiatric disorders in general.

The rapid periodic presentation of visual stimuli during electroencephalographic (EEG) recording, also known as EEG frequency tagging or steady-state visual evoked potentials [see

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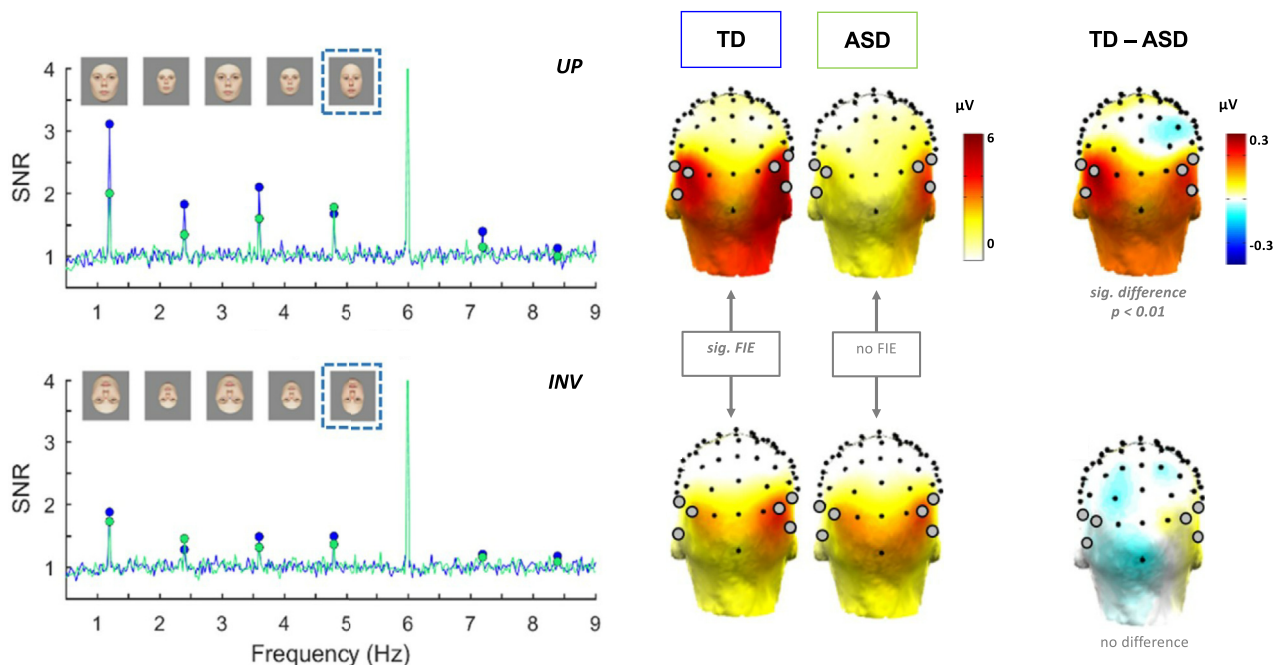


Figure 1. An oddball fast periodic visual stimulation paradigm reveals multiple dissociations in the face individuation response in boys 8 to 12 years of age who either are typically developing (TD) or have autism spectrum disorder (ASD). The FI response at 1.2 Hz and harmonics (2.4 Hz, 3.6 Hz, etc.) for upright (UP) faces is significantly larger in the TD than the ASD group (here expressed in signal-to-noise ratio [SNR] in the electroencephalography frequency spectrum). However, the groups do not differ in their general visual response at 6 Hz or their weaker individuation response to inverted (INV) faces. Moreover, only the TD group shows a significant response decrease with face inversion (face inversion effect [FIE]). Data from the frequency spectra are taken from a bilateral occipitotemporal region of interest shown on the head topographies on the right panel. [Adapted from Vettori *et al.* (9). CC BY license (<http://creativecommons.org/licenses/by/4.0/>).]

Norcia *et al.* (7) for review], may be particularly promising in this context. Compared with standard ERP measures, including stimulus repetition effects as indexed by “mismatch negativity-like” components, this approach affords great advantages in terms of objectivity in identification and quantification of responses in the frequency domain of the EEG spectrum, as well as high sensitivity (i.e., high signal-to-noise ratio) (7). Moreover, different stimuli can be presented concurrently at different stimulation frequency rates, allowing for the monitoring of automatic attentional biases to social stimuli. For instance, there is recent evidence that simultaneously presenting face and house stimuli flickering at different frequencies (6 Hz and 7.5 Hz, counterbalanced across stimulation sequences) while participants engage in an orthogonal task leads to a reduced advantage in the neural response to faces in children with ASD compared with neurotypical children (8).

Most significantly, face stimulus repetition effects have also been obtained within a few minutes of recording with an oddball paradigm, showing large reductions of responses in a group of 23 children with ASD (9). In this latter study, the same unfamiliar facial identity is repeated for about 40 seconds of stimulation at a rapid rate of 6 Hz (i.e., 6 stimuli/s). The face stimulus varies in size at every stimulation cycle, and different face identities appear every 5 stimuli, i.e., at 1.2 Hz. While the 6-Hz response reflecting the general neural response to the visual stimulation does not differ between ASD and neurotypical children, neural responses indexing unfamiliar face

individuation at 1.2 Hz are substantially reduced in individuals with ASD (9) (Figure 1). This difference vanishes when faces are presented upside-down because of the lack of a significant electrophysiological face inversion effect in ASD (Figure 1). Impressively, this result is obtained in less than 4 minutes of EEG recordings, which, given that the bulk of the response focused on a few electrodes over the right occipitotemporal cortex, could be performed after only a brief time of electrode placement. In another recent study relying on the same type of approach, reduced neural responses to rapid fearful expression discrimination have also been found, predicting clinical status with an 83% accuracy at the individual level (10).

Beyond providing original evidence for a selective, high-level impairment in face individuation and facial expression discrimination—and not (merely) in the “raw” neural response to faces as also reflected by the N170 parameters in ASD—the objectivity, high sensitivity, and reliability of this implicit approach for rapid assessment of social functioning with faces may open new perspectives for ASD diagnosis in clinical settings. Admittedly, there is still a long way to go before the promise of this type of index as an early biomarker of the ASD deficit could be fulfilled. In particular, whether they are sensitive to the heterogeneity of social functioning and treatment effects as assessed in Key and Corbett’s study (3) remains, of course, an open question, but there is now hope that it will be addressed in a growing number of studies with an alternative EEG approach in the years to come.

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Article Information

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