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Psychophysiological and Eye-tracking Markers of Speech and Language Processing in Neurodevelopmental Disorders: New Options for Difficult to Test Populations

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Abstract

It can be challenging to accurately assess speech and language processing in preverbal or minimally verbal individuals with neurodevelopmental disabilities (NDD) using standardized behavioral tools. Event-related potential and eye tracking methods offer novel means to objectively document receptive language processing without requiring purposeful behavioral responses. Working around many of the cognitive, motor, or social difficulties in NDDs, these tools allow for minimally invasive, passive assessment of language processing and generate continuous scores that may have utility as biomarkers of individual differences and indicators of treatment effectiveness. Researchers should consider including physiological measures in assessment batteries to allow for more precise capture of language processing in individuals for whom it may not behaviorally apparent.

Keywords

developmental disabilities; ERP; eye tracking; language; minimally verbal; speech

Speech and language processing abilities contribute significantly to the adaptive functioning of persons with neurodevelopmental disorders (NDDs) and are frequent treatment targets. However, behavioral assessments of language processing, especially receptive language – both examiner-directed and parent reports – are often dependent on individuals' ability to produce prompt, reliable overt responses to task instructions (e.g., pointing, answering questions, following directions). Consequently, the resulting scores may confound communication difficulties with limitations in social reciprocity, attention span, or motor function, underestimating speech and language skills at the early developmental stages (e.g., preverbal children) or in individuals with more severe disabilities (e.g., minimally verbal

persons). The associated high incidence of floor effects on behavioral measures may inhibit the detection of developmental or treatment-related changes in persons with NDDs.

To address this limitation, researchers conducting phenotyping and treatment studies of persons with NDDs are increasingly turning to alternative measures of receptive communication that minimize demands on purposeful behavioral responses. Psychophysiological methods, in particular, event-related potentials (ERPs), and tracking of spontaneous eye movements, are gaining popularity due to their wide accessibility, relatively low costs, and high temporal resolution suitable for investigating speech and language processing as it unfolds in real time. In this article, we will review applications of ERP and eye tracking methods to investigate receptive language in non-speaking (i.e., minimally verbal or preverbal) persons with NDDs. These populations are severely understudied due to current measurement limitations and thus are in particular need of novel assessment methods (Tager-Flusberg & Kasari, 2013).

Brain-Based Approaches to Language Processing

Recordings of ongoing brain activity are becoming increasingly common in NDD research due to the minimal behavioral and cognitive demands they place on participants while providing new insights into the neural mechanisms that might underlie clinical symptoms. ERPs reflect changes in ongoing brain activity in response to a stimulus chosen to selectively evoke specific neural processes (e.g., comprehension), thereby facilitating a clinically relevant interpretation of the observed neural responses. Importantly, many auditory ERP paradigms elicit the desired neural processes without requiring the participant to actively engage with the stimuli, provide a behavioral response or even stay awake, making passive listening ERPs feasible from the earliest stages of development and across all levels of adaptive functioning. Differences in the size, timing, and topographic distribution of the ERP responses are interpreted to index various aspects of information processing, from stimulus onset detection to recognition and comprehension, independent of the participants' ability to complete standardized behavioral assessments. Some of the traditional behavioral tests (e.g., Peabody Picture Vocabulary Test) already have been adapted for use with the ERPs (see Connolly & D'Arcy, 2000 for review), with the caveat that greater precision in controlling stimulus features (e.g., intensity, duration, complexity) is required. Extensive history of using ERP paradigms in populations with NDDs has allowed for the establishment of guidelines for optimal data collection procedures (e.g., Webb et al., 2015).

Auditory ERPs are frequently used to help identify potential mechanisms underlying communication difficulties in NDDs. Following the extensive evidence in preverbal infants connecting reduced neural differentiation of speech sounds to later language and cognitive outcomes (e.g., Molfese & Molfese, 1994; Maitre et al., 2013), studies targeting receptive language in minimally verbal individuals examined the ability to discriminate vowels and consonant-vowel syllables. An oddball design, where repeated presentations of one sound (i.e., standard condition) are occasionally interrupted by instances of a contrasting sound (i.e., deviant), offers an opportunity to assess stimulus differentiation during passive listening. If the change in sounds is detected at the cortical level, the less frequent sound is

expected to elicit an ERP response with larger amplitude. The mismatch negativity (MMN) (occurring between 100–300 ms; Näätänen et al., 2014) and the P3a (occurring between 250–400ms; Friedman et al., 2001) reflect preattentive change detection and spontaneous orienting to a novel stimulus, respectively, and can be used in nonspeaking participants.

Analysis of vowel discrimination noted that minimally verbal children with autism (8–12 years) exhibit significant delays in the MMN latency compared to children with autism and less severe language impairment or typical controls (Matsuzaki et al., 2019). The results were interpreted to suggest that the observed communication deficits reflect a maturational delay. In a study using spoken syllable contrasts, Kuhl and colleagues (2005) observed reduced MMN amplitudes in preschoolers with autism and demonstrated that atypical speech sound processing was specific to participants exhibiting reduced behavioral preference for child-directed speech, indicative of broader challenges with social orienting. The same children also scored lower on a parent-reported measure of expressive language.

Beyond vowels and syllables, ERP paradigms can use more complex stimuli such as words or pseudowords to more precisely characterize receptive language processing in NDDs. By examining the difference between neural responses to spoken words and meaningless pseudowords, investigators can tap the early processes that are central to receptive language development, even in very young children with substantial developmental delays. Research in typical infants and children has established that known word recognition is evidenced by more negative ERP response amplitudes compared to pseudowords within 200–500 ms after stimulus onset, particularly at temporal and parietal sites over the left hemisphere, and can be observed as early as 13 months of age (Mills et al., 1997, 2004). Application of such word recognition paradigms to studies of preverbal toddlers with autism (Kuhl et al., 2013; Sandbank et al., 2017), and nonspeaking girls with Rett syndrome (Key et al., 2019), provided valuable insights into receptive language processes in these populations that would not have been gained through behavioral measures alone. For example, girls with Rett syndrome (4–11 years) distinguish known words from nonwords during passive listening, but may rely on atypical right-hemisphere processes to do so (Key et al., 2019). Of note, individual differences in the left-hemisphere ERP responses to words accounted for 30% of variability in receptive language skills. In toddlers with autism, more typical left-lateralized ERP responses to known words compared to novel nonwords were predictive of better receptive language, cognition, and adaptive functioning at preschool and early school age (Kuhl et al., 2013). Using a similar protocol to probe receptive processing in minimally verbal children with autism, Sandbank et al. (2017) demonstrated that the magnitude of the word-nonword discrimination response in the individual participants varied based on the number of stimulus words known by each child. This finding provided further support for the validity of passive listening word-pseudoword ERP paradigms as a measure of receptive vocabulary in persons with NDDs.

Studies interested in evaluating semantic processing more directly frequently employ the N400 response. It manifests across midline central and parietal sites as a larger negative peak for semantically incongruent relative to congruent stimuli around 400 ms after stimulus onset (Kutas & Federmeier, 2011). While the N400 response is most commonly elicited using sentences in which the final word does or does not fit the preceding context, the

feasibility of such paradigms in persons with NDDs would depend on the individual's vocabulary size, working memory capacity, and attention span. Alternatively, the N400 can also be observed for spoken stimuli when the semantic context is established by another word or a picture. The word- or picture-word pair design places fewer demands on working memory and has been successfully used to document lexico-semantic processing in nonspeaking persons with NDDs (e.g., Byrne et al., 1995). Recent studies in minimally verbal children with autism (3–7 years) reported absent N400 responses for the spoken words that did not match the pictures when the data were analyzed at the group level, while at the individual level, 40% of the sample demonstrated the more typical N400 responses (Cantiani et al., 2016). Of note, the early auditory P1 amplitudes for the stimulus words were largely intact. This pattern of findings suggests that minimally verbal children with ASD process the basic acoustic features of speech, but may not integrate the word's semantic content with the immediate context (e.g., pictures). In school-age minimally verbal children with ASD (5–11 years), analysis of the N400 responses provided objective evidence that semantic processing is present but delayed, suggesting less efficient lexical access and reduced information integration compared to typical peers (DiStefano et al., 2019).

In addition to word and sentence comprehension, social-emotional processing of spoken inputs can also be documented using auditory ERPs. Studies examining processing of stimuli with personal significance (e.g., own vs. novel names; words uttered by a familiar vs. unknown voice) provided new insights into the potential effects of specific genetic alterations (e.g., excessive vs. insufficient MeCP2 protein availability) on social-communicative functioning in nonverbal children with MECP2 duplication and in Rett syndrome, respectively (Peters et al., 2015, 2017). In particular, the MECP2 duplication group exhibited typical cortical responses to their own names (evidenced by increased positive amplitudes within 450–750ms) and to familiar voices (increased induced gamma power between 600–800ms). Conversely, in girls with Rett syndrome, larger ERP responses were observed for the recently familiarized stimuli (stranger names presented repeatedly during the test session) as well as for novel voices. Of note, studies in animal models of Rett syndrome also noted increased preference for social novelty (Schaevitz et al., 2010). The lack of ERP enhancement in response to own name was also reported in minimally verbal children and adults with Angelman syndrome (Key & Jones, 2018) despite their capacity for within-session auditory learning (Key et al., 2018). These results highlighted heterogeneity in the extent of self-referential processing among minimally verbal individuals with NDDs who exhibit functional auditory attention. Across these studies, more typical ERP responses to own name were associated with caregiver reports of more adaptive communicative and social functioning.

The reviewed auditory ERP studies demonstrate that passive listening paradigms using a variety of speech stimuli are feasible in minimally verbal children and adults with NDDs and can inform about receptive communication abilities across multiple levels of analysis, from basic perceptual analysis of individual speech sounds to word-level comprehension. In addition to detecting group-level similarities and differences, the auditory ERPs are sensitive to individual differences and associated with concurrent behavioral performance or future developmental outcomes. Thus, auditory ERPs to spoken stimuli can be considered as potential candidate biomarkers, whose utility for characterizing typical, atypical, and

compensatory neural processes, as well as for determining early risk or treatment outcomes, should be examined more closely.

Eye-Gaze Studies of Language Processing

Eye gaze measures offer another opportunity to assess receptive language skills in persons with NDDs. Modern eye trackers require no physical contact with the participant and capture gaze through corneal reflections without the need for head-mounted gear. In the absence of specialized equipment, gaze can be also coded manually from video recordings of participant's eyes.

A robust body of empirical evidence has shown that spoken language implicitly guides children's attention to named aspects of the environment (e.g., objects, actions). Thus, eye movements are a natural human behavior that can provide evidence of language comprehension without requiring any explicit training regarding the child's expected response. Clinicians have long used eye gaze to informally assess basic comprehension in persons with NDD—particularly those who experience challenges pointing, following directions, or providing verbal responses to an examiner's question (responses that are often required in traditional standardized language assessments). For example, a clinician may hold up two objects (e.g., a ball and a shoe) and ask a child to identify one of them (e.g., *Where's the ball?*). The child's gaze to the named object can provide evidence that they comprehend a given word, independent of any pointing, reaching, or verbal response they may also produce.

The looking-while-listening paradigm (Fernald et al., 2008) is a research method that represents this type of informal clinical testing in a controlled, experimental context. In a standard task, two images (e.g., a ball and shoe) are presented on a screen with an auditory cue (e.g., *Where's the ball?*). Unlike behavioral assessments, which usually score items on a 'pass/fail' basis, eye-gaze measures provide graded information about the accuracy and efficiency of language processing. Increased looks to the named image over the course of the trial index comprehension and could be used to estimate vocabulary size. The speed with which gaze is shifted from the distractor toward the named object reflects processing speed. This fine-grained characterization of individual strengths and weaknesses increases the likelihood of capturing subtle differences in receptive language skills that may be overlooked by traditional measures—which, in turn, could lead to more optimal intervention and treatment target selection and serve as sensitive outcome measures in clinical trials.

The looking-while-listening procedure has been used extensively with young children with typical development (Fernald & Hurtado, 2006; Lew-Williams & Fernald, 2007) to capture word comprehension in infants as young as 6 to 9 months of age (Bergelson & Swingley, 2012). The feasibility of the looking-while-listening procedure and similar eye-gaze measures has also been established in clinical populations, including children with language impairment (McMurray et al., 2010), children born pre-term (Marchman et al., 2015), and young children with ASD (Bavin, Kidd, et al., 2016; Goodwin et al., 2012; Venker et al., 2013). Recent studies have shown that eye-gaze measures are feasible for use with children with NDD and may be particularly useful for minimally verbal participants (Plesa-Skwerer

et al., 2016), who are often excluded from research due to the difficulties associated with accurate assessment.

Furthermore, eye-gaze patterns during receptive language processing have been shown to correlate with traditional measures of language ability in children with ASD, which supports the validity of eye-gaze measures for evaluating receptive language (Tovar et al., 2014; Venker et al., 2013). Eye-gaze measures may also reveal emerging comprehension in children with ASD that is not yet apparent in traditional language assessments (Venker et al., 2016), which aligns with findings in typical development (Houston-Price et al., 2007). Similarly, eye-tracking data can be used in high-risk infants to monitor early language development and predict risk of ASD or communication disorders (Chita-Tegmark et al., 2015). Importantly, eye-gaze data are interpretable at the individual level, making them a promising approach for consideration in a clinical setting or treatment trial design.

With their reliance on attention to visual stimuli (e.g., identifying a described image among four options), the traditional format of receptive language assessments lends itself well to adaptations using eye-gaze measures. For example, Brady and colleagues (Brady et al., 2014) adapted the Peabody Picture Vocabulary Test, 4th Edition, a common receptive vocabulary assessment, to an eye-tracking paradigm and evaluated its utility in children with and without ASD. Children in both groups looked significantly more at target images (rather than competitors) when they had also successfully identified those images during traditional pointing-based evaluation. However, children with ASD did not look significantly more at target images for items they had previously gotten incorrect, which supports the potential for eye-gaze measures to distinguish known from unknown words. The field will likely continue to see adaptations of existing receptive language assessments, including those that assess more complex vocabulary (e.g., abstract nouns) and grammatical concepts.

In addition, a variety of novel eye-gaze assessments of receptive language that complement traditional measures are being developed. Beyond nouns, eye-gaze paradigms can be used to assess a variety of other language constructs with associated visual representations, including verbs (Bavin, Kidd, et al., 2016; Venker et al., 2019), adjectives, pronouns, word order, grammatical endings, and social language (Plesa Skwerer et al., 2015). For example, Tovar and colleagues (2014) designed an eye-gaze paradigm to examine comprehension of grammatical morphemes (past tense *-ed* and present tense *-ing*) in four-year-old children with ASD. As a group, the children with ASD demonstrated comprehension of grammatical morphology, and the children who showed better understanding of *-ing* were those with stronger language skills on other measures. Bavin, Prendergast and colleagues (2016) investigated how school-age children with ASD process sentences containing adjectives, nouns, and prepositional phrases (e.g., *Look at the little girl with a flower*) by presenting a more complex visual environment with both related and unrelated competitor images. Although the children with ASD showed slower overall language processing than the children with TD, both groups took advantage of grammatical information to support language processing.

Methodological Considerations

Despite their growing popularity, ERP and eye-gaze methods are not a universal solution to the challenges of receptive language assessment in NDDs. Both require specialized equipment and software, as well as trained personnel. These methods are also vulnerable to data loss due to complications related to participation (e.g., difficulty with EEG sensor placement or attentional focus), excessive motor artifacts, and missing data (e.g., looks away from the stimulus display). However, there are steps to take to help account for these issues and increase the likelihood of collecting robust, reliable, and generalizable results.

Participant cooperation with testing is a major factor in the success of the study and is particularly important for studies in rare NDDs, where the available sample sizes are often small. The novelty of the experience associated with the physical equipment required for ERP (e.g., electrode caps) can be overwhelming. To date, several effective options for maximizing participant comfort and cooperation during data collection have emerged, including desensitization protocols (e.g., exposure to the equipment and testing environment prior to data collection) and behavioral supports (e.g., tangible reinforcements, minimized distractions) (e.g., Roesler et al., 2013; Chorna et al., 2019).

Even passive paradigms without an overt task response require participants to engage in certain behaviors, such as sitting quietly, being still, and/or looking at the stimuli. Active involvement of caregivers who are briefed on the goals and challenges of the measurement process can maximize data acquisition success. Additionally, it is important to ensure that the participants are appropriately informed about the events of the study. For young children and minimally verbal individuals, this can be achieved via visual schedules, picture books describing the procedures, and social narratives (e.g., Venker & Kover, 2015). Maximizing participants' engagement during the visit allows the greatest likelihood of success in deriving valid measures of receptive language (Killing & Bishop, 2008). One of the benefits of ERP and eye-gaze paradigms is that they are often much shorter than a standardized behavioral assessment and therefore align well with participants' physical and mental endurance.

Another issue that requires careful consideration is the number of trials needed to achieve valid results. A common point of criticism for ERP and eye-gaze studies is the rate of data loss, as analyses often include less than 50% of the possible trials. However, it is important to take into account whether the final data set still meets the minimal data quantity requirements for meaningful interpretation. Increasingly, study design recommendations are based on objective evidence from psychometric studies used to identify the optimal number of trials (e.g., Duncan et al., 2009; Nyström et al., 2013). The investigators combine such information with the knowledge about the behavioral and cognitive characteristics of their study population (e.g., ability to sit still, length of attention span) in order to determine the optimal number of trials needed to maximize signal-to-noise ratio and acquire reliable data after accounting for the possible artifacts (e.g., Venker & Kover, 2015).

The approach to data processing is also an important factor to consider. Until recently, most ERP and eye-gaze studies relied on manual data review to derive the desired dependent

measures. While producing informative and often replicated findings, the process was time-consuming and idiosyncratic. The increasing availability of sophisticated computational tools has led many equipment manufacturers as well as individual investigators to seek and develop more automated processing pipelines (e.g., Gabard-Durnam et al., 2018) that could standardize data handling within and across research groups. The evaluation of the effectiveness of such novel approaches is currently ongoing, and data emerging from the studies involving populations with NDDs suggest that completely abandoning manual processing may be premature (e.g., Venker et al., 2020).

Finally, data interpretation in psychophysiological studies is often focused on group differences (e.g., between persons with NDDs and typical controls or between various subgroups within an NDD, etc.). As the field moves toward the use of EPR and eye-gaze data as biomarkers, the need for individually interpretable results is growing. Data from eye-gaze paradigms such as the looking-while-listening procedure are already interpretable at the level of single subjects, and analyses of the ERP data increasingly consider individual differences (e.g., Sandbank et al., 2017). Another issue is related to the extent of interpretation. ERPs and eye-gaze data provide measures of neural functioning, but inform about the underlying anatomic substrate only indirectly (e.g., via source analysis – e.g., Ortiz-Mantilla et al., 2019). Other imaging techniques (e.g., fMRI) are better positioned to obtain the relevant information about the changes in brain structures associated with various NDDs and with functional changes across development or following treatment.

Future Directions

Increasingly creative task designs for assessing speech and language processing in NDDs coupled with modern technology allow ERPs and eye tracking to gradually become more mainstream approaches in both clinical and research settings. Building upon the extensive published ERP and eye tracking findings in typical populations, as well as the growing body of corresponding evidence in NDDs, the next step is to identify the most promising measures and systematically evaluate their psychometric properties (e.g., Farzin et al., 2011) and sensitivity to individual differences and treatment effects.

Technological and methodological advances are continuing to expand the types of information eye-gaze and brain-based methods can provide about receptive language processing. In recent years, pupil size has emerged as an indicator of cognitive load during language (i.e., lexical, syntactic) processing in typical adult populations (Sirois & Brisson, 2014; Tromp et al., 2016). Pupillometry has been used to measure face processing, emotional reactivity, and visual search processes in NDDs, and future research may also reveal it to be a sensitive indicator of subtle language processing differences in these populations. It may also be possible for future work to combine eye-tracking and ERP methods to gather more comprehensive information about language processing (Ledoux et al., 2016), though methodological considerations must continue to be investigated to maximize data quality. Similarly, additional insights about language processing in the brain can be achieved by analyzing electrophysiological data not only as the ERP components but also in frequency domain. Different stages of speech processing and language comprehension rely on different EEG frequency bands, and analyses of functional

connectivity between electrodes (e.g., using coherence or phase locking measures) at rest or during a task performance can inform about the brain networks supporting optimal receptive communication abilities (see Gaudet et al., 2020 for review).

In conclusion, the lack of objective assessments that effectively capture individual differences in speech and language processing of preverbal or minimally verbal persons with NDDs is often cited as the limiting factor in consideration for clinical trials. Measures of brain activity and eye tracking are sensitive to subtle differences in receptive language skills, even when they are not (yet) apparent in performance on the traditional behavioral assessments. Therefore, these novel methods are starting to fill in the measurement gap and pave the way toward direct and individualized assessments of language comprehension in persons with NDDs, which in turn will lead toward new interventions that specifically target communication and language deficits.

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