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Event-related potential index of age-related differences in memory processes in adults with Down syndrome

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Abstract

A major goal of aging research is to identify early markers of age-related cognitive decline. Persons with Down syndrome (DS) experience accelerated aging and high risks for dementia, making them a valuable albeit understudied model for testing such markers. This study examined event-related potential (ERP) indices of visual memory in younger (19–25 years) and older (35–40 years) adults with DS using a passive viewing paradigm that did not require memorization or behavioral responses. ERPs were recorded in response to unfamiliar urban and nature scenes, with some images presented once and others repeated multiple times. Within 600 to 900 milliseconds after stimulus onset, repeated stimuli elicited more positive amplitudes in younger participants, indicating stimulus recognition. ERPs of older adults did not show such increases, suggesting reduced memory functioning. ERP indices were unrelated to participants' intellectual functioning, but did correlate with age and caregiver-reported lethargy/withdrawal behaviors. Passive ERP measures of memory processes are sensitive to early stages of cognitive decline in DS and are promising markers of cognitive risk for future aging studies.

Keywords

Aging; Down syndrome; ERP; Learning; Memory

1. Introduction

Similar to the general population, persons with intellectual disabilities are living longer, including those with Down syndrome (DS), or trisomy 21, the most common known chromosomal cause of intellectual disability. Life expectancy in DS now averages 58 to 60 years, and adults over age 40 or 50 years now comprise the majority of those with DS living in Scotland and Australia (Torr et al., 2010). Unlike others, however, individuals with DS are at a higher risk for age-related declines in cognitive functioning because of their extra copy of the amyloid precursor protein gene (APP) on chromosome 21 (Millan Sanchez et al., 2012). The overexpression of APP leads to an increase in brain deposition of β -amyloid ($A\beta$), with subsequent plaque and tangle development, the neuropathologic signature of Alzheimer's disease (AD) (Hyman et al., 1995; Mann, 1993; Wisniewski et al., 1985). Despite these ubiquitous neural features, not all adults with DS manifest the clinical

symptoms of AD, with 50% showing dementia by age 60 years (for a review, see Zigman and Lott, 2007).

Treatment studies of AD in DS are relatively sparse and have yet to report positive outcomes, underscoring the need echoed in the broader AD field for earlier detection and treatment of mild or subtle cognitive changes, long before the onset of clinical symptoms associated with AD. Because of their lifelong intellectual disabilities, however, it is difficult to determine the earliest signs of age-associated cognitive changes in adults with DS (Nieuwenhuis-Mark, 2009). Changes in memory processes are robust early warning signs of possible dementia in typical adults; but in persons with DS, memory, particularly auditory and verbal memory, is an area of relative phenotypic weakness (Chapman and Hesketh, 2000) that emerges early in development, well before age-related changes in adulthood. Also, many of the standardized memory tasks used to track cognition and to identify dementia in the general population are too demanding for those with DS, resulting in floor-level performances and reduced sensitivity distinguishing age-related effects from existent intellectual disabilities. Alternative methods are thus needed to assess cognitive changes in persons with DS, as well as the impact of these on behavioral and adaptive functioning.

In the typical population, age-related declines in memory or other cognitive functions are associated with changes in brain functioning, and these are typically present before any behavioral evidence of aging effects. Although adapted cognitive and behavioral test batteries for adults with DS are now available (Edgin et al., 2010), these still require significant cooperation and overt behavioral responses from the participants. Furthermore, increasing evidence suggests that cognitive changes associated with later dementia begin many years before the clinical diagnosis, the preclinical period when treatments are likely to be most effective (see Sperling et al., 2011 for review). Therefore, biologically based measures, such as recordings of brain activity, may offer an opportunity to detect shifts in brain functioning that likely occur before the emergence of observable behavioral symptoms or changes in formal test scores. Such brain changes significantly affect cortical and subcortical brain systems. In typical populations, changes in the frontal region include decreased dopamine, noradrenaline, and serotonin, with declines in the volume and function of the prefrontal cortex (Hedden and Gabrieli, 2004). These in turn correlate with age-related declines in episodic memory, working memory, and novelty detection (West, 2001). Aging-related differences were also reported in the prefrontal cortex of individuals with DS (Kesslak et al., 1994; Lögdberg and Brun, 1993), including the earliest evidence of amyloid depositions (Azizeh et al., 2000).

Another aging-related change involves a loss of volume in the entorhinal cortex (a relay between the hippocampus and association cortices), the hippocampus proper (Braak et al., 1993), and parahippocampal regions (Burgmans et al., 2011). The entorhinal cortex is likely involved in the encoding and processing sequences of events, including novelty detection (Crottaz-Herbette et al., 2005), whereas parahippocampal cortex has been implicated in memory for scenes (Hayes et al., 2007). Entorhinal, hippocampal and parahippocampal structural changes have also been found in older adults with DS (Nadel, 2003; Teipel and Hampel, 2006). Therefore, examining brain functioning during tasks targeting memory processes that rely on these structures may be an effective way to identify early markers of aging in DS.

Scalp-recorded event-related potentials (ERPs), a brief temporary change in the ongoing brain activity in a response to a specific stimulus, have been extensively used to examine brain mechanisms supporting cognitive functioning. Because their millisecond-level resolution is comparable to the speed of many cognitive processes, ERPs have been widely used to examine both automatic (e.g., sensory) and controlled (e.g., memory, attention)

stages of information processing (Proverbio and Zani, 2003; Russeler et al., 2005). Waveform shapes and specific peak characteristics change with age, and thus allow the tracking of maturation- and aging-related effects, making ERPs an effective tool for studying typical and atypical development across the lifespan. In addition to the excellent temporal sensitivity, another major advantage of ERPs is their ability to provide information about cognitive functioning even in the absence of overt verbal or motor responses. Together, these characteristics make ERPs especially valuable for persons with limited abilities to comprehend instructions or to provide reliable overt behavioral responses. Thus, we selected ERPs as the primary measure of age-related differences in memory processes in adults with DS.

To our knowledge, only 2 previous ERP studies have examined memory processes in adults with DS. Using an auditory oddball paradigm in which a rare target stimulus appeared among frequent distracters, Blackwood and colleagues (1988) reported a marked delay in the parietal P3 latency to target sounds in adults with DS starting at 37 years of age (see also St. Clair and Blackwood, 1985). In a follow-up longitudinal study, Muir et al. (1988) observed that individuals with DS who experienced clinically meaningful cognitive declines over a 2-year period had delays in P3 latency of three standard deviations or greater than the group mean. Even so, the oddball tasks used in these studies required deliberate attention to the stimuli and involved various memory and motivation processes, thus placing sizeable cognitive demands on adults with DS. Furthermore, auditory stimuli in oddball or other tasks can be problematic, as persons with DS are prone to hearing loss (Esbensen, 2010).

Using event-related fMRI with healthy controls, Jessen et al. (2002) demonstrated that a passive viewing task targeting automatic novelty detection, or discriminating between novel and familiar stimuli, elicited different activation of brain structures typically involved in memory processes. The authors created a visual paradigm in which most of the stimuli (color photographs of complex indoor and outdoor scenes) were presented only once, whereas a small subset of pictures was repeated several times throughout the test session. To ensure attention to the stimuli, participants were asked to respond with a button press every time a distinct probe stimulus was presented. Compared to the images shown only once, the repeated stimuli were associated with reduced activation in the occipital, inferior temporal, and right parietal regions, as well as in the bilateral anterior hippocampus, a structure previously noted for involvement in active novelty detection tasks (Dolan and Fletcher, 1997; Menon et al., 2000).

Increased familiarity resulting from repeated presentations of identical stimuli reflects a basic form of learning and memory (Yonelinas, 2002). Altered responses to this type of learning via repeated stimuli are seen in persons with AD (Fleischman et al., 1999; Olichney et al., 2006) and in adults with memory difficulties (Olichney, 2002; Olichney et al., 2000). Indeed, these measures of learning over repeated trials are robust predictors of conversion to AD in adults with memory problems (Albert et al., 2001). The present study thus used neural responses to passive viewing of repeated trials versus single-presentation items as a particularly promising and effective way to examine memory changes in adults with DS.

ERP studies of stimulus repetition effects in typical populations have used both words and pictures in the context of deliberate memorization and recall, as well as in familiarity and recognition paradigms. Findings consistently demonstrate that differences between repeated (“old,” learned) and single (“new,” not learned) items were reflected mainly in the amplitude of the late waveform components, such as frontal N400 and posterior P600, where repeated stimuli were associated with more positive responses (Curran and Cleary, 2003; Duarte et al., 2004).

The functional significance of these memory indices varies. The frontal N400 effect onsets at 300 to 400 milliseconds poststimulus and reflects general stimulus familiarity with “old” items eliciting smaller, more positive N400 effects (Curran, 2004; Friedman and Johnson, 2000). The parietal P600 effect is present within 400 to 900 milliseconds after stimulus onset and is thought to reflect recall of information, with the “old” items associated with a larger, more positive peak (Nessler et al., 2001; Wilding, 2000). The P600 response can be enhanced by depth of cognitive processing (Rugg et al., 2000) and by the amount of retrieved episodic information (see Friedman and Johnson, 2000, for a review).

The present study examined age-related differences in memory in adults with DS using the repetition detection paradigm. Two groups were examined: younger adults 19 to 25 years old who were functioning at a typical level for DS; and middle-aged adults 35 to 40 years old who were at higher risk for cognitive decline. Using a passive memory paradigm similar to that of Jessen et al. (2002), we examined frontal N400 and posterior P600 ERP indices of memory processes. We hypothesized that, compared to responses elicited by repeated stimuli, “new” stimuli, or images shown only once, would be associated with more negative frontal N400 and less positive posterior P600 responses. Furthermore, we expected that younger versus older participants would demonstrate better memory for the repeated stimuli, as indexed by greater differences in ERP amplitudes to repeated versus new stimuli. Finally, assuming that ERP measures of memory index age-related declines in functioning, we expected to find correlations between participants' ERP measures of memory and their adaptive behavior. Specifically, we expected that ERP indices of familiarity/recognition for repeated stimuli would be related to better everyday adaptive functioning.

2. Method

2.1. Participants

Twenty-two adolescents and adults with DS (11 male and 11 female; mean age = 27.37, standard deviation [SD] = 8.68 years) participated in the study (characteristics listed in Table 1). Two participants were left-handed, the rest were right-handed (mean laterality quotient = 0.75 ± 0.45) as determined by Edinburgh Handedness Inventory (Oldfield, 1971). Two additional participants were excluded from the study because of poor-quality electroencephalographic (EEG) data ($n = 1$) or refusal to cooperate with the EEG procedures ($n = 1$). All participants had normal or corrected-to-normal vision.

IQ was assessed by the Kaufman Brief Intelligence Test–2 (K-BIT–2; Kaufman and Kaufman, 2004), which was individually administered by trained research assistants. The mean total IQ for the sample was 51.32 (SD = 10.31), with comparable performance in verbal versus nonverbal domains, mean = 55.55, SD = 12.44 and mean = 53.09, SD = 10.83, respectively.

Participants comprised 2 age groups. The younger group included 13 participants (8 male and 5 female) 19 to 25 years of age, whereas the older group had 9 individuals (3 male and 6 female) 35 to 40 years of age. The 2 age groups did not differ in intellectual functioning, but caregivers reported higher levels of adaptive behavior skills in the younger versus older age groups (see Table 1).

Parents or guardians of participants provided written informed consent, and all participants provided their assent. The study was conducted with approval from the Institutional Review Board of Vanderbilt University.

2.2. Stimuli

Stimuli included 50 unfamiliar pictures and a drawing of a yellow “smiley face.” The unfamiliar stimuli were 50 color photographs of complex indoor and outdoor scenes, including pictures of objects and animals but excluding pictures of human faces. Ten of the unfamiliar pictures were randomly selected to be repeated 5 times throughout the experiment, yielding a unique set of 50 repeated pictures for each participant. To keep attention focused on the stimuli, a drawing of a yellow smiley face was presented 20 times throughout the session (brain responses to this stimulus were not included in the analysis). The onscreen size of the pictures was 16 cm high and 20 cm wide. From the viewing distance of 90 cm, the stimuli subtended visual angles of 10.16° (h) $\times$ 12.68° (w). The yellow smiley face was 14.5 cm (9.21°) in diameter.

2.3. Electrodes

A high-density array of 128 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net; EGI, Inc, Eugene, OR) was used to record the ERPs. Electrode impedance levels were at or below 40 kOhm as checked before and after testing. During testing data were sampled at 250 Hz with the filters set to 0.1 to 100 Hz. All electrodes were referred to Cz (vertex) and then re-referenced offline during data analysis to an average reference, the recommended reference for high-density electrode arrays (Picton et al., 2000) that has also been used successfully in prior ERP studies of memory (Curran and Cleary, 2003).

2.4. ERP procedure

All stimuli were presented in random order for 1500 milli-seconds with a random interstimulus interval of 1300 to 1600 milliseconds to prevent habituation and development of trial onset expectations. To encourage attention to the stimuli, participants were asked to press a response button when they saw the smiley face. Stimulus presentation was controlled by E-prime (v.2.0; PST, Inc, Pittsburgh, PA). The entire task included 110 trials and lasted approximately 7 minutes. A researcher was present in the room to monitor participants' behavior. If participants became inattentive or restless, stimulus presentation was suspended until they participant were ready to continue with the task.

2.5. Behavioral assessments

2.5.1. IQ—All participants were administered the Kaufman Brief Intelligence Test–2 (K-BIT–2; Kaufman and Kaufman, 2004), which provides verbal, nonverbal, and overall IQ standard scores. This measure was used to assess whether possible age-related differences in ERP performance could instead be attributed to potential IQ differences across age groups. Standardized K-BIT2 scores have a mean of 100 and an SD of 15.

2.5.2. Adaptive functioning—Caregivers of all participants completed the Parent/Caregiver Rating Form of the Vineland Adaptive Behavior Scales–II (VABS-II) (Sparrow et al., 2005). The VABS-II assesses a range of behaviors needed for personal or social self-sufficiency. The standardized scores (mean = 100, SD = 15) for the domains of Communication, Socialization, and Daily Living Skills were selected a priori because they measure constructs that tap areas of functioning most likely to change in the aging process of adults with DS.

2.5.3. Aberrant Behavior Checklist—Community—Caregivers of all participants completed the Aberrant Behavior Checklist—Community (ABC) (Aman and Singh, 1994), a widely used, 58-item survey of problem behaviors in persons with intellectual disabilities. The ABC yields 5 domain scores: irritability, lethargy/withdrawal, stereotypy, hyperactivity, and inappropriate speech.

2.6. Data analysis

2.6.1. Behavioral data—To determine whether participants attended to the stimuli, the accuracy and reaction times of the responses to the smiley face probes were submitted to a 1-way analysis of variance (ANOVA) with age group as the between-subject factor.

2.6.2. ERP data—Collected EEGs were filtered using a 30-Hz low-pass filter. Individual ERPs were derived by segmenting the ongoing EEG on stimulus onset to include a 100-milliseconds prestimulus baseline and a 900-milliseconds post-stimulus interval. The resulting trials were grouped into presented once (“new”) and repeated (“old”) categories. To better characterize the time course of memory development, the repeated trials were further sub-divided into 2 categories including the first and the last 25 repeated trials, hereafter called “old-1” and “old-2”.

All trials contaminated by ocular and movement artifacts were excluded from further analysis using an automated screening algorithm in NetStation followed by a manual review. The automated screening criteria were set as follows: for the eye channels, voltage greater than 140 μ V was interpreted as an eye blink, and voltage greater than 55 μ V was considered to reflect eye movements. Any channel with voltage exceeding 200 μ V was marked as bad. Data for electrodes with poor signal quality within a trial were reconstructed using spherical spline interpolation procedures. If more than 15% of the electrodes within a trial were deemed to be bad, the entire trial was discarded. The retention rates were comparable across conditions and groups (younger participants: new = 19.00 ± 4.82 ; old-1 = 13.07 ± 3.15 ; old-2 = 11.71 ± 1.82 ; Older participants: new = 19.22 ± 7.60 ; old-1 = 13.00 ± 2.40 ; old-2 = 12.33 ± 3.57).

After artifact screening, individual ERPs were averaged, re-referenced to an average reference, and baseline corrected by subtracting the average microvolt value across the 100-millisecond prestimulus interval from the post-stimulus segment. To reduce the number of electrodes in the analysis, data from 128 electrodes were submitted to a spatial principal components analysis (sPCA), an objective and replicable statistical approach that identified a small set of “virtual electrodes” (Fig. 1), each representing a spatially contiguous group of electrodes with similar ERP waveforms (Spencer et al., 1999). Specific electrodes comprising each cluster were identified using the criterion of factor loadings of $|0.6|$ or greater. Only electrode clusters corresponding to the locations previously identified as optimal for the N400 (frontal, central) and posterior P600 responses (parietal, occipital) were used in the statistical analyses.

Next, mean ERP amplitudes were derived for the frontal N400 in the 350- to 500-millisecond window, and for the P600 in the 400- to 600- and 600- to 900-millisecond post-stimulus intervals. Because prior studies identified repetition-related effects mainly for the amplitude of the ERP responses, latency measures were not included in the analyses. The specific time intervals were selected a priori based on temporal windows used in previously published ERP studies of recognition and recall in visual paradigms (Curran, 2004; Duarte et al., 2004). The resulting values were averaged across the electrodes within each of the sPCA-identified clusters (Table 2) and entered into separate repeated-measures ANOVAs with Age group as the between-subject factor and Condition (3: new, old-1, old-2) $\times$ Electrode Cluster (4: frontal, central, occipito-parietal, right parietal) within-subject clusters, with the Huynh-Feldt correction.

3. Results

3.1. Behavioral data

Responses to attention probes (smiley face) revealed that all participants maintained attention to the stimuli during the test session (mean accuracy = 99%, SD = 3%, mean reaction time = 720.54 milliseconds, SD = 289.89 milliseconds). Although no age group differences were found in accuracy rate, older adults responded slower than the younger group (880.09 vs. 590.00 milliseconds, respectively; $F_{1,18} = 6.354, p = 0.021$).

Reaction times to attention probes did not correlate with overall IQ ($r = -0.301, p = 0.210$). However, RTs were instead negatively related to Socialization and Daily Living subscales of VABS-II, where better adaptive functioning in these domains was associated with faster RTs ($r = -0.738, p < 0.001$ and $r = -0.607, p = 0.006$, respectively).

3.2. ERP data

There were no significant age or condition effects for the 350- to 500- and 400- to 600-millisecond temporal windows. The later 600- to 900-millisecond interval was characterized by a Condition $\times$ Age Group interaction ($F_{2,42} = 3.942, p = 0.031$, partial $\eta^2 = 0.158$) (Fig. 2). Follow-up analyses indicated that there were no significant Age group differences in response to any particular stimulus type. However, within-group, pair-wise t tests of new versus old stimulus discrimination indicated that only the younger participants with DS demonstrated a difference in response amplitude to repeated stimuli versus those pre-sented once. Specifically, stimuli in the old-2 category were associated with more positive amplitudes than new items ($t_{13} = 3.506, p = 0.004, d = 0.937$). No such condition differences were detected for the older group.

3.3. ERP connections with cognition and behavior

We limited analyses of brain-behavior connections to the difference scores between P600 amplitudes for new items (presented once) and those in the old-1 or old-2 categories. There were no significant correlations between these ERP variables and probe RT, handedness, K-BIT2 IQ, or adaptive behavior on the VABS-II.

Differences in the ERP amplitudes for the old-2 versus new stimuli correlated negatively with age, such that increasing age was associated with reduced condition differences in P600 amplitude ($r = -0.611, p = 0.003$). The same ERP difference was negatively correlated with the ABC lethargy/withdrawal subscale ($r = -0.497, p = 0.026$), suggesting that greater memory-related differences in ERPs were related to fewer concerns regarding lethargy/withdrawal.

4. Discussion

This study is the first to use brain responses during a passive viewing task to identify age-related differences in memory processes in younger and older adults with DS. By using ERP indices of repetition detection, we avoided potential confounds between memory performance and the lowered intellectual functioning that characterizes this population.

We hypothesized that “new” stimuli (images shown only once) would be associated with a more negative anterior N400 and less positive posterior P600 responses compared to those elicited by the repeated stimuli. Furthermore, we expected that younger participants would demonstrate better memory for the repeated stimuli than older adults, as evidenced by greater difference in ERP amplitudes to repeated versus new stimuli. Results partially supported these hypotheses.

Although there were no condition differences for the frontal N400 response, stimulus repetition effects were evident in the P600 time range, but only in the younger participants with DS. These young adults demonstrated larger mean amplitudes in response to old-2 stimuli compared to the new images, which is thought to reflect recognition of the repeated images. This result was not image specific because a different set of images was used for the repeated condition for each participant. In line with the functional interpretation of the P600 response in typical populations (Rugg et al., 1998), we consider these old–new amplitude differences to reflect memory trace development for the repeated stimuli. Our task was deliberately designed to be passive and nonverbal, and therefore we did not collect any behavioral evidence of explicit recollection of the stimuli. However, our proposed interpretation of the ERP results is supported by findings from prior studies requiring active memorization and recognition/recall, in which old/new ERP differences were absent for old items incorrectly classified as new (i.e., not remembered) or by new items incorrectly judged as old (Wilding and Rugg, 1997).

The lack of the frontal N400 response, thought to reflect stimulus familiarity in typical populations, could be attributed to the absence of an explicit stimulus evaluation component in our study procedures. In previous studies of the anterior N400, participants were asked to actively study a set of stimuli and then identify them as “old” when presented in the mix of new (not studied) items. A frontal old/new ERP effect was observed only for correctly categorized studied stimuli (Wilding and Rugg, 1997) and was larger in the context of greater judgment certainty (Azimian-Faridani and Wilding, 2004). In our experimental design, there was no “study” phase, and participants were instructed only to view the images without an explicit request to memorize them or to detect repetitions. Thus, not having an explicit evaluative component of stimuli is likely responsible for the lack of the old/new distinction in ERP amplitudes in the 350- to 500-millisecond temporal window.

In contrast to the N400, P600 indices of memory varied with age, such that old versus new stimulus differences were observed in younger but not older participants with DS. This finding should not be interpreted as the complete absence of memory for repeated stimuli in the older group. It is possible that the older adults evidenced a delayed response to the stimuli, beyond the 900-millisecond window included in the analysis. However, age differences in ERPs within 600 to 900 milliseconds after repeated versus single stimulus presentations may reflect the earlier evidence of reduced memory functioning, such as the absence of a memory effect (e.g., due to a shift in latency or a complete absence) in the time window where it is detectable in younger participants. As such, the ERP differences identified in the present study are likely to be highly informative as a biomarker of cognitive decline.

Beyond age, greater ERP evidence of repetition recognition (determined by the differences in response to new vs. repeated stimuli in the P600 range) was associated with fewer lethargy/withdrawal concerns on the ABC. Thus, individual differences in ERP responses to repeated versus novel stimuli correlated with caregiver reports of participants' functioning in specific domains that are salient in the DS aging process.

Of note is the absence of correlations between ERP indices of memory and participants' IQ scores. Thus, the passive task and neural measures of stimulus processing successfully evaluated basic memory processes independent of participants' levels of intellectual functioning.

Although it is novel, this study has several limitations. Our sample size was not atypical for an ERP study, yet it was relatively small, especially in the older age range. Also, the younger and older groups were different (albeit not significantly) in the distribution of male

and female participants, even though the number of participants of each sex in the overall sample was equal. Although there were no significant sex effects on ERPs or behavioral measures in this study, future studies will need to consider possible sex differences in the course of aging-related cognitive changes. Also, we did not include a typical comparison group. The goal of this study was to examine whether a passive, nonverbal memory assessment using ERPs could be used to detect age-related differences in cognitive functioning. Persons with DS experience accelerated onset of aging and thus were an optimal sample for the purpose of the study. However, future studies will need to include other populations (with and without intellectual disabilities) to examine the specificity of the reported findings. Finally, our study represented just a single snapshot of memory processes in participants. Future longitudinal studies are needed to test the power of the ERP markers identified in the present study to predict age-related behavioral or cognitive decline. These future studies are particularly important because brain evidence of reduced cognitive functioning is typically present in advance of behavioral symptoms. It will also be important to examine the time course of memory trace development within the task. In the present study, we arbitrarily split the repeated trials in 2 halves, with the old-1 group including the first presentation of the repeated stimuli, which could contribute to the reduced difference in ERPs for the old-1 versus new conditions. Identifying the optimal number of stimulus repetitions would further increase the utility of our paradigm as a biomarker of cognitive functioning.

Despite these several weaknesses, our findings suggest that ERPs are a promising cognitive marker of aging in adults with DS. The noninvasive nature and relatively low cost of the ERPs, as well as the low cognitive demand of the passive task, make our assessment approach particularly well suited for repeated applications over the course of development. Future studies can use these approaches to objectively monitor shifts in neural functioning in adults with DS, which may open new doors to earlier treatments of age-related functional declines in this vulnerable population.

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Fig. 1.
Electrode clusters identified by spatial principal components analysis and used in the statistical analyses.

Fig. 2. Event-related potentials (ERP) waveforms averaged across 4 analyzed electrode clusters for the 3 stimulus conditions recorded in younger (A) and older (B) participants with Down syndrome (DS).

Table 1
Characteristics of study participants

	Age 19–25 y		Age 35–40 y		Total		p Value*
	Mean	SD	Mean	SD	Mean	SD	
Sex (female/male)	13 (5/8)		9 (6/3)		22 (11/11)		0.193
Age (y)	20.37	0.98	37.49	1.13	27.37	8.68	<0.001
Handedness	0.61	0.55	0.95	0.08	0.75	0.45	0.086
KBIT							
IQ	51.15	10.68	51.56	10.37	51.32	10.31	0.931
Verbal	57.38	12.59	52.89	12.44	55.55	12.44	0.418
Nonverbal	53.31	9.38	52.78	13.26	53.09	10.83	0.913
VABS-II							
Communication	69.09	11.33	45.67	17.90	58.55	18.58	0.004
Daily living	66.00	9.15	50.78	12.29	59.48	12.88	0.004
Socialization	76.92	12.28	64.33	10.26	71.52	12.87	0.022
ABC							
Irritability	1.00	2.19	2.00	2.45	1.45	2.31	0.326
Lethargy/withdrawal	0.82	1.25	3.67	3.20	2.10	2.69	0.171
Stereotypy	0.73	1.35	0.89	2.32	0.80	1.79	0.973
Hyperactivity	2.27	3.32	1.22	1.92	1.80	2.76	0.401
Inappropriate speech	0.64	1.12	1.44	2.55	1.00	1.89	0.305

Key: ABC, Aberrant Behavior Checklist; KBIT, Kaufman Brief Intelligence Test; SD, standard deviation; VABS-II, Vineland Adaptive Behavior Scales-II.

* The values in bold are significant.

Table 2
Mean (SD) amplitudes for younger and older participants with Down syndrome, by stimulus condition and electrode cluster

	350–500 ms		400–600 ms		600–900 ms	
	Age 19–25 y	Age 35–40 y	Age 19–25 y	Age 35–40 y	Age 19–25 y	Age 35–40 y
New						
F	–13.83 (7.81)	–8.04 (5.42)	–13.21 (8.08)	–7.40 (5.61)	–7.49 (7.34)	–1.87 (3.68)
C	–6.97 (3.53)	–4.37 (3.88)	–6.69 (3.19)	–4.07 (3.14)	–4.60 (2.37)	–1.47 (1.90)
OP	13.22 (5.99)	9.16 (5.18)	11.86 (5.72)	8.13 (5.21)	5.67 (5.51)	1.85 (4.05)
RP	8.13 (5.73)	6.12 (4.16)	7.95 (5.51)	5.77 (4.44)	4.73 (4.30)	2.18 (2.87)
Old-1						
F	–13.08 (10.04)	–6.51 (3.84)	–11.88 (9.75)	–6.19 (4.01)	–5.43 (9.02)	0.07 (4.58)
C	–6.92 (4.41)	–5.02 (2.99)	–6.71 (4.28)	–4.74 (2.54)	–3.59 (3.76)	–2.39 (1.82)
OP	13.29 (7.52)	9.00 (3.63)	11.57 (7.52)	8.01 (3.49)	4.41 (7.23)	1.27 (3.05)
RP	8.11 (6.20)	4.31 (3.03)	7.90 (6.26)	4.15 (2.99)	5.03 (6.38)	1.04 (3.32)
Old-2						
F	–12.88 (8.70)	–9.36 (4.75)	–11.57 (7.98)	–8.22 (5.12)	–4.02 (6.85)	–2.50 (2.06)
C	–5.25 (3.55)	–3.57 (1.86)	–4.82 (3.14)	–2.89 (1.56)	–2.49 (3.12)	–1.48 (1.70)
OP	12.20 (7.10)	9.86 (4.60)	10.50 (6.30)	8.34 (5.47)	3.62 (5.59)	1.70 (3.30)
RP	8.83 (6.46)	4.75 (4.93)	8.80 (6.22)	4.25 (4.99)	4.94 (4.57)	1.08 (3.17)

Key: F, frontal electrode cluster; C, central electrode cluster; New, stimuli presented once; Old-1, first 25 repetitions of selected stimuli; Old-2, second 25 repetitions of selected stimuli; OP, occipito-parietal electrode cluster; RP, right parietal electrode cluster; SD, standard deviation.