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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.

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 (Aβ), 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

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(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 post-stimulus and reflects general stimulus familiarity with "old" items elicting 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