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Age-related decline in differentiated neural responses to rare target versus frequent standard stimuli

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Abstract

One mechanism hypothesized to contribute to cognitive aging is the failure to recruit specialized neural modules and generate differentiated neural responses to various classes of stimuli. Here, ERPs were used to examine the extent to which target and standard stimulus types were processed differently by well-matched adults ages 19–99. Subjects responded to designated visual target letters under low and high load conditions. Temporospatial PCA was used to parse the P3b component, an index of categorization/memory updating. The P3b amplitude difference between targets and standards decreased substantially as a function of age. Dedifferentiation began in middle age, and continued into old-old age. The reduced differentiation of neural responses was driven by an age-related decline in the size of the P3b to targets and an age-related increase in the P3b to standards. Larger P3b amplitude to standards among older subjects was associated with higher executive capacity and better task performance. In summary, dedifferentiation begins relatively early in adulthood and progresses in a linear fashion throughout the lifespan. The age-related augmentation of the P3b to standards appears to reflect a compensatory mechanism that helps maintain task performance.

Keywords

Cognitive Aging; Dedifferentiation; Compensatory Activity; ERPs; P3b; Temporospatial PCA

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1. Introduction

As individuals grow older, there appears to be a decrease in the specificity of activation of neural modules in response to different kinds of stimuli, such as target vs. non-target letters or numbers, images of faces vs. non-faces, and cued vs. non-cued locations (Curran, Hills, Patterson, & Strauss, 2001; Hahn, Wild-Wall, & Falkenstein, 2011; Kenemans, Smulders, & Kok, 1995; Looren de Jong, Kok, & van Rooy, 1988; Lorenzo-Lopez, Amenedo, Pazo-Alvarez, & Cadaveira, 2007; Park et al., 2012). This age-related loss of neural specialization has been indexed by comparing neural responses to different stimulus types and by measuring changes in the distribution of neural activity recruited to carry out task demands (Cabeza, Anderson, Locantore, & McIntosh, 2002; Lorenzo-Lopez et al., 2007).

Several functional neuroimaging techniques, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and event-related potentials (ERPs) have been leveraged to demonstrate a loss of neural specialization with age. For example, in a recent fMRI study, Park et al. (2012) showed images of faces and houses to adult subjects while measuring activity in two brain regions: the fusiform face area and the extended face network. In young adults, these two brain regions were preferentially activated in response to faces. Relative to young subjects, old subjects exhibited greater activation of the fusiform face area in response to non-faces (houses) and less activation in the extended face network in response to faces. These results suggest that observed reductions in specialization may be the combined result of decreased specificity in some regions and diminished sensitivity in others.

Cabeza et al. (2002) used PET in a verbal source memory task to examine changes in hemispheric asymmetry with age. They compared young adults to old adults who were divided into high- and low-performing groups based on standardized memory test scores. Young adults and low-performing old adults recruited a similar region of the right prefrontal cortex, whereas high-performing old adults exhibited bilateral prefrontal activity. The authors suggest that the recruitment of bilateral frontal areas served as compensatory activity, allowing those subjects to maintain performance more like their younger counterparts. This interpretation supports the compensation hypothesis of cognitive aging, which posits that the recruitment of additional brain regions to carry out the task reflects an advantageous compensatory mechanism to counter a decline in neurophysiologic processing (Cabeza et al., 2002; Cabeza et al., 2004). In contrast, Li and Lindenberger (1999) have argued that the aging process leads to a deterioration in the brain's ability to recruit specialized neural mechanisms to carry out a task, reducing the signal-to-noise ratio in cognitive operations and decreasing processing efficiency. The dedifferentiation hypothesis, as this has been labeled, emphasizes the deleterious nature of these age-related changes.

ERPs, specifically the P3b component, have been used to study age-related changes in the generation of differentiated neural activity. The P3b component is a posteriorly-distributed component peaking between ~400 and 600 ms that reflects the categorization of an event in accordance with task demands, the updating of working memory once an event has been categorized, or the bridge between stimulus evaluation and response selection (Daffner et al., 2011a; Donchin, 1981; Donchin & Coles, 1988; Knight & Scabini, 1998; Kok, 2001;

Verleger, 2008; Verleger, Jaskowski, & Wascher, 2005). In young adults, repetitive standard events elicit minimal or no P3b response. By contrast, young adults produce a robust P3b component in response to rare target events (Dien, 2012; Dien, Spencer, & Donchin, 2004; Spencer, Dien, & Donchin, 1999; Spencer, Dien, & Donchin, 2001). The generation of highly differentiated P3b responses to targets vs. standards in young adults provides the context for examining the extent to which this pattern of processing changes in older adults.

In previous work, we compared P3b responses to letter stimuli under attend and ignore conditions that were based on a non-spatial feature (color) (Alperin et al., 2013). We found that young adults generated a robust P3b in response to designated target letters in the attended but not ignored color, demonstrating a clearly differentiated neural response between conditions. In contrast, older subjects generated a P3b of similar magnitude to target letter forms under both conditions, i.e., no differentiation. Hahn et al. (2011) used the P3b to examine age-associated changes in stimulus processing in attend vs. ignore conditions that were defined by spatial location. They used a spatial attention paradigm that required subjects to respond to designated target letters, but only when they appeared in a cued location. Young subjects generated a much larger P3b to target letters in cued than non-cued locations, indicating a differentiated neural response to stimulus types that were supposed to be attended vs. ignored. Older subjects generated a P3b component with the same amplitude in response to target letter forms in both cued and non-cued locations. Results from these studies suggest an age-related loss of differentiation in P3b responses to stimuli under attend vs. ignore conditions across tasks that manipulate either spatial or non-spatial attention.

Several outstanding issues in research on dedifferentiation remain. First, many ERP studies that have examined age-related dedifferentiation, including our own, compared responses to the same class of stimuli under attend vs. ignore conditions (Alperin et al., 2013; Hahn et al., 2011; Lorenzo-Lopez et al., 2007), but have not investigated responses to different classes of stimuli under an attend condition only. Second, almost all prior reports have limited their investigation to young adults in their 20s and young-old adults in their 60s and 70s (Alperin et al., 2013; Cabeza et al., 2002; Curran et al., 2001; Hahn et al., 2011; Looren de Jong et al., 1988; Lorenzo-Lopez et al., 2007; Vallesi, Stuss, McIntosh, & Picton, 2009), leaving open questions about when in the lifespan dedifferentiation begins and whether it continues to progress in oldold age. Third, most prior studies have not explicitly tried to match different age groups in terms of cognitive capacity or performance on the experimental task (Curran et al., 2001; Hahn et al., 2011; Looren de Jong et al., 1988), making it problematic to interpret whether differences in neural activity between groups were due to age or other factors such as executive capacity, perceived task difficulty, or task performance. Fourth, most previous studies have included tasks with only one level of difficulty (Curran et al., 2001; Hahn et al., 2011; Looren de Jong et al., 1988; Lorenzo-Lopez et al., 2007), which does not provide the opportunity to address the issue of whether an age-related reduction in differentiated neural responses is a function of task demand.

The current study addressed these limitations. The P3b was used to examine age-related differences in the specificity of neural response to two different attended stimulus types, presented sequentially, that varied in task salience: infrequent target letters and frequent

standard letters. To expand the age-range investigated beyond those used in previous studies, Middle-aged (40–60) and Old-Old (80+) participants were included in addition to Young (18–32) and Young-Old (65–79) subjects. Groups were matched in terms of cognitive capacity by inclusion criteria limiting participants to individuals whose neuropsychological test performance was in the top third relative to age-appropriate norms. Level of difficulty was manipulated by incorporating a low demand task (one target stimulus) and a high demand task (multiple target stimuli). In addition, the relationship between neural dedifferentiation and task performance was explicitly addressed.

Almost all studies investigating age-related changes in the P3b analyze their data through the traditional measurement of averaged ERP waveforms (Friedman, Kazmerski, & Fabiani, 1997; Kok, 2000; Polich, 1996). Though valuable, this method of analysis is not well suited for parsing the P3b component from spatially or temporally overlapping neural activity, such as the anterior P3a or the posterior slow wave. To address this issue, it is important to employ techniques that will aid in decomposing averaged waveforms (Alperin, Mott, Rentz, Holcomb, & Daffner, 2014). Here, we used temporospatial principal component analysis (PCA), following a method developed by Dien (2012). PCA is a data-driven method that decomposes an ERP waveform into its underlying components and is particularly useful in separating spatially and/or temporally overlapping components. Therefore, data from PCA is more likely to represent the activity associated with the P3b, and not reflect input from other overlapping components. The P3b factor obtained from the PCA was used to compute what we will label the target minus standard Stimulus Amplitude Difference Value (SADV). This enabled us to statistically assess age-related changes in the differential P3b responses to the two stimulus types.

Analysis of the SADV alone did not allow us to determine whether age-related changes in stimulus differentiation resulted from diminished processing of targets, augmented processing of standards, or both. To address this issue, we also examined age-associated differences in neural responses to targets and standards separately. A decrease in the P3b response to targets among older adults has commonly been reported (Anderer, Pascual-Marqui, Semlitsch, & Saletu, 1998; Fabiani & Friedman, 1995; Fabiani, Friedman, & Cheng, 1998; Li, Gratton, Fabiani, & Knight, 2013; O'Connell et al., 2012; Richardson, Bucks, & Hogan, 2011). Although age-associated differences in P3b responses to standard events have generally not been emphasized in the literature, we have found an increase in P3 responses to standard stimuli with age in cognitively high performing adults (Daffner et al., 2005; Riis et al., 2008).

Based on the existing literature, we predicted that older subjects would produce less differentiated neural responses than their younger counterparts, as measured by a P3b target minus standard SADV. We hypothesized that an age-related decline in differentiated neural responses would become significant by young-old age and would progress through old-old age (Daffner et al., 2011b). The extent to which middle-aged subjects would exhibit differences in processing relative to young subjects was unclear. Although there has been relatively limited study of middle-aged adults, available evidence would suggest that such individuals already demonstrate structural and functional brain changes (Brickman et al., 2006; Gunstad et al., 2006; Park et al., 2012; Pfefferbaum et al., 2000; Riis et al., 2008; Salat

et al., 2004). We anticipated that the reduction in the SADV would reflect both an age-related decrease in the P3b to targets and an increase in the P3b to standards. If this prediction were confirmed, we hypothesized that an augmented P3b response to standards might represent a compensatory response, with increased appropriation of resources helping to maintain task performance. This hypothesis was tested by determining whether a larger P3b to standard stimuli predicted better task performance and higher executive functioning among older individuals. Finally, we anticipated that augmenting task load would lead to less differentiated neural responses between target and standard stimuli, and that this effect would be more pronounced in the older groups.

2. Results

2.1 Participants

A total of 64 subjects were included in the study. See Table 1 for a summary of subject characteristics. The Young (Y) group included 12 subjects between ages 19 and 25. The Middle-aged (M) group included 14 subjects between ages 40 and 60. The Young-Old (YO) group included 15 subjects between ages 67 and 79. The Old-Old (OO) group included 23 subjects between ages 80 and 99. An additional 2 Young, 3 Middle-aged, 3 Young-Old, and 3 Old-Old subjects participated in the experiment but were excluded due to excessively noisy ERP data. The number of subjects in the Old-Old group was larger than the other three groups, which was deemed prudent given the increased noise and variability present in the data of old subjects (Li & Lindenberger, 1999; Li, Lindenberger, & Sikstrom, 2001). Of note, there were no differences across groups in gender, education, estimated intelligence quotient (IQ), Mini-Mental State Examination (MMSE), or executive capacity relative to age-appropriate norms.

2.2 Behavior

Accuracy and mean reaction time (RT) data are presented in Table 2. An ANOVA on accuracy revealed an effect of memory load, $F(1,60) = 28.09$, $p < .001$, but no effect of age group, $F(3,60) = .90$, $p = .45$, or memory load $\times$ age group interaction, $F(3,60) = 1.06$, $p = .37$. Performance was better on the low load task ($M = 96.42\%$, $SD = 5.54\%$) than the high load task ($M = 91.17\%$, $SD = 7.87\%$). An ANOVA of mean RTs revealed an effect of age group, $F(3,60) = 2.91$, $p = .04$, and memory load, $F(1,60) = 256.55$, $p < .001$, but no memory load $\times$ age group interaction, $F(3,60) = .80$, $p = .50$. Young adult subjects generated shorter RTs than the other groups. Subjects responded faster in the low load task ($M = 532$ ms, $SD = 69$ ms) than the high load task ($M = 631$ ms, $SD = 66$ ms). Regression analyses did not suggest a linear relationship between age and accuracy, or between age and RT.

2.3 Averaged Waveforms

Figures 1a and 1b illustrate the grand average waveforms in response to target and standard stimuli for all groups under low and high memory load at midline electrode sites Cz and Pz, respectively.

2.4 Principal Component Analysis (PCA)

The initial temporal PCA yielded 10 temporal factors (TF) which accounted for 94.99% of the variance. The one temporal factor of a priori interest was a positivity peaking at 441 ms (TF2) that accounted for 23.09% of the variance. A spatial PCA was performed on the temporal factor and 12 spatial factors (SF) were retained. Due to its centro-posterior topography, spatial factor 1 (SF1) was consistent with the P3b component. TF2SF1 accounted for 9.04% of the total variance, and 39.15% of the variance within TF2. Figures 2a and 2b depict the topography of TF2SF1 for all age groups in response to target and standard stimulus types, respectively.^{1,2}

2.5 Regression Analyses

2.5.1 TF2SF1 SADV (Targets – Standards)—Both linear and nonlinear regression models were explored. However, because nonlinear models explained no more of the variance than the linear model, the simplest one (based on linear regression) is presented here. There was an inverse linear relationship between age and the size of the SADV under low, $r^2 = .34$, $r = -.58$, $p < .001$, and high, $r^2 = .26$, $r = -.51$, $p < .001$, memory load; the older the subject, the smaller the SADV. Because older subjects had longer RTs than Young subjects, all of these analyses were re-run using RT as a covariate. This did not affect the pattern of results, low load: $r^2 = .31$, $r = -.56$, $p < .001$; high load: $r^2 = .24$, $r = -.49$, $p < .001$. In addition, although groups were matched for executive capacity, it was deemed prudent to re-run these analyses using executive capacity score as a covariate. This also did not affect the pattern of results, low load: $r^2 = .34$, $r = -.58$, $p < .001$; high load: $r^2 = .27$, $r = -.52$, $p < .001$. See Figure 3a for scatter plots illustrating the relationship between age and the SADV.

2.5.2 TF2SF1 to Targets and Standards Separately—Age inversely correlated with the P3b to target stimuli under low, $r^2 = .19$, $r = -.44$, $p < .001$, and high memory load, $r^2 = .10$, $r = -.31$, $p = .01$, such that the older the subject, the smaller the P3b to targets. This relationship survived controlling for either executive capacity score, low load: $r^2 = .19$, $r = -.44$, $p < .001$; high load: $r^2 = .09$, $r = -.30$, $p = .02$, or RT, low load: $r^2 = .18$, $r = -.42$, $p < .001$; high load: $r^2 = .06$, $r = -.25$, $p = .04$. Age was positively correlated with the size of the P3b to standard stimuli under both low, $r^2 = .06$, $r = .25$, $p = .04$, and high, $r^2 = .07$, $r = .26$, $p = .04$, memory load; the older the subject, the larger the P3b to standards.³ This relationship remained significant after controlling for either executive capacity score, low load: $r^2 = .08$, $r = .29$, $p = .02$; high load: $r^2 = .10$, $r = .31$, $p = .01$, or RT, low load: $r^2 = .08$,

¹Additional PCAs were run on each age group separately in order to ensure that group differences were not due to a misallocation of variance related to latency differences in P3b across groups. Each of the four separate PCAs demonstrated a factor consistent with the P3b component. The results of these analyses demonstrated the same overall pattern of age-associated dedifferentiation as was observed for the PCA that included all four age groups. Therefore, the results of these PCAs are not presented here, and the single PCA that incorporated all four age groups is the focus of our manuscript.

²To address whether the difference in the P3b response to targets and standards was driven by their variation in frequency, we ran a PCA that included foil stimuli, which were non-target letters that occurred with the low frequency of targets, in addition to target and standard stimuli. A factor, TF2SF1, consistent with the P3b was identified. An ANOVA demonstrated no difference between the size of the P3b to standards and the P3b to foils, $F(1,60) = .006$, $p = .940$, with no interaction between stimulus type and age group. Across subject groups, the relationship between the P3b to targets and foils was the same as that between targets and standards (Young: targets > foils, $p < .001$; Middle: targets > foils $p < .001$; Young-Old: targets = foils $p = .59$; Old-Old: targets = foils $p = .38$). These results lead us to conclude that it is unlikely that differences in frequency between targets and standards are contributing to our findings.

$r = .29$, $p = .02$; high load: $r^2 = .13$, $r = .36$, $p = .004$. Figure 3b illustrates scatter plots of the relationship between age and the size of the P3b to targets and standards.

To test our hypothesis that the age-related increase in the P3b to standards represented compensatory activity, we examined the relationship between the P3b amplitude to standards and measures of task performance and executive capacity (see section 4.1 for an explanation of executive capacity). The size of the P3b to standards predicted task performance under the high load, accuracy: $r^2 = .07$, $r = .27$, $p = .03$; mean RT: $r^2 = .10$, $r = -.32$, $p = .01$.⁴ These correlations survived controlling for age, accuracy: $r^2 = .08$, $r = .28$, $p = .03$; mean RT: $r^2 = .14$, $r = -.37$, $p = .003$. In addition, the P3b to standards was positively correlated with a composite measure of executive function, low load: $r^2 = .08$, $r = .29$, $p = .02$; high load: $r^2 = .12$, $r = .35$, $p = .004$. This correlation survived controlling for age, low load: $r^2 = .08$, $r = .29$, $p = .03$; high load: $r^2 = .14$, $r = .37$, $p = .004$.

Interestingly, we found a positive correlation between the P3b response to standards and the P3b response to targets, low load: $r^2 = .08$, $r = .29$, $p = .02$; high load: $r^2 = .19$, $r = .44$, $p < .001$. This relationship was still significant after controlling for age, low load: $r^2 = .21$, $r = .46$, $p < .001$; high load: $r^2 = .32$, $r = .57$, $p < .001$. In summary, a larger P3b response to standards predicted a larger P3b response to targets.

Because there was a correlation between the P3b to standards and the P3b to targets, multiple regression analysis was used to explore whether these factors were independently associated with the variance in the age of subjects. Together, the two variables were associated with 36% of the variance in age under the low load, $r^2 = .36$, $F(2,63) = 16.75$, $p < .001$, and 29% under the high load, $r^2 = .29$, $F(2,63) = 12.66$, $p < .001$. Each variable made a reliable independent contribution, with the P3b to targets being slightly more predictive of age, low load: $\beta = -.56$, $p < .001$; high load: $\beta = -.53$, $p < .001$, than the P3b to standards, low load: $\beta = .42$, $p < .001$; high load: $\beta = .49$, $p < .001$.

2.6 ANOVAs

ANOVAs were utilized to determine whether memory load modulated age-related differences in the size of the P3b component. An ANOVA was run on the amplitude values of TF2SF1, the P3b factor, with stimulus type and memory load as the within-subject variables and age group as the between-subject variable. There was no overall effect of age group, $F(3,60) = 1.48$, $p = .23$, an effect of stimulus type, $F(1,60) = 53.49$, $p < .001$, and an effect of memory load, $F(1,60) = 68.81$, $p < .001$. Of particular interest, there was a 2-way

³To further assess the impact of RT on the P3b to standards, a median split was performed on each age group based on reaction time. An ANOVA on mean RTs showed that the fastest half of the Young-Old and Old-Old groups had shorter RTs than the slowest half of the Young and Middle-aged groups, $F(1,26) = 18.62$, $p < .001$. Follow-up comparisons showed that individually, the two younger groups had longer RTs than the two older groups ($Y > YO$ $p = .02$, $Y > OO$ $p = .006$, $M > YO$ $p < .001$, $M > OO$ $p < .001$). An ANOVA was run on the size of the P3b to standards comparing the slowest half of the younger two groups with the fastest half of the older two groups. There was still an effect of age group, $F(1,26) = 3.62$, $p = .02$, such that the P3b to standards increased in size with age ($Y < M$ $p = .07$, $Y < YO$ $p = .02$, $Y < OO$ $p = .008$, $M = YO$ $p = .36$, $M = OO$ $p = .19$, $YO = OO$ $p = .78$).

⁴The relationship between the P3b to standards and the false alarm rate to standards was also examined. False alarms were generally very infrequent, especially under low memory load. For this reason, the high memory load was the focus of these analyses. The false alarm data were not normally distributed (Shapiro-Wilk test of normality $p < .001$), which led to the use of a non-parametric test, Spearman's rho. It was found that the size of the P3b to standards inversely correlated with the total false alarms to standards under the attend and ignore conditions, $\rho = -.30$, $p = .02$. This relationship was re-examined with only the Young-Old and Old-Old subjects, and again an inverse correlation was found, $\rho = -.32$, $p < .05$.

interaction between stimulus type and age group, $F(3,60) = 11.35$, $p < .001$, and between memory load and stimulus type, $F(1,60) = 105.30$, $p < .001$, and a 3-way interaction between memory load, stimulus type, and age group, $F(3,60) = 3.49$, $p = .02$. The stimulus type effect was such that the P3b to targets was larger than the P3b to standards. The load effect was due to the P3b being larger under low load than high load.

The stimulus type $\times$ age group interaction was explained by a stimulus type effect that differed across the four age groups. The Young and Middle-aged groups had a robust effect of stimulus type, such that the P3b to targets was larger than the P3b to standards, Y: $F(1,11) = 85.74$, $p < .001$, $\eta^2 = .89$; M: $F(1,13) = 35.09$, $p < .001$, $\eta^2 = .73$, while the Young-Old and Old-Old groups had no effect of stimulus type, YO: $F(1,14) = .35$, $p = .56$, $\eta^2 = .02$; OO: $F(1,22) = 1.86$, $p = .19$, $\eta^2 = .08$. Note, also, that the magnitude of the stimulus type effect for the Middle-aged group was smaller than for the Young group. This was confirmed by a 2 stimulus type $\times$ 2 memory load $\times$ 2 age group ANOVA on the Young and Middle-aged groups alone, which revealed a stimulus type $\times$ age group interaction, $F(1,24) = 8.93$, $p = .006$. This interaction was present because the two groups did not differ in the size of their P3b response to targets, $F(1,24) = .53$, $p = .47$, but Middle-aged subjects generated a much larger P3b to standards than Young subjects, $F(1,24) = 16.85$, $p < .001$ (Figures 1a and 2b illustrate this point).

The memory load $\times$ stimulus type interaction was present because there was a load effect for targets, $F(1,60) = 113.39$, $p < .001$, such that the P3b was larger under low load than high load, but no load effect for standards, $F(1,60) = 1.01$, $p = .32$. The interaction can also be explained by the magnitude of the effect of stimulus type (targets > standards) being greater under low load, $F(1,60) = 90.99$, $p < .001$, $\eta^2 = .60$, than high load, $F(1,60) = 9.48$, $p = .003$, $\eta^2 = .14$.

The 3-way interaction between memory load, stimulus type, and age group was present because the reduction in the difference in P3b amplitude between targets and standards under the high memory load, as measured by the stimulus type $\times$ memory load interaction, was smaller for the two older groups, Y: $F(1,11) = 37.30$, $p < .001$, $\eta^2 = .77$; M: $F(1,13) = 91.32$, $p < .001$, $\eta^2 = .88$; YO: $F(1,14) = 6.04$, $p = .03$, $\eta^2 = .30$; OO: $F(1,22) = 26.29$, $p < .001$, $\eta^2 = .54$.

3. Discussion

The goal of the current study was to examine the extent to which individuals across the adult lifespan process targets and standards in a stimulus-type specific manner. By definition, there are fundamental differences between target and standard stimulus types. The early processing of both classes of stimuli is likely to be similar and include operations involved in stimulus registration, selection, and identification (Dien et al., 2004). However, in optimal neural systems like those found in healthy young adults, one would expect the later processing of targets and standards, as indexed by the P3b, to diverge.

In contrast to the class of frequent standard stimuli, rare target stimuli are salient and most critical to the assigned goal of a task. As Petersen and Posner (2012) have argued, the

moment of target detection seems to involve a capturing of awareness that triggers interference throughout the brain, preventing immediate detection of another target. They suggest that this state may represent focal attention acting as the entryway to the "global work space frequently associated with consciousness" (p. 76). The description of this process dovetails with several hypotheses about the P3b component as an index of the transfer of pertinent information to consciousness (Picton, 1992), or the rapid neural inhibition of on-going activity to facilitate transmission of stimulus/task information (Polich, 2007). The P3b is often linked to the categorization process itself (Daffner et al., 2011a; Knight & Scabini, 1998; Kok, 2001) or to operations associated with the updating of working memory and revision of expectations for stimuli that are categorized as task relevant (Dien et al., 2004; Donchin & Coles, 1988). The need for context updating is theoretically much greater after categorizing a rare target than a frequent standard stimulus.

As expected, young adults produced highly differentiated P3b responses to targets and standards. Analysis of the target minus standard SADV showed that aging is associated with reduced differentiation of neural responses to targets and standards. Changes in the pattern of neural activity across groups cannot simply be attributed to group differences in executive capacity or accuracy on the experimental task, which were well-matched, but are more likely linked to the aging process itself (Daffner et al., 2011a; Riis et al., 2008; Schneider-Garces et al., 2009). This is supported by the fact that controlling for executive capacity score did not impact the relationships between the P3b and age.

We attempted to match behavior by asking the older two groups to respond to four target letters in the high load task while asking the younger two groups to respond to five target letters. Although this approach succeeded in matching groups for task accuracy, the older subjects still had longer RTs. There is evidence to suggest that the P3b component mainly indexes stimulus evaluation (Kutas, McCarthy, & Donchin, 1977; McCarthy & Donchin, 1981), or perhaps the transition to response selection (Verleger et al., 2005), but not response execution itself. Motor programming and output is slowed in aging (Kolev, Falkenstein, & Yordanova, 2006; Roggeveen, Prime, & Ward, 2007). Reducing the number of target letters in the high load task for the older two groups may not have been sufficient to compensate for delayed motor execution in older adults. Because of this group difference it was important to assess whether variance in RT could account for some of the age-related differences observed for the P3b. It seems unlikely that group differences in RT can explain group differences in the P3b because controlling for RT did not affect the correlations between the P3b and age. In addition, using a median split to compare the slowest old to the fastest young subjects did not impact the pattern of results.

Regression analyses suggested that the age-related decline in differentiation is linear in nature, beginning by middle-age and progressing into old-old age. These results add to the literature indicating that age-associated changes in indices of cerebral function may be present by middle age (Brickman et al., 2006; Gunstad et al., 2006; Park et al., 2012; Pfefferbaum et al., 2000; Riis et al., 2008; Salat et al., 2004) and continue into old-old age (Daffner et al., 2011b; Kemps & Newson, 2006; Lindenberger & Baltes, 1997; Singer, Lindenberger, & Baltes, 2003; Singer, Verhaeghen, Ghisletta, Lindenberger, & Baltes, 2003).

Assessing the effects of age on the P3b to targets and standards separately allowed us to investigate the extent to which changes in the P3b to each stimulus type may have contributed to the decrease in a differentiated response. The age-associated decline of the SADV was driven by both an age-related reduction in the size of the P3b to targets and an age-related increase in the size of the P3b to standards, with a larger contribution coming from the former process. In addition, there was evidence that dedifferentiation had already begun in the Middle-aged group, as the difference between the two stimulus types was smaller for the Middle-aged group than for the Young group. This finding was driven by an increased P3b to standard stimuli among Middle-aged subjects.

The age-related reduction in the P3b to targets is in agreement with many reports in the literature (Anderer et al., 1998; Fabiani & Friedman, 1995; Fabiani et al., 1998; Li et al., 2013; O'Connell et al., 2012; Richardson et al., 2011) and may reflect attenuation of the categorization process or the ability to update working memory after a target has been detected (Daffner et al., 2011a; Donchin, 1981; Donchin & Coles, 1988; Knight & Scabini, 1998; Kok, 2001). Prior work has indicated that cognitive operations like sustaining attention on a task may compete for a shared pool of limited resources with the categorization/updating process (Daffner et al., 2011a). At lower levels of task demand, older adults may need to divert resources to these other operations, leaving fewer resources for the categorization/updating process, which is indexed by a reduced P3b amplitude.

It is not clear whether the age-related increase in the P3b to standards reflects a detrimental or compensatory response. At a minimum, the processing strategy used by old adults is less optimal and less efficient than that used by young adults. One possibility is that the increase in the P3b to standards represents an impairment in decision making or categorization/context updating processes, as standards are being treated more like targets. This would be an inefficient way to utilize resources and would be consistent with the view of dedifferentiation as being a detrimental process (Li & Lindenberger, 1999). Alternatively, the augmentation of the P3b to standards could represent a compensatory response, with the increased allocation of resources allowing older subjects to perform better on the task, perhaps by increasing resource appropriation for categorization or context updating (Donchin, 1981; Donchin & Coles, 1988; Knight & Scabini, 1998; Kok, 2001), or by strengthening the bridge between stimulus evaluation and response selection (Verleger, 2008; Verleger, 2010; Verleger et al., 2005). This would be consistent with the compensatory hypothesis of dedifferentiation (Cabeza, 2002; Cabeza et al., 2004).

Similar to other investigators (Cabeza, 2002; Riis et al., 2008), we addressed the question of maladaptive response vs. compensatory mechanism by examining its relationship to task performance and executive functioning. If the increase in P3b to standards represents a detrimental response, we would expect that older adults who perform worse would generate a larger P3b response to standards. In contrast, if it reflects a compensatory process, we would anticipate that older adults who perform the best will demonstrate the largest P3b response to standards. For example, in Cabeza's study (2002), recruitment of bilateral frontal activity by old adults is less efficient than the recruitment of only one hemisphere by young adults, but is still considered compensatory because it is associated with better performance than observed in older adults who do not recruit both hemispheres.

There is evidence from the current study that the augmentation in the P3b to standard stimuli may represent a compensatory mechanism that aided in the successful completion of the task, which would support the compensation hypothesis (Cabeza et al., 2002). A larger P3b to standards correlated with increased accuracy, reduced RT, and higher executive capacity. Correlation analyses also suggested that a larger P3b to standards was associated with fewer false alarms to standards. However, the correlations with behavior were only significant under the high load. This may be due to the low load task being easy enough to result in limited variance in performance across subjects. Future work incorporating a larger number of subjects with more varied levels of executive capacity and task performance would help to either support or refute the correlations with behavior. The correlations that were observed are particularly noteworthy because the subject pool for this study only included individuals whose composite neuropsychological scores were in the top third, as defined by age-matched norms, which likely limited the variance in behavioral measures. The results are suggestive that the enlarged P3b to standards may support task performance, rather than detract from it.

An increased P3b to standards implies that older subjects are allocating more resources than their younger counterparts to the cognitive operations indexed by this component. This implies that in order to correctly refrain from responding to standards, they have to appropriate more resources towards categorization, context updating, or the delivery of stimulus information to select responses. Increased allocation of these resources (as indexed by a larger P3b amplitude to standards) was associated with fewer false alarms. Addressing why older subjects need these extra cognitive resources to be as accurate as younger subjects is beyond the scope of the current paper, but may be related to impairments in early stimulus processing and/or the delivery of degraded information for late selection and stimulus categorization (Alperin et al., 2013).

Notably, if the P3b to standards does represent a compensatory mechanism, it still did not prevent older subjects from having longer RTs in the high load task than the Young group. This finding does not necessarily contradict the idea of compensation, as alternative ways to process stimuli may scaffold task accuracy, but be less efficient and therefore lead to longer RTs. In fact, a larger P3b to standards was associated with shorter RTs, suggesting that it may represent compensatory activity. RT reflects the speed of both stimulus evaluation and motor execution, and many studies have shown age-related impairments in and slowing of motor function (Kolev et al., 2006; Roggeveen et al., 2007). Therefore it is possible that while the enlarged P3b to standards compensates for other impaired processes, it cannot completely make up for RT slowing caused by motor impairments.

It is important to note that although the age-related changes in the P3b to targets and standards are moving in opposite directions, the P3b component itself presumably indexes the same underlying cognitive operations regardless of stimulus type. One way to make sense of this paradox is to frame the issue in terms of resource availability and processing demands. For example, our lab and others have suggested that when task demands increase, subjects may initially generate a larger P3b response to target stimuli, but as the demands increase further, the size of the P3b may diminish (Daffner et al., 2011a). Older subjects allocate more resources at lower levels of demand and deplete their resources earlier as the

demands increase. We have suggested that the decision-making/updating operations indexed by the P3b depend on the same limited resources as those linked to sustaining attention (as indexed by the posterior slow wave) (Daffner et al., 2011a). Tasks that are more difficult for subjects require greater sustained attention, which seems to siphon resources from operations indexed by the P3b. We suspect that older adults may be at a point along the resource availability/task demand curve that is associated with a reduction in the size of the P3b to target stimuli. However, because the resource demands for standards remain lower than for targets, they still have sufficient resources to generate a larger P3b response to standard stimuli than their younger counterparts, who can process standards using fewer resources. Based on this perspective, we would predict that as task demands become increasingly difficult, young adult subjects may exhibit an increase in the size of the P3b to standards and old subjects may demonstrate a decline in the size of their P3b to standards, a hypothesis that could be tested experimentally.

The production of a larger P3b to standards was also associated with the generation of a larger P3b response to targets. We suspect that this relationship is a reflection of the internal consistency in the amount of resources a person appropriates to carry out the operations indexed by the P3b component. Individuals who allocate more resources to the processing of standards also appear to allocate more resources to targets than subjects who overall appropriate fewer resources for P3b processes. Notably, multiple linear regression suggests that both the P3b to targets and the P3b to standards predict age independently of each other.

In accordance with our prediction, increasing task load resulted in greater dedifferentiation across all age groups, as indexed by a reduced difference between the P3b to targets vs. standards. The reduction in the differentiated P3b response under the high load appears to be driven by the decrease in amplitude of the P3b to targets, since there was no load effect on the P3b to standards. Contrary to our expectation, the magnitude of the load effect on dedifferentiation was smaller among older subjects. This finding may be due to the fact that compared to their younger counterparts, older subjects already generated a smaller P3b to targets under low load, limiting the possible extent of further reduction under the high load task.

The current investigation was designed to match different age groups in terms of high executive capacity. This approach strengthens the argument that the observed differences between groups were due to the aging process and not differences in executive capacity. It also reduced the likelihood that subjects in our Old-Old group were suffering from early dementia or mild cognitive impairment, which would have confounded normal with diseased cognitive aging. Future studies should incorporate subjects with average executive capacity and a wider range of task performance, while being careful to exclude individuals with evidence of mild cognitive impairment or other neurological disease. This approach will improve the generalizability of our findings and allow us to more directly address whether the age-related differences observed in the current study, such as the augmentation of the P3b to standards, are best understood as reflecting a compensatory or detrimental process. If compensatory, one would expect that older adults with high executive capacity would generate a larger P3b response to standards than their lower executive capacity counterparts (Cabeza et al., 2002; Riis et al., 2008).

Further investigations should explore potential relationships between earlier cognitive operations and P3b differentiation. It would also be useful to gather longitudinal data, rather than cross-sectional, in order to track the progression of dedifferentiation in an individual over time and determine its relationship to changes in behavioral performance (Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012). Finally, it would be helpful to include participants in their 30s, as this age group was not represented in the current study. Including these ages would help to verify the early age of onset and linear nature of the progression of neural dedifferentiation.

4. Methods

4.1 Participants

Recruitment of subjects took place through community announcements in the Boston metropolitan area, including the Harvard Cooperative Study on Aging. All subjects underwent informed consent approved by the Partners Human Research Committee and a detailed screening evaluation that included a structured interview to obtain a medical, neurological, and psychiatric history; a formal neurological examination; a neuropsychological test battery; and questionnaires surveying mood, activity, and socioeconomic status.

To be included in this study, participants had to be between the ages of 18 and 32 (Young), 40 and 60 (Middle-aged), 65 and 79 (Young-Old), or 80 and older (Old-Old), be English-speaking, have ≥ 12 years of education, have an MMSE (Folstein, Folstein, & McHugh, 1975) score ≥ 26, and an estimated IQ on the American Modification of the National Adult Reading Test (AMNART) (Ryan & Paolo, 1992) ≥ 100. Subjects were excluded if they had a history of CNS diseases or major psychiatric disorders based on DSM-IV criteria (American Psychiatric Association, 1994), focal abnormalities on neurological examination consistent with a CNS lesion, a history of clinically significant medical or audiological diseases, corrected visual acuity worse than 20/40 (as tested using a Snellen wall chart), a Beck Depression Inventory (Beck & Steer, 1987) score ≥ 10 (for Young and Middle-aged subjects) or a Geriatric Depression Scale (Yesavage et al., 1982) score ≥ 10 (for Young-Old and Old-Old subjects), or were unable to distinguish between the colors red and blue. Subjects were paid for their time.

A special effort was made to minimize group differences in cognitive abilities and task performance in order to appropriately interpret age-related changes in neural activity. Otherwise, observed differences between groups could be due not to age, but to other factors (Alperin et al., 2013; Daffner et al., 2011b; Daselaar & Cabeza, 2005; Riis et al., 2008). Because there is strong evidence that selective attention reflects top-down control mechanisms (de Fockert, Rees, Frith, & Lavie, 2001; Gazzaley et al., 2008; Rissman, Gazzaley, & D'Esposito, 2009; Zanto, Rubens, Thangavel, & Gazzaley, 2011), age groups were matched in terms of executive capacity. Although there is no universally accepted operational definition of executive functions, we adopted the position of many investigators who emphasize processes that include working memory, initiation, monitoring, and inhibition, and advocate the use of at least several neuropsychological tests to assess this complex group of functions (Chan, Shum, Touloupoulou, & Chen, 2008; Delis, Kaplan, &

Kramer, 2001; Spreen & Strauss, 1998). We selected tests that had well established norms across a wide range of ages. Tests of executive functions included: 1) Digit Span Backward subtest of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (Wechsler, 2008), which measures maintenance and manipulation operations of working memory; 2) Controlled Oral Word Association Test (COWAT) (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996), which indexes initiation, self-generation, and monitoring; 3) WAIS-IV Letter-Number Sequencing, which assesses maintenance, monitoring, and manipulation; 4) WAIS-IV Digit-Symbol Coding, which assesses sustained attention/persistence, cognitive speed, and efficiency; 5) Trail-Making Test Parts A and B (Reitan & Wolfson, 1985), which measures planning/sequencing, set shifting, and inhibition.

Performance across these tests was averaged to create a composite score of executive capacity, which was used to match the four age groups. Consistent with suggestions in the literature on aging, the groups were matched according to percentile scores relative to ageappropriate norms rather than raw scores (Daffner et al., 2007; Daffner et al., 2006; Daselaar & Cabeza, 2005; Riis et al., 2008). Our previous work (Daffner et al., 2006; Riis et al., 2008) indicates that age-related changes in information processing, as measured by ERPs, differ between individuals with high and average executive capacity, suggesting that these groups need to be analyzed separately. For the current study, our focus was on adults with high executive capacity, whose composite neuropsychological score was in the top third (67th percentile) as defined by age-matched norms.

4.2 Experimental Procedure

The experiment consisted of a visual oddball task in which subjects were shown a series of letters presented in either the color red or the color blue, and were asked to respond by button press to infrequent target letters. In the low load task, subjects were required to respond to one specific target letter. In the high load task, subjects were required to respond by button press to four (for Young-Old and Old-Old) or five (for Young and Middle-aged) specific target letters. Task demands were made easier for old subjects in order to minimize group differences in performance. In this way, differences in neural activity were more likely to be due to differences in age and not performance. The number of target letters chosen for each age group was based on pilot data. Subjects were instructed to pay attention to letters appearing in the designated color while ignoring letters appearing in the other color, and to respond by button press to target letters appearing in the designated color only. Subjects were asked to respond as quickly and as accurately as possible to target letters. Practice trials preceded each set of experimental trials. The hand used for the target response was counterbalanced across subjects, as was the attended color.

Each task included 800 stimulus trials divided into 8 blocks. Stimuli appeared one at a time within a fixation box that subtended a visual angle of $\sim 3.5^\circ \times 3.5^\circ$ and remained at the center of a high-resolution computer monitor at all times. Visual stimuli subtended an angle of 2.5° along their longest dimension and were presented for 250 ms. Half of the stimuli appeared in the color red and half in the color blue, in randomized order. Target stimuli (7.5% in attend color; 7.5% in ignore color) were designated upper case letters. Non-target upper case letters accounted for 70% of the stimuli presented. Non-target letters included

frequent standard stimuli (55% overall; 27.5% in each color) and infrequent “foils” (15% overall, 7.5% in each color). Foils were a category of non-target letters which were presented as infrequently as target letters. Fillers accounted for the remainder of the stimuli presented. The inter-stimulus interval (ISI) varied randomly between 815–1015 ms (mean ~915 ms) (see Figure 4). For analytic purposes, trials were further categorized in terms of whether the stimuli presented were in the attend or the ignore color. The attend condition consisted of all stimuli in the designated color; the ignore condition consisted of all stimuli in the non-designated color. Of note, the current study only examined the P3 activity in response to target and standard stimuli presented under the attend condition (see Alperin et al., 2013 for results comparing the attend vs. ignore condition).

4.3 ERP Recordings

An Active Two electrode cap (Behavioral Brain Sciences Center, Birmingham, UK) was used to hold to the scalp a full array of 128 Ag-AgCl BioSemi (Amsterdam, The Netherlands) “active” electrodes whose locations were based on a pre-configured montage. Electrodes were arranged in equidistant concentric circles from the 10–20 position Cz. In addition to the 128 electrodes on the scalp, 6 mini bio-potential electrodes were placed over the left and right mastoid, beneath each eye, and next to the outer canthi of the eyes to check for eye blinks and vertical and horizontal eye movements. EEG activity was digitized at a sampling rate of 512 Hz.

4.4 Data Analysis

Demographic variables and overall percentile performance on the neuropsychological tests for the four groups were compared using ANOVAs. We measured mean RT and accuracy rates. A response was considered a hit if it occurred 200–1000 ms after stimulus presentation. Target Hits were defined as target stimuli correctly responded to, while False Alarms were defined as stimuli incorrectly identified as targets. Accuracy was calculated as Percent Target Hits – Percent False Alarms.

EEG data were analyzed using ERPLAB (Lopez-Calderon & Luck, 2014; www.erpinfo.org/erplab) and EEGLAB (Delorme & Makeig, 2004; <http://sccn.ucsd.edu/eeglab>) toolboxes that operate within the MATLAB framework. Raw EEG data were resampled to 256 Hz and referenced off-line to the algebraic average of the right and left mastoids. EEG signals were filtered using an IIR filter with a bandwidth of .03–40 Hz (12 dB/octave roll-off). Eye artifacts were removed through an independent component analysis. Individual bad channels were corrected with the EEGLAB interpolation function. EEG epochs for the two stimulus types (target and standard) across two attention conditions (attend and ignore) were averaged separately. The sampling epoch for each trial lasted for 1200 ms, including a 200 ms pre-stimulus period that was used to baseline correct the ERP epochs. Trials were discarded from the analyses if they contained baseline drift or movement artifacts greater than 90 μ V. Only trials with correct responses were included in the analyses.

4.4.1 Temporospatial Principal Component Analysis (PCA)—Temporospatial PCA takes advantage of PCA's ability to parse components both temporally and spatially by breaking down each temporal principal component into a series of spatially distinct

components (Dien, 2012). Here, a temporospatial PCA (temporal PCA followed by a spatial PCA) was conducted on all subjects' individual ERP averages at all 134 electrode sites, following the recommendation of Dien (2012). ERPs from all four age groups to target and standard stimuli under the attend and ignore conditions for both low and high load were included in the analysis. Utilizing the ERP PCA toolkit 2.39 (Dien, 2010), a Promax rotation was used and a covariance matrix and Kaiser normalization were applied to the data (Alperin et al., 2014). Each dataset consisted of 307 time points between –200 and 1000 ms. The number of factors generated for each PCA was restricted using a parallel test. In accordance with the literature, a factor consistent with the P3b was identified based on visual inspection of its timing, voltage, and topography (see section 3.3) (Dien, Spencer, & Donchin, 2003; Goldstein, Spencer, & Donchin, 2002; Spencer et al., 1999; Spencer et al., 2001). The Stimulus Amplitude Difference Value (SADV) was computed by subtracting the factor amplitude values in response to standards from those in response to targets. Amplitude values were submitted to statistical analysis using regression and ANOVA.

4.4.2 Statistical Analysis—Regression analyses were run to determine the relationship between the size of the target – standard SADV and age. Regression analyses were also run to test hypotheses about the relationships between the P3b factor in response to standards and age, task performance, and neuropsychological test scores. Families of multiple comparisons were accounted for using the Holm-Bonferroni method. To determine whether level of task difficulty modulated these relationships, the size of the P3b factor was analyzed using ANOVA, with memory load and stimulus type as the within-subject variables and age group as the between-subject variable. Behavioral performance across groups under low and high memory loads was compared using ANOVA, with memory load as the within-subject variable and age group as the between-subject variable. The Greenhouse-Geisser correction was applied for all ANOVAs with greater than 1 degree of freedom.

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- Age-related reduction in the degree of differentiated neural responses was examined
- PCA used to measure P3b to targets vs. standards in adults ages 19–99
- Linear decrease with age in P3b amplitude difference between targets and standards
- Dedifferentiation driven by decreased P3b to targets and increased P3b to standards
- Larger P3b to standards linked to better task performance and executive function

Figure 1.

Grand average ERP waveforms for each age group in response to targets and standards under both memory loads at midline electrode sites **a)** Cz and **b)** Pz. Note that the scale differs between targets and standards.

Figure 2. Scalp topographies of PCA factor TF2SF1 (P3b) for each age group under both memory loads in response to **a)** targets and **b)** standards. Note that the scales differ for targets and standards. Also, for targets, the scales differ between high and low memory load.

Figure 3.

Scatter plots showing the relationships between **a**) age and the SADV under both memory loads and **b**) age and the size of TF2SF1 (P3b) to targets and standards, collapsed across memory load. Note that the scales differ between scatterplots.

Figure 4.
Illustration of an experimental run.

Table 1

Subject Characteristics (Mean (SD))

	Young	Middle	Young-Old	Old-Old
Number of Subjects	12	14	15	23
Gender (female:male)	7:5	8:6	9:6	16:7
Age	22.58 (1.73)	50.64 (6.89)	73.93 (3.67)	84.83 (4.55)
Years of Education	15.88 (1.65)	17.14 (2.03)	16.47 (3.72)	16.09 (3.10)
AMNART (Estimated IQ)	119.08 (4.83)	123.50 (5.50)	121.13 (8.53)	122.55 (7.20)
Executive Capacity (%ile)	80.33 (8.44)	82.76 (7.06)	81.50 (7.54)	80.31 (14.96)
MMSE	29.92 (.29)	29.64 (.63)	29.53 (.74)	29.13 (1.29)

Table 2

Accuracy and Mean RT (Mean (SD))

	Young	Middle	Young-Old	Old-Old
Accuracy (%)				
Low Load	96.88 (5.96)	98.74 (1.74)	96.96 (2.63)	94.45 (7.50)
High Load	91.73 (7.32)	90.21 (6.55)	93.09 (4.97)	90.20 (10.25)
Mean RT (ms)				
Low Load	487 (38)	566 (81)	528 (63)	539 (67)
High Load	592 (40)	647 (78)	631 (59)	642 (70)