EFFECTS OF DISTRACTER NOVELTY ON ATTENTIONAL ORIENTING IN HEALTHY AGING AND PARKINSON'S DISEASE: AN EVENT-RELATED POTENTIAL (ERP) STUDY

By

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Novel events are preferentially processed in the brain in order to facilitate adaptive responses to a dynamic, changing world. However, much is still unknown about the mechanisms that give rise to attentional orienting toward novel events in the brain. Healthy aging and Parkinson's disease (PD) have been previously associated with deficits in novelty processing, which is mediated by neural networks that give rise to preferential processing for novel distracters. In order to better characterize the nature of these attentional mechanisms, two event-related potential (ERP) experiments were conducted in young adults, older adults, and PD patients. The experiments manipulated the novelty characteristics of task-irrelevant distracters that were presented in the context of a three-stimulus oddball task. This task allowed for the examination of both distracter- and target-related processing as a function of distracter novelty. As expected, novel distracters differentially engaged the visual attention system in ways that were not seen for non-novel distracters. However, older adults and PD patients showed impairments in their attentional orienting responses toward novel stimuli. These deficits in distracter processing were associated with a number of other cognitive and emotional symptoms, and further gave rise to impairments in target-related processing. Notably, older adults and PD

patients exhibited weaker processing of attentional targets and a frontal shift in their ERP reflections of target processing, which is consistent with a frontally-mediated deficit in memory updating for the targets. Taken together, the results of these experiments provide strong evidence that novel events receive preferential neural processing in ways that are influenced by the stimulus features that characterize the event, as well as the functional integrity of specialized attentional orienting networks in the brain. Older adults and PD patients appear to be less engaged with new information, yet more susceptible to the interfering effects of novel distracters. These findings help to clarify the ways in which stimulus characteristics affect attentional orienting to unexpected events, along with the impacts that healthy aging and PD have on this process.

CHAPTER 1
GENERAL INTRODUCTION AND METHODS

General Introduction

Flexible allocation of attention is a vital cognitive process that facilitates adaptation to changing environmental demands. Novel events can serve as either potential sources of engagement, irrelevant distracters that are ignored, or obstacles that block the achievement of one's goals. Adaptive responding to novel events is necessary to successfully navigate through unexpected cognitive and emotional challenges. Unfortunately, life is wrought with factors that can interfere with our ability to efficiently process novelty. Healthy aging brings about neurophysiological changes that are associated with compromised cognitive processing. Alterations in the dopaminergic systems in healthy aging may be responsible in part for some of the executive functioning deficits that preferentially impact frontal lobe functioning and complex attentional processing in old age (Raz, 2000; Woodruff-Pak, 1997). As a result, it has been suggested that neurodegenerative diseases like Parkinson's disease (PD) may provide a useful clinical model for understanding some of the cognitive deficits of healthy aging, primarily because the dopamine deficits that characterize PD may disrupt frontal-striatal circuitry in ways that are similar to age-related frontal dysfunction (Cabeza, 2001). Declines in attentional processing have been observed in healthy aging (McDowd & Shaw, 2000) and PD (Poliakoff et al., 2003), yet the nature of these attentional impairments is not always consistent (Kingstone et al., 2002). In PD, emotional symptoms frequently accompany cognitive and motor deficits, and there is suggestion that some of these problems are associated with impairments in novelty processing. Because of these reasons, PD provides a unique clinical opportunity to examine the relationships between novelty processing, executive functioning, emotional dysfunction, and the underlying neuropathology within this clinical condition.

The overall goals of this dissertation research are to better understand how novelty is processed in the brain, and how healthy aging and PD affect the ability to respond appropriately to novel events. Specifically, I will address three research questions:

1. At what point(s) during attentional processing do novel events receive preferential engagement?
2. How does healthy aging and/or Parkinson's disease impact the preferential processing of novelty?
3. How is novelty processing related to other forms of cognitive and emotional functioning in young adults, healthy aging, and Parkinson's disease?

In order to address my first research question, it is necessary to utilize a tool that is able to index neural activity with rapid (millisecond) fidelity in a non-invasive manner. Of current psychophysiological methodologies, one of the best approaches for characterizing rapid changes of this sort is to measure scalp-based event-related potentials (ERPs). Not surprisingly, there is a rich history of ERP research on the topic of novelty processing. After a review of ERPs and how they can be used to study attentional processing of novelty, I will discuss specific impairments that have been observed in the way that older adults and PD patients process novel events. This chapter will then conclude with an overview of the general methods used in the two experiments that follow.

Scalp-Recorded Event-Related Potentials (ERPs)

Over the last forty years, advances in electrophysiology have enabled new kinds of questions to be addressed about the neural systems and processes that underlie many forms of cognition. The electroencephalogram (EEG) is the record of the volume-conducted electrical activity of the brain measured by scalp electrodes (Davidson, Jackson, & Larson, 2000). Electrical activity recorded from the EEG can be averaged in association with the presentation of specific events of interest. Initially, the event-related response associated with the presentation

of a stimulus is embedded in the ongoing EEG activity. Extracting an ERP waveform associated with a specific stimulus is accomplished by averaging multiple samples of the EEG that are time-locked to repeated occurrences of the stimulus (Fabiani, Gratton, & Coles, 2000). Assuming that the underlying brain activity remains constant during the same conditions of an experiment, there is a benefit of averaging in that the ERPs should remain somewhat consistent from trial to trial, while the ongoing background EEG is random and is averaged out of the resulting waveform (Otten & Rugg, 2005).

ERPs are highly sensitive to changes in neural activity on the level of milliseconds (ms), making them the "gold standard" among noninvasive imaging methods in terms of temporal resolution (Fabiani et al., 2000). ERP waveforms usually consist of discrete voltage deflections that can either be positive- or negative-going. Specific "components" of ERP waveforms are usually named in accordance with their polarity (positive or negative) and peak latency (in ms). A common example is "P300," which refers to an ERP component with a positive peak that has latency of approximately 300 ms post-stimulus onset. Since the P300 is typically the third positive peak after a stimulus, this component is also frequently called the "P3," particularly when specific subcomponents of this potential are examined.

Novelty Processing and the P300

The P300 was first described over four decades ago (Sutton, Braren, Zubin, & John, 1965), and it has become one of the most highly studied components in the ERP literature. Various experimental paradigms elicit the P300, including simple paradigms when a participant responds to a single target stimulus (Figure 1-1A). A traditional two-stimulus "oddball" task presents an infrequent target in the background of a more frequent "standard" stimulus (Figure 1-1B). A larger P300 is evoked by the infrequent target compared to the standard background stimulus. Additionally, P300 amplitude varies systematically with the proportion of infrequent events (e.g.,

Duncan-Johnson & Donchin, 1977). These two-stimulus oddball findings are frequently taken to suggest that subjective probability (i.e., expectancy) controls the amplitude of the P300 (Fabiani et al., 2000).

Three-stimulus oddball tasks present an infrequent target in the background of a frequently occurring standard stimulus and an infrequently occurring distracter stimulus (Figure 1-1C). In these three-stimulus oddball paradigms, two subcomponents of the P300 are typically seen. The P3a is evoked most prominently by infrequent, task-irrelevant distracter stimuli when the stimulus discrimination between target and standard stimuli is difficult (Polich & Comerchero, 2003). In these paradigms, distracter stimuli are contextually novel, meaning that they are not expected given the parameters (i.e., attentional goals) of the task, and participants are typically instructed to not respond to them. The stimulus features of the distracters may either be novel (i.e., unfamiliar stimuli that are unique for each trial) or non-novel (i.e., repeating across trials). The P3a has often been interpreted as reflecting an orienting reflex toward unexpected events (Simons & Perlstein, 1997), which is believed to be a fundamental biological mechanism that influences exploratory behavior and is critical for survival and evolution (Sokolov, 1963). The P3a component reflects attentional orienting toward distracters with a frontocentral maximum amplitude distribution, while a different component called the P3b is typically evoked most prominently by task-relevant target stimuli, with a more posterior parietal distribution (Snyder & Hillyard, 1976; Squires, Squires, & Hillyard, 1975).

By manipulating the nature of stimulus features of distracters in three-stimulus oddball tasks, some researchers have concluded that distracter stimuli that are more novel and complex elicit a P3a component with a greater frontal distribution compared to distracters that are simple and repeating (Cycowicz & Friedman, 2004). However, others have compared novel and non-

novel distracter effects and concluded that the resulting P3a components are virtually indistinguishable from each other (Simons, Graham, Miles, & Chen, 2001; Simons & Perlstein, 1997). However, it is important to note that experiment-specific variables (e.g., task difficulty, perceptual distinctiveness of stimuli, etc.) play a large role in dictating P3 responses during oddball tasks (e.g., Comerchero & Polich, 1998), making some cross-study comparisons difficult. In order to best integrate findings from different researchers and methodologies in this paper, P3 responses will generally be identified as "distracter-related" or "target-related," rather than P3a or P3b.

Novelty Processing and the N2

For several decades, the N2 has been commonly observed in association with the P3 component. This N2 response (sometimes called N2b) typically has frontocentral distribution and occurs prior to a P3 response to a distracter (J. R. Folstein & Van Petten, 2008). Early three-stimulus oddball studies found that the N2 is impacted by the complexity of novel stimuli, such that simple novel distracters elicited a smaller N2 response than those that are more complex (Courchesne, Hillyard, & Galambos, 1975). More recent studies often overlook the effects of novelty on N2 amplitude, in favor of focusing exclusively on P3 responses. For example, when examining the difference between novel and non-novel distracters, Polich and Comerchero (2003) did not discuss any impact on the N2 component. However, analysis of the figures from this study suggests that the N2 was enhanced by distracter novelty features to a greater degree than the P3 component, which showed nearly identical amplitudes from novel and non-novel distracters.

One study found interesting effects on N2 responses by utilizing different variants of the three-stimulus oddball paradigm that manipulated the degree of stimulus complexity in the targets, distracters, and standard stimuli (Daffner, Mesulam, Scinto, Calvo et al., 2000). These

results included two key findings regarding the nature of N2 responses to novelty. First, simple distracters elicited larger N2 amplitudes when presented in the context of contrasting stimulus features – complex targets and standard stimuli – relative to targets and standards that were also simple. Furthermore, unusual distracters evoked larger N2s than simple, familiar distracters. These findings suggest that the N2 novelty effect can arise for two different reasons: 1) deviation from a predominant stimulus category, and 2) novel stimulus features (i.e., departures from long-term familiarity; see J. R. Folstein & Van Petten, 2008). In a recent extension of this paradigm, Chong and colleagues (2008) examined the effect of characterizing novel designs as task-relevant items to explore, rather than task-irrelevant distracters to ignore. They found that the N2 processed the novel stimuli equally regardless of their task relevancy, suggesting that the N2 reflects a more automatic detection of unfamiliar novel stimuli that is not modulated by top-down influences. Conversely, the P3 and late slow waves evoked by novel stimuli were larger when viewed as a task-relevant exploration, suggesting that these later stages of processing involve more a voluntary allocation of processing resources to novel events.

Novelty Processing and Early Sensory Potentials

The visual P1 (80-130 ms) is generated by extrastriate visual cortex and reflects early sensory processing (Clark & Hillyard, 1996). The visual N1 (140-200 ms) arises from multiple neural generators in secondary visual cortex and downstream association cortices in the temporal and parietal lobes (Di Russo, Martinez, Sereno, Pitzalis, & Hillyard, 2002). Spatial attention leads to amplification of these two early sensory potentials, yet attentional selection based on nonspatial features such as color and shape is not associated with changes in the P1 or N1. Instead, this form of feature selection is associated with a large negative potential over the occipital lobe called the "selection negativity" (SN) that begins 140-180 ms after stimulus onset and is believed to be generated by the dorsal occipital cortex and posterior fusiform gyrus

(Hillyard & Anllo-Vento, 1998). An interesting combination of spatial and feature detection is reflected in a later, more frontally-distributed P2 response (180-300 ms), which is modulated by both spatial attention as well as feature detection such as color processing (O'Donnell, Swearer, Smith, Hokama, & McCarley, 1997). Since oddball paradigms often manipulate stimulus features based on color or shape, the SN and P2 effects may become relevant for interpreting results about novelty effects. Because of their exogenous nature, however, P1, N1, SN, and P2 responses are rarely reported in studies employing novelty oddball tasks. Nevertheless, there is evidence that certain kinds of novel distracters elicit enhancements of P2 amplitudes, even in the context of brain injury or healthy aging (Czigler & Balazs, 2005; R. T. Knight, 1997). The effects of novelty on these early potentials are likely to vary across studies in accordance with specific stimulus features that have been selected for experimental novelty manipulations.

A Neuroanatomical Model of Attentional Orienting

Early investigation of hippocampal activity using depth electrodes suggested that the P300 is partly generated by structures of the medial temporal lobe (Halgren et al., 1980). Patients with lesions to the frontal lobe or hippocampal region have shown disruptions in P3 potentials to distracter stimuli (Daffner, Mesulam, Scinto, Acar et al., 2000; R. Knight, 1996; R. T. Knight, 1984), suggesting that engagement of both frontal and hippocampal regions is necessary for the mechanisms of attentional processing that give rise to a distracter-related P3 potential. Intracranial electrophysiological recordings in epilepsy patients have shown that P3-like ERP responses to novel distracters are amplified in the regions of the inferior frontal sulcus, anterior cingulate cortex (ACC), temporoparietal and inferior temporal cortex, and the posterior hippocampus (Baudena, Halgren, Heit, & Clarke, 1995; Halgren, Baudena, Clarke, Heit, Liegeois et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic et al., 1995). Interestingly, it has also been proposed that the frontal activity that gives rise to distracter-related P3 is mediated

by dopaminergic activity, while the target-related P3 is believed to be mediated by norepinephrine activity in the parietal lobe (Polich & Criado, 2006). The neural generators of novelty N2 effects are largely unclear, as few informative studies have sought to explicitly examine the neural substrate underlying this component (J. R. Folstein & Van Petten, 2008).

Building on the data available from research in humans and animals, Corbetta and Shulman (2002) have proposed that visual attention is mediated by two partially segregated networks in the brain – one system includes parietal and superior frontal cortex and is engaged in top-down selection for stimuli and responses, and another bottom-up system activated by distracters, which includes tempoparietal and inferior frontal cortex. According to this model, the bottom-up system is specialized for the detection of behaviorally relevant stimuli (particularly when they are unexpected) and can interrupt the functioning of the top-down system in order to direct attention toward salient events.

This model has been partially supported by a recent fMRI study which found that both target and distracters engaged a common ventrolateral frontoparietal network, while distracters alone activated a dorsolateral frontoparietal network (Bledowski, Prvulovic, Goebel, Zanella, & Linden, 2004). Similar evidence was obtained from a bi-field visual selective attention task, which found that novel stimuli engaged activity in a broad network of brain regions, including the superior and middle frontal gyrus, temporal-parietal junction, superior parietal lobe, cingulate cortex, hippocampus, and fusiform gyrus (Yamaguchi, Hale, D'Esposito, & Knight, 2004). Interestingly, prefrontal and hippocampal regions were activated regardless of whether these stimuli were presented in the attended hemifield, and these regions were the only ones that showed habituation over repeated exposures to the novel stimuli. These imaging findings converge on the clinical data to suggest that prefrontal and hippocampal regions are critically

involved in attentional orienting and carry out an automatic process of detection and habituation to unexpected distracters, which can occur in the absence of controlled attention, and possibly even disrupt top-down cognitive processes that were in place prior to the encounter with the distracter.

Summary and Implications of Novelty Processing

With their excellent temporal resolution, ERPs are well suited for examining rapid changes in brain function that accompany attentional processing of novelty. Novelty has been shown to enhance distracter-related N2 and P3 responses; however, this novelty can arise from two different types of settings. When stimuli are perceived as unfamiliar, they are judged to be novel as a result of their deviation from a long-term context. Novel distracters of this sort elicit larger P3 and N2 amplitudes, presumably reflecting a common attentional orienting reflex that is driven by a bottom-up visual processing system. This system relies in part on long-term memory stores in the brain to maintain a sense of familiarity that can be used as a backdrop on which to evaluate new events that are encountered. One critical question that is not completely resolved in the literature is how much unfamiliarity is necessary to maximize the attentional orienting network(s) in the brain.

In addition, distracter-related N2 and P3 components can also respond to deviations from a short-term experimental context (i.e., mismatch of expectations), even in the absence of long-term familiarity violations. This has not been explored as much in the literature, but has tremendous relevancy for individuals who fail to show normal levels of preferential processing of novel information. Most studies have found that older adults have difficulty engaging in attentional orienting, and patients with frontal lobe deficits typically show even greater impairments. For the benefit of these patients, it is important to understand these alterations in attentional processing and determine if anything can be done to improve them. If left unchecked,

these deficits could have many real-world implications for these individuals, including a host of negative cognitive and/or emotional problems. Additionally, knowledge gained from studying individuals with novelty processing deficits may spark new insights about neural mechanisms of visual attention and various types of executive function. With these considerations in mind, it is important to appreciate the previous research that has investigated novelty processing in healthy aging and Parkinson's disease, which will be the focus of the remainder of this paper.

ERP Studies of Novelty in Healthy Aging

ERP studies examining the performance of healthy older adults in oddball paradigms have found a consistent increase in P3 latency to both target and distracter stimuli in all modalities and across both two- and three-stimulus oddball tasks (Anderer, Semlitsch, & Saletu, 1996; Fabiani & Friedman, 1995; Fjell & Walhovd, 2001; Friedman, Simpson, & Hamberger, 1993; Polich, 1996). These increases in P3 latency are likely to be reflective of age-related slowing of memory updating processes that are required to correctly identify and respond to task-relevant targets (Polich, 1996). Numerous studies have also found that the P3 amplitudes elicited by target and distracter stimuli decrease with age (Anderer et al., 1996; Fabiani & Friedman, 1995; Kok, 2000), which are believed to reflect alterations in the degree to which attentional resources are allocated to stimuli (Fjell & Walhovd, 2001).

Older adults show a posterior-to-anterior shift in target-related P3 responses with age, which leads to a more evenly distributed scalp topography for this component (Friedman, Kazmerski, & Fabiani, 1997). Fabiani, Friedman, and Cheng (1998) found that older adults exhibited individual differences in the distribution of target P3 responses in an auditory oddball task. While younger adults showed a posterior-maximal scalp topography for the target stimuli, some older adults had a frontal-maximal P3 scalp distribution for the targets. These older adults who showed frontal P3 scalp distributions for targets performed more poorly on tests of

executive functioning such as the Wisconsin Card Sorting Test and Verbal Fluency relative to older adults who showed posterior-maximal scalp topographies. These findings suggest that changes in P3 scalp topography may be reflective of underlying frontal lobe dysfunction in healthy aging. More specifically, it has been suggested that older adults have more difficulty creating categorical templates of their attentional targets in working memory, which contributes to these ERP differences in target-related P3 potentials (Fabiani & Friedman, 1995; Friedman, Kazmerski, & Cycowicz, 1998).

The shift to a more frontally oriented topography has also been seen for distracter-related P3 responses, which also appears to be associated with an age-related increase in the false-alarm rate, suggesting a decline in frontal lobe activity with increasing age (Friedman et al., 1993). Fjell and Walhovd (2004) recently conducted a visual three-stimulus oddball study to further explore the effects of age on P3 potentials. They found that the distracter-related P3 amplitudes were more susceptible to age-related declines than target-related P3. The most pronounced impairments in distracter-related P3 potentials were seen in central and posterior electrode sites, with less pronounced changes seen in frontal sites. Furthermore, they found that the age-related changes in P3 to distracters were linear in nature, suggesting a gradual and steady decline across the adult lifespan. Interestingly, Czigler and Balazs (2005) also found age-related reductions in N2 amplitudes to novel events, while P2 novelty enhancements were still present in old adults. Taken together, these findings suggest that the attentional orienting reflex toward novel stimuli declines with age, while earlier stages of feature discrimination remain intact.

Recently, a new line of research has called into question some of the conclusions that were previously given to account for age-related changes in P3 to target and distracter stimuli. Daffner and colleagues (2005) have argued that previous research in this area has not properly

controlled for differences in the level of cognitive status between age groups. When testing cognitively high-performing old, middle-aged, and young adults, they found no age-related differences in P3 latency or amplitude but instead observed a larger, more frontally distributed P3 in old adults. When compared to younger adults, the older adults in this study exhibited larger P3 amplitudes for novel, target, and standard stimuli. These findings suggest that higher functioning older adults may employ increased resources and more effortful frontal activity in order to enhance their attentional processing. However, this phenomenon was non-specific in this study, and does not appear to be associated with changes in the attentional processing that were specific to targets or novel events. Importantly, these effects need to be qualified with the fact that the oddball task used in this study is systematically different than most other oddball paradigms in the literature, as participants make responses to all stimuli and thereby have different task demands placed on them. Nonetheless, these initial findings have been replicated (Daffner et al., 2006), and suggest that old adults who are cognitively high functioning exhibit preserved (and possibly even increased) preferential processing for novel events.

ERP Studies of Novelty in Parkinson's Disease

ERP studies in Parkinson's disease have found that PD patients with dementia show prolonged P3 latencies, while PD patients without dementia show P3 latencies within the normal range (Ebmeier et al., 1992; Goodin & Aminoff, 1987; Graham, Yiannikas, Gordon, Coyle, & Morris, 1990). However, prolonged P3 latencies have also been reported in PD patients without dementia, and these latencies are correlated with patient age and stage of the disease (Stanzione et al., 1998), along with age of symptom onset (Wang, Kuroiwa, & Kamitani, 1999). Although most studies employing the oddball paradigm have found normal P3 responses in non-demented PD patients, target-related P3 latency has been reported to be correlated with general cognitive functioning in PD patients (Bodis-Wollner et al., 1995; O'Donnell, Squires, Martz, Chen, &

Phay, 1987). Target-related P3 latency and amplitude have both been shown to correlate with multiple neuropsychological measures, including tests of attention, visuoconstructional skills, verbal fluency, memory, and executive function (Chen, Lin, Liu, Tai, & Lai, 2006). Target-related P3 amplitude has also been shown to correlate with severity of gait disturbance (Wang et al., 1999). In auditory three-stimulus oddball tasks, deficits in both distracter- and target-related P3 responses have been observed in PD patients (Lagopoulos et al., 1998), leading the authors to conclude that PD is associated with impairments in both automatic orienting and controlled attentional processing.

Only one study has examined the ERP reflections of novel distracter processing in PD. Using a three-stimulus auditory oddball task, Tsuchiya, Yamaguchi, and Kobayashi (2000) found that PD patients exhibited impaired P3 responses to both targets and novel distracters. Distracter-related P3 amplitude was diminished over frontal scalp sites and correlated with poorer performance on a modified version of the Wisconsin Card Sorting Test. This finding suggests that novelty processing deficits in PD may be related to executive functioning deficits that are typically elevated in this population (Dubois & Pillon, 1997). Importantly, executive dysfunction in PD has been associated with emotional symptoms, including depression (Costa, Peppe, Carlesimo, Pasqualetti, & Caltagirone, 2006) and apathy (Isella et al., 2002). Tsuchiya and colleagues (2000) did not measure emotional symptoms in their sample of PD patients, which is problematic since depression, anxiety, and apathy are often elevated in this group (Isella et al., 2002; McDonald, Richard, & DeLong, 2003; Walsh & Bennett, 2001). This omission is also unfortunate because apathy has been significantly associated with reduced P3 amplitudes to novel distracters in other neurological populations, including Alzheimer's disease (Daffner et al., 2001), cortical stroke (Daffner, Mesulam, Scinto, Acar et al., 2000; R. T. Knight, 1984), and

subcortical stroke (Yamagata, Yamaguchi, & Kobayashi, 2004). Furthermore, some researchers have found that anxiety symptoms increase in PD patients when they experience the "off" state of dopaminergic therapy (Menza, Sage, Marshall, Cody, & Duvoisin, 1990; Siemers, Shekhar, Quaid, & Dickson, 1993), while others have reported no relationship between anxiety and motor symptoms in PD (Stein, Heuser, Juncos, & Uhde, 1990). Since distracter-related P3 potentials may be mediated by dopamine (Polich & Criado, 2006), it is possible that these ERP responses may also be associated with anxiety and motor symptoms in PD. However, the relationship between distracter-related P3 potentials, anxiety, and motor symptoms not been previously studied in prior research in PD.

Summary and Rationale for the Current Project

Despite extensive research efforts over the past few decades, a number of issues are still unclear as to how novel events receive preferential processing in the brain. At the heart of these issues is the unavoidable problem that novel distracter processing is highly influenced by experiment-specific task demands. Therefore, it can be difficult to reconcile divergent findings from different researchers using different stimuli and/or task parameters. It can also be difficult to draw conclusions about the implications of novelty processing when relatively few researchers adequately examine relationships between ERP reflections of novelty processing and broader levels of cognitive functioning.

Comparisons across the lifespan have offered many insights into the neural mechanisms of novelty processing and how these are associated with aging. Older adults generally exhibit declines in distracter-related processing (N2 and P3) which are suggestive of impaired attentional orienting. Additionally, the categorization of task-relevant information is also altered in older adults, such that target-related P3 responses become more frontally-distributed in a way that is consistent with frontal lobe decline requiring greater compensatory activations. However,

individual differences appear to affect these general findings, such that cognitively high functioning older adults may show different patterns of distracter- and target-processing. Importantly, no studies to date have explicitly examined the role of distracter novelty on these aging effects. As a result, it is not clear if age-related deficits in attentional orienting and target-related processing interact with stimulus novelty, which may have important implications for the way in which these deficits are understood.

Studies of Parkinson's disease patients also have much to offer to our understanding of novelty processing. PD patients have been shown to be impaired in both attentional orienting to distracters and task-relevant processing of targets. Importantly, novel distracters fail to receive preferential processing in PD patients relative to age-matched controls, and these deficits are correlated with executive functioning symptoms. However, the nature of novelty processing deficits in PD has not been studied extensively, and no relationships with emotional symptoms have been explored in this group.

With these considerations in mind, this dissertation research will address three different aims and test the following hypotheses:

1) Specific Aim 1: Examine the effects of novelty on distracter processing and examine the neural timecourse of preferential engagement with novel events.

    - Hypothesis 1: Distracters will be associated with preferential engagement that is greater and begins earlier in the visual processing stream when distracters are novel and highly salient.

2) Specific Aim 2: Examine the impact that healthy aging and Parkinson's disease have on novelty processing.

    - Hypothesis 2: Healthy aging will be associated with intact early preferential processing of novelty (i.e., SN and P2) but impairments in attentional orienting (i.e,. N2 and P3).

    - Hypothesis 3: Relative to age-matched controls, Parkinson's disease patients will show reductions in the preferential processing of novel distracters (i.e., N2 and P3).

3) Specific Aim 3: Explore the relationships between novelty processing and other domains of function.

- Hypothesis 4: Participants from all groups will show relationships between measures of executive functioning and distracter-related processing. In addition, patterns of novelty processing in PD patients will be associated with motor and emotional symptoms.

General Methods

ERP Stimuli and Task

Stimuli and procedures for the three-stimulus oddball task were modified from Polich and Comerchero (2003). A total of 600 stimuli were randomly presented against a black background, 70% of which were standard stimuli, 15% of which were targets, and 15% of which were distracters. Participants received four blocks of 150 trials with three breaks in between. Standard stimuli, to which the participants were told not to respond, consisted of small grey circles measuring 2 inches in diameter. Target stimuli were medium-sized grey circles, measuring 3 inches, and participants were instructed to press a button when they saw these stimuli. Distracter stimuli, to which the participants were told not to respond, were large squares measuring 4.5 inches in diameter. A moderate difference between the targets and standards and the large difference between the targets and distracters was chosen to maximize the P3 response (see Comerchero & Polich, 1998) while also maximizing task accuracy. Each stimulus was presented for 75 milliseconds (ms), with a 2 second inter-stimulus interval. A practice task consisting of 10 stimuli was presented in advance to ascertain that all participants can discriminate targets from standards. This practice task was repeated until all participants achieved 80% correct responses.

Distracter novelty was manipulated by stimulus features contained within the large squares. Half of the distracters were grey, like the targets and standards, and were identical in appearance throughout the experiment. The other distracters contained colorful fractal designs

that were unique and only occurred once over the course of the experiment (see Figure 1-2 for an example). These novel distracter designs were generated by Tiera-Zon software (http://www.ktaza.com/fractal/). Both types of distracters were the same size, and were presented in different trial blocks to allow the opportunity to examine block-related effects of the distracters on the other stimuli. Half of the participants completed the novel distracter blocks first and third, while the other participants completed novel distracter blocks second and fourth. Presentation order of novel and non-novel distracter blocks was counterbalanced across participants.

Neuropsychological Measures

Participants completed a short battery of neuropsychological tests to assess cognitive and emotional functioning. The Mini-Mental State Exam (MMSE; M. F. Folstein, Folstein, & McHugh, 1975) was used to screen for dementia and other global cognitive problems. Additionally, participants were administered the Trail Making Test A and B (Trails; Reitan & Wolfson, 1995), Digit Symbol and Digit Span subtests from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997), Stroop Color and Word Test (Golden, 1978), Controlled Oral Word Association Test (Benton & Hamsher, 1989), Boston Naming Test-Second Edition-Short Form (Kaplan, Goodglass, & Weintraub, 2001), and Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Of the executive functioning measures, Trails B provides an assessment of divided attention and cognitive flexibility, Digit Symbol measures psychomotor speed and complex sustained attention, the Stroop Color and Word Test measures inhibition, selective attention, and response conflict, and the Wisconsin Card Sorting Test measures abstract problem-solving and set-shifting (Lezak, Howieson, & Loring, 2004).

Emotional Measures

Participants also completed a short set of self-report questionnaires to assess emotional functioning. The State-Trait Anxiety Inventory (STAI; Speilberger, Gorusch, Lushene, Vagg, & Jacobs, 1983) was used to provide information regarding the participants' general levels of anxiety as manifest in temporary states of distress and more long-term personality traits. The Beck Depression Inventory-Second Edition (BDI-II; Beck, 1996) was used to assess for elevated levels of depression symptoms. Unfortunately, the BDI-II was not normed on older adults, and contains items assessing somatic symptoms of depression that may lead to inflated scores in the elderly. Therefore, the Geriatric Depression Scale (GDS; Yesavage et al., 1983) was used in addition to the BDI-II to assess depression symptoms. Unlike the BDI-II, the GDS was normed on an elderly population and was designed to avoid somatic symptoms that complicate diagnosis in the presence of comorbid, age-related medical conditions (Blazer, 2002). Finally a modified Apathy Evaluation Scale (AES; Starkstein et al., 1992) was used to assess self-reported apathy symptoms.

EEG Acquisition and Reduction

EEG was recorded from 64 scalp sites using a 64-channel geodesic sensor net and amplified at 20K using an Electrical Geodesics Incorporated (EGI; Eugene, Oregon) amplifier system (nominal bandpass .10 – 100Hz). Electrode placements enabled recording vertical and horizontal eye movements reflected in electro-oculographic (EOG) activity. EEG was initially referenced to Cz and digitized continuously at 250 Hz with a 16-bit analog-to-digital converter. A right posterior electrode served as common ground. Impedance of electrodes was generally maintained below 50 kΩ, consistent with procedures suggested by the manufacturer.

Following the recording session, EEG was then re-referenced into a virtual montage using Brain Electrical Source Analysis software (BESA version 5.2; Scherg, 1990). This montage

used a combined ears reference and calculated EEG data from electrode sites based on the International 10-10 system, several of which were interpolated from the original 64 channels on the EGI net (see Figure 1-4). The electrodes used in statistical analyses consisted of midline sites Fz, Cz, Pz, and Oz. Of note, the Fpz electrode was interpolated from a mixture of channels 6 and 11, Fz was interpolated from channels 3 and 8, and Oz was interpolated from channels 37, 38, and 40. Cz and Pz activity corresponded with the recordings taken from the vertex reference and channel 34, respectively. EEG data were then adjusted for movement, electromyographic muscle artifact, electro-ocular eye movement, and blink artifacts using computer algorithms in BESA. EEG activity was excluded from the remaining data using threshold criteria that maximized the number of trials accepted from each individual. The average voltage threshold that was used for excluding trials was 109.2 μV (*SD*: 2.5, range: 100-150) μV. Point-to-point transitions were not allowed to exceed 75 μV.

Individual-subject event-related potentials (ERPs) were extracted and averaged together from the ongoing EEG recording in discrete temporal windows that coincide with the onset of each stimulus. ERP averages from each participant were then calculated separately for standards, targets, and distracters. Stimulus-locked epochs were extracted with a duration of 200 ms prior to stimulus presentation and 800 ms post-stimulus presentation. All averaged ERP epochs were baseline-corrected using a 200 ms window prior to stimulus onset and digitally filtered at 30 Hz low-pass and a .1 Hz high-pass. All ERP components were scored on peak amplitude and peak latencies during a specified time window. Time windows used for scoring the different ERP components were as follows: occipital SN: 100-200 ms, central P2: 120-240 ms, frontal N2: 175-350 ms, and midline P3: 300-650 ms.

Data Analysis

Independent and paired samples t-tests were performed to examine between-group and within-group differences on neuropsychological and oddball task behavioral data. Detection accuracy data that were not normally distributed underwent arcsine transformation (Neter, Wasserman, & Kutner, 1985), which can correct for skewedness caused by low probability of error rates on the task. For analyses involving RT, median RTs were employed for correct responses (Ratcliff, 1993). ERP peak amplitudes and latencies were examined with 2-Group (young, older) x 3-Stimulus (standard, target, distracter) x 3-Electrode Site (Fz, Cz, Pz) x 2-Distracter (novel, non-novel) repeated measures analyses of variance (ANOVAs). In line with a priori hypotheses, planned contrasts were used to decompose interaction effects. When applicable, these contrasts utilized orthogonal polynomial comparisons across different stimulus conditions and electrode sites. To assist in interpretation of these contrasts, factors were always entered into ANOVAs in the same order. Electrode site was always ordered in an anterior-to-posterior fashion (Fz, Cz, Pz). Stimulus type was always ordered in a manner consistent with increasing novelty (standard, target, distracter). Orthogonal contrast vector rules specified linear contrasts over electrode site and stimulus type separately, using weights of -1, 0, +1. Quadratic contrasts were then defined applied to electrode site and stimulus type, using weights of +1, -2, +1. Visual examples of orthogonal contrasts used in ERP data analysis can be seen in Figure 1-3. Linear trends observed over electrode site indicated that the ERP amplitude was greatest in either frontal (Fz) or posterior (Pz) channels. Quadratic trends over electrode site reflected equal amplitude in frontal (Fz) and posterior (Pz) channels but a different amplitude at the central site (Cz). Linear trends were observed over stimulus type indicated that ERP amplitude was greatest for either distracters or standard stimuli. Quadratic trends over stimulus type reflected equal amplitudes elicited by standard and distracter stimuli but different amplitude evoked by targets.

In addition to planned contrasts, follow-up post-hoc comparisons were made using Bonferroni corrections for multiple comparisons. The Huynh-Feldt epsilon adjustment (Huynh & Feldt, 1976) was used for all repeated measures ANOVAs with greater than 1 degree of freedom; uncorrected degrees of freedom and corrected *p*-values are reported.

For analyses that yielded significant interactions with electrode site, ERP amplitudes from the three stimulus conditions were normalized and then re-analyzed. Component amplitudes were *z*-score transformed across the three stimulus conditions to eliminate the main effect of electrode site, which placed the stimulus-related amplitudes on the same metric scale (see Kounios & Holcomb, 1994) and equated the sensitivity to detect differences across conditions at the different recording sites.

Along with analyses of peak amplitude and latency data, some ERP components were subjected to difference wave calculations. Difference waves for each participant were computed by subtracting the individual participant's average waveforms from two conditions of interest. These computations allowed for a comparison of the effects of a particular stimulus condition after controlling for the effects of another. These difference waves were visually inspected for topographic differences over the scalp, and analyzed by calculating the mean amplitude over a time window where the condition-related differences were maximal. These calculations were made at the scalp site where the original ERP component had a maximal distribution. Pearson correlation coefficients were then used to measure the relationships between difference wave amplitudes and neuropsychological data of interest. Hierarchical regression models were also used to assess the individual contributions of certain neuropsychological predictor variables on ERP difference wave responses.

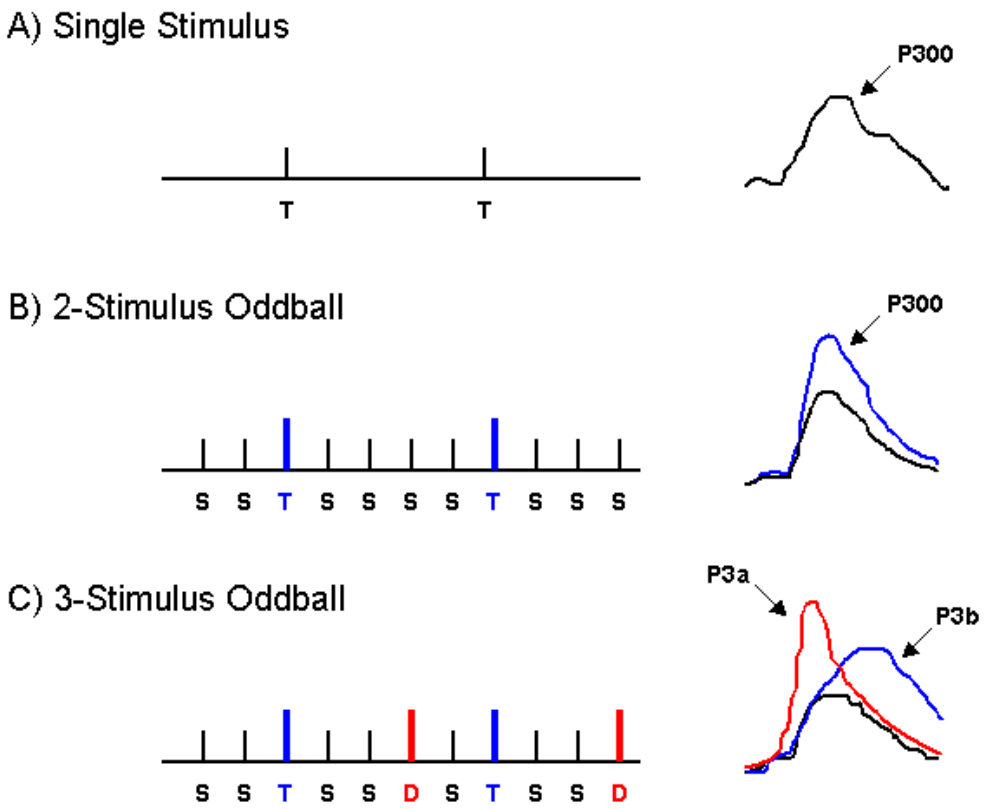

Figure 1-1. Schematic illustration of different paradigms that elicit the P300. (A) A P300 deflection is elicited target stimuli that require a response. (B) 2-stimulus oddball tasks generate a larger P300 to an infrequent target stimulus, relative to a frequent non-target (standard). (C) In 3-stimulus oddball tasks, P3a potentials are elicited by infrequent distracter stimuli, while P3b potentials are evoked by infrequent target stimuli. Note: T = target, S = standard, and D = distracter. Adapted from Polich and Criado (2006).

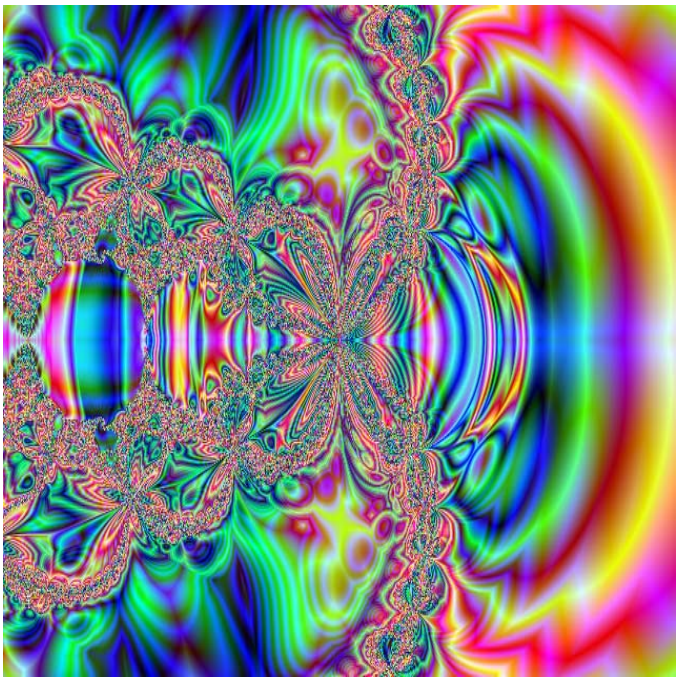

Figure 1-2. Sample fractal design used as a novel distracter in the oddball task.

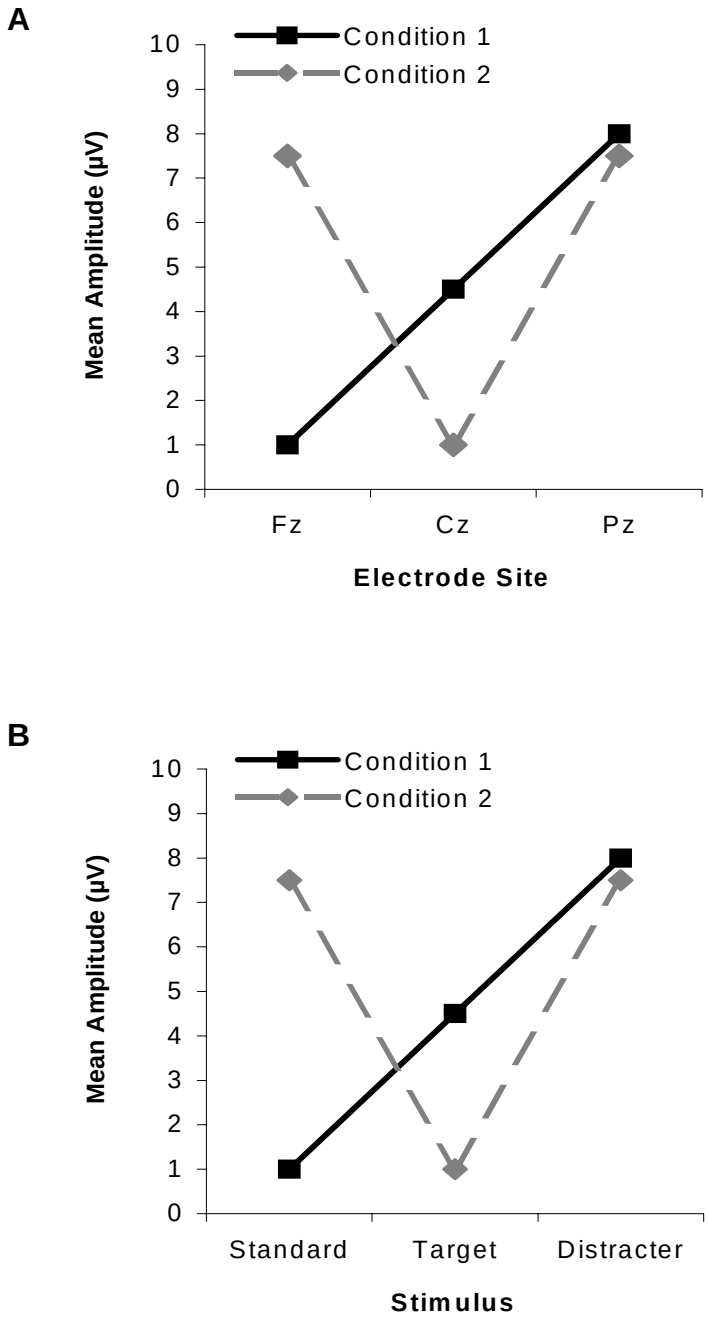

Figure 1-3. Examples of planned comparisons used in ERP data analysis. (A) Orthogonal contrasts reveal a linear trend over electrode site for Condition 1, with greatest amplitude over the posterior site (Pz). Condition 2 shows a quadratic trend over electrode site, with greater amplitudes over frontal and posterior sites (Fz, Pz) relative to central (Cz). (B) Orthogonal contrasts reveal a linear trend over stimulus type for Condition 1, with greatest amplitude elicited by distracters. Condition 2 shows a quadratic trend over stimuli, with greater amplitudes evoked by standards and distracters relative to targets.

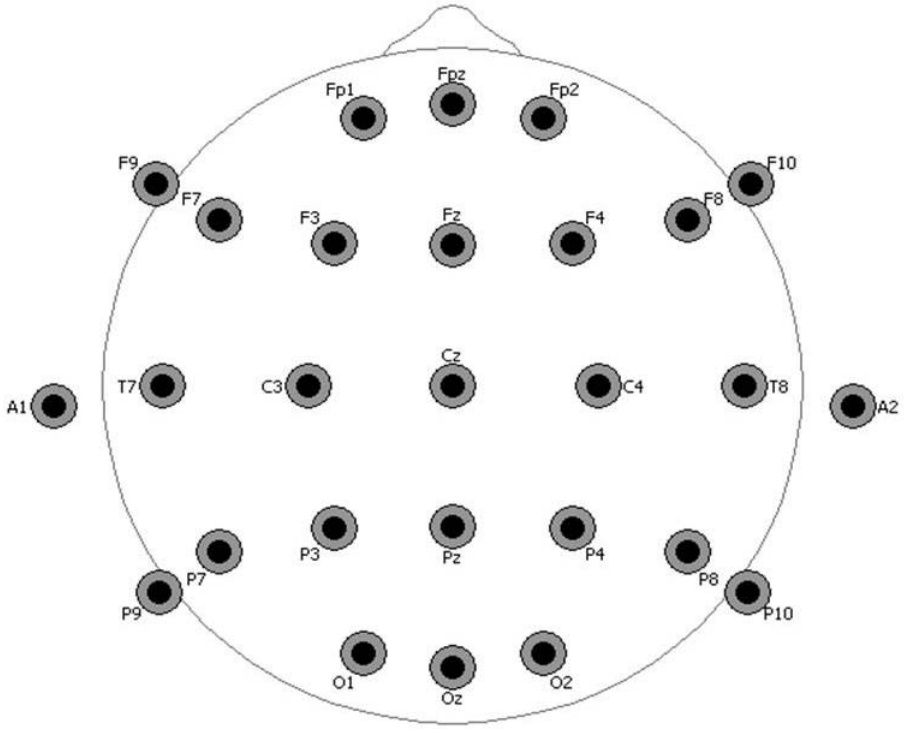

Figure 1-4. Montage used for the EEG analyses, showing international 10–10 positions interpolated from the 64-channel geodesic sensor net (EGI; Eugene, Oregon). Primary sites of interest were midline sites Fz, Cz, Pz, and Oz.

CHAPTER 2
EXPERIMENT 1: THE IMPACT OF HEALTHY AGING ON PREFERENTIAL NOVELTY PROCESSING

Overview and Predictions

Experiment 1 was conducted to examine the effects of distracter novelty on ERP reflections of attentional orienting and determine if healthy aging impacts these effects. The inclusion of both young and older age groups also allowed for the examination of interacting effects of age and novelty on attentional orienting. In addition, it was anticipated that the colorful properties of the novel distracters would differentially engage early visual attention with greater SN and P2 amplitudes relative to non-novel distracters. It was also predicted that young participants would show selective attentional orienting effects to distracters in the form of increased N2 and distracter P3 amplitudes relative to targets and standard stimuli. In line with previous P3 findings on novel versus non-novel distracters (Polich & Comerchero, 2003), novel distracters were not expected to differ from non-novel distracters on overall P3 characteristics. However, novel distracters were expected to receive greater preferential processing than non-novel distracters, as reflected in N2 amplitudes that have been shown to be more sensitive to unfamiliar stimuli (Daffner, Mesulam, Scinto, Calvo et al., 2000).

With regard to predicted effects of age, older participants were expected to show decreased attentional orienting toward distracters, meaning that distracter-related P3 and N2 amplitudes would be attenuated relative to the young group. Contrary to predictions for the young group, a novelty enhancement effect of N2 was not expected in older participants, due to their overall impairments in attentional orienting. However, novelty-related P2 and SN enhancements were expected to be intact in the older participants, since the neural processes that give rise to these components are rooted in sensory discrimination, which should be preserved into old age. All participants were expected to show correlations between distracter-standard difference waves

and measures of executive functioning, particularly those that assess working memory (Digit Span) and inhibition (Stroop Interference).

Methods

Participants

Twenty-two young participants (ages 18-35) and twenty older participants (ages 49-77) were recruited for this study. The two groups were matched for gender ($\chi^2 = .22$, $p > .70$) and handedness ($\chi^2 = .001$, $p > .90$), although older participants had a higher mean level of education compared to those in the young group, $t(35) = -3.5$, $p = .001$. Of the young participants, 22 completed all the cognitive measures while 11 completed only a limited battery of the MMSE, Trails A and B, Digit Symbol, Stroop, and WCST. All of the older participants completed all measures. All participants were screened for the presence of psychiatric illness, learning disability, neurological disease, or history of other major medical problems affecting cognition. Table 2-1 provides demographic and neuropsychological data for the participants.

Procedures

After informed consent was obtained, participants began an experimental session which lasted approximately 3 hours. Two participants (one in each group) needed to divide their session over two days due to scheduling difficulties, but all other individuals completed all tasks in the same experimental session. Participants received either financial compensation ($10 per hour) or course credit for their participation.

Results

Behavioral Data

Oddball task performance

Behavioral data from the oddball task are presented in Table 2-2. A 2-Group x 2-Distracter ANOVA was performed on reaction time to targets, which revealed no significant

effect of distracter type or group x distracter interaction. When the two groups were analyzed separately with paired samples *t*-tests, however, reaction time to targets was found to be affected by distracter type for older participants, $t(14) = 2.6$, $p < .05$, with faster responses during trial blocks that presented novel distracters. In order to correct for high levels of skewedness caused by the low probability of errors on the task, error rates were subjected to arcsine transformation and then analyzed using a 2-Group x 3-Stimulus x 2-Distracter Type ANOVA. There was a main effect of stimulus type on accuracy, $F(2,34) = 34.3$, $p < .001$, $\eta^2 = .50$, such that false alarms to distracters were more common than incorrect target responses, which were in turn more common than false alarms to standards (*ps* < .05). Distracter type also exerted a main effect on accuracy, $F(2,34) = 70.2$, $p < .001$, $\eta^2 = .67$, and significantly interacted with stimulus type, $F(2,34) = 48.8$, $p < .001$, $\eta^2 = .59$, such that false alarms to distracters were elevated during trial blocks that presented novel distracters.

Cognitive and emotional functioning

The participant groups performed comparably on the MMSE, Boston Naming Test, Controlled Word Association Test, Semantic Fluency, Digit Span, and the Wisconsin Card Sorting Test, while endorsing similar levels of emotional symptoms. Young participants out-performed older participants on Trails A and B, Digit Symbol Coding, and Stroop Color Word Naming (*ps* < .01). Although no individuals met diagnostic criteria for any psychiatric disorder, two members of each group obtained a score on the AES that was above the conventional clinical cutoff for apathy (14).

Event-Related Potential Data

Standard stimuli waveforms contained an average ($\pm$ *SD*) of 167.8 $\pm$ 22.6 trials (range: 113-204), while target waveforms contained 35.5 $\pm$ 5.2 trials (range: 24-46) and distracter waveforms contained 34.7 $\pm$ 5.1 (range: 20-44). A 2-Group x 3-Stimulus x 2-Distracter

ANOVA confirmed that there were no group- or distracter-related differences in the number of trials comprising the waveforms. Stimulus-locked ERP waveforms from the oddball task can be seen in Figures 2-1 and 2-2. Mean ERP amplitude and latency data are presented in Tables 2-3 through 2-6.

SN component

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of SN amplitude revealed a significant main effect of group, $F(1,35) = 7.2$, $p = .01$, $\eta^2 = .17$, with older participants exhibiting greater negative amplitudes compared to young participants. There was also a main effect of stimulus type, $F(2,70) = 34.8$, $p < .001$, $\eta^2 = .50$, with maximal amplitude to distracters ($ps < .001$). A main effect of distracter type was also significant, $F(1,35) = 21.9$, $p < .001$, $\eta^2 = .39$, which was qualified by a significant stimulus x distracter interaction, $F(1,35) = 23.4$, $p < .001$, $\eta^2 = .40$. SN amplitude was dramatically larger for novel distracters relative to non-novel ($p < .001$), as shown in Figure 4-3.

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of SN peak latency revealed significant main effects of stimulus, $F(2,70) = 5.0$, $p = .01$, $\eta^2 = .13$ and distracter, $F(1,35) = 4.5$, $p < .05$, $\eta^2 = .11$. Additionally, distracter type interacted significantly with a linear trend over stimulus, $F(1,35) = 6.5$, $p < .05$, $\eta^2 = .16$, such that SN latencies were faster for novel distracters than non-novel ($p < .01$), as shown in fig 2-3. SN latencies did not differ across group.

P2 component

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of central P2 amplitude revealed significant main effects of group, $F(1,35) = 12.3$, $p = .001$, $\eta^2 = .26$, stimulus, $F(2,70) = 20.8$, $p < .001$, $\eta^2 = .37$, and distracter, $F(1,35) = 4.5$, $p < .05$, $\eta^2 = .11$. A significant linear trend over stimulus interacted with distracter, $F(1,35) = 4.5$, $p < .05$, $\eta^2 = .11$, such that distracter-related P2 amplitudes were larger during when the distracters were novel. When examining the group x

stimulus x distracter interaction for a similar polynomial trend, a significant quadratic trend over stimulus type was found to interact with group and distracter, $F(1,35) = 4.5$, $p < .05$, $\eta^2 = .11$. Older participants exhibited larger distracter-related P2 amplitudes in the novel distracter block, while young participants did not show this novelty enhancement (Figure 2-4).

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of P2 latency revealed a significant effect of stimulus, $F(2,70) = 7.4$, $p = .001$, $\eta^2 = .17$, and a stimulus x distracter interaction, $F(2,70) = 4.0$, $p < .05$, $\eta^2 = .10$. Distracter-related P2 latency was shorter for both participant groups when the distracters were novel. P2 latency did not vary across group.

N2 component

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of frontal N2 amplitude revealed significant main effects of group, $F(1,35) = 36.5$, $p < .001$, $\eta^2 = .51$ and stimulus, $F(2,70) = 4.7$, $p < .05$, $\eta^2 = .12$, the latter of which was qualified by a significant stimulus x distracter interaction, $F(2,35) = 4.6$, $p < .05$, $\eta^2 = .12$. Novel distracters elicited larger N2 components than targets and standard stimuli ($ps < .01$) but this effect was not seen for non-novel distracters. To assess for group differences in this novelty effect, data were subjected to polynomial trend contrasts of stimulus type across distracter and group. A significant interaction of group x quadratic trend over stimulus x distracter emerged, $F(1,35) = 4.1$, $p < .05$, $\eta^2 = .11$, revealing that distracter-related N2 amplitudes were enhanced by novelty in young participants only (see Figure 2-5).

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of frontal N2 latency detected a significant group x distracter interaction, $F(1,35) = 16.9$, $p < .001$, $\eta^2 = .33$, in which older participants had longer N2 latencies to stimuli as a whole than young when the trial block presented novel distracters.

P3 component

A 2-Group x 3-Stimulus x 3-Site x 2-Distracter ANOVA of P3 amplitude revealed main effects group, stimulus, and electrode site, as seen in Table 2-7. Peak P3 amplitudes were larger for young participants compared to older participants. Follow-up comparisons across participants revealed that distracter-related P3 amplitudes were larger than those from targets ($p < .001$), which were in turn larger than those evoked by standards ($p < .001$). As expected, a group x stimulus interaction was significant, with young participants exhibiting larger P3 amplitudes from target and distracter stimuli relative to older adults, as shown in Figure 2-6. Importantly, there was also a significant group x quadratic trend over stimulus x distracter interaction, with older participants exhibiting smaller amplitudes for targets during the novel distracter block relative to young participants. There were also significant group x site, stimulus x site, and group x stimulus x site interactions in the data.

The stimulus x site interaction remained significant following amplitude normalization. Standard P3 amplitudes were equal across site, while target P3 amplitudes maintained a maximal posterior distribution, larger for the parietal site than the frontal ($p < .001$). Conversely, distracter P3 amplitudes displayed a maximal anterior distribution, larger for the frontal site than the parietal ($p < .001$). The group x stimulus x site interaction was also significant in the normalized data, with young participants demonstrating a more posteriorly distributed target-related P3 response and older participants showing anteriorly distributed P3 to targets, as shown in Figure 2-7. Both groups showed a central maximum for their distracter-related P3 responses.

A 2-Group x 3-Stimulus x 3-Site x 2-Distracter ANOVA of P3 latency was also performed, with significant results shown in table 2-8. A significant group x stimulus x site interaction found that older participants exhibited prolonged P3 latency for targets over the parietal site. Additionally, a group x stimulus x distracter interaction revealed that relative to

older participants, young participants' target-related P3 latencies were shorter when non-novel distracters were presented ($p < .001$) and distracter-related P3 latencies were shorter for novel distracters ($p < .01$).

Difference waves

In order to isolate the endogenous components that were more specific to processing distracters, difference waves were calculated by subtracting the standard stimulus ERP waveforms from those elicited by distracters. Similarly, target difference waves were calculated by subtracting the standard stimulus ERP waveforms from those elicited by targets. Distracter and target difference waves were calculated for each age group, and these difference waves showed maximal positive amplitudes with a latency of approximately 400 ms, seen in Figures 2-8 and 2-9. This corresponds approximately with P3 latencies of the peak amplitude seen in the original distracter and target waveforms. Mean amplitudes of these difference waves were calculated using a time window from 380-420 ms in order to quantify these condition-specific effects.

For distracter difference waves, a 2-Group x 3-Site x 2-Distracter ANOVA revealed main effects of group, $F(1,35) = 4.3$, $p < .05$, $\eta^2 = .11$, electrode site, $F(2,70) = 17.7$, $p < .001$, $\eta^2 = .34$, and a group x site interaction, $F(2,70) = 11.6$, $p < .001$, $\eta^2 = .25$. Young participants exhibited difference waves that had larger positive amplitudes over central and parietal sites relative to older participants ($ps < .05$). For target difference waves, a 2-Group x 3-Site x 2-Distracter ANOVA revealed main effects of distracter, $F(2,70) = 4.9$, $p < .05$, $\eta^2 = .12$ and electrode site, $F(2,70) = 8.6$, $p < .001$, $\eta^2 = .20$, along with a group x site interaction, $F(2,70) = 17.3$, $p < .001$, $\eta^2 = .33$, and a group x distracter interaction, $F(2,70) = 4.1$, $p = .05$, $\eta^2 = .11$. Relative to young participants, members of the older group had smaller positive amplitudes for

the target difference wave over the parietal site ($p < .01$), and their overall responses were reduced during trial blocks presenting novel distracters ($p < .05$).

Relationship with neuropsychological performance

Several demographic and neuropsychological variables correlated with distracter and target difference wave amplitudes, as shown in Table 2-9. Age correlated with target-standard amplitudes for novel distracter blocks only, while digit span backwards correlated with novel and non-novel distracter-standard amplitudes. Digit Symbol performance correlated with target and distracter difference wave amplitudes regardless of distracter novelty. Phonemic fluency performance correlated with non-novel distracter amplitudes. Surprisingly, education level was negatively correlated with novel and non-novel distracter-related P3 responses, suggesting perhaps that lengthy doctoral programs (and/or never-ending dissertation projects) may lead to blunted attentional orienting.

The most interesting of these correlations is the finding that age was significantly correlated with target responses only when targets were presented in the context of novel distracters. In order to further examine these age-target relationships, hierarchical regression models were used to predict target difference wave amplitudes for novel and non-novel distracter blocks separately. Both models entered Digit Symbol score in step 1 (since this performance on this measure was consistently correlated with target difference waves during both distracter blocks) and age in step 2. As shown in Table 2-10, the initial model with Digit Symbol performance as the lone predictor explained 12% of the variance in target amplitude from novel distracter trials. The addition of age significantly added to the model, accounting for an additional 10% of the variance and causing Digit Symbol to lose its significance as a predictor of target amplitude. Table 2-11 shows the effects when taking this same regression approach with target amplitudes from the non-novel distracter block, Digit Symbol score explained a similar

amount of initial variance (11%) as the lone predictor. However, the addition of age did not significantly add to this model, and Digit Symbol remained a significant predictor of target amplitude even after accounting for its shared variance with age. Taken together, these regression results illustrate that the effect of age on target processing was unique to novel distracter trials only.

Discussion

In this experiment, distracters of differing levels of novelty were presented in the context of a three-stimulus oddball task. The novel distracters were designed to be deviant in both short-term context (i.e., infrequent, unexpected, task-irrelevant) and stimulus features (i.e., colorful, complex patterns) such as to maximize preferential processing that begins in early stages of visual processing. The non-novel distracters were designed to elicit attentional orienting without the same degree of early preferential processing as the novel stimuli. The first goal was to observe the effects of distracter novelty on ERP reflections of attentional orienting. The second goal was to observe the effects of healthy aging on these patterns of preferential engagement of novel stimuli.

As hypothesized, novel distracters differentially engaged the visual attention system in ways that non-novel distracters did not. Novel distracters elicited robust SN responses with larger amplitudes and shorter latencies than non-novel distracters. Similarly, P2 responses to novel distracters were larger and faster than those for non-novel distracters. These results were driven by the salient color patterns contained within the novel distracters that made them distinct from the other grey stimuli in the task. These early stages of attentional processing are not specific to a novelty response, per se, but nonetheless provide a manipulation check which assures that these stimuli were receiving the maximal level of engagement from the start.

Attentional orienting to novel events is hypothesized to take place in two different sets of processes that are reflected in different ERP components. In line with predictions, the first stage of attentional orienting was selectively engaged by novel distracters in this experiment, resulting in larger N2 amplitudes. Non-novel distracters elicited N2 amplitudes that were no different from targets. This finding offers a dramatic contrast to what was seen for the second stage of attentional orienting which gave rise to the P3 response. Distracter stimuli as a whole elicited larger P3 amplitudes than targets, regardless of their degree of novelty. However, no additional preferential processing occurred due to increased novelty in the colorful distracters. These results provide support for the distinction between N2 and P3 as reflecting different stages of attentional orienting.

As expected, older adults in this experiment showed similar patterns to young for the early preferential processing reflected in SN and P2. In fact, older participants exhibited larger SN amplitudes and enhanced P2 responses for novel distracters relative to young participants. Although it is consistent with previous research for older adults to show P2 novelty enhancements that are equal to that of young adults (Czigler & Balazs, 2005), it was not expected for older participants in this study to exhibit greater P2 amplitudes. This finding has not been reported in any other known studies examining novelty processing in aging; however, these results may be explained in terms of an increased susceptibility to involuntary capture of attention in the older adults. Andres, Parmentier and Excera (2006) found that older adults showed a larger distraction effect for task irrelevant sounds and attributed this to a greater capture of attention due to deficits in frontal lobe filtering of irrelevant information. Consistent with this explanation, the older adults in this experiment may have exhibited larger SN and P2 amplitudes because of an impaired ability to inhibit attentional capture to the novel distracters. It

is noteworthy that this attentional capture was limited only to these early components, and did not lead to a subsequent enhancement of attentional orienting in N2 or P3 responses in the older adults.

In line with predictions, older participants showed deficits in attentional orienting. In contrast to young participants, older adults failed to show an enhanced N2 response to novel distracters. Older adults also showed less preferential processing reflected in P3 responses for infrequent stimuli as a whole (targets and distracters). These effects are striking given the nature of their enhanced processing of novel distracters, reflected in the SN and P2 components that occur earlier in the visual processing stream. This finding is important since attentional orienting relies in part on a healthy frontal lobe, while early visual processing is more dependent on posterior cortical areas. Of additional note is the way that older participants processed targets during the oddball task. P3 response to targets had a frontally maximal distribution in the older adults, relative to a parietally maximal distribution for young adults. This finding replicates a host of prior studies (e.g,. Friedman et al., 1997), and provides evidence that the older participants needed to activate greater frontally-mediated processing resources in order to successfully respond to the targets. Overall, these findings suggest that the older adults in this study had alterations in frontal lobe contributions to attentional processing while exhibiting intact posterior visual processing.

In the face of these expected age-related findings, it is interesting to note how the older participants' target-related processing was influenced by the type of distracter that was presented. During blocks involving novel distracters, older adults demonstrated reduced P3 processing of targets relative to young adults. In other words, older participants were more distracted by the novel distracters than young, and this impact caused selective impairments on

target-related P3 processing. Paradoxically, their reaction times to targets during these blocks actually decreased – a replication of a surprising finding first reported by Fabiani and Friedman (1995). It is possible that this occurred because the older adults in this study recruited greater frontal resources as they processed the targets, and these additional resources enabled them to respond to them more quickly. Regardless, the hierarchical regression results illustrate that age was a significant predictor of target processing when novel distracters were presented and accounted for more variance than performance on a complex attention task (Digit Symbol). In contrast, age was not a significant predictor of target processing for trials in which the distracters were not novel.

Taken together, these results suggest that older participants in this experiment processed target trials differently from young participants when novel distracters were present. Increased frontal involvement in older adults was likely needed to offset a reduced ability to maintain memory templates for the target stimuli, as suggested by previous studies (e.g., Fabiani & Friedman, 1995; Friedman et al., 1998). What makes the findings of this experiment unique is that the novelty of the distracters played a role in how easily targets were processed (i.e., how easily their memory templates were maintained). This is the first study of its kind that has detected a link between the degree of distracter novelty and the ease with which targets are categorized.

Table 2-1. Mean and standard deviation (*SD*) demographic and neuropsychological data for young and older participants.

	Young		Older		
	Mean	(*SD*)	Mean	(*SD*)	*p*
Demographics					
Age (years)	21.6	(3.2)	65.0	(9.5)	< .001
Education (years)	14.7	(.9)	17.4	(3.3)	.001
Female (%)	55	--	47	--	*ns*
Right-Handed (%)	86	--	87	--	*ns*
Cognitive Functioning					
MMSE	29.0	(1.1)	28.5	(1.5)	*ns*
Boston Naming Test	55.8	(3.7)	57.1	(3.8)	*ns*
COWA (FAS)	37.3	(10.4)	44.6	(12.0)	*ns*
Semantic Fluency (Animals)	22.8	(3.0)	22.1	(5.3)	*ns*
Digit Span Forward	7.2	(1.0)	7.1	(1.3)	*ns*
Digit Span Backward	5.1	(1.3)	5.5	(1.4)	*ns*
Trails A (sec)	20.7	(4.7)	28.0	(10.3)	< .01
Trails B (sec)	48.6	(17.2)	65.0	(28.0)	< .05
Digit Symbol	89.2	(12.9)	75.6	(13.3)	< .01
Stroop Word Reading	101.9	(14.1)	99.3	(13.0)	*ns*
Stroop Color Naming	79.7	(13.6)	73.5	(15.3)	*ns*
Stroop Color Word Naming	47.1	(12.4)	38.6	(11.5)	< .05
WCST Categories Completed	5.8	(.9)	5.7	(1.0)	*ns*
WCST Total Errors	18.2	(17.0)	18.7	(15.0)	*ns*
WCST Perseverative Errors	8.8	(5.2)	10.5	(9.1)	*ns*
WCST Set Failure	.1	(.4)	.3	(.6)	*ns*
Emotional Functioning					
BDI-II	2.1	(2.8)	2.8	(3.3)	*ns*
GDS	1.6	(2.1)	.9	(1.3)	*ns*
AES	8.1	(4.1)	7.9	(4.9)	*ns*
STAI - State	26.9	(5.4)	27.5	(7.5)	*ns*
STAI - Trait	30.5	(5.8)	27.7	(5.7)	*ns*

Table 2-2. Mean reaction time and accuracy data from the oddball task

	Young		Older		
	Mean	(*SD*)	Mean	(*SD*)	*p*
Non-Novel Distracter					
Reaction time to targets (ms)	468	(80)	478	(69)	*ns*
Target response errors (%)	2.3	(3.9)	1.6	(2.2)	*ns*
False alarm to distracters (%)	.5	(1.6)	.5	(.9)	*ns*
False alarm to standards (%)	.1	(.2)	.1	(.3)	*ns*
Novel Distracter					
Reaction time to targets (ms)	466	(75)	462	(73)	*ns*
Target response errors (%)	1.4	(2.1)	1.5	(3.1)	*ns*
False alarm to distracters (%)	4.7	(.7)	4.6	(.6)	*ns*
False alarm to standards (%)	.1	(.3)	.3	(.5)	*ns*

Table 2-3. Peak amplitudes (μV) from young participants for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	-1.0	(2.0)	-.80	(2.8)	-7.1	(6.1)
	Non-Novel	-.7	(2.0)	-1.2	(3.0)	-1.0	(3.4)
Cz	P2						
	Novel	2.0	(1.9)	3.1	(3.6)	4.0	(3.4)
	Non-Novel	1.8	(1.8)	1.9	(2.2)	3.2	(2.9)
Fz	N2						
	Novel	-2.9	(1.6)	-2.7	(2.2)	-5.1	(2.7)
	Non-Novel	-2.8	(1.5)	-3.7	(2.5)	-3.5	(2.9)
Fz	P3 (Frontal)						
	Novel	4.5	(3.1)	8.2	(3.8)	10.1	(6.1)
	Non-Novel	4.7	(3.1)	6.6	(3.5)	9.6	(5.6)
Cz	P3 (Central)						
	Novel	8.2	(4.4)	13.9	(5.1)	17.5	(8.5)
	Non-Novel	8.6	(4.2)	12.2	(4.5)	17.3	(8.0)
Pz	P3 (Parietal)						
	Novel	8.3	(3.9)	16.2	(4.9)	16.5	(6.2)
	Non-Novel	8.1	(3.3)	14.3	(4.1)	16.0	(7.1)

Table 2-4. Peak latencies (ms) from young participants for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	154.7	(34.5)	151.8	(35.4)	134.9	(20.3)
	Non-Novel	154.0	(37.1)	157.1	(28.2)	156.2	(32.7)
Cz	P2						
	Novel	209.8	(37.2)	183.8	(39.4)	160.0	(30.0)
	Non-Novel	208.2	(39.6)	190.4	(46.3)	188.9	(43.1)
Fz	N2						
	Novel	216.2	(43.2)	221.4	(49.1)	236.2	(34.0)
	Non-Novel	234.2	(52.0)	232.5	(47.3)	234.0	(42.3)
Fz	P3 (Frontal)						
	Novel	394.7	(48.9)	411.6	(84.8)	377.8	(35.0)
	Non-Novel	406.9	(71.5)	376.4	(48.8)	405.1	(57.1)
Cz	P3 (Central)						
	Novel	390.5	(58.2)	451.4	(105.8)	380.4	(49.7)
	Non-Novel	415.3	(83.6)	366.4	(30.3)	400.9	(68.3)
Pz	P3 (Parietal)						
	Novel	375.4	(81.8)	444.9	(86.9)	376.9	(30.3)
	Non-Novel	418.9	(86.5)	350.7	(46.3)	388.5	(91.9)

Table 2-5. Peak amplitudes (μV) from older participants for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	-1.9	(1.9)	-3.0	(2.6)	-8.7	(5.2)
	Non-Novel	-2.4	(1.3)	-2.9	(2.2)	-4.8	(3.5)
Cz	P2						
	Novel	4.1	(2.3)	4.5	(2.5)	7.4	(3.6)
	Non-Novel	4.3	(2.0)	5.0	(2.0)	5.7	(3.4)
Fz	N2						
	Novel	-.09	(1.5)	-.21	(1.8)	-.67	(3.2)
	Non-Novel	.00	(1.4)	.04	(1.5)	-.10	(2.1)
Fz	P3 (Frontal)						
	Novel	5.3	(2.2)	8.9	(3.8)	10.4	(3.8)
	Non-Novel	5.4	(2.1)	9.5	(4.3)	10.3	(3.5)
Cz	P3 (Central)						
	Novel	8.5	(3.3)	10.4	(6.2)	14.9	(5.9)
	Non-Novel	8.9	(3.4)	10.6	(6.5)	14.2	(5.4)
Pz	P3 (Parietal)						
	Novel	7.7	(3.4)	10.9	(6.4)	12.9	(4.9)
	Non-Novel	8.0	(3.0)	10.6	(6.6)	11.4	(5.3)

Table 2-6. Peak latencies (ms) from older participants for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	160.0	(21.8)	155.7	(21.9)	147.7	(13.6)
	Non-Novel	161.6	(23.5)	156.0	(20.8)	152.0	(18.5)
Cz	P2						
	Novel	195.7	(45.4)	185.3	(37.1)	173.9	(30.0)
	Non-Novel	197.3	(42.5)	171.2	(40.5)	189.6	(43.1)
Fz	N2						
	Novel	216.3	(50.9)	243.2	(49.7)	240.5	(37.9)
	Non-Novel	202.4	(28.9)	218.1	(43.2)	212.8	(38.3)
Fz	P3 (Frontal)						
	Novel	409.9	(43.0)	437.9	(58.6)	418.7	(48.9)
	Non-Novel	392.5	(47.8)	417.6	(49.9)	430.9	(50.3)
Cz	P3 (Central)						
	Novel	391.7	(47.5)	472.3	(85.3)	424.8	(48.1)
	Non-Novel	381.9	(36.4)	438.1	(66.0)	421.6	(34.5)
Pz	P3 (Parietal)						
	Novel	388.3	(61.3)	482.4	(91.5)	425.9	(72.2)
	Non-Novel	383.5	(59.4)	487.5	(94.4)	410.7	(69.1)

Table 2-7. Summary of the 2-Group x 3-Stimulus x 3-Site x 2-Distracter ANOVAs performed on P3 peak amplitude data.

	Amplitude			Normalized Amplitude		
	F	*p*	η^2	*F*	*p*	η^2
Group[a]						
Stimulus[b]	51.7	<.001	.60			
Site[b]	68.4	<.001	.66			
Distracter[a]						
G x Stim[a]	4.3	<.05	.11			
G x Site[b]	12.4	<.001	.26			
G x D[a]						
S x S[c]	14.0	<.001	.29	5.1	.004	.13
Stim x D[b]						
Site x D[b]						
G x S x S[c]	8.4	<.001	.19	4.3	.009	.11
G x Stim x D[b]						
G x Site x D[b]						
S x S x D[c]						
G x S x S x D[c]						

[a]df = 1,35, [b]df = 2,70, [c]df = 4,140

Table 2-8. Summary of the 2-Group x 3-Stimulus x 3-Site x 2-Block ANOVAs performed on P3 peak latency data.

	Latency		
	F	*p*	η^2
Group[a]	4.1	.05	.11
Stimulus[b]	8.7	<.001	.20
Site[b]			
Block[a]	6.5	<.05	.16
G x Stim[b]	8.6	<.001	.20
G x Site[b]			
G x B[a]			
Stim x Site[c]	4.7	.001	.12
Stim x B[b]	9.1	<.001	.21
Site x B[b]			
G x Stim x Site[c]	2.7	<.05	.07
G x Stim x B[b]	6.1	<.01	.15
G x Site x B[b]			
Stim x Site x B[a]	5.5	<.05	.14
G x Stim x Site x B[a]	4.7	<.05	.12

[a]df = 1,35, [b]df = 2,70, [c]df = 4,140

Table 2-9. Significant correlations between P3 difference waves and neuropsychological measures for young and older groups combined.

	Distracter – Standard		Target – Standard	
	Novel	Non-Novel	Novel	Non-Novel
Age			-.45**	-.19
Education	-.47**	-.38*		
Digit Span Backwards	-.39*	-.37*		
Digit Symbol	.38*	.45**	.34*	.37*
COWA	-.10	-.36*		

*$p < .05$, **$p < .01$

Table 2-10. Summary of hierarchical regression analysis for variables predicting the amplitude of the target-standard difference wave from novel distracter trials.

	B	*SE B*	*β*
Step 1			
Constant	-8.58	5.01	
Digit Symbol	.127	.06	.34*
Step 2			
Constant	1.29	6.71	
Digit Symbol	.05	.07	.14
Age	-.09	.04	-.38*

Note R^2 = .12 for Step 1 ($p < .05$); ΔR^2 = .10 for Step 2 ($p < .05$).
*$p < .05$.

Table 2-11. Summary of hierarchical regression analysis for variables predicting the amplitude of the target-standard difference wave from non-novel distracter trials.

	B	*SE B*	*β*
Step 1			
Constant	-9.38	4.56	
Digit Symbol	.13	.05	.34*
Step 2			
Constant	-9.79	6.50	
Digit Symbol	.13	.07	.38*
Age	<.01	.04	.02

Note R^2 = .11 for Step 1 ($p < .05$); $\Delta R^2 < .01$ for Step 2 ($p > .90$).
*$p = .05$.

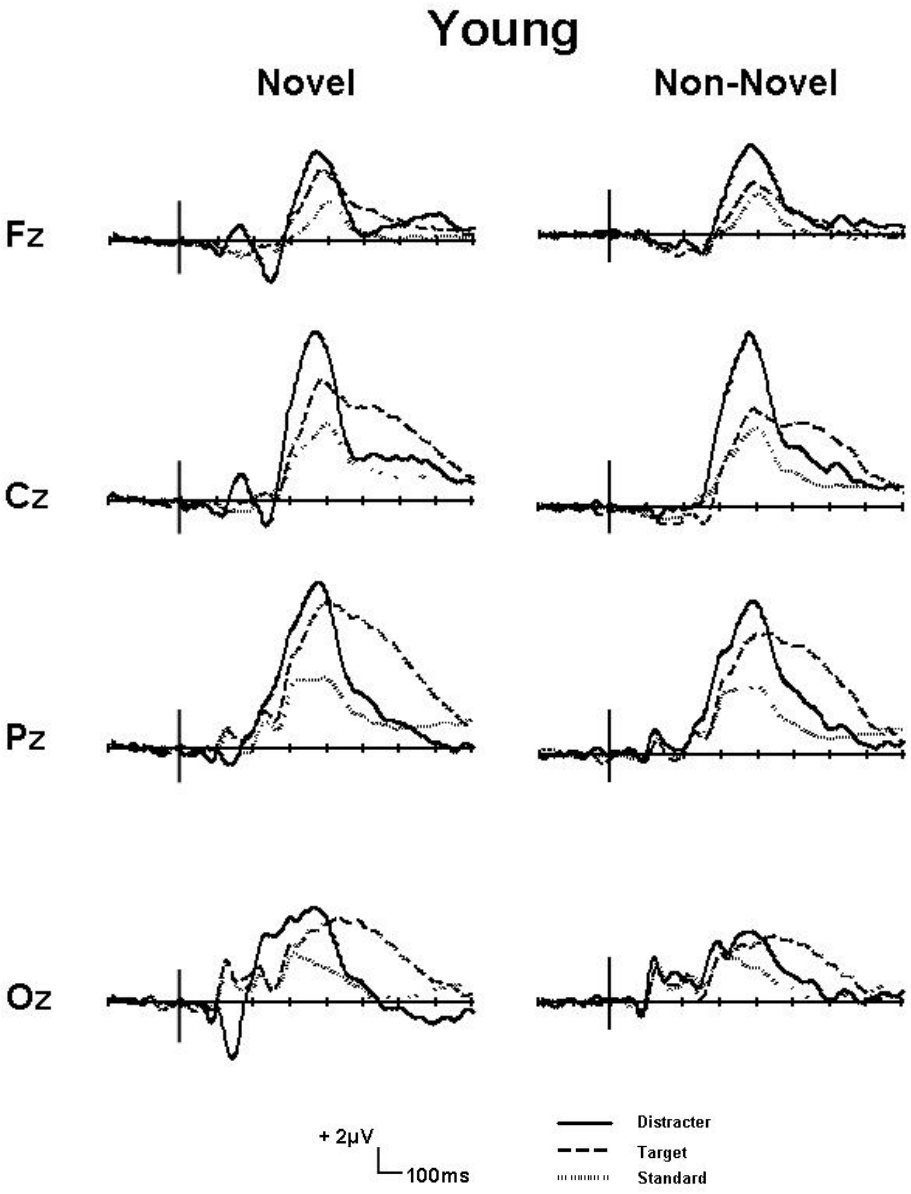

Figure 2-1. Grand-averaged standard, target, and distracter ERPs from the midline electrodes for young adults. Microvolts on the *y*-axis, milliseconds on the *x*-axis.

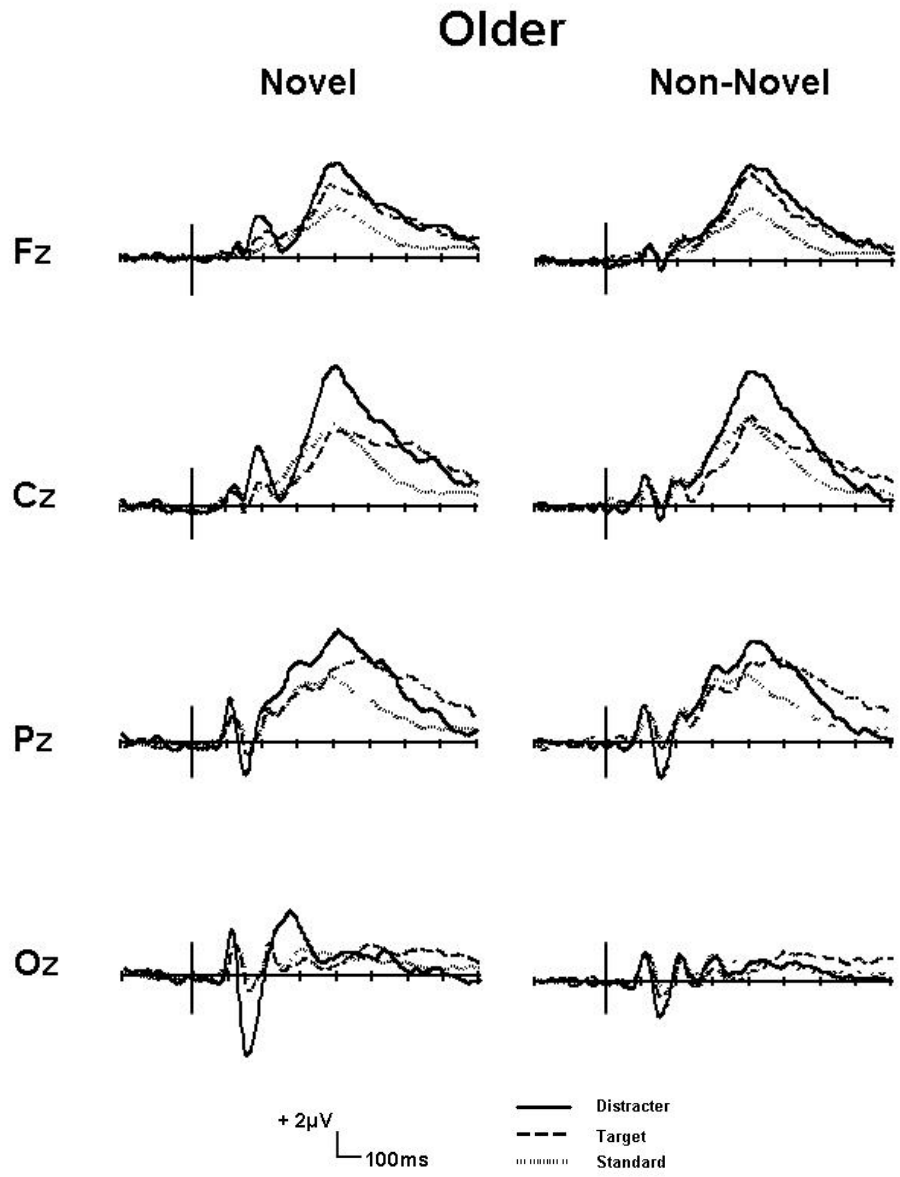

Figure 2-2. Grand-averaged standard, target, and distracter ERPs from the midline electrodes for older adults. Microvolts on the *y*-axis, milliseconds on the *x*-axis.

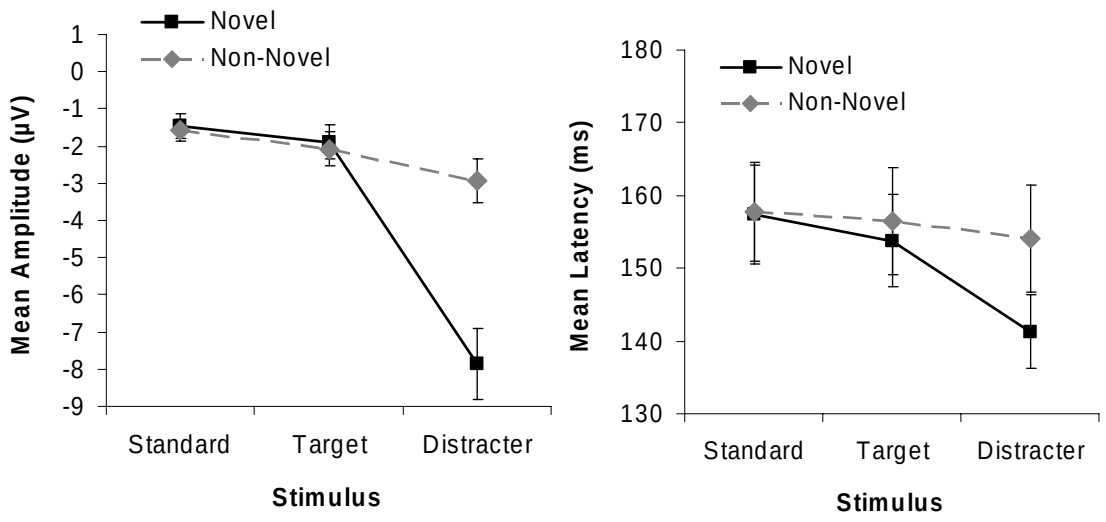

Figure 2-3. Mean amplitudes and latencies for the SN component as a function of stimulus condition and distracter type. Note: error bars reflect standard error of the mean.

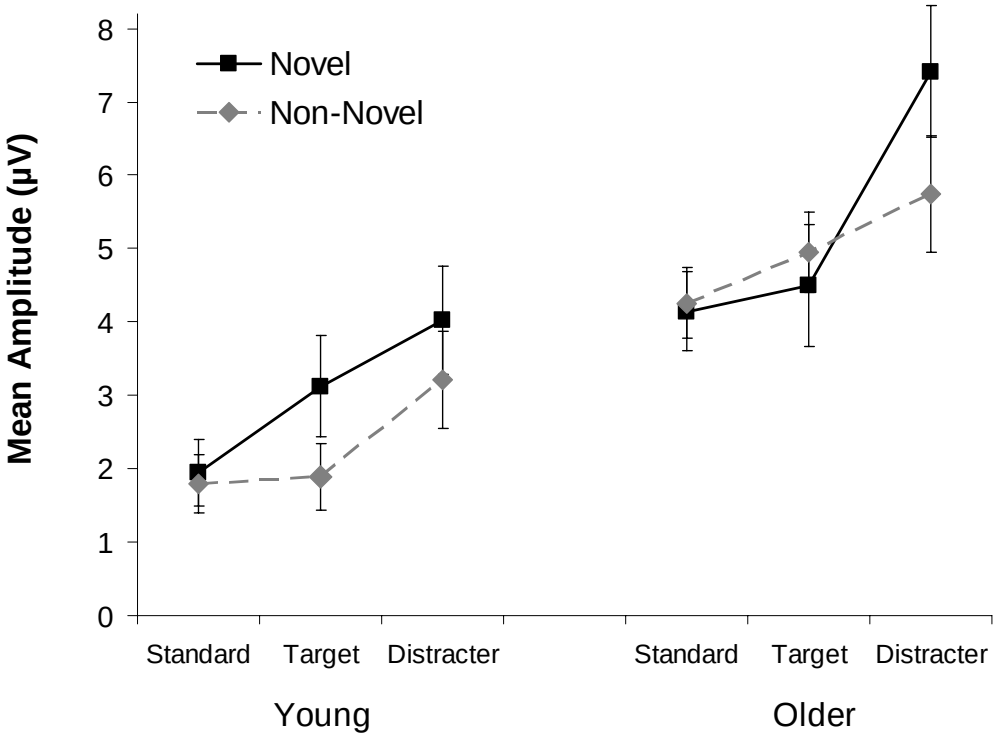

Figure 2-4. Mean amplitudes and latencies for the P2 component as a function of stimulus condition and distracter type for the two participant groups. Note: error bars reflect standard error of the mean.

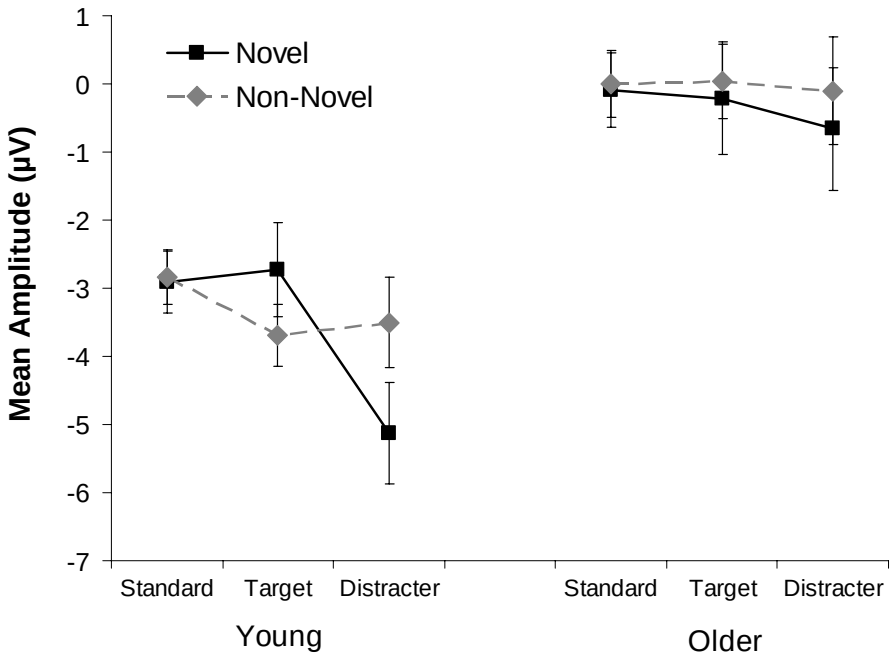

Figure 2-5. Mean amplitudes for the N2 component as a function of stimulus condition and distracter type for the two participant groups. Note: error bars reflect standard error of the mean.

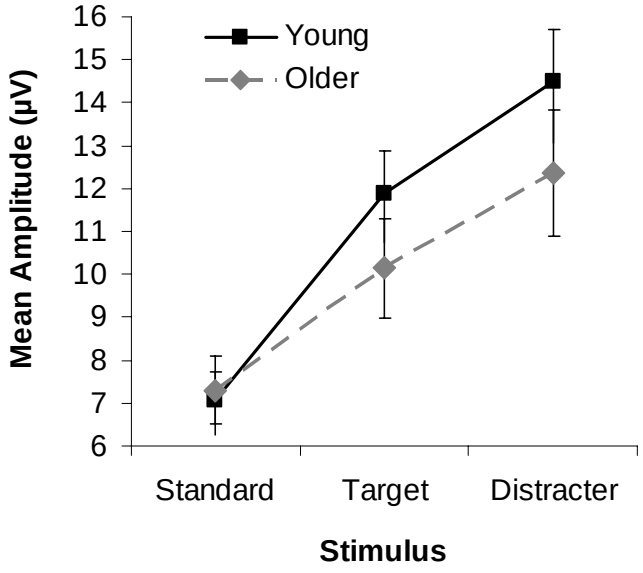

Figure 2-6. Mean amplitudes for the P3 component as a function of stimulus condition for young and older participants. Note: error bars reflect standard error of the mean.

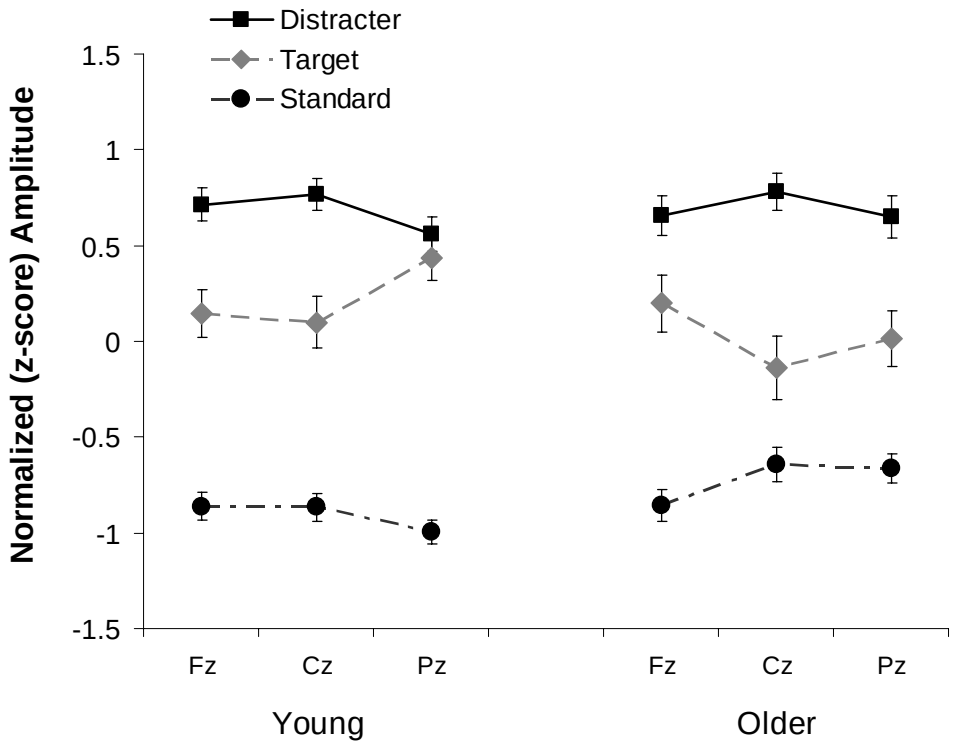

Figure 2-7. Normalized (z-score) ERP amplitudes for the P3 as a function of electrode site and stimulus condition for young and older participants. Note: error bars reflect standard error of the mean.

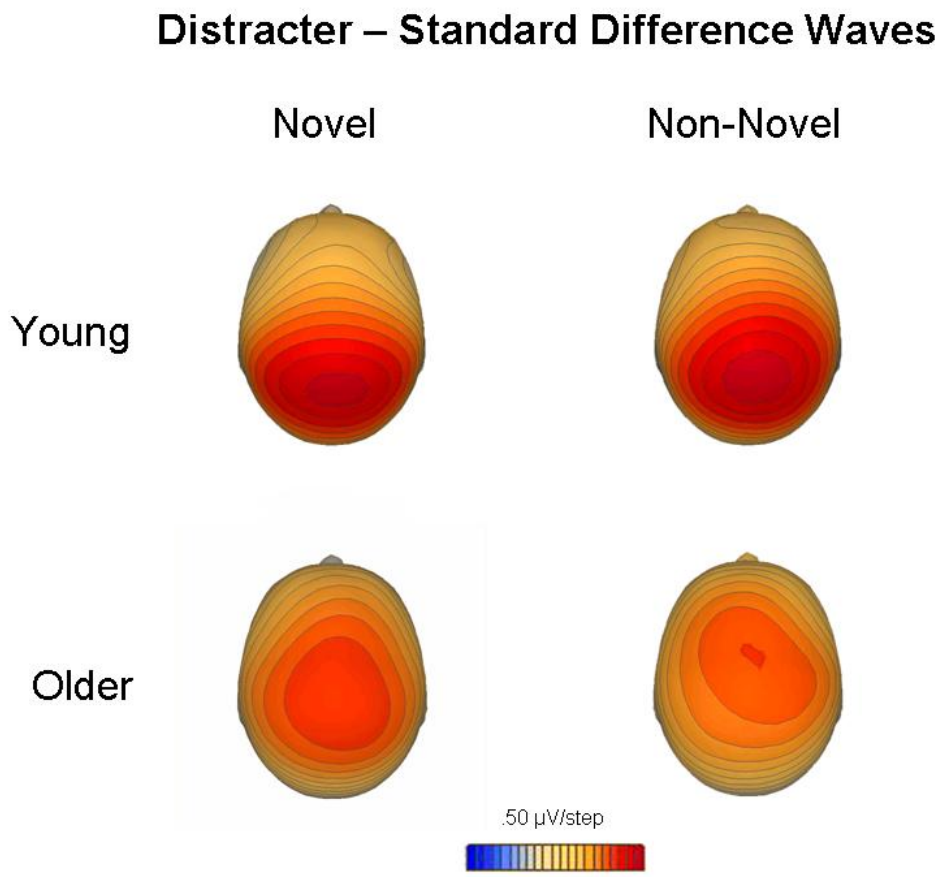

Figure 2-8. Spherical spline voltage maps for the difference waves of distracter – standard stimulus across participant groups, taken at 400 ms.

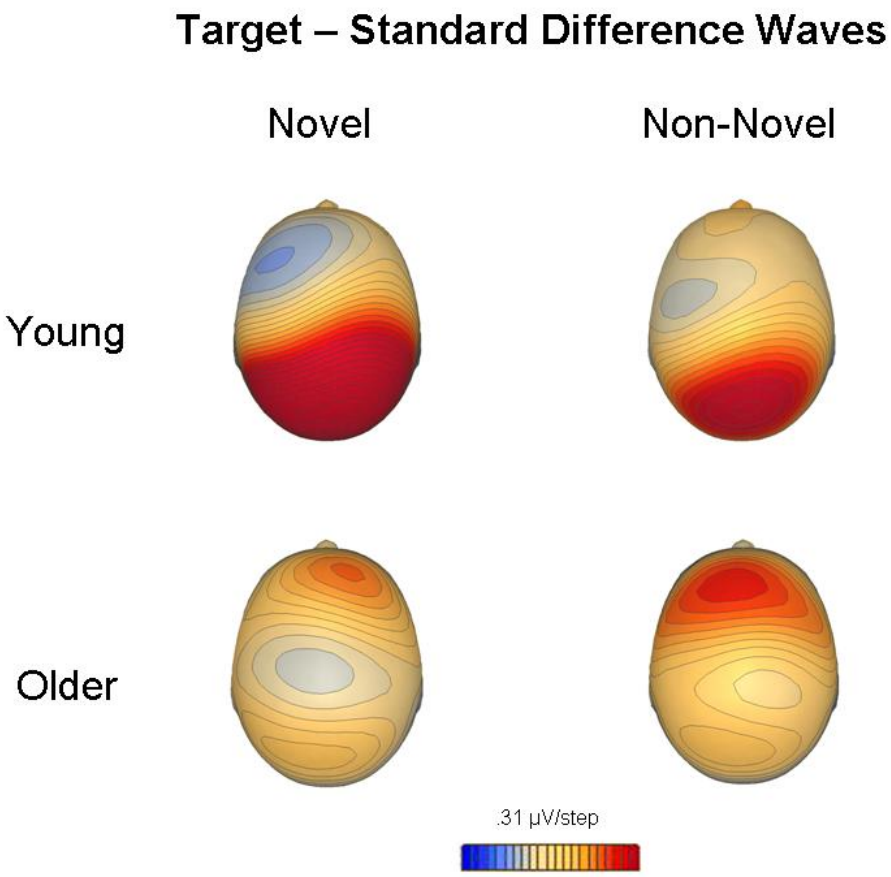

Figure 2-9. Spherical spline voltage maps for the difference waves of target – standard stimulus across participant groups, taken at 400 ms.

CHAPTER 3
EXPERIMENT 2: THE IMPACT OF PARKINSON'S DISEASE ON PREFERENTIAL NOVELTY PROCESSING

Overview and Predictions

Experiment 2 was conducted to examine the effects of Parkinson's disease on ERP reflections of attentional orienting. In line with previous findings, it was predicted that PD patients would show decreased attentional orienting (reflected in N2 and P3 amplitudes) toward novel distracters relative to controls. Given the fact that older adults from Experiment 2 showed reduced effects of distracter novelty on their N2 and P3 responses, it was not expected that these ERP components would differ as a function of distracter novelty for PD patients. However, it was anticipated that target-related processing would be impacted in PD patients in a way similar to that of the older adults from Experiment 1. Assuming that age-related frontal lobe changes give rise to impaired target processing, then it would seem likely that fronto-striatal disruptions in PD would lead to even more alterations in target P3 processing when novel distracters are present. Despite these expected changes in the PD group, early sensory processing was still expected to elicit greater SN and P2 amplitudes relative to non-novel distracters.

Along with differences in N2 and P3 responses, PD patients were also expected to show correlations between novel distracter processing and measures of apathy and executive functioning, while controls were expected to show relationships only between distracter processing and executive functioning. More specifically, distracter amplitudes in PD patients were expected to correlate with self-reported symptoms of apathy (AES), while participants as a whole were expected to show correlations between distracter amplitudes and performance on the Stroop test, Digit Symbol, Trails B, and the Wisconsin Card Sorting Test.

Methods

Participants

Participants for this study were sixteen patients with idiopathic Parkinson's disease and fifteen healthy age-matched controls. Exclusionary criteria for the control participants were the presence of psychiatric illness, learning disability, or history of neurological disease or head injury. To be included in the PD group, patients needed to meet diagnostic criteria for PD and be free of dementia or any other medical illness that would potentially suppress their cognitive performance. The clinical criteria for diagnosis of idiopathic PD included at least two of four cardinal motor signs (akinesia, bradykinesia, resting tremor, rigidity; Hughes, Ben-Shlomo, Daniel, & Lees, 1992) and a history of demonstrated therapeutic response to dopamine replacement therapy, as indicated by a marked improvement in motor signs measured by the United Parkinson Disease Rating Scale-Third Edition (UPDRS; Fahn & Elton, 1987). In this study, all PD patients obtained a score of 25 or higher on the MMSE (M. F. Folstein et al., 1975). Additional dementia screening was done with the Dementia Rating Scale (Mattis, 1988), on which patients generally did very well (mean $\pm$ *SD* = 136.6 $\pm$ 6.5).

Control participants were recruited from the community. Parkinson's disease patients were recruited through the Movement Disorders Center of the University of Florida. Patients received standard measures for staging their motor symptoms and disease course, including the motor subscale of the UPDRS and a modified Hoehn-Yahr scale (Hoehn & Yahr, 1967). Whenever possible, patients were evaluated with the UPDRS "on" and "off" medication. Of the sixteen PD patients, seven received Hoehn-Yahr scores of 2, two were given the score of 2.5, two were scored as 3, and one was a 4. Demographic and neuropsychological data for the participants can be seen in Table 3-1.

Procedures

All participants provided informed consent prior to the experimental session. For members of the healthy control group, the experiment took place in one session that lasted approximately 3 hours (except for two participants who needed to divide their session over two days due to scheduling difficulties). In contrast, most PD patients participated in the study over the course of two days which helped to prevent fatigue from adversely affecting their results. Patients were not given a full motor assessment at the time of testing for this experiment; however, data from UPDRS and modified Hoehn-Yahr scales were collected during a prior visit to the Movement Disorders Center that took place within one calendar year of the experimental session. Controls received financial compensation at the rate of $10 per hour for their participation. PD patients were not paid, but willingly volunteered to participate in conjunction with their visits to the Movement Disorders Center.

Results

Behavioral Data

Oddball task performance

Behavioral data from the oddball task are presented in Table 3-2. A 2-Group x 2-Distracter ANOVA was performed on reaction time to targets, which revealed no significant effect of distracter type or group x distracter interaction. When the two groups were analyzed separately with paired samples t-tests, however, reaction time to targets was found to be affected by distracter type for controls, $t(14) = 2.6$, $p < .05$, with faster responses during trial blocks that presented novel distracters. In order to correct for high levels of skewedness caused by the low probability of errors on the task, error rates were subjected to arcsine transformation and then analyzed using a 2-Group x 3-Stimulus x 2-Distracter ANOVA. Response accuracy showed a group x distracter interaction, $F(2,29) = 5.8$, $p < .05$, $\eta^2 = .17$, such that controls showed a

decline in overall stimulus accuracy when novel distracters were presented, while PD patients showed the opposite pattern. Distracter type also significantly interacted with stimulus type, $F(2,58) = 15.2$, $p < .001$, $\eta^2 = .34$. Follow-up comparisons revealed that false alarms to distracters were greater than both false alarms to standards and target misses, but only when distracters were novel (*ps* < .001).

Cognitive and emotional functioning

The participant groups performed comparably on the MMSE, Boston Naming Test, Controlled Word Association Test, Semantic Fluency, and Digit Span, while PD patients exhibited decreased performance on Trails A and B, Digit Symbol, Stroop Word reading, and the Wisconsin Card Sorting Test (*ps* < .01). PD patients also exhibited more symptoms of depression (BDI and GDS) and anxiety (state and trait) than controls (*ps* < .01). PD patients reported elevated levels of apathy symptoms relative to controls, but this difference was not statistically significant. Four PD patients and two controls obtained a score on the AES that was above the conventional clinical cutoff for apathy (14).

Event-Related Potential Data

Standard stimuli waveforms contained an average ($\pm$ *SD*) of 167.8 $\pm$ 25.3 trials (range: 97-204), while target waveforms contained 33.7 $\pm$ 7.4 trials (range: 18-46) and distracter waveforms contained 35.4 $\pm$ 6.0 (range: 20-44). A 2-Group x 3-Stimulus x 2-Distracter ANOVA confirmed that there were no group- or distracter-related differences in the number of trials comprising the waveforms. Stimulus-locked ERP waveforms from the oddball task can be seen in Figures 3-1 and 3-2. Mean ERP amplitude and latency data are presented in Tables 3-3 through 3-6.

SN component

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of SN amplitude revealed a significant main effect of group, $F(1,29) = 4.8$, $p < .05$, $\eta^2 = .14$, with controls exhibiting greater SN

amplitudes compared to PD patients. There was also a main effect of stimulus, $F(2,58) = 27.6$, $p < .001$, $\eta^2 = .49$, with distracters eliciting the maximal SN. Additionally, a main effect of distracter was also significant, $F(1,29) = 18.4$, $p < .001$, $\eta^2 = .39$, which was qualified by a significant stimulus x distracter interaction, $F(1,29) = 11.7$, $p = .001$, $\eta^2 = .29$. Distracters as a whole elicited larger SN amplitudes than targets and standards (*ps* < .05), but this effect was enhanced when the distracters were novel (*ps* < .001), as shown in Figure 3-3.

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of SN peak latency revealed significant group x stimulus interaction, $F(2,58) = 11.6$, $p < .001$, $\eta^2 = .29$, such that distracter-related SN responses in PD patients were prolonged relative to other stimuli, while controls did not show this pattern. There was also a stimulus x distracter type interaction, $F(2,58) = 3.9$, $p < .05$, $\eta^2 = .12$, that was qualified by a group x linear trend over stimulus x distracter type interaction, $F(1,29) = 5.1$, $p < .05$, $\eta^2 = .15$. For controls, distracters were processed with faster SN responses than other stimuli, particularly when the distracters were novel. Although PD patients were slower with their overall SN responses to distracters relative to other stimuli, they still processed novel distracters more quickly than non-novel distracters ($p < .01$).

P2 component

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of P2 amplitude revealed a significant main effect of group, $F(1,29) = 6.6$, $p < .05$, $\eta^2 = .19$, with controls exhibiting greater P2 amplitudes compared to PD patients. There was also a main effect of stimulus, $F(2,58) = 22.7$, $p < .001$, $\eta^2 = .44$, as P2 amplitude was greater for distracters than any other type of stimulus (*ps* < .001). As shown in Figure 3-4, a significant stimulus x distracter interaction also emerged, $F(1,33) = 14.8$, $p = .001$, $\eta^2 = .34$, such that distracter-related P2 amplitudes were larger during when the distracters were novel. There were no group differences in this stimulus x distracter interaction.

A 2-Group x 3-Stimulus x 2-Distracter ANOVA was conducted on P2 latency, but no main effects or interactions were found.

N2 component

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of frontal N2 amplitude revealed a significant linear trend over stimulus, $F(1,29) = 5.2$, $p < .05$, $\eta^2 = .15$, with maximal N2 amplitude evoked by distracters, followed by targets, and then standard stimuli.

A 2-Group x 3-Stimulus x 2-Distracter ANOVA of frontal N2 latency found a generalized significant main effect of distracter, such that N2 responses from all stimuli that were presented in novel distracter blocks exhibited longer peak latency relative to non-novel distracter blocks, $F(1,29) = 12.3$, $p < .01$, $\eta^2 = .30$.

P3 component

A 2-Group x 3-Stimulus x 3-Site x 2-Distracter ANOVA of P3 amplitudes revealed significant main effects of stimulus and electrode site, as shown in Table 3-7. Target- and distracter-related P3 amplitudes did not differ but were both larger than standard stimuli (*ps* < .001). Overall amplitudes were smaller at Fz relative to central and parietal sites (*ps* < .01). Significant stimulus x site and site x distracter interactions were subjected to follow-up analyses using normalized amplitude data.

The site x distracter interaction was no longer significant following amplitude normalization. However, the stimulus x site interaction remained significant with normalized data, demonstrating a quadratic trend over stimulus that interacted with a quadratic trend over electrode site, $F(1,29) = 13.5$, $p = .001$, $\eta^2 = .32$. P3 distribution was maximal for distracters at the central site, while target-related amplitude was maximal at frontal and parietal sites (see Figure 3-5).

A 2-Group x 3-Stimulus x 3-Site x 2- Distracter ANOVA on P3 latency data revealed a main effect of stimulus and stimulus x site interaction, as shown in table 3-8. Overall, target-related P3 responses were the slowest to reach peak latency (*ps* < .05), and this effect was most pronounced at the parietal site (*ps* < .01), as shown in Figure 3-6. Taken together with the amplitude data, these results show that PD patients' P3 responses were generally affected by distracter novelty in the same way as healthy controls.

Difference waves

In order to isolate the endogenous components more specific to processing distracters and targets, difference waves were calculated by subtracting the standard stimulus ERP waveforms from those elicited by distracters and targets. Novel and non-novel distracter type difference waves were calculated for each group, and these difference waves showed maximal positive amplitudes with a latency of approximately 400 ms, shown in Figure 3-7. This corresponds with P3 latencies of the peak amplitude seen in the original distracter and target waveforms. Mean amplitudes of these difference waves were calculated using a time window from 380-420 ms.

For distracter difference waves, a 2-Group x 3-Site x 2-Distracter ANOVA revealed a main effect of electrode site, $F(2,70) = 5.7$, $p < .01$, $\eta^2 = .16$, and a site x distracter interaction, $F(2,70) = 4.0$, $p < .05$, $\eta^2 = .12$. Distracters elicited a centrally-distributed maximal difference wave, and the site that showed the largest novelty enhancement was the parietal site. For target difference waves, a 2-Group x 3-Site x 2-Distracter ANOVA revealed only a main effect of electrode site, $F(2,70) = 5.1$, $p < .05$, $\eta^2 = .15$, with frontal and parietal sites showing larger amplitudes than central for both groups (*ps* < .05).

Relationship with neuropsychological performance

Several significant correlations were found between neuropsychological measures and difference waves for distracters and targets, as shown in Table 3-9. Controls showed correlations

between digit span backward and the distracter-standard difference wave amplitude, while Digit Symbol performance was correlated with the target-standard difference wave amplitude. Similarly to Experiment 1, education level was also negatively correlated with distracter-standard difference amplitude in the control group.

PD patients showed a large number of correlations between distracter-standard difference wave amplitude and measures of cognition, emotional symptoms, and motor symptom severity. It was interesting to note that several of these correlations were stronger for novel distracters, while others were stronger for non-novel distracters. Notably, Stroop interference score and Digit Symbol correlated had positive correlations with non-novel distracter difference wave amplitudes, while apathy and trait anxiety symptoms correlated negatively with amplitudes from novel distracter difference waves. Of the emotional measures given, only state anxiety symptoms correlated with non-novel distracter difference waves. Additionally, target-standard difference wave amplitude correlated with scores on the GDS and Wisconsin Card Sorting Test.

In order to assess the unique relationships between distracter processing and neuropsychological measures, hierarchical regression models were conducted. The first model included three different measures of emotional symptoms as predictors for the novel distracter-standard difference wave amplitude, as shown in Table 3-10. Apathy score from the AES was selected for step 1 of this model because of the previous research showing a relationship between apathy and distracter P3 amplitudes in other neurological populations. BDI score was then added to the model in order to determine if apathy exhibited a relationship with distracter processing that was unique from that of depression, followed by the trait anxiety score from the STAI. The initial model with apathy score as the lone predictor explained 54% of the variance in novel distracter-standard difference wave amplitude. The addition of BDI and STAI trait anxiety

factors into the regression did not account for any additional variance in distracter-related amplitude.

In order to better understand the unexpected significant correlation between anxiety and novel distracter P3 amplitude, additional hierarchical regression models were conducted to determine if motor symptoms accounted for this relationship. Trait anxiety was included as a predictor for the novel distracter-standard difference wave amplitude in the first step, with motor symptoms taken from the Hoehn-Yahr Scale and UPDRS (both on meds) included in the second step. As shown in Table 3-11, the initial model with trait anxiety as the lone predictor explained 73% of the variance in novel distracter difference wave amplitude, yet the addition of motor symptoms did not account for any additional variance. When examining the role of state anxiety in predicting non-novel distracter difference wave amplitude, a similar result was found. As shown in Table 3-12, state anxiety explained 47% of the variance in non-novel distracter amplitude, and the addition of motor symptoms did not account for any additional variance. As a result, state and trait anxiety emerged as significant predictors of distracter processing, even after controlling for effects of motor symptoms.

Discussion

This experiment used the same parameters as Experiment 1 to examine the ways in which novel stimuli are preferentially processed in Parkinson's disease. The first goal was to observe the effects of distracter novelty on ERP reflections of attentional orienting and determine if PD patients differ in novelty processing relative to age-matched controls. The second goal was to explore the relationships between novelty processing and broader symptoms in PD.

As predicted, novel distracters engaged the early visual attention system in ways that were not seen for non-novel distracters. PD patients showed larger SN and P2 responses to novel distracters compared to non-novel distracters, although both of these effects were smaller for PD

patients compared to controls. However, no differences were found between PD patients and controls with regard to the effects of distracter novelty on attentional orienting or target-related processing. N2 responses were larger for distracters than targets, but did not differ between groups. Both groups also showed a lack of P3 enhancement from distracters and similar scalp distributions of overall P3 responses. Distracters were associated with a maximal response over the parietal electrode, while target-related P3 responses showed scalp distributions that were large at both frontal and parietal sites, an effect that is commonly observed in older adults (e.g., Fabiani & Friedman, 1995).

Contrary to predictions, these findings suggest that PD patients do not experience additional deficits in attentional orienting or target processing beyond those associated with healthy aging. Differences did emerge, however, when examining the relationships between P3 responses and measures of neuropsychological and neurological functioning. PD patients showed correlations between distracter processing and a much broader range of symptoms that fell into distinct cognitive, emotional, and motor categories. In line with predictions, all of the cognitive factors that correlated with distracter processing were measures of executive functioning (Stroop interference, Digit Symbol, verbal fluency, and Trails B). Of the emotional measures, apathy and trait anxiety correlated with novel distracter processing, while motor symptom severity scores correlated with both novel and non-novel distracter responses.

The negative correlation between novel distracter P3 and apathy scores was expected, given previous reports that other neurological patients with damage to frontal or subcortical regions show this same relationship (Daffner et al., 2001; R. T. Knight, 1984; Yamagata et al., 2004). Subsequent analysis with hierarchical regression found that the relationship between apathy and novelty distracter P3 amplitude remained significant after accounting for the effects

of depression. Furthermore, trait anxiety did not explain any additional variance in novel distracter processing beyond that of apathy and depression. However, trait and state anxiety emerged as significant predictors of distracter processing above and beyond that accounted for by motor symptoms. This is an interesting finding, since there has been some data linking anxiety and motor fluctuations in PD, with some studies finding increased anxiety symptoms when patients are in the "off" state of dopaminergic therapy (Menza et al., 1990; Siemers et al., 1993). Unfortunately, since PD patients typically spread their participation across different days to prevent fatigue, the data from the STAI, motor symptom scales, and EEG experiment were not collected at the same time. As a result, the precise temporal relationship between distracter processing and momentary fluctuations in anxiety or motor symptoms could not be fully assessed with the current study.

Target-related P3 responses in PD patients correlated with depression symptoms endorsed on the GDS and measures of WCST performance (categories completed, perseverative errors). Although many cognitive processes are required for success on the WCST, this task is generally understood to measure executive functioning (Lezak et al., 2004). Impairment on the WCST has previously been associated with distracter-related P3 processing in PD (Tsuchiya et al., 2000), so it was somewhat unexpected that WCST performance correlated with target-related P3 amplitude in this study. When examining the relationships between distracter-related processing and neuropsychological measures, stroop interference and Digit Symbol performance both correlated strongly with non-novel distracter processing. However, these cognitive measures had virtually no correlation with novel distracter processing. The opposite finding was the case for apathy and trait anxiety scores, which correlated strongly with novel distracter processing only.

The reason for these different correlation patterns is not clear; however, it is possible that the divergent relationships with distracter novelty were influenced by task-related differences caused by the experimental manipulation of distracter novelty. Analysis of false alarm rates to distracters revealed that PD patients committed more errors when the distracters were novel (6.0%) than when they were not (4.7%). Furthermore, controls were over 10 times more likely to commit a false alarm to a novel distracter than one that was non-novel. ERPs were taken only from correct trials, so distracter false alarms did not directly contribute to differences in the ERP waveforms. However, the fact that participants were more likely to generate false alarms when the distracters were novel suggests that the two distracter conditions required differing degrees of inhibition. It would be logical that the more challenging response inhibition condition (trial blocks containing novel distracters) would require cognitive processes similar to that measured neuropsychological tasks like Stroop, WCST, or Digit Symbol that tap inhibition and other related executive functioning abilities. Instead, the data seem to be suggesting another story. Novel distracter processing was most strongly correlated with apathy, trait anxiety, and motor symptom severity.

Perhaps the relationship between novel distracter processing and neuropsychological measures were lacking because the inhibitory processes required to prevent false alarms of novel distracters are not as simple or unitary as they are for non-novel distracters. Furthermore, it is possible that additional neural resources were required to successfully inhibit a false alarm to the novel distracters (due to increased perceptual salience), and these extra resources might be beyond the scope of the P3 to measure. Whatever the reason behind these particular findings, these correlation patterns raise the possibility that novelty processing may interact with broader cognitive and emotional functions in ways that are more complex than first thought.

Table 3-1. Mean and standard deviation (*SD*) demographic and neuropsychological data for controls and PD participants.

	Controls (n=15)		PD Patients (n=16)		
	Mean	(*SD*)	Mean	(*SD*)	*p*
Demographics					
Age (years)	65.0	(9.5)	63.5	(8.7)	*ns*
Education (years)	17.4	(3.3)	13.7	(3.1)	< .01
Female (%)	47	--	25	--	*ns*
Right-Handed (%)	87	--	100	--	*ns*
Cognitive Functioning					
MMSE	28.5	(1.5)	29.2	(1.1)	*ns*
Dementia Rating Scale	--	--	136.6	(6.5)	
Boston Naming Test	57.1	(3.8)	56.6	(2.3)	*ns*
COWA (FAS)	44.6	(12.0)	37.1	(14.9)	*ns*
Semantic Fluency (Animals)	22.1	(5.3)	19.3	(6.5)	*ns*
Digit Span Forward	7.1	(1.3)	7.0	(1.1)	*ns*
Digit Span Backward	5.5	(1.4)	5.6	(1.4)	*ns*
Trails A (sec)	28.0	(10.3)	47.3	(25.7)	.01
Trails B (sec)	65.0	(28.0)	119	(55.6)	< .01
Digit Symbol	75.6	(13.3)	49.4	(16.8)	< .001
Stroop Word Reading	99.3	(13.0)	83.9	(15.5)	< .001
Stroop Color Naming	73.5	(15.3)	63.3	(13.8)	*ns*
Stroop Color Word Naming	38.6	(11.5)	32.3	(11.4)	*ns*
WCST Categories Completed	5.7	(1.0)	3.7	(1.9)	.001
WCST Total Errors	18.7	(15.0)	40.4	(19.3)	< .01
WCST Perseverative Errors	10.5	(9.1)	22.9	(12.5)	< .01
WCST Set Failure	.3	(.6)	1.3	(.9)	.001
Emotional Functioning					
BDI-II	2.8	(3.3)	11.7	(8.1)	.001
GDS	.9	(1.3)	8.0	(7.9)	< .01
AES	7.9	(4.9)	10.4	(8.0)	*ns*
STAI - State	27.5	(7.5)	39.1	(11.3)	< .01
STAI - Trait	27.7	(5.7)	39.1	(12.3)	< .01
Disease Characteristics					
Duration of Symptoms (yrs)	--	--	10.4	(2.82)	--
UPDRS Motor – On Meds	--	--	26.2	(13.2)	--
Hoehn-Yahr Scale – On Meds	--	--	2.4	(.6)	--
UPDRS Motor – Off Meds	--	--	34.1	(12.4)	--
LED	--	--	1129.0	(637.8)	--
Antidepressant Medications (%)	--	--	37.5	--	--

Table 3-2. Behavioral data from the oddball task.

	Controls		PD Patients		
	Mean	(*SD*)	Mean	(*SD*)	*p*
Non-Novel Distracter					
Reaction time to targets (ms)	478	(69)	476	(97)	*ns*
Target response errors (%)	1.6	(2.2)	9.1	(10.1)	*< .01*
False alarm to distracters (%)	.4	(.9)	4.7	(9.8)	*ns*
False alarm to standards (%)	.1	(.3)	4.2	(8.8)	*ns*
Novel Distracter					
Reaction time to targets (ms)	462	(73)	483	(72)	*ns*
Target response errors (%)	1.5	(3.1)	4.8	(7.3)	*ns*
False alarm to distracters (%)	4.6	(.6)	6.0	(3.5)	*ns*
False alarm to standards (%)	.3	(.5)	2.2	(4.3)	*ns*

Table 3-3. Peak amplitudes (μV) from the control group for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	-1.9	(1.9)	-3.0	(2.6)	-8.7	(5.2)
	Non-Novel	-2.4	(1.3)	-2.9	(2.2)	-4.8	(3.5)
Cz	P2						
	Novel	4.1	(2.3)	4.5	(2.5)	7.4	(3.6)
	Non-Novel	4.3	(2.0)	5.0	(2.0)	5.7	(3.4)
Fz	N2						
	Novel	-.09	(1.5)	-.21	(1.8)	-.67	(3.2)
	Non-Novel	.00	(1.4)	.04	(1.5)	-.10	(2.1)
Fz	P3 (Frontal)						
	Novel	5.3	(2.2)	8.9	(3.8)	10.4	(3.8)
	Non-Novel	5.4	(2.1)	9.5	(4.3)	10.3	(3.5)
Cz	P3 (Central)						
	Novel	8.5	(3.3)	10.4	(6.2)	14.9	(5.9)
	Non-Novel	8.9	(3.4)	10.6	(6.5)	14.2	(5.4)
Pz	P3 (Parietal)						
	Novel	7.7	(3.4)	10.9	(6.4)	12.9	(4.9)
	Non-Novel	8.0	(3.0)	10.6	(6.6)	11.4	(5.3)

Table 3-4. Peak amplitudes (μV) from PD patients for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	-1.0	(2.9)	-2.1	(3.4)	-4.3	(4.7)
	Non-Novel	-.90	(2.4)	-1.2	(3.0)	-2.4	(3.7)
Cz	P2						
	Novel	2.5	(1.7)	2.2	(3.0)	5.5	(3.4)
	Non-Novel	2.3	(1.8)	3.0	(2.7)	3.0	(3.2)
Fz	N2						
	Novel	-1.3	(1.8)	-2.2	(3.3)	-2.5	(3.7)
	Non-Novel	-1.6	(1.7)	-1.3	(3.1)	-2.7	(2.7)
Fz	P3 (Frontal)						
	Novel	5.6	(2.8)	8.0	(5.3)	9.0	(4.6)
	Non-Novel	5.6	(2.6)	9.6	(5.2)	9.2	(4.9)
Cz	P3 (Central)						
	Novel	7.1	(3.4)	8.5	(6.6)	11.1	(4.8)
	Non-Novel	7.1	(3.6)	10.3	(7.8)	11.1	(6.1)
Pz	P3 (Parietal)						
	Novel	7.0	(3.4)	9.6	(6.4)	10.8	(4.5)
	Non-Novel	6.9	(3.5)	11.2	(5.7)	10.1	(5.2)

Table 3-5. Peak latencies (ms) from controls for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	160.0	(21.8)	155.7	(21.9)	147.7	(13.6)
	Non-Novel	161.6	(23.5)	156.0	(20.8)	152.0	(18.5)
Cz	P2						
	Novel	195.7	(45.4)	185.3	(37.1)	173.9	(30.0)
	Non-Novel	197.3	(42.5)	171.2	(40.5)	189.6	(43.1)
Fz	N2						
	Novel	216.3	(50.9)	243.2	(49.7)	240.5	(37.9)
	Non-Novel	202.4	(28.9)	218.1	(43.2)	212.8	(38.3)
Fz	P3 (Frontal)						
	Novel	409.9	(43.0)	437.9	(58.6)	418.7	(48.9)
	Non-Novel	392.5	(47.8)	417.6	(49.9)	430.9	(50.3)
Cz	P3 (Central)						
	Novel	391.7	(47.5)	472.3	(85.3)	424.8	(48.1)
	Non-Novel	381.9	(36.4)	438.1	(66.0)	421.6	(34.5)
Pz	P3 (Parietal)						
	Novel	388.3	(61.3)	482.4	(91.5)	425.9	(72.2)
	Non-Novel	383.5	(59.4)	487.5	(94.4)	410.7	(69.1)

Table 3-6. Peak latencies (ms) from PD patients for each stimulus type across novel and non-novel distracter blocks.

Electrode Site		Standard		Target		Distracter	
		Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)
Oz	SN						
	Novel	150.3	(33.6)	144.3	(35.0)	151.5	(19.8)
	Non-Novel	139.8	(34.3)	144.0	(33.6)	164.5	(19.9)
Cz	P2						
	Novel	167.0	(44.4)	167.0	(39.0)	171.3	(31.3)
	Non-Novel	177.3	(46.6)	176.5	(43.7)	168.0	(50.3)
Fz	N2						
	Novel	244.3	(44.3)	237.8	(40.9)	250.5	(31.6)
	Non-Novel	234.0	(36.8)	228.3	(45.5)	232.0	(45.2)
Fz	P3 (Frontal)						
	Novel	416.3	(59.9)	462.0	(95.3)	453.3	(81.1)
	Non-Novel	415.3	(69.6)	446.3	(91.7)	432.0	(76.6)
Cz	P3 (Central)						
	Novel	436.5	(87.3)	463.3	(121.6)	431.0	(72.7)
	Non-Novel	425.3	(90.7)	454.5	(121.6)	422.5	(71.5)
Pz	P3 (Parietal)						
	Novel	379.5	(61.7)	447.8	(112.9)	393.0	(76.7)
	Non-Novel	397.5	(76.5)	444.8	(89.8)	409.8	(78.5)

Table 3-7. Summary of the 2-Group x 3-Stimulus x 3-Site x 2-Distracter ANOVAs performed on P3 peak amplitude data.

	Amplitude			Normalized Amplitude		
	F	*p*	η^2	*F*	*p*	η^2
Group[a]						
Stimulus[b]	22.7	<.001	.44			
Site[b]	14.1	<.001	.33			
Distracter[a]						
G x Stim[b]						
G x Site						
G x D[a]						
Stim x Site[c]	8.5	<.001	.23	3.1	< .05	.10
Stim x D[b]						
Site x D[b]	3.5	<.05	.11			
G x S x S[c]						
G x Stim x D[a]						
G x Site x D[b]						
S x S x D[c]						
G x S x S x D[c]						

[a]df = 1,29, [b]df = 2,58, [c]df = 4,116

Table 3-8. Summary of the 2-Group x 3-Stimulus x 3-Site x 2-Distracter ANOVAs performed on P3 peak latency data.

	Latency		
	F	*p*	η^2
Group[a]			
Stimulus[b]	11.9	<.001	.29
Site[b]			
Distracter[a]			
G x Stim[b]			
G x Site			
G x D[a]			
Stim x Site[c]	4.0	<.01	.12
Stim x D[b]			
Site x D[b]			
G x S x S[c]			
G x Stim x D[a]			
G x Site x D[b]			
S x S x D[c]			
G x S x S x D[c]			

[a]df = 1,29, [b]df = 2,58, [c]df = 4,116

Table 3-9. Significant correlations between difference waves and neuropsychological measures for control and PD groups separately.

	Distracter – Standard		Target – Standard	
	Novel	Non-Novel	Novel	Non-Novel
Controls				
Education	-.72***	-.61*		
Digit Span Backward	-.35	-.55*		
Digit Symbol			.62*	.57*
PD Patients				
Cognitive				
Stroop Interference	.14	.71**		
Digit Symbol	.11	.55*		
Animal Fluency	.37	.51*		
Trails B	-.55*	-.27		
WCST Categories			-.56*	-.57*
WCST Persev Errors			-.65*	-.59*
Emotional				
AES	-.61**	-.30		
BDI	-.41	-.10		
STAI – Trait	-.65**	-.44		
STAI – State	-.37	-.61*		
GDS	-.43	-.20	.57*	.39
Motor				
UPDRS	-.54*	-.61*		
Hoehn-Yahr	-.63*	-.28		

*$p < .05$, **$p < .01$, ***$p < .001$

Table 3-10.Summary of hierarchical regression analysis for variables predicting the amplitude of the novel Distracter-Standard difference wave.

	B	*SE B*	*β*
Step 1			
Constant	6.40	.98	
AES	-.28	.07	-.73**
Step 2			
Constant	6.19	1.12	
AES	-.33	.14	-.87*
BDI	.063	.14	.16
Step 3			
Constant	7.02	3.00	
AES	-.31	.18	-.79
BDI	.08	.16	.21
STAI – Trait Anxiety	-.04	.12	-.14

Note R^2 = .54 for Step 1 (p < .01); ΔR^2 = .007 for Step 2; ΔR^2 = .004 for Step 3 (ps >.65).
*p < .05, **p < .01.

Table 3-11.Summary of hierarchical regression analysis for variables predicting the amplitude of the novel Distracter-Standard difference wave.

	B	*SE B*	*β*
Step 1			
Constant	10.72	1.74	
STAI – Trait Anxiety	-.209	.04	-.86**
Step 2			
Constant	11.56	2.32	
STAI – Trait Anxiety	-.19	.06	-.80*
Hoehn-Yahr Scale (on meds)	.03	.07	.10
UPDRS (on meds)	-.87	1.29	-.19

Note R^2 = .73 for Step 1 (p = .001); ΔR^2 = ..02 for Step 2 (p > .80).
*p < .05, ** p < .01.

Table 3-12.Summary of hierarchical regression analysis for variables predicting the amplitude of the non-novel Distracter-Standard difference wave.

	B	*SE B*	*β*
Step 1			
Constant	10.06	2.98	
STAI – State Anxiety	-.21	.08	-.69*
Step 2			
Constant	8.12	3.87	
STAI – Trait Anxiety	-.23	.09	-.75*
Hoehn-Yahr Scale (on meds)	-.07	.11	-.22
UPDRS (on meds)	1.81	1.86	.34

Note $R^2 = .47$ for Step 1 ($p < .05$); $\Delta R^2 = .06$ for Step 2 ($p > .60$).
*$p < .05$.

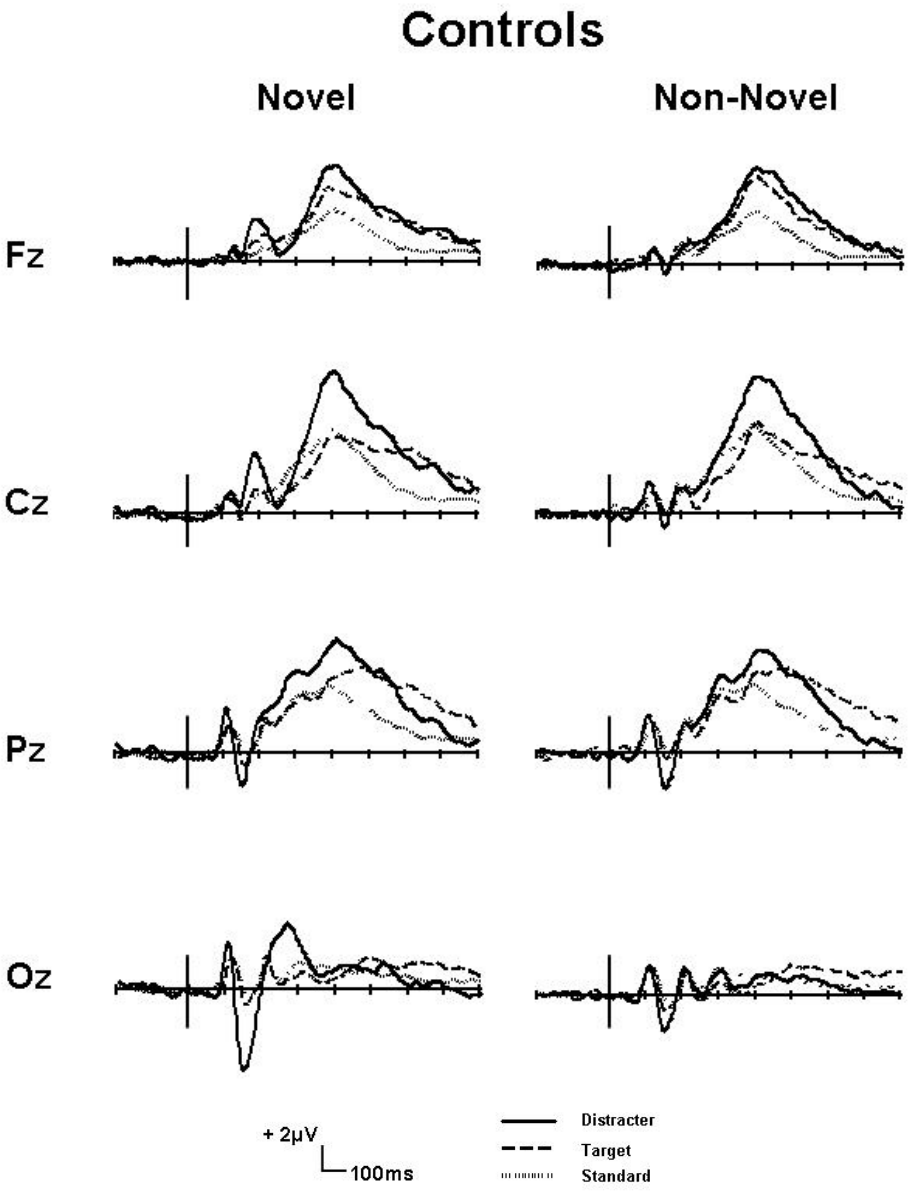

Figure 3-1. Grand-averaged standard, target, and distracter ERPs from the midline electrodes for healthy controls. Microvolts on the *y*-axis, milliseconds on the *x*-axis.

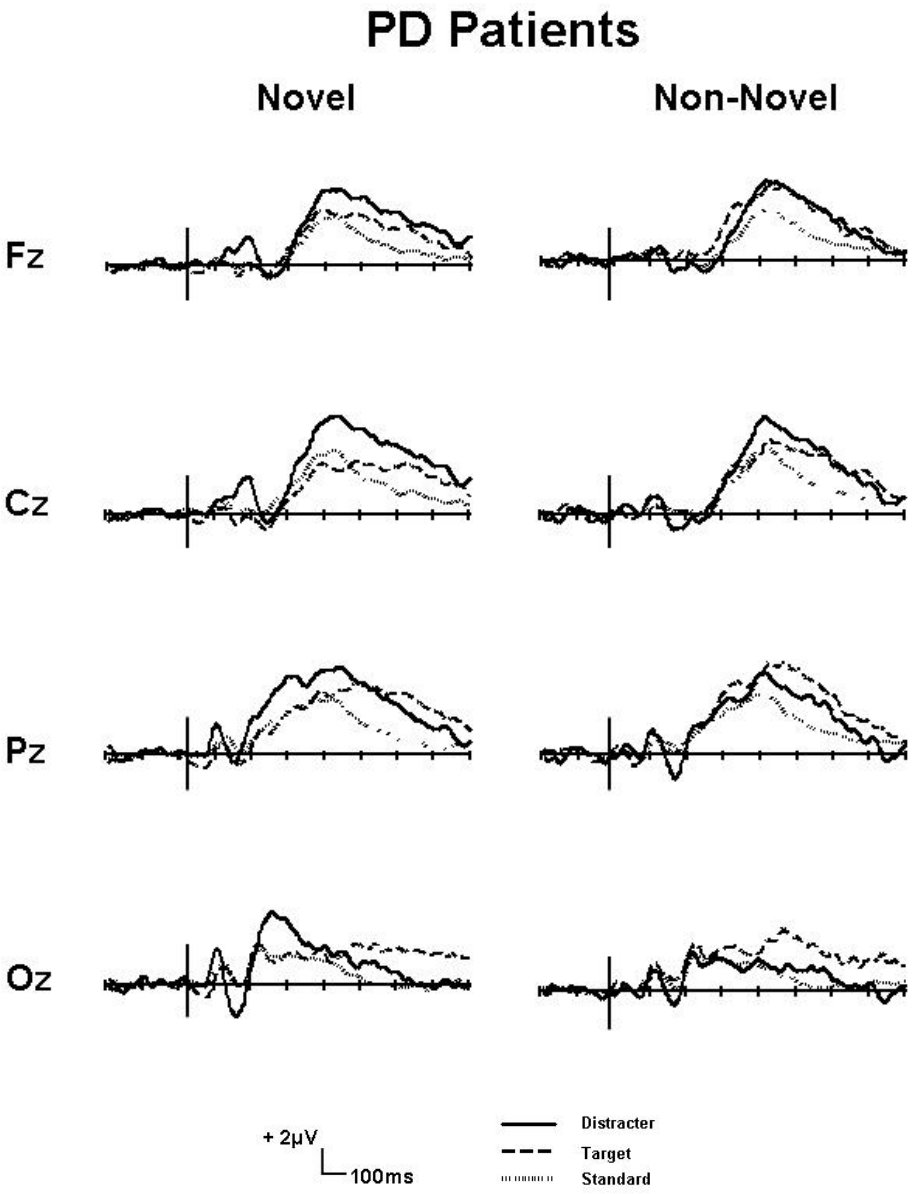

Figure 3-2. Grand-averaged standard, target, and distracter ERPs from the midline electrodes for PD patients. Microvolts on the *y*-axis, milliseconds on the *x*-axis.

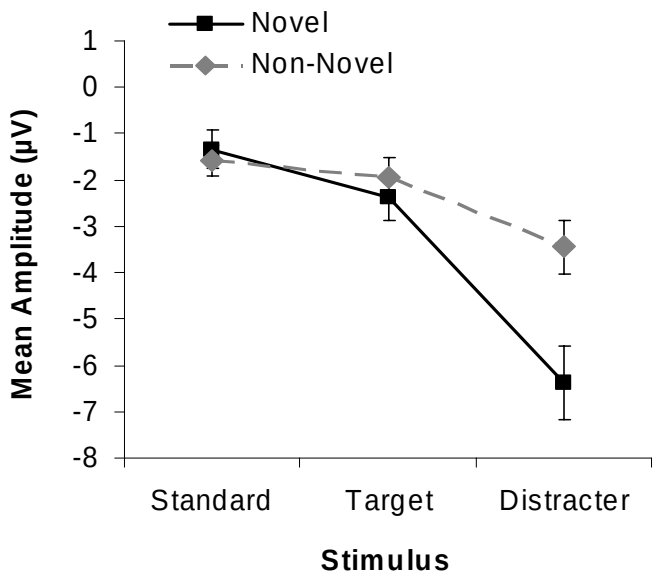

Figure 3-3. Mean amplitudes for the SN component as a function of stimulus condition and distracter type. Note: Error bars reflect standard error of the mean.

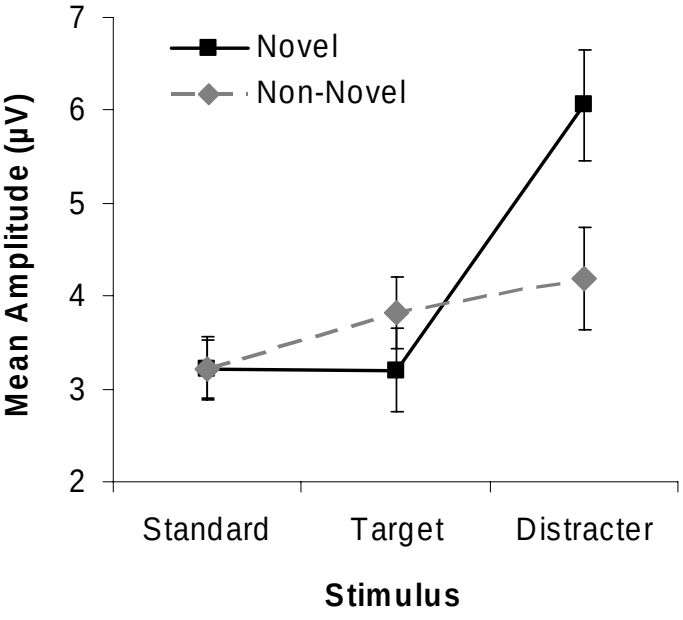

Figure 3-4. Mean amplitudes for the P2 component as a function of stimulus condition and distracter type. Note: Error bars reflect standard error of the mean.

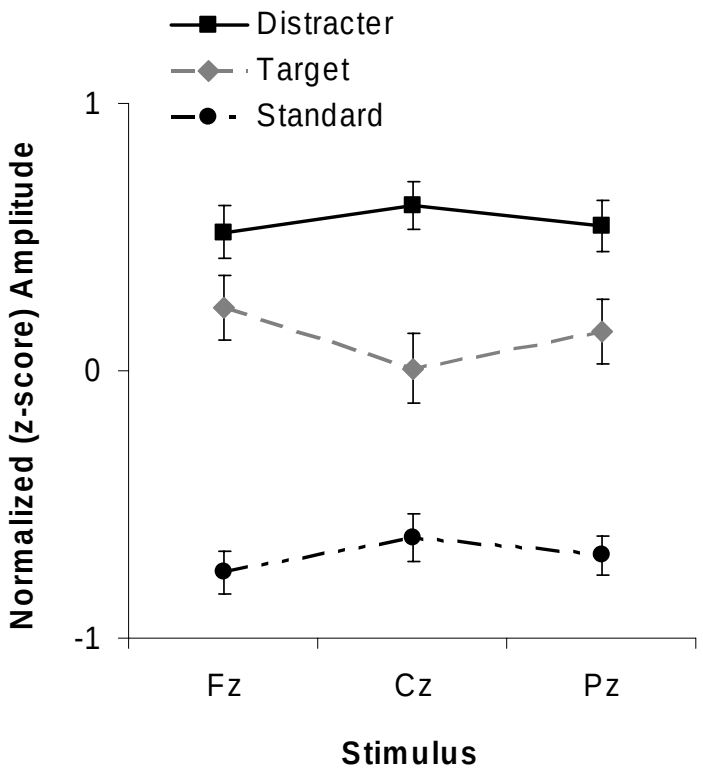

Figure 3-5. Normalized (z-score) ERP amplitudes for the P3 as a function of electrode site and stimulus condition for both groups combined. Note: Error bars reflect standard error of the mean.

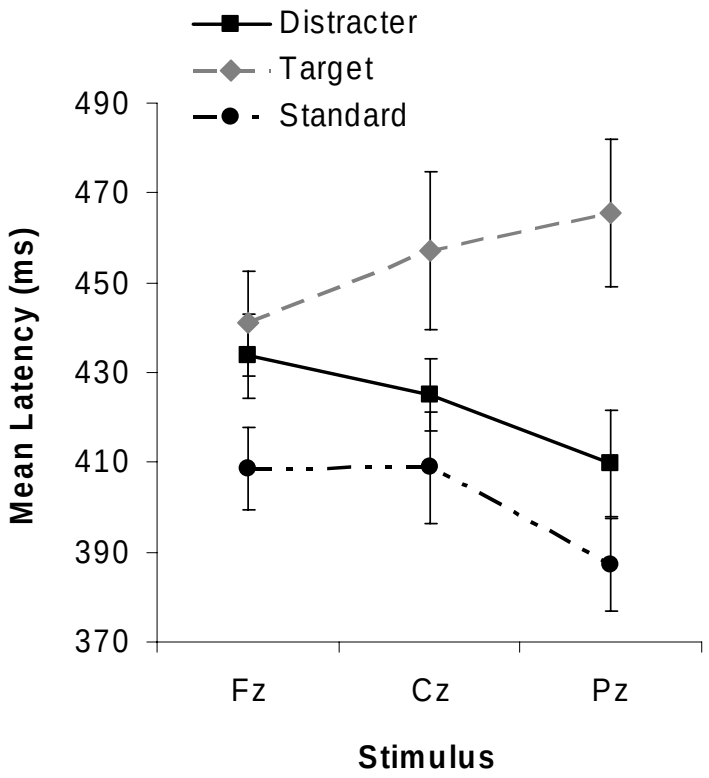

Figure 3-6. ERP latencies for the P3 as a function of electrode site and stimulus condition for both groups combined. Note: Error bars reflect standard error of the mean.

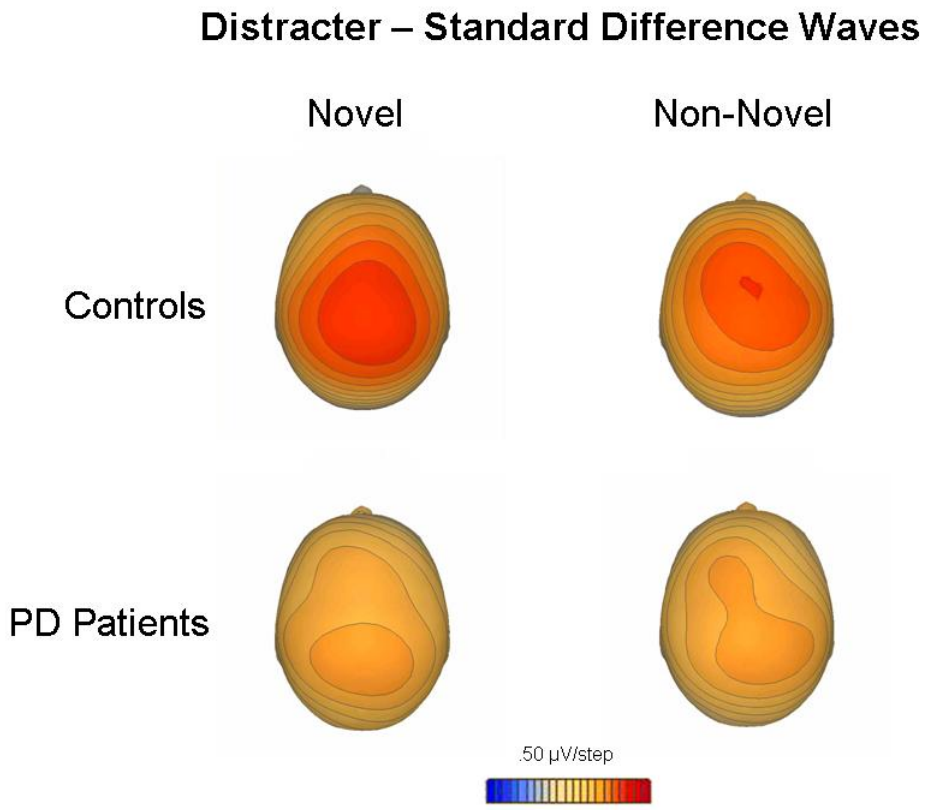

Figure 3-7. Spherical spline voltage maps for the difference waves of distracter – standard stimulus across participant groups, taken at 400 ms.

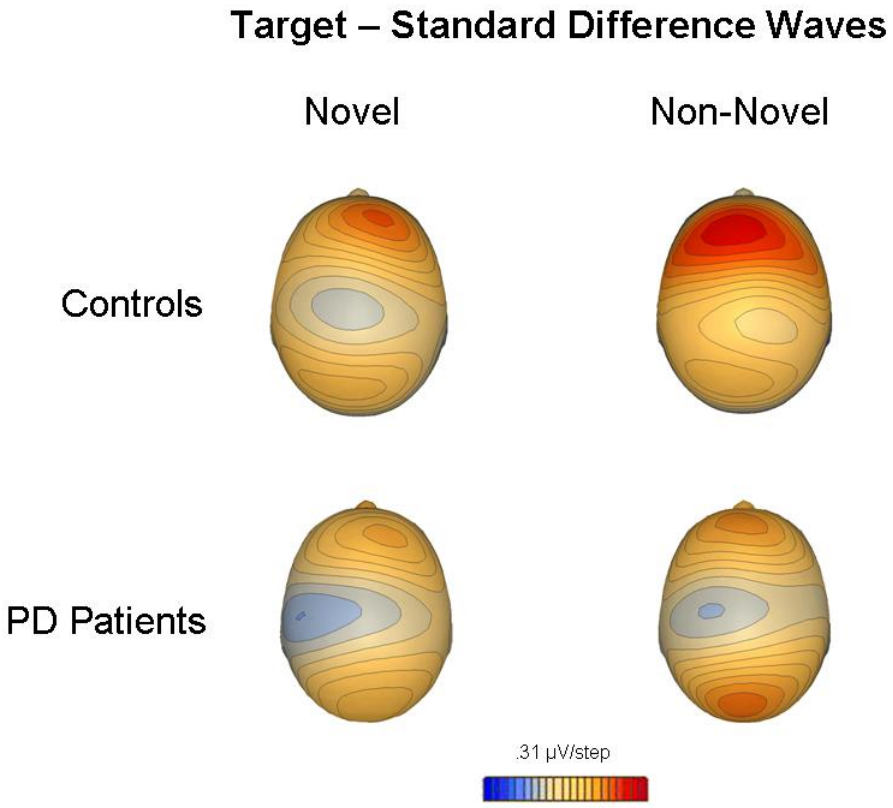

Figure 3-8. Spherical spline voltage maps for the difference waves of target – standard stimulus across participant groups, taken at 400 ms.

CHAPTER 4
GENERAL DISCUSSION

These two experiments examined novelty processing across young and older adults and between Parksinson's disease patients and age-matched controls. By manipulating distracter features, it was possible to examine the effects of novelty on attentional orienting to unexpected events. The first aim of this project was to examine the effects of novelty on distracter processing and examine the neural timecourse of preferential engagement with novel events in healthy young adults. As predicted, distracting novel stimuli that contained colorful designs were associated with preferential processing that began early in visual processing, reflected in SN and P2 component enhancements. Also in line with predictions, these novelty features did not change the preferential processing reflected in the P3 component, yet N2 was enhanced beyond the level seen for non-novel distracters. This supports the notion that the N2 reflects subprocesses of attentional orienting which serve as an index of stimulus unfamiliarity (Daffner, Mesulam, Scinto, Calvo et al., 2000). While this N2 enhancement effect has been seen in previous studies, it has not been reported in conjunction with the early components of visual attention (SN, P2) that were also enhanced for novel distracters. Furthermore, this finding is important since N2 differences have only rarely been studied in older adults and PD patients.

The second aim was to examine the impact of healthy aging and Parkinson's disease on novelty processing. Both healthy older adults and PD patients failed to exhibit N2 enhancements in response to novelty, even when distracters were highly novel and preferentially engaged early visual attention (SN, P2). The reasons for these deficits are not entirely clear, but are likely related to compromised frontal lobe structures that are part of the network that mediates attentional orienting. Indeed, frontal shifts in target-related scalp distribution were seen for the older adults and PD patients, suggesting that they required additional frontal lobe resources to

perform the task. Even so, older participants' target P3 responses were selectively altered by the presence of novel distracters, suggesting that the increase in task-irrelevant novelty processing disrupted their ability to maintain memory templates of task-relevant stimuli.

Contrary to expectations, PD patients and healthy age-matched controls did not significantly differ in their ERP reflections of attentional orienting (N2, P3). P3 amplitudes were slightly smaller in the PD group compared to controls, but this difference did not reach statistical significance. Although impairments in novelty P3 amplitudes have previously been reported in this clinical population (Tsuchiya et al., 2000), the results of the current study are not supportive of a definitive impairment in attentional orienting in PD that goes beyond the general effects of aging. However, PD patients did exhibit differences from controls in the manner with which their attentional orienting measures (P3 amplitude) were associated with other forms of cognitive and emotional processing.

The third aim of this project was to explore the relationships between novelty processing and other domains of psychological function. In Experiment 1, young and older adults showed similar relationships between measures of executive function and distracter-related P3 processing. In Experiment 2, PD patients generated P3 responses to novel distracters that were negatively correlated with apathy scores (even while accounting for symptoms of depression), such that patients who were more apathetic demonstrated smaller P3 amplitudes in response to the novel distracters. This finding was predicted, given previous reports that other neurological disorders are characterized by this same relationship (Daffner, Mesulam, Scinto, Acar et al., 2000; Daffner et al., 2001; R. T. Knight, 1984; Yamagata et al., 2004). Another interesting finding was that anxiety was negatively associated with distracter-related P3 amplitudes, even while controlling for motor symptoms. Finally, it was notable that some neuropsychological

measures only correlated with novel distracter P3 amplitudes in PD patients, while others correlated only with responses evoked from non-novel distracters. Unfortunately, the current project was not statistically powered for an in-depth analysis of these relationships. However, these dissociations could reflect meaningful differences in the way that novelty processing interacts with broader psychological functioning and should be explored further in future research.

Although novelty processing is often conceptualized as an automatic reflex that orients attention toward unexpected events, a recent study found that novelty effects are vulnerable to top-down modulation. Using a three-stimulus oddball task similar to the one involved in this project, Chong and colleagues (2008) included an interesting condition in which participants were instructed to visually explore the novel stimuli as task-relevant "invitations" for further processing, rather than ignoring them as task irrelevant distracters. This condition led to enhanced novelty processing, as reflected in larger P3 amplitudes, and provided dramatic evidence that changes in context – both experimentally and personally derived – can have dramatic changes on how novel information is processed. The results of the current study clearly support this notion that individual differences in psychological functioning are strongly associated with ERP reflections of novelty processing, as apathy and anxiety were found to explain large portions of the variance in distracter P3 amplitudes.

This project possessed several weaknesses that need be taken into account when generalizing conclusions. First of all, the mean age of the older participants was 65, yet this age varied considerably within the group (range: 49-77). It would have been desirable to limit the sample to a more homogenous age range so that the findings could be better generalized and compared to other aging studies that had more restrictive age ranges. Similarly, the PD patient

group also suffered from limitations in that the sample size was relatively small in relation to the heterogeneity of symptoms presented. Furthermore, all PD patients were recruited from clinical/research settings affiliated with an academic medical center. Many of these patients were participating in other research/clinical evaluations in conjunction with their participation in this project. Therefore, certain levels of symptoms (e.g., apathy, cognitive dysfunction) may have been subject to a selection bias. As a result, the PD-related findings may not generalize to all PD patients. However, both of these limitations should have actually worked against the hypotheses and made it more difficult to obtain significant age- and PD-related effects; therefore, participant characteristics of the older and PD groups do not appear to be a major obstacle in interpreting the results of this study. On the contrary, they speak to the robustness of the age- and PD-related findings that were obtained.

Another limitation is that no estimates of IQ were obtained from participants during this study, which may have been helpful for interpreting results in light of global cognitive abilities. This became an important weakness as the study reached its completion, since young and older age groups could not be balanced in terms of overall education level. While education is not believed to have been a major confound in the current project, it is possible that it influenced some of the group-related differences, particularly with regard to the relationships between P3 responses and other cognitive variables. A measure of IQ could have provided a way to ensure that global cognitive abilities were similar across groups. As a screening tool, the MMSE was not likely sensitive enough to provide this level of information. Nevertheless, other studies similar to this have also suffered from group differences in education, which appears to be somewhat inevitable when investigating aging (e.g., Daffner et al., 2005).

This project also contained numerous methodological strengths. First, the concept of novelty was operationalized successfully by using two sets of task-irrelevant distracters that differed in their degree of novelty features. The experimental manipulation of distracter novelty allowed for concrete conclusions to be drawn about the effects of novelty on attentional processing across the three participant groups. The novel stimuli were designed in such as a way as to maximize their likelihood of receiving preferential processing in all stages of visual processing. This high degree of perceptual salience led to measurable differences in early visual processing that could then be used for comparison with the subsequent attentional orienting processes. These stimuli generated dramatic effects on early visual processing in all participant groups, verifying that the impairments of attentional orienting in select groups could not be explained in terms of a generalized attentional deficit.

Another clear strength was the use of ERPs to characterize the rapid changes in neural processing that occurred during the oddball task. ERPs were used as a way as to probe the processing resources devoted to different stages of attentional processing and offered insights into the underlying neural mechanisms in ways that behavioral data alone could not achieve. Importantly, a large number of neuropsychological tests were also administered, providing the opportunity for maximal convergence of research findings across different methods.

Overall, the overarching goal of this dissertation was to better understand how novelty is processed in the brain and examine how healthy aging and Parkinson's disease impact novelty processing. The results of these two experiments have provided strong evidence that novel events receive preferential neural processing in ways that are governed by both the features that characterize the event, as well as the features that characterize the individual. Neurophysiological changes in older adults and PD patients give rise to novelty processing

deficits in these two groups, which can be precisely measured with ERPs. Future research is needed to continue characterizing the nature of these deficits and the relationships they have with broader psychological functioning.

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BIOGRAPHICAL SKETCH

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