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Sensory Gating in Patients With Alzheimer's Disease and Their Biological Children

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Research has shown that sensory gating is largely modualted by acetylcholine. Diminished levels of acetylcholine and sensory gating deficits have been reported in research involving Alzheimer's disease (AD) patients. However, there has been little investigation into those with a family history (FH+) of AD. The rationale of this study was to determine whether sensory gating impairments could distinguish those with early AD from individuals with increased risk for the disease while replicating previous findings of gating abnormalities in AD patients. Using the paried-click paradigm, evoked potentials were recorded from 4 groups of 20 subjects per group (AD, older controls, FH+, FH–). The results showed that while the AD group demonstrated sensory gating abnormalities, the FH+ group did not when compared to their peers with no family history of the disease (FH–). These results are discussed in relation to previous findings reporting P300 abnormalities in the FH+ group.

Keywords: Alzheimer's disease; sensory gating; P50; at risk

Alzheimer's disease (AD) is becoming highly prevalent in the increasingly aged population of the United States, affecting nearly 4.5 million Americans annually.[1] AD is a progressive form of dementia that affects parts of the brain that control memory, language, and executive abilities, and it is the most commonly diagnosed form of dementia. Because of the devastating impact of AD on patients and caregivers' lives and on the infrastructure of the health care system, the clinical characteristics, pathology, and risk factors associated with this disease have received well-deserved attention over the past 25 years. Finding preclinical markers and additional risk factors of AD can prospectively lead to a more accurate identification of individuals who will ultimately develop the disease, allowing treatments to be initiated earlier and helping to reduce the near $100 billion annual cost to care for patients with AD.[2] Currently, treatments are being developed to treat the underlying pathology of AD.[3,4] Current thinking is that pathology may be present 10 to 15 years before clinical presentation or diagnosis,[5] and finding preclinical markers of the disease is of paramount importance.

AD is characterized by neuritic plaques, neurofibrillary tangles, and a presynaptic deficit in acetylcholine.[6] Furthermore, it has been reported that patients with AD show disrupted basal forebrain cholinergic pathways,[7] and some patients reveal associated alpha-7 receptor loss.[8] This cholinergic dysfunction has been linked to behavioral disturbances[6] and cognitive deficits such as attention and working memory impairments.[9,10] Studies examining the efficacy of cholinesterase inhibitor therapy in patients with AD suggest that behavioral disturbances such as distractibility, agitation, hallucinations,

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delusions, overactivity, and anxiety can be reduced when taking the medication.[11-13]

Research examining patients in the preclinical and early stages of AD suggest that cytopathological changes occur in one of the brain's largest cholinergic centers, the nucleus basalis.[14] However, it is currently unknown at what point in the disease process this cytopathology takes place. Mesulam and colleagues[14] suggest that although the number of cholinergic neurons in the nucleus basalis of patients with mild cognitive impairment (MCI) is not reduced when compared to age-matched controls, these neurons are at pretangle stages of cytopathology and are unlikely to function normally. Mesulam et al further suggest that early neurofibrillary tangle formations have been shown to interfere with protein synthesis and energy metabolism and that normal whole-brain acetylcholine levels do not ensure the integrity of cholinergic innervation of the cortex. Because the nucleus basalis is known to be the main source of acetylcholine to the cortex, cytopathology in a single nucleus basalis neuron may have widespread consequences on cortical cholinergic innervation.[14] There has been recent evidence supporting the idea that cholinergic cells are dysfunctional in MCI and early stages of the disease. A positron emission tomography (PET) study completed by Herholz et al[15] showed a significant reduction in cerebral acetylcholinesterase in the brains of patients with MCI.

Neurophysiologists have studied cholinergic function using the exogenously evoked auditory P50 component.[16] P50 has been used to examine the ability of the brain to inhibit irrelevant sensory input in a wide range of healthy and neurologically impaired populations.[17] The term *sensory gating*, commonly associated with the P50 component, refers to the inhibition of a stimulus-related neuronal response if the stimulus is preceded by a warning stimulus.[18] Studies have demonstrated that the habituation of repetitive, irrelevant sensory stimuli is an essential function of the human brain that keeps higher cortical centers from being flooded with this sensory information.[17] Disruption in this sensory gating process could impair the brain's ability to select, process, and store important information or stimuli.[19] Animal studies[20] and postmortem studies of patients with schizophrenia[21] reveal that sensory gating may be mediated by the α-7 subunit of the cholinergic nicotinic receptor. Grunwald et al[17] identified the neural correlates of the gating process, reporting that sensory gating may be a multistep process, with an early phase subserved by the temporoparietal and prefrontal cortex and a later phase mediated by the hippocampus.

In research paradigms, sensory gating is examined using the auditory paired-click paradigm, also known as the conditioning-test paradigm. P50 differences are assessed by measuring the amplitude of the P50 potential to the test click (second click) as compared to the conditioning click (first click) of a paired-click paradigm. Researchers then typically produce a ratio called the sensory gating ratio by dividing the test click amplitude by the conditioning click amplitude (click 2/click 1).[22] Responses to the conditioning click can also be compared to ensure that any deficit in sensory gating is not due to some nonspecific changes in the brain that affect sensory-evoked responses. In effect, the conditioning click can act as an internal control measure for between-group comparisons.

Data suggest that P50 sensory gating heavily involves the cholinergic system.[16,21,23,24] Leonard et al[24] proposed that interneurons and pyramidal neurons receive cholinergic input from the septum (which is connected to important structures involved in AD such as the hippocampus and fornix) and that the blockade of the septal cholinergic input removes the inhibitory effect of the interneurons, allowing pyramidal cells to fire in response to irrelevant repetitive stimuli. Freedman et al[25] support this finding by reporting that the cholinergic agonist nicotine improves gating in individuals who exhibit the P50 gating deficit, whereas antagonists of the α-7 nicotinic receptor block P50 inhibition, impairing gating. Furthermore, several studies have examined the direct link between P50 and scopolamine, which temporarily blocks muscarinic cholinergic receptors in the brain. Results of these studies also suggest that these cholinergic receptors modulate P50, and they have reported that cholinergic contribution to preattentive auditory processing underlies stimulus-change detection.[16,23,26,27]

Studies investigating the P50 component in the AD/MCI process have found a diminished ability to gate irrelevant repetitive stimuli. Most research examining patients with AD has found disrupted sensory gating.[18,26,28,29] Jessen and colleagues[18] concluded that disturbed sensory gating in patients with AD results from cholinergic dysfunction and possibly from α-7 nicotinic receptor loss. One study, however, found no significant differences in P50 ratios between patients with AD and an age-matched

control group.[30] Investigations into the early stages of cognitive impairment linked to AD have also found sensory gating deficits in patients with MCI.[31,32] Irimajiri et al[32] suggest that changes in the cholinergic system may be associated with the modulation of cortical activities, such as sensory gating, in MCI and AD.

While these initial studies have examined the P50 component in patients with AD and MCI, there have been no investigations of the P50 in individuals at risk for AD. As disease-modifying therapies are being tested and pathology may develop years before any clinical symptoms, investigation of at-risk individuals is of great interest. Estimates put familial risk for AD from 35% to 65% for first-degree relatives.[33] Reiman et al[34] found that participants at genetic risk for AD demonstrated abnormally low rates of metabolism bilaterally in the posterior cingulate, parietal, temporal, and prefrontal cortex several decades before the possible onset of dementia. Finding new risk factors, preclinical evidence, and diagnostic markers for AD is critical to understanding the disease process and developing new treatment strategies. The present study examined the possibility of neurophysiological evidence of cytopathology in cholinergic neurons as manifested by changes in sensory gating in patients with mild AD and their first-degree relatives. The current study may elucidate whether cholinergic innervation to the cortex is disrupted in individuals with genetic risk for AD but without any cognitive or behavioral manifestations of the disease.

Methods

Participants

Eighty community-dwelling participants were recruited for 1 of 4 experimental groups: an Alzheimer's disease (AD) group, an age- and gender-matched healthy older adult control (OC) group, a first-generation AD offspring group (positive family history, FH+), and an age- and gender-matched control group for the FH+ group (no family history, FH–). Participants in the AD group were recruited in pairs with a biological child, establishing a true genetic link between AD patient and their offspring. Families were recruited to participate only as AD patient/adult-child pairs, and to control for cumulative risk, FH+ participants had only 1 parent diagnosed with the disease.

Each of the 4 groups contained 20 participants. The AD group, which was recruited by local neurology services, contained individuals with a National Institute of Neurological and Communicative Diseases–Alzheimer's Disease and Related Disorders Association diagnosis of AD and a Mini-Mental State Examination (MMSE)[35] score between 18 and 26. Diagnoses were made based on neuroimaging, neuropsychological testing, and clinical impression. The age of AD patients ranged from 64 to 87 years ($\bar{x}$ = 74.90, SD = 5.63). There were 11 female and 9 male AD patients whose MMSE scores ranged from 18 to 25 ($\bar{x}$ = 21.20, SD = 2.48). Two of the original 20 AD patients could not complete the electroencephalogram (EEG) evaluation because of incontinence and agitation during the data collection phase; these patients were dismissed from the experiment and replaced by 2 new AD participants. Of the final 20 AD patients used in the analysis, 18 were taking a cholinesterase inhibitor. The older controls were matched with the AD patients using the criteria of same gender and within 3 years of age to the AD patient. The older controls ranged in age from 66 to 85 years, with a mean of 74.35 (SD = 5.42) years. There were 9 women and 11 men, with MMSE scores ranging from 28 to 30 ($\bar{x}$ = 28.35, SD = 0.86). The AD and OC groups differed on gender because 2 of the initial AD subjects were excluded from the study. The 2 male AD subjects who were excluded were replaced by 2 female subjects, which shifted the gender matching slightly.

The FH+ group was composed of 20 asymptomatic healthy adults ranging in age from 38 to 62 years ($\bar{x}$ = 53.15, SD = 4.45) and composed of 13 women and 7 men, with MMSE scores ranging from 29 to 30 ($\bar{x}$ = 29.17, SD = 0.71). Finally, the FH– group was composed of healthy adults ranging in age from 39 to 66 years, with a mean age of 54.10 (SD = 4.97). Similarly to the 2 older groups, the FH– group was matched by the criteria of gender and within 3 years of age to the FH+ subject. There were 13 women and 7 men, with MMSE scores ranging from 29 to 30 ($\bar{x}$ = 29.77, SD = 0.42). Each participant in the study read and signed institutional review board–approved consent forms before participating.

A complete interview of all participants was conducted to screen for individuals with a history of psychiatric or neurological disorders (eg, Parkinson's disease, depression, schizophrenia, bipolar disorder, multiple sclerosis), past cerebrovascular accidents or transient ischemic attacks, excessive alcohol use, and current use of psychotropic medications. Participants

with a significant psychiatric history or diagnosed neurological disease and those taking narcotics, benzodiazepines, or neuroleptic medications were excluded from the study. In addition, participants in the older control group and the AD group were examined by neurology services for possible uncorrected hearing or vision problems. Subjects were excluded from the study for any uncorrected hearing of vision problems.

Stimuli and Procedures

The MMSE assessment of all participants was completed immediately before the laboratory session. Subjects were seated on a reclining chair in a well-lit, sound-attenuated room, with an observation window and camera. Event-related potentials (ERPs) were recorded from 2 electrode sites located frontally, centrally, and parietally on the head (electrode sites Fz, Cz, and Pz of the International 10-20 system of electrode placement). The scalp was lightly abraded, and Grass Instruments (West Warwick, RI) silver cup EEG electrodes were attached to the head. Electrodes were referenced to linked mastoid EEG electrodes. Electrode-skin impedances were held below 5 kΩ. Silver/silver chloride Sensormedics (Viasys Healthcare, Conshohocken, Pa) mini-biopotential electrodes were placed above each participant's left eyebrow and directly below the left eye to record the electro-oculogram (EOG). Any epoch coinciding with EOG activity greater than 75 μV was excluded from the participant's average.

The P50 paired-click paradigm was performed in 2 blocks of 60 paired-click trials each. The 2 blocks were collapsed for data analysis purposes, resulting in all participants' having at least 90 artifact-free trials available for data analysis. Each click was 3 milliseconds in duration, with an interclick interval of 500 milliseconds in a methodology similar to Yee and White.[36] The interval between each click pair was approximately 8 seconds. A Visual Basic (Microsoft, Redmond, Wash) program specifically programmed for click generation and presentation of the paired-click paradigm was employed for the experiment. Each click was presented at a standardized volume of 70 dB above auditory threshold through a speaker placed on a table directly behind the subject. Auditory threshold was determined by using a standard ANSI Mannix Economy SLM (Mannix Testing and Measurement, Lynbrook, NY). Sampling occurred for 900 milliseconds total for each click pair, beginning 100 milliseconds before the first click presentation. The sampling process continued throughout the paired-click paradigm, ending 300 milliseconds after the second click. The analog-to-digital conversion board maintained a sampling rate of 1000 Hz. EEG was recorded using Grass Instruments 7P511J wide-band AC preamplifiers, with a frequency bandwidth of 0.03 Hz to 85 Hz (12-dB octave), with a 60-Hz notch filter on each amplifier. EOG was recorded with a Grass 7P5B Wide Band AC preamplifier. Data were recorded and stored for each electrode site individually. The analog-to-digital process, presentation of stimuli, data collection, and postprocessing of data were programmed in Visual Basic 4.0 and Keithley Metrabyte VTX (Keithley Instruments, Inc, Cleveland, Ohio) and completed on a standard Dell desktop PC.

P50 Identification

The amplitude of the first P50 component was defined as the most positive peak voltage that occurred between 40 and 80 milliseconds after the onset of the conditioning click and was labeled "CC." The amplitude of the second P50 component was defined as the most positive peak voltage that occurred between 40 and 80 milliseconds after the test click and was labeled "TC." Latency values were determined for each click and were defined as the time from stimulus onset to the point of maximum positive amplitude occurring between 40 and 80 milliseconds after stimulus onset. The conditioning click in the paired-click set started a new sampling epoch. The computer program was designed to begin sampling EEG data at all locations (Fz, Cz, and Pz) 100 milliseconds before the onset of the first click and ending 300 milliseconds after the second click. The 100 milliseconds before stimulus onset was used as a prestimulus baseline to zero center the waveform. A Data Translation (Marlboro, Mass) 2801-A laboratory interface board within a PC computer digitized EEG recordings. Averaged data were digitally filtering from 10 to 50 Hz to remove any influence of the N100 or P200 components.[37] A sensory gating ratio was computed for each subject to quantify the degree of sensory gating by dividing the testing click by the conditioning click (click 2/click 1). It should be noted that the higher the sensory gating ratio, the worse subjects are performing. Sensory gating and P50 data were analyzed using analysis of variance (ANOVA). Pearson correlations

Table 1. Mean Amplitudes and Sensory Gating Ratios for All Groups at Site Cz

	Amplitude		
	Click 1	Click 2	Gating Ratio
Alzheimer's disease	6.57 (2.2)	5.88 (2.3)	0.89
Older adult control	6.91 (2.1)	3.61 (1.4)	0.52
Positive family history	7.21 (1.9)	4.57 (2.4)	0.63
No family history	7.22 (2.0)	3.13 (1.2)	0.43

All amplitudes are in microvolts (SD).

Table 2. Mean Latency Times for All Groups at Site Cz

	Latency	
	Click 1	Click 2
Alzheimer's disease	54 (8.2)	54 (8.0)
Older adult control	54 (7.2)	50 (7.0)
Positive family history	56 (5.8)	54 (7.3)
No family history	56 (5.3)	53 (5.9)

All latency times are in milliseconds (SD).

were used to examine the possible effect of disease severity on P50 sensory gating ratio.

Results

There were no significant results found at sites Fz or Pz. Since the P50 suppression effect is most pronounced at site Cz, data will be reported at this site only. Table 1 includes the mean amplitude data and sensory gating ratios for all groups at site Cz, and Table 2 includes the mean latency data for all groups at site Cz. Figure 1 shows the P50 waveforms for all groups. In addition to completing 2 ANOVAs for sensory gating ratios (AD vs OC; FH+ vs FH–), 2 ANOVAs were used to compare responses to the conditioning click, to ensure that both groups share the same baseline in which to compare the test click.

First, we present the analysis for the AD and the older control groups. No significant difference in amplitude, $F(1, 38) = 0.550$, $P = .463$, or latency, $F(1, 38) = 0.486$, $P = .490$, response to the conditioning click was found between the AD group and the OC group. That there are similar neural responses to the conditioning click suggests that any differences observed in the test click are attributable to differences in sensory gating and not to nonspecific changes in the brain such as cortical atrophy. The 1-way ANOVA between the AD and OC groups for the sensory gating ratio (TC/CC) revealed that the AD group demonstrated significantly diminished ability to appropriately reduce the response to the testing click (click 2), leading to a larger sensory gating ratio when compared to the healthy older controls, $F(1, 38) = 6.377$, $P = .016$. Using η^2 as the measure of effect size, group accounted for 14.4% of the variance in the P50 sensory gating ratio between the AD and OC groups. The Pearson's correlation of disease severity and sensory gating ratio within the AD group was not significant ($r = 0.231$, $P = .326$).

Next, we present the analysis for the positive (FH+) and negative (FH–) family history groups. Like the AD and OC groups, there were no differences in amplitude, $F(1, 38) = 0.054$, $P = .817$, or latency, $F(1, 38) = 0.278$, $P = .601$, response to the conditioning click. However, in contrast to the difference in sensory gating ratio observed between the patients with AD and the older controls, the 1-way ANOVA revealed no difference in the sensory gating ratio in the children of the patients compared to their young control group, $F(1, 38) = 1.230$, $P = .274$. An analysis of effect size between the FH+ and FH– groups using η^2 revealed only 3.1% of the variance was attributable to group.

Discussion

The present investigation has provided 2 main results relevant to sensory gating in AD. Results revealed that the patients with AD demonstrated significantly impaired sensory gating when compared to an age- and gender-matched control group, consistent with previous research.[18,25,28,29] However, the biological asymptomatic children (FH+) of these patients showed normal sensory gating. It has been suggested that observed P50 suppression deficits in patients with AD and MCI might result from the presynaptic cholinergic deficit commonly associated with the disease.[18,26] Cholinergic deficiency consisting of reduced levels of acetylcholine, choline acetyltransferase, and acetylcholinesterase is the most consistent and significant biochemical change in AD.[38] The fact that patients with AD show abnormal sensory gating and those with relatively higher risk for the disease do not suggests that perhaps P50 is disrupted when AD pathology is significant

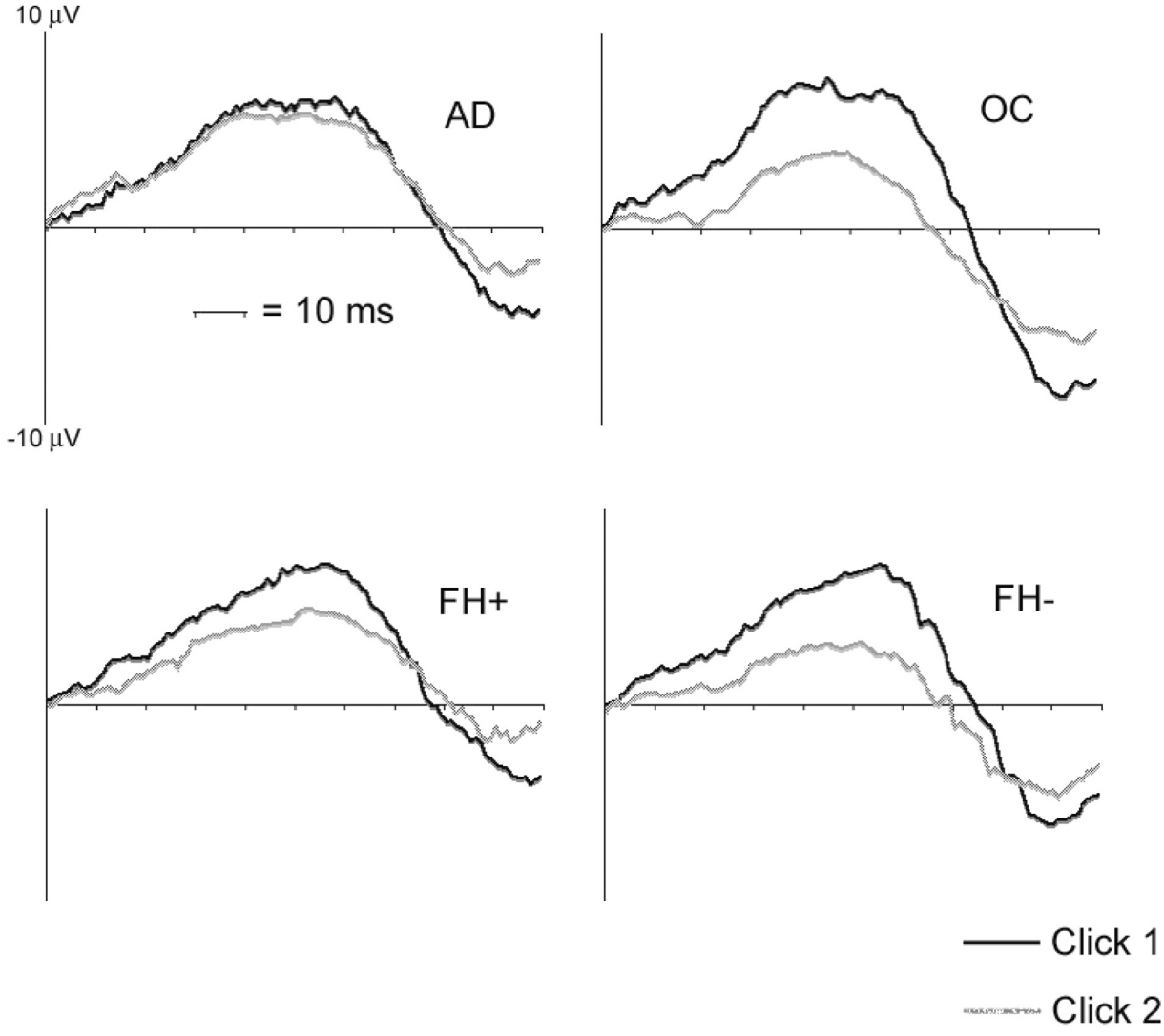

Figure 1. P50 waveforms for all groups at electrode site Cz. Each tick mark of the x-axis represents 10 milliseconds of the total 100-millisecond epoch. The y-axis is in μV from –-10 to 10 μV. AD = Alzheimer's disease; OC = older adult control; FH+ = positive family history; FH– = no family history.

enough to cause damage to the cholinergic system in the brain.

This argument is also supported by studies investigating patients with MCI. AD has a long preclinical period during which β-amyloid plaques and neurofibrillary tangles gradually accumulate in the brain without causing clinically detectable impairments.[39,40] Neuropathological studies report that the extent of neuronal death and accumulation of β-amyloid plaque in MCI are similar quantitatively to early AD,[40-43] suggesting that MCI may be a transitional stage of the disease.[32] A recent PET study demonstrated that patients with MCI show diminished levels of acetylcholinesterase when compared to healthy subjects.[15] Furthermore, a recent study reported that patients with MCI, like the patients with mild AD in our study, demonstrate sensory gating abnormalities.[32]

One of the current difficulties for clinicians is the ability to distinguish individuals with high risk from those in the preclinical or early stages of the disease. Even with expensive technology, such as PET, the early diagnosis of AD can be confounded by changes that occur in healthy individuals at risk for the disease.[34] While we know that 35% to 65% of the biological children of patients with AD will ultimately develop the disease, the current study found that they are not demonstrating neurophysiological deficits associated with cholinergic dysfunction at a

point nearly 10 to 15 years from possible symptom onset. A previous study from this laboratory found that both patients with AD and their biological children demonstrate significantly smaller P300 amplitudes and longer P300 latency times compared to control participants.[44] That P50 was normal despite demonstrating abnormal P300 amplitudes and latency times in the FH+ is particularly interesting and may provide some insight into the disease process. As suggested by Ally et al,[44] P300 abnormalities in the FH+ group might reveal subtle preclinical changes in functions associated with P300, such as attention and working memory, but may not be indicative of the systematic cholinergic dysfunction that accompanies AD. One explanation is that higher risk associated with P300 abnormalities may be related to neurophysiological changes other than cholinergic dysfunction. The current P50 investigation suggests that perhaps P300 can better be defined as a risk factor for developing the disease, rather than a preclinical marker of the early stages of AD, as it appears to be sensitive to those who have a relatively increased risk of developing the disease. P50, by contrast, appears to be a bit more specific for those who are developing signs and symptoms of AD due to cholinergic impairment. Thus, obtaining a sensory gating ratio using P50 may be helpful to distinguish those individuals who are showing very early signs of AD from those who are simply at risk for the disease.

Last, we would like to comment on a few possible limitations in the current study. One argument for not finding a significant difference between the FH+ and the FH– groups is that there is a possible lack of power. However, an examination of effect size using η^2 between the FH+ and FH– groups reveals that only 3.1% of the variance was explained by group. In contrast, the effect size between the AD and healthy older control group shows that 14.4% of the variance was explained by group. Furthermore, we examined the effect size of group in a previous study from this laboratory that shows that the FH+ group demonstrated significantly smaller P300 amplitudes and longer P300 latency times compared to the FH– group.[44] In that study of the biological children of AD patients, 18.7% of the variance was explained by group. Thus, we do not feel as though the lack of significance between the FH+ and FH– groups was simply due to a lack of power. In the current study, we also did not find a correlation between the sensory gating ratio and disease severity as measured by the MMSE. This result may be attributable to the imprecision of the MMSE as a neuropsychological measure of the underlying disease severity. Another investigation examining correlations between sensory gating and a more comprehensive neuropsychological testing battery is encouraged.

In summary, the current investigation examined sensory gating in patients with AD and their biological children. As expected, AD patients demonstrated impaired sensory gating compared to age and gender-matched controls. The biological children of these AD patients did not, however, show impaired sensory gating compared to their peers. Sensory gating has been reported to be a neurophysiological measure of cholinergic function in the brain. The results of the current study suggest that while patients with mild AD demonstrate neurophysiological changes suggestive of cholinergic dysfunction, the FH+ (higher risk) group does not show changes associated with impaired cholinergic function. One direction for future research may be to examine the effects of treatment with cholinesterase inhibitor therapy on sensory gating.

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