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Deficit in Sensorimotor Gating in Alzheimer's Disease (AD): Measuring Pre Pulse Inhibition (PPI) as a Measure of Liability to AD

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Abstract

Alzheimer's disease a heterogeneous disorder and genetic factors play an important role in its pathogenesis. Deficits in attention and information processing have been recognised as early features of AD. The Pre Pulse Inhibition of the startle reflex (PPI) is a measure of attention; sensorimotor gating and information processing that are deficient in AD.

Method: The performance of twenty subjects with mild AD, twenty first-degree siblings and thirty healthy controls on the PPI paradigm was examined as well as we provided the first report of PPI performance in first-degree siblings and linked this to *APOE* ε4.

Results: Reactivity, onset and peak latencies and PPI 120 were impaired in patients with AD. Siblings showed similar reactivity, slow processing and onset latency to AD cases. The PPI showed a significant difference in PPI 120 between cases and controls. Siblings behaved half-way between cases and controls. In the cases group, subjects without *APOE* ε4 variant seemed to be more reactive than those with *APOE* ε4 variant. The presence of *APOE* ε4 variant has significantly affected onset and peak latency at ISI-120ms.

Conclusion: The effect of PPI confirmed that sensorimotor gating is deficient in early AD. First degree siblings of AD cases have shown some failure of inhibition compared to healthy controls. PPI may be used as a part of battery of biomarkers in aiding clinical diagnosis and early detection of subjects at risk of developing AD such as first-degree siblings.

Keywords: Alzheimer's disease; Prepulse inhibition; Startle response, *APOE* ε**4**

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Introduction

Alzheimer's Disease (AD) is characterised by long preclinical period during which cognitive deficits are detectable [1]. Memory impairment is the most prominent clinical feature of early stage AD and overlaps with deficits in attention and executive function to produce the characteristic features of the disease [2]. Patients in the mild to moderate stages of the disease frequently fail to direct attention to novel or interesting aspects of their environment [3]. The lack of inhibition of competing and conflicting responses, known as sensorimotor gating, has been shown to be the most affected aspect of selective attention in early AD [4,5]. A number of studies have shown that AD patients are more prone to the effects of interference from distracters due to impaired inhibitory mechanisms [6,7], suggesting that deficits in selective attention may be due to a failure in inhibitory versus facilitatory processes.

Pre Pulse Inhibition (PPI) of the startle reflex offers one way of assessing attention deficits and sensorimotor gating problems in early AD. PPI is a neurological phenomenon where a weaker pre stimulus (prepulse) inhibits the reaction of an organism to a subsequent strong startling stimulus (pulse) [8,9]. Deficits in PPI manifest in the inability to filter out irrelevant information, and produce sensorimotor gating impairment [10]. Closing of the eyelid in a blink response is a well-established index of the startle reflex [11]. It has been suggested that startle PPI could be used as a biological marker for amnestic MCI and mild AD [12]; however impairments in PPI and sensorimotor gating have not been fully established [13]. The *APOE* ε4 allele is a major risk factor for late-onset AD and has been shown to be associated with startle response in *APOE* transgenic/knockout mouse models of AD [14].

This study sought to examine the performance of subjects with mild AD compared to healthy

controls on the PPI paradigm. We used a family design to compare unaffected siblings of AD sufferers to AD cases and healthy controls. First degree relatives of AD sufferers are enriched for risk factors of AD but do not yet have the disease. This is the first study to investigate PPI in unaffected first-degree relatives of AD patients and we did this because impairment in first degree relatives may be a marker for conversion to AD. We also characterized all individuals for *APOE* genotype, to determine if PPI and sensimotor gating are associated with *APOE* ε4 genotype.

Methodology

Participants were recruited as part of the Medical Research Council Genetic Resource for AD and comprised 20 subjects with mild late-onset AD (Mini-Mental State Examination Score (MMSE) 20 -25; aged ≥ 65 years), 20 unaffected siblings of AD cases and thirty age and gender matched healthy controls. All AD cases were diagnosed according to NINCDS-ADRDA criteria for probable AD using an assessment battery that has a proven positive predictive value of 95% for the detection of AD neuropathology [15]. Healthy controls and siblings were screened for cognitive decline using the MMSE adopting a cut off score of 25 or above, and were carefully matched to AD cases to take account of age, sex, and geographical location. First-degree siblings of AD were identified through their participating pro bands and aged 65 years or over. Healthy controls had no family history of AD.

APOE genotyping was performed using standard PCR methods.

Semi structured interviews were completed with all study participants. The assessment interview included: Mini Mental State Examination (MMSE) [16]; Cambridge Mental Disorders of the Elderly Examination (CAMDEX) [17]; Blessed Dementia Scale (BDS) [18]; Bristol Activities of Daily Living Scale (B-ADL) [19]; Webster Rating Scale [20]; Global Deterioration Scale [21]; Cornell Scale for Depression in Dementia [22]; Neuro Psychiatric Inventory (NPI) [23]. Informants were interviewed to confirm the data collected from AD cases. Cases also had an MRI scan of the brain to aid diagnoses.

Previous research has shown that psychopathology (such as psychosis and depression), medication use and smoking can affect the startle response. As such subjects with a personal history of psychiatric illness, neurological disturbances, head injury, smoking or habitual alcohol/substance abuse were excluded. No subjects were taking medications known to affect the central nervous system or the startle paradigm at the time of the study. The study was approved by the Multi-Centre Ethics Committee for Wales. All participants were able to give written, informed consent and were willing to participate in the study.

The PPI was administered to all participants. Prior to testing, subjects were screened for hearing deficits using an Amplivox 160 Screening Audiometer with standard exclusion criteria for impairment (30-40dB at 1 KHz).

Participants were seated in a comfortable chair. To record startle activity of the muscle in response to the startling stimuli two small sensors were placed below and to the right of their right eye, over the orbicularis oculi muscle. A ground sensor was placed behind the right ear over the mastoid. The right eye was used for all subjects. The skin was cleaned and gently abraded with Omni prep (D.O. Weaver and Co.) to lower the skin resistance and reduce recording noise. All subjects included in this study were responsive.

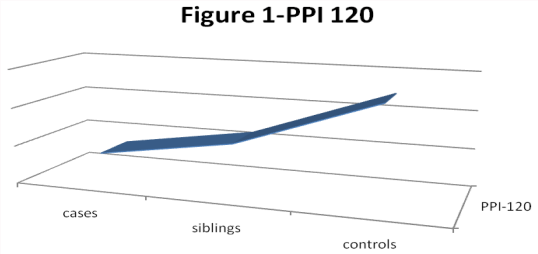

Figure 1: Siblings to behave half-way between cases and controls.

The acoustic stimuli were delivered, recorded and scored by a computerised startle response system (SR-Lab, San Diego Instruments). Acoustic stimuli were presented binaurally through headphones (TDH-39-P, Maico). Each test session began with a 2-minute acclimation period consisting of 70-dB [A] broadband noise, which continued as the background noise throughout the entire session. Participants received 51 trials in each session. An initial pulse alone trial (40 ms in duration and 115 dB [A] white noise) was followed by 50 trials. This consists of 10 prepulse-to-pulse intervals (pulse alone, 30, 60, 120 and 2000 ms) presented in a random order that was identical for all participants. The prepulse-to-pulse intervals were measured from the offset of the prepulse to the onset of the pulse. The prepulse was a 20ms burst of white noise at 86 dB [A]; the pulse was a 40ms burst of white noise at 115 dB [A]. The mean inter-trial interval was 15s.

Startle responsiveness is the ability to respond to the startling stimulus and was measured by electromyography. Startle reflex was measured by examining whether subjects demonstrated a response of greater than 10 digital units to the initial block containing only pulse-alone trials. If the subject responded the magnitude of the response can be quantified to define a measure of startle reactivity. Reactivity was analysed by examining the first initial pulse amplitude (a measure of initial reactivity) and mean of other pulse. The temporal characteristics of the response were examined by assessing the startle latency, or the latency to the onset or peak of the response. Habituation of the startle response was assessed as the decrement in startle response amplitude over time after repeated stimulus presentations that occurs across a testing session. Habituation was tested separately on mean pulse-alone from block one to block three (first three trials), and from block one to block ten (the whole trials). Prepulse inhibition was assessed by calculating percentage change in amplitude from pulse-alone to the various prepulse trials. PPI was calculated by the following formula:

(Mean amplitude of pulse alone trials-Mean amplitude of prepulse trials) / Mean amplitude of pulse alone trials.

Repeated measures ANOVAs and multiple linear regression models were used to determine group effects on PPI and latencies controlling for *APOE* genotype, age and gender. If the overall *F*-value was found statistically significant, comparisons among groups were made according to Tukey HSD test. Using a sample size of 70 participants this study had 80% power to detect mean differences between groups ($P<0.05$) on measures of prepulse inhibition with an effect size of greater than equal to 0.44. All statistical analysis of the data was carried out using SPSS version 16.

Results

Clinical and demographic characteristics can be found in Table

Table 1: Demographic characteristics for each group.

	% Female	Mean Age (SD)	Range Age	Mean MMSE	Range MMSE	% e4 carriers
Cases	70	80.4 (7.2)	66-94	23.3	19-26	50%
Siblings	60	78.3 (4.6)	69-88	28.3	24-30	35%
Controls	56.7	79.3 (6.3)	66-93	28.6	27-30	26%

1. The groups did not differ significantly in terms of age or gender ($P>0.05$). A higher prevalence of the *APOE* ε4 allele was observed among AD cases (50% vs. 26%, $X^2=6.533$, $p<.01$) and siblings (35% vs. 26%, $X^2=1.800$, $p>.05$) when compared to controls.

Startle amplitude

We observed a significant main group effect on reactivity, in terms of both initial startle amplitude (F (2, 69)=39.745, $P<0.001$) and mean startle amplitude ($F=52.636$, $P<0.001$). A significant difference ($P<0.001$) in mean and initial pulse amplitude was observed between AD cases (initial pulse amplitude=228.75; mean pulse amplitude=219.72) when compared to both siblings (initial pulse amplitude=151.40; mean pulse amplitude=152.86) and controls (initial pulse amplitude=130.20; mean pulse amplitude=115.68).

Overall, *APOE* ε4 carriers (mean (SD) = 168.17 (59.03)) were more reactive than non-carriers (mean (SD)= 155.81 (54.71)). ANOVAs showed no significant interaction with *APOE* ε4, F (1, 1)=.677, $p>0.05$ and no significant interaction between reactivity, *APOE* ε4 and groups, F (2, 2)=1.336, $p>0.05$. Between subjects effects was also non-significant, F (1) =.356, $p>0.05$.

Onset and peak latencies

There was a significant main effect of groups on *onset* latency, F (2)=8.016, $p<0.01$. Analysis of the results by Tukeys HSD test revealed no significant difference in onset latencies between cases and siblings ($P>0.05$), but a significantly increased onset latency when comparing controls with both cases ($P=.001$) and siblings ($P=.003$). Significant main effects were also observed for *peak* latencies, F (2)=5.217, $p<0.01$. Significant differences in peak latencies were observed when comparing cases with both siblings (P=0.021) and controls (P=0.003). Peak latencies did not differ significantly between siblings and controls ($P=.580$).

We observed a significant effect for the presence of *APOE* ε4 on onset latencies at ISI 120, β=.426, t (19)=3.066, $p<0.01$ and peak latencies at ISI 120, β=.583, t (19)=2.424, $p<0.05$.

There was no interaction between age and gender with group on onset and peak latencies ($P>0.05$). However, gender had significantly affected onset latencies and peak latency at ISI-30ms ($p<0.05$).

Prepulse modification

We have observed a significant main effect for PPI within-subjects, F (2, 3)=3.353, P<0.05. There was no significant difference between the groups in terms of PPI 30, PPI 60 and PPI 2000 ($p>0.05$). Tukey's post hoc analysis of PPI 120 showed a significant difference between cases and controls, $P<0.01$. There was a trend for siblings to behave half-way between cases and controls (Figure 1).

We did not observe a significant association between *APOE* ε4 genotype and PPI, F (1, 3)=0.440, $P>0.05$. Likewise there was no significant interaction between *APOE* ε4 and group, F (2, 6)=.595, $p>0.05$. The absence of *APOE* ε4 was significant in PPI 120, β=.490, t (40)=3.283, $p<0.01$. Tukey's post hoc analyses between groups, *APOE* ε4 and PPI-120 showed a significant effect between cases and controls, $p<0.01$. However, the presence of *APOE* ε4 showed no significant effect on PPI-120 ($p>0.05$). No interaction or main effect was found between prepulse inhibition and age and gender.

Habituation

The rates of habituation found in the test session were as follows: cases -101.70 % (SE=1.458), siblings -94.70 % (SE=2.559) and Controls -108.80% (SE=3.141). ANOVA showed a highly significant difference between the groups, F (2, 67)=.6.813, $P<0.01$. Post hoc Tukey's multiple comparisons showed a significant difference between siblings and controls, $p<.01$. However, there was no significant difference in habituation between cases and both siblings, and controls, $p>.05$. ANOVAs of habituation for both the first three trials and all trials showed that there was no significant main effect for habituation within-subjects but a significant between subjects' effects, $p<0.01$.

The rate of habituation found in the test session for *APOE* ε4 present was -103.60% (SE=14.05) and *APOE* ε4 absent was -102.27% (SE= 14.72). We have observed no significant main effect within-subjects and no significant between subjects effects of habituation (first three trials and all trials) and *APOE* ε4.

There was also no significant interaction between habituation and age or gender; and no significant between subjects' effects.

Discussion

Alzheimer's disease (AD) is the commonest cause of dementia in the elderly. Increased age, initial subjective memory complaints, female gender and the presence of apolipo protein E4 allele are risk factors for the development of AD [24]. Deficits in attention and information processing have been recognised as early features of AD. The inability to filter out irrelevant stimuli can lead to information processing deficit and cognitive overload.

The Pre Pulse Inhibition of the startle reflex (PPI) has been utilized as a measure of attention and sensorimotor gating [8]. Unfortunately, the research on AD and PPI is scanty.

A limitation in previous research in humans using the PPI in individuals with AD is the lack of testing in first-degree siblings specially that a positive family history is an important risk for future development of AD. Another limitation is the lack of *APOE* ε4 testing despite the fact that it is an important risk factor for the development of late onset AD.

In terms of reactivity, the results of this study showed that AD cases group were more reactive than siblings and healthy controls. The data on reactivity contradicts the findings by [12,13] who found no significant difference between healthy controls, mild cognitive impairment and AD patients. However, the two groups of researchers did not include first-degree siblings and did not test for *APOE* ε4. The overall direction of the effect of *APOE* ε4 on reactivity was consistent with the finding by [14].

Onset latency showed that both siblings and cases of AD behaved

similarly and showed slower onset latencies compared to healthy controls. The presence of *APOE* ε4 variant has significantly affected onset latencies at ISI 120ms. Post hoc analysis showed no difference between siblings and cases. Onset latencies showed similar findings in AD cases and their first-degree siblings and that AD cases showed slower processing of information as compared to healthy controls. *APOE* ε4 and female gender were associated with these effects in both siblings and AD cases.

On the other hand, peak latencies showed that both siblings and healthy controls behaved similarly and showed faster latencies in comparison to AD cases. The presence of *APOE* ε4 variant has significantly affected peak latency at ISI-120ms. Post hoc analysis showed a significant effect between controls and both cases and siblings. These results agree with the findings by [13] who found a significant difference between healthy controls and AD patients in latency to peak.

The absence of *APOE* ε4 has significantly affected PPI 120 between cases and controls. The reduction in PPI 120 in AD cases reflects the reduction in inhibition. AD cases show failure of inhibition at the ISI 120 ms due to failure of sensory motor gating. This means impaired information processing and reduction of processing of and distraction by irrelevant stimuli. They also take longer to assess information which requires more attention.

This study showed that the results on PPI in AD cases may be associated with *APOE* ε4. This finding supports Hartman et al. [14] findings that showed that the *APOE* ε4 mice were profoundly impaired in PPI which suggested that they have difficulties in executing correct responses that are dependent on accurately recalling recent events. Hejl et al. [13] did not found interaction between PPI and the groups; however, they could not exclude the possibility of a small reduction in PPI in mild AD. Furthermore, Ueki et al. [12] found sensorimotor gating deficits in mild AD patients compared to controls. Also, Janus *et al.* (2000) showed that AD patients demonstrated reduced sensory gating.

The effect of PPI in this study confirms that sensorimotor gating is deficient in early AD and that first-degree siblings of individuals of AD showed some failure of inhibition compared to healthy controls. Swerdlow et al. [25] argued that the inability to successfully inhibit irrelevant sensory information may have significant cognitive implication. Geyer et al. [26] suggested that sensory gating deficiency leads to high distractibility.

The PPI is an operational measure of sensorimotor gating and it reflects a reduced sensitivity to the inhibitory effects of the prepulse or a diminished influence of inhibitory forebrain circuitry on the primary startle circuit Swerdlow et al. [27]. Different neural circuits have been shown to be activated during PPI including brainstem circuits and forebrain circuits. The PPI has also been shown to be modulated by cholinergic, glutamate and dopaminergic receptors. These were shown to be impaired in AD.

The PPI supports the inability of participants to filter out or inhibit irrelevant information. Furthermore, the PPI appears to be able to tap some of the genetic vulnerability to AD and their first-degree siblings as it has been found in AD cases in association with *APOE* ε4. Disturbances in cognition in AD may result from impaired automatic preconscious and controlled inhibitory mechanisms that regulate sensorimotor and cognitive information reaching consciousness. Deficits in PPI at ISI 60 and 120 ms reflect inhibition of information at the boundary between unconscious and conscious processing Swerdlow et al. [28].

In terms of habituation, siblings were the least to habituate in comparison to cases and healthy controls. This difference in habituation could not be explained by *APOE* ε4. An explanation of this difference can be the modulating effect of emotionality, anxiety and arousal factors. First-degree Siblings of AD individuals may be more anxious as they have a higher risk of developing the disease. Anticipating the results of testing and the fear component of developing AD may affect their habituation [29,30].

There have been a number of reports about the differential effects of age and gender on PPI. It has been found that men exhibit more PPI than women [31,32]. Ellwanger et al. [4] showed a reduction in inhibitory processes with age. Our study showed no significant interaction with age and gender on reactivity, latency to onset and peak, PPI and habituation. However, men showed faster onset and peak latencies.

One possible limitation of this study is the sample size specially the lack of *APOE* ε4 alleles. This could explain the lack of significant results we observed in some results in the study. A future research that has larger sample size and ascertain subjects with *APOE* ε4 allele would be advisable to fully assess the impact of *APOE* ε4 on the PPI paradigm. It is also important to consider the practical application of recruiting subjects specially that about one third of participants may not respond to the startle paradigm. Another limitation is the lack of other ethnic groups. The individual differences such as IQ, social class, level of education as residual confounding factors were controlled for by the randomisation of the PPI paradigm, matching them in the different groups and the use of multiple regression and multivariate test statistics. Also, the PPI paradigm requires minimal motivation of the subjects.

A longitudinal study testing different stages of the illness with adequate sample size and high effect size may be able to track changes in startle responses in AD patients. A larger study testing first-degree siblings of AD cases would be beneficial in testing our findings and the validity of PPI as a biomarker in AD. The correlation, between PPI and ERP in those at increased risk for developing AD, needs to be considered in future research. Also, it is important to pursue a study to test the impact of psychotic and behavioural disturbances in AD patients on the PPI paradigm. The PPI has been proven to be an important tool in helping understanding the cognitive impairment in AD. It may possible that the PPI can be used in evaluating the effects of new drugs or AB immunization in normalizing deficits in AD.

The startle response is sensitive, reliable, reproducible, non-invasive measure of central nervous system activity and it has been used in a wide variety of research and clinical settings. The PPI can be a valuable adjunct to clinical investigation in establishing the diagnosis of mild to moderate AD. Moreover, it has the advantage of being free of risk for the subject and is relatively inexpensive. An important feature of the startle response is that it is easily measured and reflects changes in attentional processes and sensorimotor gating which is disturbed in AD.

The PPI may serve as a biomarker, in early AD cases and first-degree siblings who are at higher risk of developing the disease, because it is objective, and highly quantitative measure of sensorimotor gating and information processing with underlying neural basis which are impaired in AD.

In conclusion, reactivity, onset and peak latencies and PPI 120 were impaired in patients with AD. Some of these findings may be associated with *APOE* ε4 allele. Siblings showed similar reactivity, slow processing and onset latency to AD cases. PPI may be used as a part of battery of biomarkers in aiding clinical diagnosis and detecting risk of developing AD in first-degree siblings.

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