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Novelty processing in younger and older adults measured using an adapted visual novelty oddball task

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Word of Thanks

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Abstract

Studies using event-related potential (ERP) suggests that the hippocampus, a medial temporal lobe (MTL) structure, can distinguish new and old stimuli. However, it remains unclear whether age deficits in MTL processes contribute to age deficits in novelty processing. The present study aimed to investigate this knowledge gap and to confirm previous findings reported by Schomaker et al. (2021) regarding the role of the MTL in novelty detection and later processing. Twenty-one patients with epilepsy with unilateral MTL resection and twenty-four matched healthy controls performed an adapted visual novelty oddball task, with two streams of stimuli presented left and right of a fixation cross, while their electroencephalogram (EEG) was recorded. The participants had to respond to infrequent target stimuli while ignoring standard and novel stimuli. Novelty detection, indexed by the N2, was reduced by MTL resections, shown by a smaller N2 for patients compared to healthy controls. Novelty processing, indexed by the P3, was not reduced in patients, shown by a larger P3 for patients compared to healthy controls. However, this might be due to collapsing of data in the patient group, since resection side was outside the scope of this study. Target processing, indexed by the P3b, was unaffected by MTL resections: no differences were found between patients and healthy controls. These results suggest that MTL structures, including the hippocampus and the amygdala, play a role in novelty processing. In contrast, MTL structures do not play a role in target processing since this was unaffected by MTL resections.

Introduction

Converging evidence from studies using event-related potential (ERP) suggests that the hippocampus can distinguish new and old stimuli (Brankačk et al., 1996; Friedman et al., 2001; Rutishauser et al., 2006; Schomaker & Meeter, 2014). Physiological novelty responses are traditionally studied using ERP while participants carry out a three-stimulus novelty oddball task (Friedman et al., 2001). The three stimuli used in this novelty oddball task are a standard stimulus, a target stimulus, and novel stimuli. The novelty-related ERP component, referred to as anterior N2 or simply N2, is believed to reflect novelty detection and is elicited between 200 and 300 milliseconds (ms) after the novel stimulus is presented (Knight, 1996). The N2 is followed by the novelty P3, believed to be related to the conscious evaluation of novel stimuli, with peaks occurring between 300 and 450 ms (Friedman et al., 2001). Different tasks elicit positive-going waves in the P3 time window, resulting in two P3 components in the P3 time window: the P3a, the novelty-related P3 component reflecting the transient allocation of attention to novel stimuli, and P3b, the target-related P3 as a measure of the stimulus evaluation process (Fjell & Walhovd, 2004). In other words, when a novel stimulus is detected, an N2 response arises (Knight, 1996). Next, the P3 response arises when the novel stimuli are being processed (Friedman et al., 2001; Fjell & Walhovd, 2004).

The hippocampus is part of the medial temporal lobe (MTL; Knight, 1996), which plays a role in detecting and processing new information (Kumaran & Maguire, 2009). Schomaker et al. (2021) investigated the role of the MTL in the detection and processing of novel stimuli. Using an adapted visual novelty oddball task, they tested a group of twenty-one patients with epilepsy who had undergone unilateral MTL resection to treat their epilepsy and twenty-six matched healthy controls. This adapted version had two lateralized stimuli streams, where stimuli could be presented on either the right or the left side, instead of one stimulus stream as used in the traditional visual oddball task. Since stimuli presented at one side are predominantly processed by the contralateral hemisphere, the lateralized stimuli design offered the opportunity to compare the detection and processing of novel stimuli in the resected side with detection and processing in the unresected side. This enabled the researchers to investigate the role of the MTL in the detection and processing of novel stimuli in a within-subject design, but also to draw comparisons between the patients and the matched healthy controls. They concluded that the MTL structures did in fact play a role in novelty detection and processing, since the ERP novelty responses in patients were reduced for novel stimuli presented contralaterally to the MTL resections.

It is important to note at this point that an amygdalohippocampectomy or a complete unilateral resection is not the only cause for damaged MTL structures. Even in healthy aging, the MTL deteriorates (Raz, 2005), a process that results in decline of recollection and memory (Daselaar et al., 2006). This decline suggests that distinguishing between old and new information is more difficult for

older adults (Bowman & Dennis, 2015). However, research reports regarding age-related differences in novelty processing are contradictory. Firstly, several studies suggest that there are indeed age-related deficits in novelty processing due to age-related MTL deterioration (Bowman & Dennis, 2015; Daffner et al., 2015; Daffner et al., 2006; Daffner et al., 2011; Düzel et al., 2010; Fjell & Walhovd, 2004; Riis et al., 2009), while other studies found no age-related differences (i.e., Behforuzi et al., 2019). Secondly, the studies that did find age-related differences are contradictory as well, specifically regarding the novelty P3 component. Some studies found that the amplitude of the P3 component was higher in older adults in comparison to younger adults (Alperin et al., 2014; Daffner et al., 2006), while other studies found that the novelty P3 component was smaller and more anterior in older adults, with a robust decline in participants above the age of 80 (Daffner et al., 2011). Finally, Fjell and Walhovd (2004) found that P3a, the transient allocation of attention to novel stimuli, was more impaired with increased age than P3b, the evaluation of the novel stimuli. In contrast, Alperin et al. (2014) did not find an impaired P3a in older adults.

There are several possible explanations for the discrepancies in findings regarding age-related differences in novelty processing. Some studies carried out measurements in different time periods and differed in terms of the age groups used for comparison. For instance, Behforuzi et al. (2019) only looked at older adults over a period of seven weeks. Other studies looked at one moment in time and compared young adults with old adults (Alperin et al., 2014) or three or more age groups (Daffner et al., 2015; Daffner et al., 2006; Daffner et al., 2011; Riis et al., 2009). Furthermore, some studies made the experimental task easier for the older adults compared to the younger adults (Alperin et al., 2014; Daffner et al., 2015), while other studies did not change the difficulty of the task (Daffner et al., 2006; Daffner et al., 2011; Riis et al., 2009). Lastly, even though all studies used a visual novelty oddball task to measure the ERPs, they did differ in one aspect of the task. Most studies used viewing duration to measure the amount of time spent focused on the stimuli, where participants could press a button when they no longer wanted to look at the presented stimuli (Behforuzi et al., 2019; Daffner et al., 2015; Daffner et al., 2006; Daffner et al., 2011). Alperin et al. (2014), on the other hand, used the button press method, where participants were asked to press a button as soon as they saw the target stimuli. Furthermore, Riis et al. (2009) used two experimental conditions: a condition where only the visual novelty oddball task was performed and a condition where, during the visual novelty oddball task, a difficult experimental task in the auditory modality had to be performed. All these differences between the various studies could have influenced the results. Specifically, task differences between younger and older adults make it difficult to identify differences in novelty detection and processing. To illustrate: task difficulty influences both the latency and the amplitude of the N2 and P3 components (Gajewski & Flakenstein, 2013; Kim et al., 2008), leading to different conclusions regarding the age-related differences in novelty processing.

Moreover, an ERP study cannot normally be used to investigate a direct link between the underlying neuronal sources and the elicited ERPs. This direct link can be investigated with an ERP study in which patients with unilateral MTL resection are compared to healthy controls, as Schomaker et al. (2021) did. Since none of the above-mentioned studies regarding age-related differences included patients with unilateral MTL resection, a knowledge gap persists as it remains unclear whether age deficits in MTL processes also contribute to age deficits in novelty processing.

The present study aimed to investigate this knowledge gap and to confirm the previous findings reported by Schomaker et al. (2021). A group of patients with epilepsy who underwent a unilateral MTL resection and an age- and sex-matched control group were tested. They performed a visual novelty oddball task while their electroencephalogram (EEG) was recorded. In contrast to the approach adopted by Knight (1996), truly novel stimuli were presented during the task, allowing us to investigate the brain's responses to novel information rather than deviant information. The visual novelty oddball task had been adapted with two streams of stimuli rather than one. The novel and standard stimuli were presented either left or right of a fixation cross, while a standard stimulus was presented on the opposite site. This lateralization of the stimuli enabled Schomaker et al. (2021) to investigate the role of the MTL in the detection and processing of novelty in a within-subject design. However, the current study did not differentiate between the ipsi- and contralateral factors for patients since its main focus lay on age-related differences in novelty detection and later processing. We investigated these differences in two age groups: younger adults (19-45 years) and older adults (>45 years). Even though most studies regarding age-related differences are focused on the processing of novel stimuli (Alperin et al., 2014; Behforuzi et al., 2019; Bowman & Dennis, 2015; Daffner et al., 2006; Daffner et al., 2011; Düzel et al., 2010; Fjell & Walhovd, 2004), we also investigated possible age-related differences regarding the detection of novel stimuli, as indexed by the anterior N2. The broad age range of the participants of the study offered us the chance to conduct this investigation.

Our first hypothesis is based on the findings obtained by Schomaker et al. (2021), where the adapted visual novelty oddball task elicited the typical novelty ERPs, measured by the novelty N2 and the novelty P3. Therefore, we hypothesized that the adapted visual novelty oddball task would elicit the typical N2 and P3 components, which would be larger for novel stimuli compared to standard stimuli. This hypothesis was tested by comparing the ERPs of the N2 and P3 components elicited by the novel and target stimuli in the healthy controls. To clarify, by comparing the N2 elicited by novel stimuli with the N2 elicited by target stimuli, it would become clear whether the N2 elicited by novelty falls within the expected time window for the N2 component. The same comparison could be made for the P3 component, making it clear whether the P3 falls within the to-be-expected time window. This would confirm that the adapted visual novelty oddball task does indeed elicit the

expected N2 and novelty P3 responses. Our second hypothesis is also based on the findings reported by Schomaker et al. (2021), where novelty detection, as indexed by the N2 component elicited by novels, and the later processing of novels, as indexed by the novelty P3 component elicited by novels, were reduced by the MTL resections. Therefore, we hypothesized that there would be a difference in novelty processing between patients and healthy controls, with a smaller N2 as well as a smaller novelty P3 for patients compared to healthy controls. Finally, following the research conducted by Fjell and Walhovd (2004) and by Alperin et al. (2014) regarding the age-related differences in novelty detection and later processing of the novel signal, we hypothesized that older adults (age > 45) would show smaller N2 and novelty P3 compared to younger adults (age 19-45).

Methods

Participants

Twenty-one patients with epilepsy who underwent a MTL resection volunteered to participate (8 female/ 13 male; age-range: 19-64; mean age: 42.2 years; standard deviation (SD) age: 13.7 years). Twenty-four healthy controls participated (14 female/10 male; age-range: 19-62; mean age: 42.3; SD age: 14.8). The healthy controls were matched with the patients on age and sex. The healthy participants had normal to corrected-to-normal vision, no history of neurological or psychiatric disorders, and no current intake of psychotropic medication. We tested a few more matched healthy controls subjects than patients to be able to remove participants if EEG data should prove to be noisy. Prior to the experiment, the participants had received an informational invitation letter and had given their consent for participation by signing the informed consent forms.

After completion of the study, participants were debriefed about the purpose of the study via a debriefing letter. Ethical approval for this study was obtained by the Psychology Research Ethics Committee (CEP) of Leiden University on the 29th of September 2020. The CEP number is '2020-09-24-J. Schomaker-V1-2649'.

Stimuli and behavioural measures

The present study had an experimental design with within-subject as well as between-subject components. The participants performed an adapted visual novelty oddball task with two streams of stimuli instead of one, presented to the left and right side of a fixation cross. During the task, three types of visual stimuli were presented: targets, novels, and standard stimuli. The target stimulus was an upwards or downwards pointing triangle, counterbalanced between participants. The novel stimuli were formed by white line drawings of non-existing objects (provided by Kirk Daffner and used in, for example, Daffner et al., 2006); these were not repeated throughout the experiment.

Finally, the standard stimuli were created by making a scatterplot of the white pixels of the novel or target stimuli in a circular formation. This was done to create standard stimuli that matched with the novel and target stimuli in terms of luminance. The response time and the hit rate to the target oddball, i.e., pressing 'b' with the right or left index finger (counterbalanced across participants), were the task-related measure.

Procedure

Participants were recruited by spreading recruitment posters and sharing the recruitment poster on social media, by means of flyers distributed in the area around Leiden University, and via a newspaper advertisement. Participants had to indicate their interest in the study via e-mail, after which they answered a short questionnaire to ensure that they were suited to participate in this experiment. Because of the COVID-19 pandemic, several COVID-19 protocols had to be followed. One day before testing, the participants were called by the researcher to administer the COVID-19 screening procedure. If the participant answered 'yes' to one of the questions, the testing had to be postponed or cancelled. If all the questions were answered with 'no', the testing could proceed as planned. On the day of testing, the participant came to the lab and the COVID-19 screening was administered again. If all questions were answered with 'no', the testing could proceed as planned. Otherwise, the participant had to go home, and the testing had to be postponed or cancelled. After the COVID-19 screening had taken place, the participant was briefed about the experiment, had a chance to ask questions, and filled in the informed consent form.

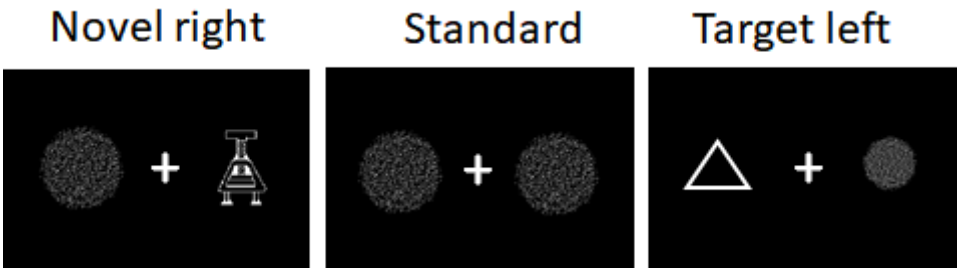
Before the experiment began, the EEG was prepared, after which the task was explained. Participants were seated in an EEG recording room and performed the novelty oddball task while their EEG was measured. Stimuli were presented on a computer screen using E-Prime, at a viewing distance of 60 cm. Participants were instructed to press 'b' with their right/left index finger (counterbalanced across subjects) as quickly as possible when the target stimulus was presented, regardless of the side the stimulus was presented on. Additionally, participants were instructed to fixate their eyes on the fixation cross and to minimize eye and head movements. They were also instructed to minimize blinking. Prior to the actual experiment, the participant first performed a practice round of 20 stimuli. After this round, the experimental task began, divided into six rounds with 70 stimuli each and lasting around five minutes. Between rounds, participants were free to take a self-paced break. The total procedure had a duration of approximately 60 minutes: 25 minutes for EEG preparation, 30 minutes for the task, and 5 minutes for debriefing.

On each trial, two visual stimuli were presented, with one stimulus on the left side and one on the right side of the fixation cross. Figure 1 presents examples of stimuli combinations, which

consisted of two standard stimuli or a standard stimulus in combination with either a novel stimulus or a target stimulus. The target and novel stimuli were presented either on the right or the left side of the fixation cross. The stimuli were presented for 2000 ms on each trial, with a fixation cross presented with a jittered duration of 800-1500 ms between trials. On standard trials, the same standard stimulus was presented on both sides of the fixation cross. Standard trials were shown more frequently (71.4%) than novel or target trials (14.3%). During a novel or target trial, a novel or target stimulus was shown on either the left or the right side during specific trials. When a novel or target stimulus was shown, on the opposite side a standard stimulus was shown. Identical luminance was reached by spreading the white pixels of the target or novel stimulus in a circle, which resulted in the same number of white pixels in the two presented stimuli.

Figure 1

Example Stimulus Combinations



Note. Left display: a novel stimulus presented on the right side with its scattered circular counterpart on the left. Middle display: example standard display is shown, with two matched scatter circles. Right display: a target on the left and its scattered circular counterpart on the right. Participants had to detect the target and respond with a button press. Stimulus displays were shown for 2000 ms, and between trials a fixation cross was shown for a jittered interval of 800 to 1500 ms. Note that pictures were rescaled for demonstrational purposes in this figure.

EEG recording and analyses

The EEG was recorded using a 32 channel Biosemi system (Biosemi, Amsterdam, the Netherlands). The electrodes used were sintered Ag/AgCI electrode tips plugged into an elastic cap (Electrocap International, Inc). The locations of the electrodes corresponded to the 10-20 system. Data for the Fz, Cz, and Pz electrode were analysed, since these are the sites where the N2, P3, and P3b have been reported to be maximal. The N2 peaks anteriorly, which is why electrode Fz was analyzed (Tarbi et al., 2011). The novelty P3 peaks central and posterior, and P3b peaks posterior, which is why Cz and Pz were analyzed (Dien et al., 2003; He et al., 2001) The EEG signal was digitized with a sampling rate of 512 Hz with a gain setting of 1000. The signal was later resampled to 500 Hz.

The electrode offset was kept below 20 microvolts during recording. The data was offline re-referenced to the average of all 32 EEG electrodes. Four external electrodes were placed to measure horizontal and vertical electrooculogram (EOG): two on the outer canthi of the eyes, one supraorbitally and one infraorbitally to one eye. These external electrodes were used to measure horizontal and vertical eye movements. These measurements were later used for the cleaning and preparation of the EEG data, to identify and remove eye movements and blinks from the dataset.

The dependent variables, novel N2, novel P3, and target P3, were derived from the EEG. The time window for the epochs was -200 – 1500 ms around stimulus onset. The data was visually inspected to remove trials with motion artifacts, eye movements, and blinks within the time windows for N2 and P3 in the electrodes of interest (Fz, Cz, and Pz). After cleaning of the dataset, a minimum of 15 and a maximum of 30 epochs (patients mean = 29.2; healthy controls mean = 28.7) were included per condition per participant for the novels and the targets. For standards, a minimum of 257 and a maximum of 300 epochs (patients mean = 289.0; healthy controls mean = 283.1) were included.

Standard signal averaging techniques (Luck, 2005) were used to calculate the ERPs relative to a prestimulus baseline of -200 to 0 ms. The main amplitudes of N2, P3, and P3b were calculated for two groups (patients; healthy controls) at three electrode sites (Fz, Cz, and Pz) for each of the conditions. The exact time window for the calculation of the main amplitudes for N2, novelty P3, and target P3b were based on the visual inspection of the grand average ERP signal. For the healthy controls, mean amplitudes were calculated for a time window of 190-260 ms for N2, 275-325 for P3, and 300-475 for target P3b. For the patients, a time window of 190-240 was used for N2, 290-340 for P3, and 275-450 for target P3b.

Statistical analyses

Schomaker et al. (2021) took the location of resection into account in their analyses, since this allowed them to investigate the differences between stimuli presented ipsilateral and contralateral to the resected side in a within-subject manner. However, in the current study, location of the resection was not taken into account. Instead, for patients the data of the N2 and P3 components were collapsed for stimuli presented contra- and ipsilaterally to the resected side, resulting in one N2 and one P3 variable for each patient instead of two of each. The collapsed N2 and P3 variables could then be more easily compared with the N2 and P3 variables for the matched healthy controls.

To measure the components of interest, the mean amplitudes were calculated for N2, novelty P3, and P3b for each Stimulus (standard; novel; target) at three electrode sites (Fz; Cz; Pz).

These mean amplitudes were then compared between the groups (patients; healthy controls) and between age groups (younger adults; older adults). The age group 'younger adults' had an age range of 19 to 45 years, followed by the 'older adults' group with an age range of 45 to 64 years. These age ranges were based on the study by Fjell and Walhovd (2004), who divided their participants in these same age groups instead of using age as a covariate. The behavioural responses, measured in terms of accuracy and response rate, were investigated with an independent samples *t*-tests (equal variances not assumed) with Group (patients; healthy controls) and Age Group (younger adults; older adults) as between-subjects factors.

To confirm if the adapted version of the visual novelty oddball task did indeed elicit the typical N2 and novelty P3 components, the ERPs elicited by novel and standard stimuli were investigated using a mixed ANOVA with Stimulus (standard; novel) and Electrode (Fz; Cz; Pz) as within-subject factors and Group (patients; healthy controls) and Age Group (younger adults; older adults) as between-subjects factor. The target stimulus was not included in this analysis, since the novelty ERPs were investigated, for which only the standard and novel stimulus are needed. This ANOVA confirmed that the lateralized version of the visual oddball task elicited the typical novelty ERPs over frontal, central, and posterior electrode sites, and it identified group differences. The N2 and P3 were investigated using mixed repeated measures ANOVAs, with Stimulus (standard; novel) and Electrode (Fz; Cz; Pz) as within-subject factors and Group (patients; healthy controls) and Age Group (younger adults; older adults) as between-subjects factor. If a group effect was found, separate repeated measures ANOVAs were run for each group with Stimulus (standard; novel; target) and Electrode (Fz; Cz; Pz) as within-subject factors.

When significant interaction effects for Electrode were found, these were further investigated using a mixed ANOVAs per Electrode (Fz; Cz; Pz) with Stimulus as a within-subject factor and Group (patients; healthy controls) as a between-subjects factor. Additionally, for electrode we reported the linear main effects to identify the peak location (anterior or posterior).

The analyses showed group and stimulus differences for the N2 component, which could lead to distorted effects on the P3 component due to the fact that N2 and P3 are of opposite polarities. In other words, if the N2 is significantly larger in one group compared to the other, the P3 that follows would start from a lower point, resulting in a less positive P3 component in that group, even though no P3 difference would exist between the two groups. Therefore, we calculated the N2-P3 complex (subtracting novel-elicited N2 from the novel-elicited P3) and conducted two additional analyses with the N2-P3 complex. Both mixed ANOVAs were conducted with Group (patients; healthy controls) and Age Group (younger adults; older adults) as between-subjects factors, and Electrode (Fz; Cz; Pz) as within-subjects factor.

Finally, to test for age differences in novelty detection and later processing, the same ANOVAs were run as described above with only the healthy participants selected, meaning without Group (patients; healthy controls) as a between-subjects factor. For each ANOVA, a Greenhouser-Geisser correction was performed when the assumption of sphericity was violated.

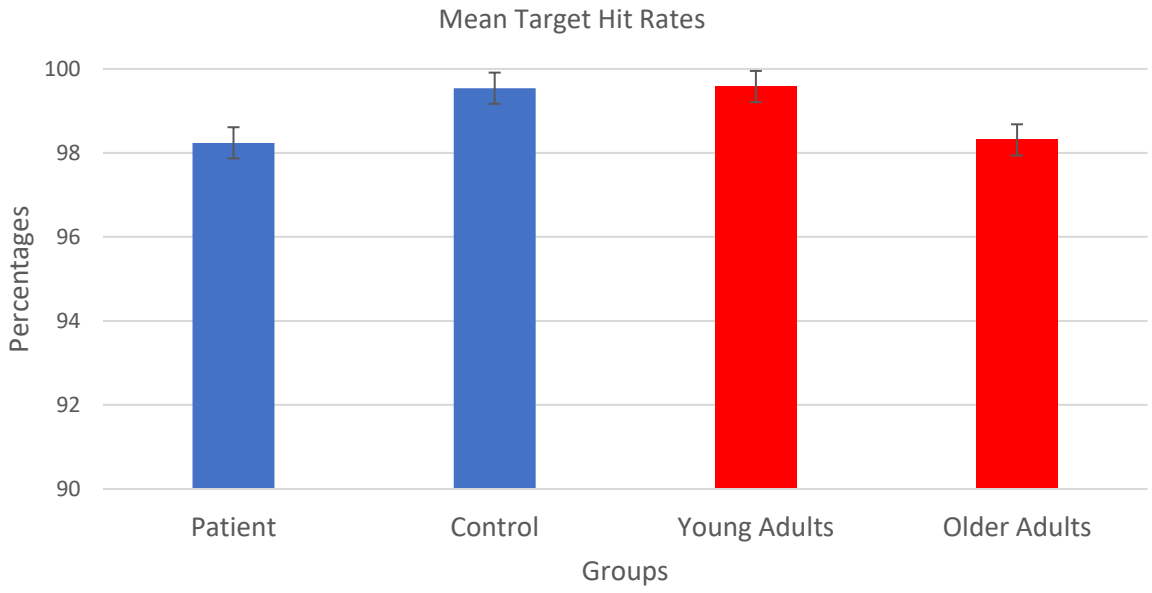
Results

Behavioural responses

Figure 2 shows differences in mean target hit rate between the different groups. No significant differences were found in target hit rate between patients (*N*=21; mean hit rate = 98.24%, SD = 4.18%) and healthy controls (*N*=24; mean hit rate = 99.54%, SD = 1.37%; *p* = .186). Furthermore, no significant differences in target hit rate were found between age groups (younger adults: *N*=22; mean hit rate = 99.58%, SD = 1.47%; older adults: *N*=23; mean hit rate = 98.31%, SD = 3.98%; *p* = .169).

Figure 2

Differences Between Mean Target Hit Rates



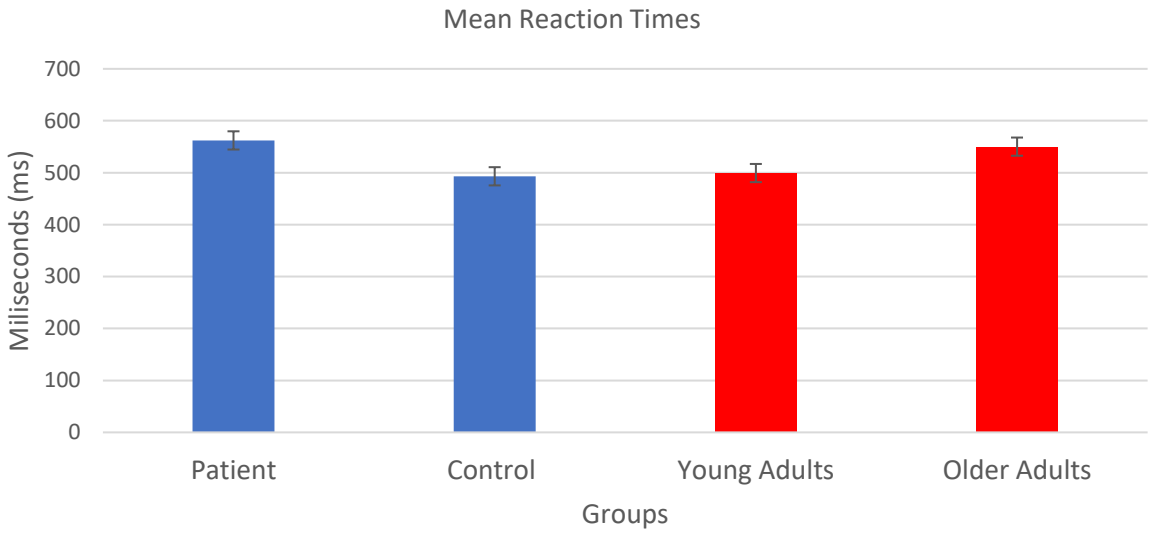
Note: The blue bars show mean target hit rates between the patient and the control group. The red bars show mean target hit rates between the young adults and the older adults.

Furthermore, as shown in Figure 3 below, a difference in reaction time (RT) was found between patients and healthy controls, where healthy controls were faster in responding to targets than patients, *t*(43) = 2.63, *p* = .012 (patients: mean RT = 562 ms, SD = 96 ms; healthy controls: mean

RT = 493 ms, SD = 80 ms). However, no difference in RT was found between age groups (younger adults: mean RT = 499 ms, SD = 86 ms; older adults: mean RT = 550 ms, SD = 96 ms; *p* = .068).

Figure 3

Differences Between Mean Reaction Times



Note. The blue bars show mean reaction times between the patient and the control group. The red bars show mean reaction times between the young adults and the older adults.

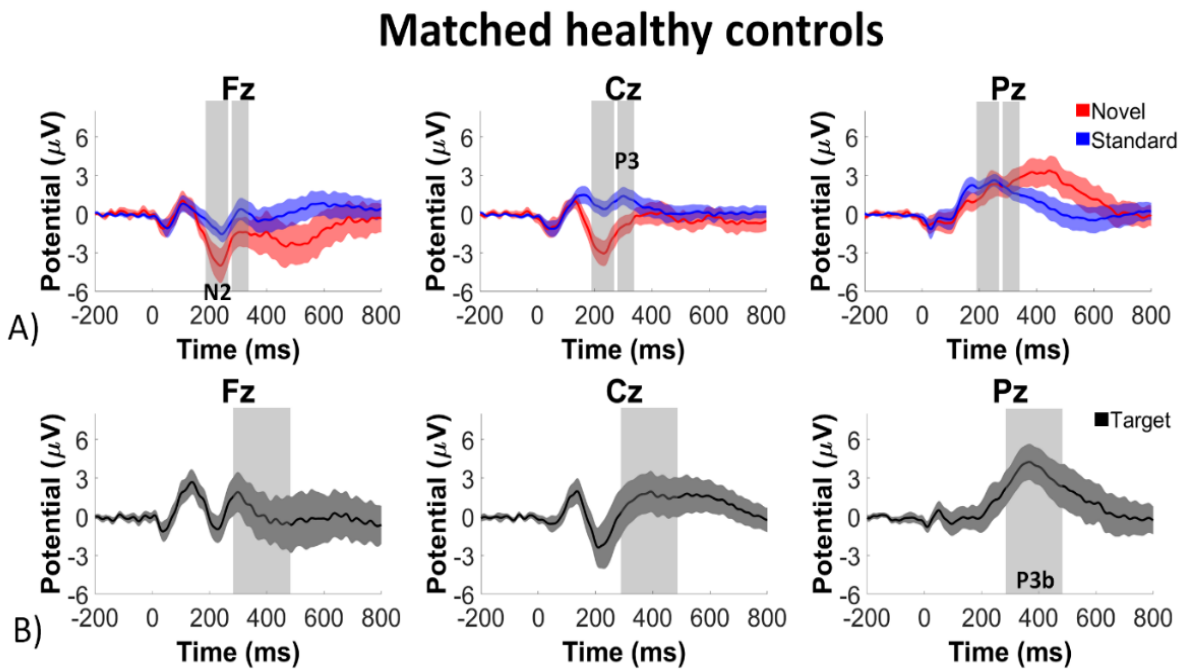
Mean ERP amplitudes

The novel stimuli elicited a negative component (N2) that peaked around 225 ms over anterior electrodes, which was followed by a positive component (P3) that peaked around 300 ms over posterior electrodes. Figure 4 shows the grand average ERPs for the matched healthy controls at Fz, Cz, and Pz, for A) standards and novels and B) targets. In Figure 5, the grand average ERPs for the patients are shown, with A) standards presented bilaterally, B) novels presented both ipsi- and contralaterally, and C) targets presented both ipsi- and contralaterally.

The topographic maps for ipsi- and contralaterally presented novels and bilaterally presented standards in patients in the N2 and P3 time windows are presented in Figure 7 below. This figure also shows the topographic maps for standards and novels in the matched healthy controls.

Figure 4

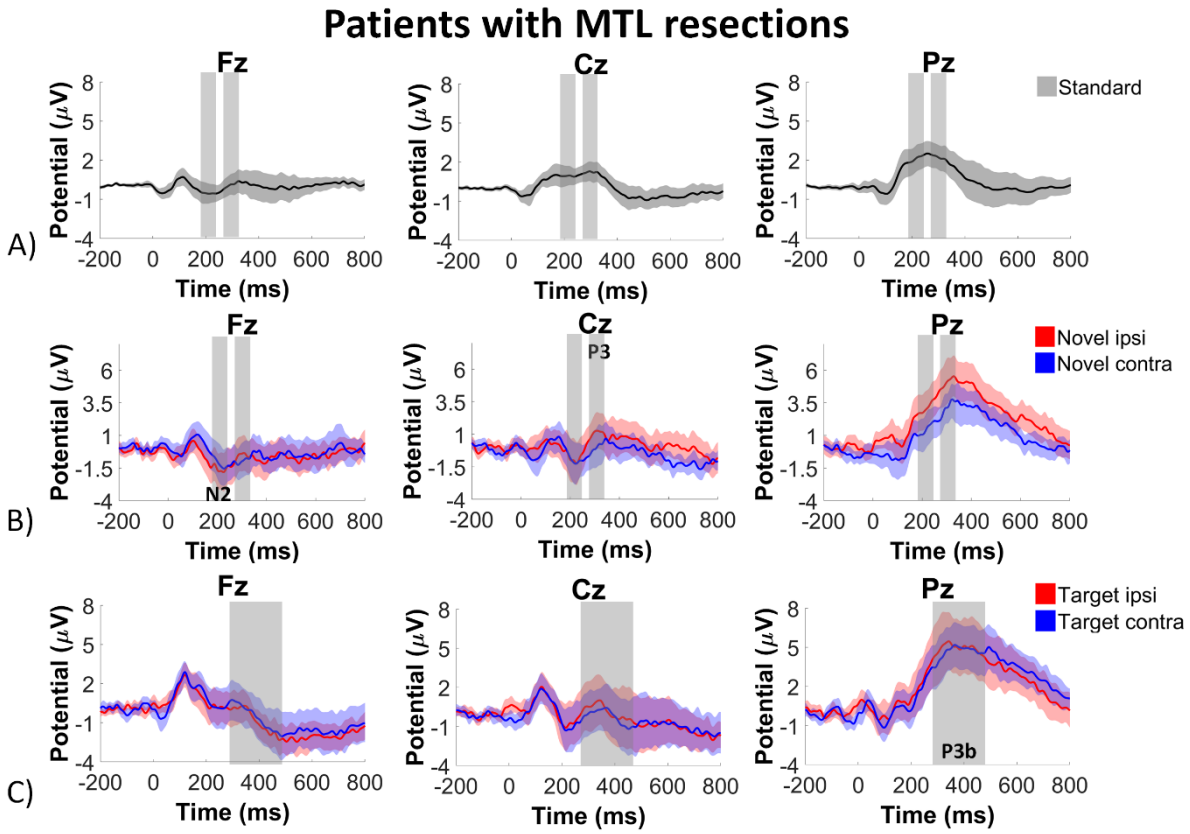
Grand average ERPs for Matched Healthy Controls



Note. Grand average ERPs for matched healthy controls at Fz, Cz, and Pz for A) standards and novels and B) targets. The grey highlights are the time windows used for the mean amplitude ERP analyses for the N2 and P3 (A) and P3B (B) components. The translucent areas show the 95% confidence intervals around the means.

Figure 5

Grand Average ERPs for Patients with Unilateral MTL Resections



Note. Grand-average ERPs for patient for A) standards, B) novels at Fz, Cz, and Pz, presented ipsi- and contralaterally, and C) targets at Fz, Cz, and Pz, presented both ipsi- and contralaterally. The grey highlights are the time windows used for the mean amplitude ERP analyses for the N2 (A), P3 (B), and P3B (C) components. The translucent areas show the 95% confidence intervals around the means.

Anterior N2

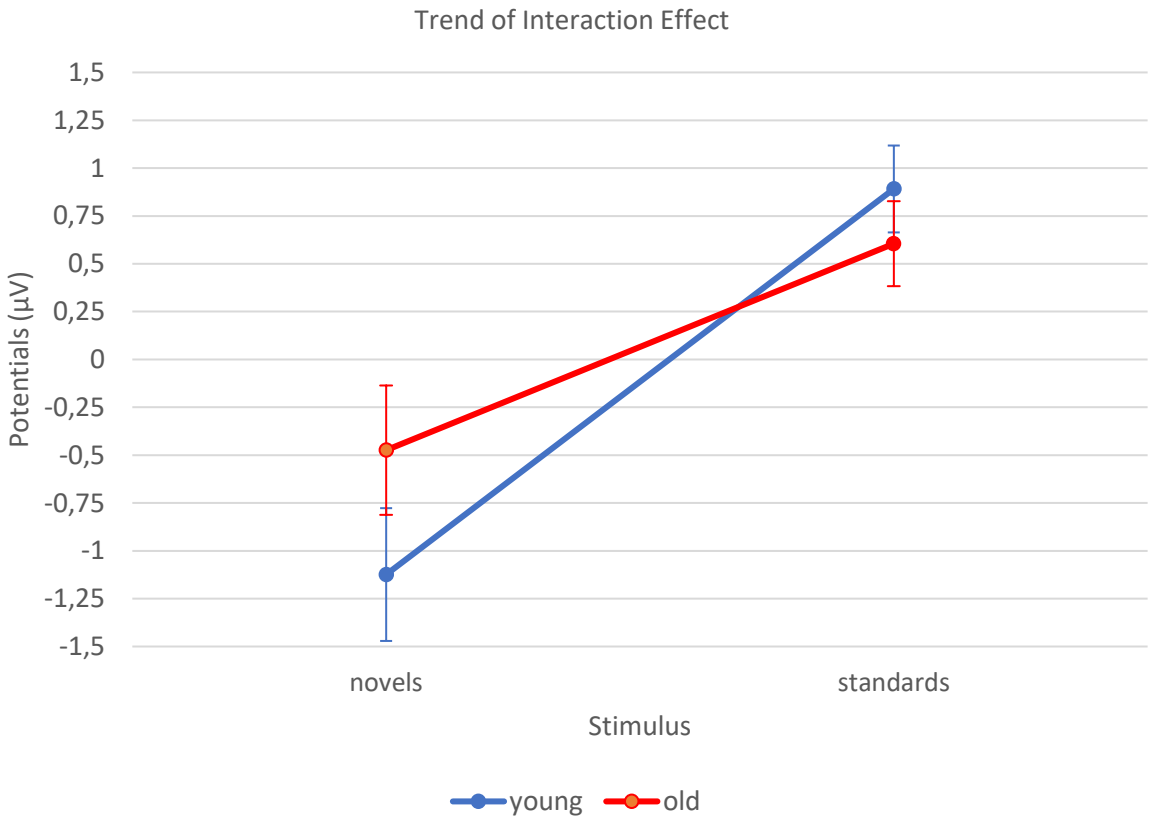
The anterior N2 was investigated with a mixed repeated measures ANOVA with Stimulus (novel; standard; target) and Electrode (Fz; Cz; Pz) as within-subject factors and Group (patient; healthy controls) and Age Group (younger adults; older adults) as between-subject factors. A main effect of stimulus type was found, with larger N2 elicited by novels compared to standards, $F(1,41) = 33.98$, $p < .001$, $\eta^2 = .45$. A linear effect over electrode was found, with N2 peaking over anterior sites, $F(1,41) = 61.89$, $p < .001$, $\eta^2 = .60$. A significant group effect was found, with larger N2 elicited by novels in matched healthy controls compared to patients, $F(1,41) = 6.81$, $p = .013$, $\eta^2 = .14$. Stimulus and Group also interacted, with larger N2 elicited by novels in matched healthy controls compared to patients and smaller differences for standards between groups, $F(1,41) = 5.54$, $p = .023$, $\eta^2 = .12$. Stimulus and electrode also interacted, $F(1.58,41) = 20.42$, $p < .001$, $\eta^2 = .33$. Furthermore, a trend could be distinguished in the interaction between stimulus and age group, $F(1,41) = 3.108$, $p = .085$,

η^2 = .07, as shown in Figure 6. Younger adults (younger adults) peaked in a more extreme manner in comparison to older adults (older adults). No other significant interactions were found (*ps* >= .298).

The interaction effect between Stimulus and Electrode was further investigated through follow-up ANOVAs comparing the effects of stimulus per electrode site (Fz, Cz, and Pz) separately. Bonferroni correction was used to correct for multiple testing. These follow-up ANOVAs showed that novel stimuli elicited a larger N2 than standards at Fz, $F(1,41) = 21.23$, $p < .001$, $\eta^2 = .34$, and Cz, $F(1,41) = 47.67$, $p < .001$, $\eta^2 = .54$, but not at Pz ($p = .41$).

Figure 6

Trend of Interaction Effect Between Stimulus and Age Group



Note. Trend of interaction effect between Stimulus (novel; standard) and Age Group (younger adults; older adults), including standard errors.

Novelty P3

The novelty P3 was investigated with the same ANOVA as used for the N2. A main effect on electrode was found, $F(1.40) = 38.24$, $p < .001$, $\eta^2 = .48$, with a linear effect of electrode, $F(1,41) = 43.79$, $p < .001$, $\eta^2 = .52$, showing that P3 peaked over posterior sites. Even though no main effects of stimulus ($p = .196$) or group ($p = .165$) were found, group and stimulus did interact, with larger novel-elicited P3 in patients and larger standard-elicited P3 in healthy controls, $F(1,41) = 16.33$, $p < .001$, η^2

= .29. Additionally, stimulus and electrode interacted, $F(1.29,41) = 21.62$, $p < .001$, $\eta^2 = .35$. No further significant interactions were found (*ps* >= .073). In healthy controls, no significant interactions with age group were found (*ps* >= .253).

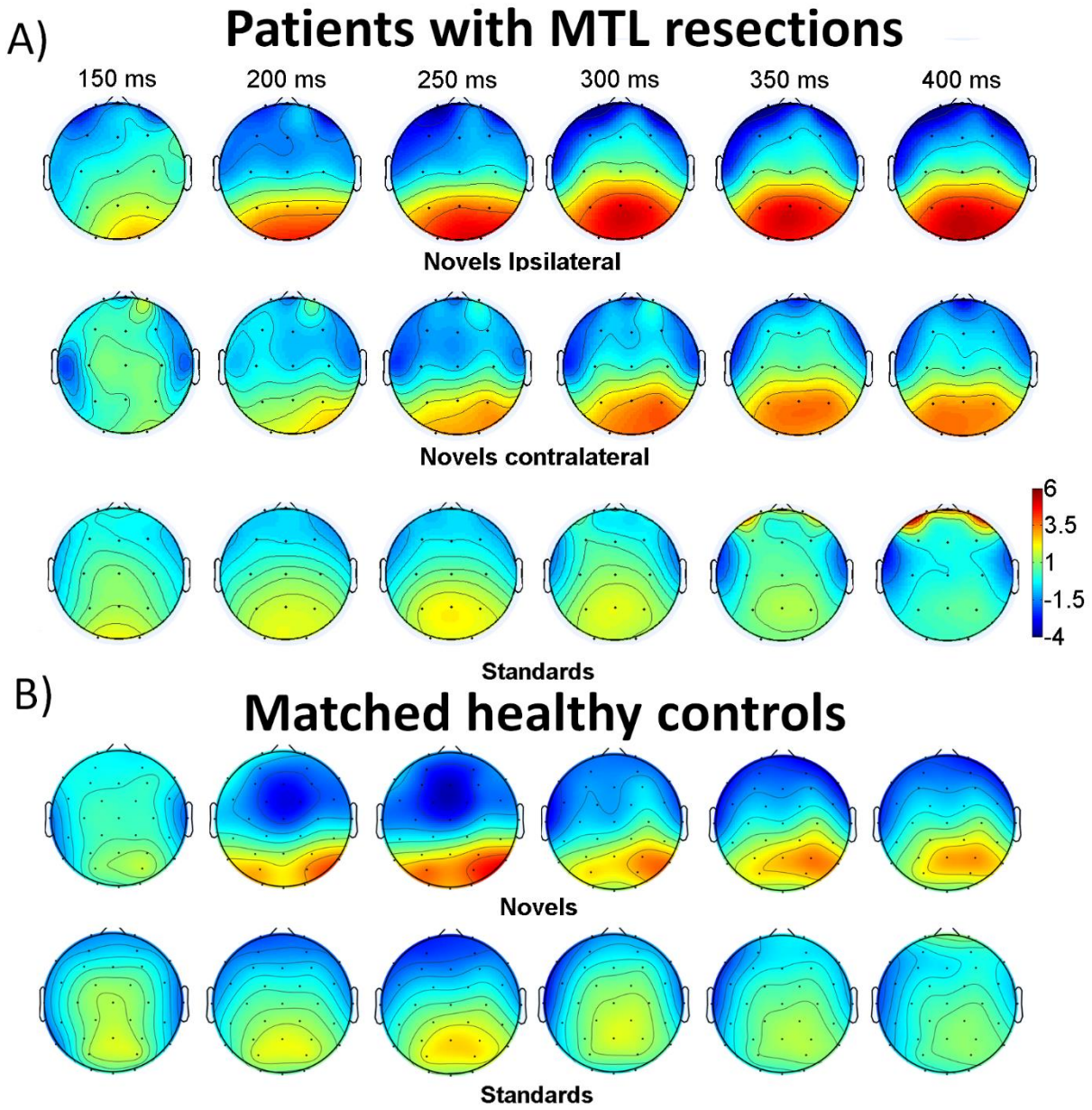
The interaction effect between stimulus and electrode was further investigated with the same follow-up ANOVAs per electrode site (Fz, Cz, and Pz) as used for the N2. These follow-up ANOVAs showed that novels elicited a larger P3 at Pz compared to standards, $F(1,41) = 16.80$, $p < .001$, $\eta^2 = .29$. This effect was reversed, with standards eliciting larger P3 compared to novels, at Fz, $F(1,41) = 9.85$, $p = .003$, $\eta^2 = .19$, and Cz, $F(1,41) = 15.52$, $p < .001$, $\eta^2 = .28$.

N2-P3 complex

The findings of a larger novel-elicited P3 for standards compared to novels and for patients compared to healthy controls might be explained by the stimulus and group effects found earlier on the novel-elicited N2, as N2 and P3 are of opposite polarities and the differences found on the novel-elicited N2 might have confounded the later novel-elicited P3 effects. For a further investigation of this effect, an additional ANOVA was run on the N2-P3 complex, where the novel-elicited N2 was subtracted from the novel-elicited P3. This ANOVA showed an interaction between electrode and group, $F(1.398,57.301) = 4.83$, $p = .021$, $\eta^2 = .11$, with a linear effect $F(1,41) = 6.18$, $p = .017$, $\eta^2 = .13$. For the matched healthy controls, a larger N2-P3 complex was found at Fz ($M = 1.707$, $SD = .355$) and smaller N2-P3 complex at Pz ($M = .786$, $SD = .330$). For patients, the linearity was reversed, with a smaller N2-P3 complex at Fz ($M = .790$, $SD = .380$) and a larger N2-P3 complex at Pz ($M = 1.732$, $SD = .353$). At Cz, there was little difference between the two groups (patients: $M = 1.523$, $SD = .415$; healthy controls: $M = 1.758$, $SD = .388$).

Figure 7

Topographic Maps for Patients and Matched Healthy Controls



Note. Topographic maps for A) novels presented ipsilaterally, contralaterally, and standards for patients with medial temporal lobe resections and B) novels and standards presented to matched healthy controls. The topographic maps are shown for 150 to 400 ms, with 50-ms intervals. The N2 and P3 components peaked in these time windows.

Target P3B

Target P3B was investigated using a repeated measures ANOVA with Electrode (Fz, Cz, Pz) as within-subject factors and with Group (patients; healthy controls) and Age Group (younger adults; older adults) as between-subject factors. A main effect on electrode was found, $F(1.43,58.71)$ =

18.45, $p < .001$, $\eta^2 = .31$, with a linear effect where P3b is largest at posterior regions (Pz) and increasingly smaller over central (Cz) and anterior (Fz) regions, $F(1,41) = 21.40$, $p < .001$, $\eta^2 = .34$. No further significant interactions were found (*ps* >= .182). For the healthy controls, no significant interactions with age group were found (*ps* >= .245).

Discussion

In this study, patients with epilepsy who had undergone unilateral MTL resections and matched healthy controls performed an adapted visual novelty oddball task while their EEG was measured. This was done to confirm the findings by Schomaker et al. (2021) regarding the role of the MTL structures in the detection and later processing of novel stimuli, and to investigate age-related differences in the detection and later processing of novel stimuli. In this adapted visual oddball task, truly novel pictures were used, in contrast to the deviant stimuli used by Knight (1996). The task was lateralized, with novel and target stimuli presented either to the left or the right side of a fixation cross. In patients the novel and target stimuli were presented to either the patients' unresected (ipsilateral) or resected (contralateral) side. This enabled Schomaker et al. (2021) to make comparisons in a within-subjects design as well as comparisons with the control group. However, since the current study focused on the comparisons between the patient group and the matched healthy controls, and between the younger and older age groups, the resection side was not taken into account. In the current study, the typical novelty component N2 was observed, with a greater novelty response at frontal and central electrode sites compared to responses to standard stimuli (Chourchesne et al., 1975). Additionally, the novelty P3 component was observed, with a greater ERP response at a posterior electrode site. This suggests that the adapted visual novelty oddball effectively elicited the typical novelty ERP components. Even though no significant effects were found between the two age groups, differences were found in novelty responses between patients and healthy controls.

The results show that novelty detection, indexed by the novel-elicited anterior N2, was reduced in patients with MTL resections, as evidenced by the smaller N2 for patients compared to controls. Normally, ERP investigations using the novelty oddball paradigm find that the amplitude of the P3 component is larger for novel stimuli in comparison to standard stimuli (Daffner et al., 2006). In addition, and rather unexpectedly, the results of this study show that processing of the novel stimuli, registered by the novelty P3, was smaller compared to the standard elicited P3 and larger for patients compared to healthy controls. This might be explained by the stimulus and group effects found earlier on N2, since N2 and P3 are of different polarities. The differences found on N2 may have confounded the later P3 effects, which is why an analysis of the N2-P3 complex (novel-elicited P3 minus novel-elicited N2) was also conducted (see Folstein & Van Petten, 2008). Interestingly, the

analysis of the N2-P3 complex showed a main effect on group. When the N2-P3 complex between patients and healthy controls was compared, opposite effects between the groups were found, with patients showing larger N2-P3 complex at posterior sites and the matched healthy controls showing larger N2-P3 complex at anterior sites. As the location of the resection was not taken into account, our data was collapsed for stimuli presented contra- and ipsilaterally to the resected side. Potentially, this could have influenced the results for the patient group, resulting in an opposite effect compared to the healthy controls. Schomaker et al. (2021) did take resection side into account, and they found different results. Even though they also found that healthy controls had a larger N2-P3 complex at anterior sites, they did not find an opposite effect for patients, since no further effect of group was observed. Because differences were found in the results of the current study compared to the results found by Schomaker et al. (2021), an additional visual inspection of the grand average ERPs of the current study was done. This visual inspection suggested that, compared to the matched healthy controls, patients indeed had a smaller peak in anterior regions contralaterally to the resected side. This suggests that the processing of novel stimuli was reduced in patients for stimuli presented contralaterally to the resected side, which is in line with what Schomaker et al. (2021) concluded. For future research, it is important to take collapsed data into account, since collapsing data from two to one variable might influence the results. Therefore, running two separate analyses where the N2-P3 complex for the contra- and ipsilateral side are separately compared to the N2-P3 complex of the matched healthy control group is preferred, since this will result in more precise and detailed information regarding differences between the two groups.

More importantly, no differences in target processing, as registered by the P3b component, were observed between patients and healthy controls. In both groups, the target P3b peaked in the posterior regions and was increasingly smaller across central and anterior regions. This shows that the group differences on the novelty N2 and N2-P3 complex are specific for novel stimuli and that the P3b was not affected by MTL resections. This is in line with findings reported by Knight (1996) which suggest that MTL structures are not required for the processing of targets. However, there are also studies that contradict these findings by arguing that the origin of the P3b component is the hippocampus (Halgren et al., 1998; Halgren, et al., 1980; McCarthy et al., 1989). This lack of consensus may be explained by the fact that these studies used different oddball tasks. The studies that point to the hippocampus as the root of the P3b component mainly used a two-stimulus oddball task, while Knight (1996) and the current study used a three-stimulus oddball task, with novel stimuli as a third category of stimuli. A possible explanation for the discrepancy between findings could be that the hippocampus only elicits a P3b component when all attention is focused on the target stimuli (Halgren et al., 1998; McCarthy et al., 1989). In a three-stimulus task, the novel stimuli are registered by the brain even when participants are asked to focus exclusively on the target stimuli.

Thus, it may be that the brain subconsciously processes the novel stimuli, which diverts part of the attention from the target stimuli towards the novel stimuli. It could therefore be concluded that the target stimuli do in fact elicit a P3b, possibly through activation of other MTL structures, but that there is insufficient attention for the target stimuli to be processed in such a way that the hippocampus is activated. However, future research is necessary to investigate the involvement of the hippocampus in the P3b ERP component in greater detail. This could be done, for instance, by comparing the target-induced ERPs of the two- and three-stimulus tasks in one single study.

Several researchers have suggested the MTL structures as the root of the novelty signal (Knight, 1996; Kumaran & Maquire, 2007). Furthermore, it is believed that the novelty N2 is affected by perceptual novelty, and that it marks an early novelty signal (Ferrari et al., 2010; Schomaker & Meeter, 2014). In the current study, differences on N2 were found between the patients with epilepsy with MTL resections and the matched healthy controls. This study showed a reduced N2 in patients compared to the healthy controls. This group difference implies that novelty detection may rely on MTL structures. These findings are in line with the findings reported by Knight (1996) which suggest that the detection of novel stimuli occurs in the hippocampus.

As stated earlier, no differences in P3b amplitudes were found between patients and healthy controls. Nonetheless, patients were slower in responding to target stimuli in comparison to the healthy controls. This may indicate that the MTL resections slowed down the target processing but did not affect P3b amplitudes. However, the finding that P3b amplitudes in patients and healthy controls were similar suggests that target processing was not affected by the history of epilepsy. In conclusion, these findings suggest that the MTL resections resulted in a specific impairment in the processing of novel stimuli.

The MTL resections in the patient group included in the current study were surgically performed using anatomical landmarks, with the aim to remove both the hippocampus and amygdala completely. This resulted in highly similar resection patterns across patients. However, the removal of not only the hippocampus but also the adjacent amygdala in 17 out of 21 patients is a limitation of the current study. Additionally, 10 out of 21 patients had undergone a maximal temporal resection, where the temporal pole, the entorhinal cortex, and the perirhinal cortex were removed as well. Despite these differences between the patients included in the current study, the patient sample was more homogeneous in comparison to that in the study conducted by Knight (1996), in which lesions occurred naturally and could extend to other regions of the brain. However, as the variation in resected brain structures was found to be insignificant and there was overlap between patients, individual differences could not be investigated, and the patient group was too small to be divided in subgroups.

The differences between patients and healthy controls in novelty processing could be explained by the resection of the hippocampus. However, it is vital to bear in mind that other MTL structures, such as the amygdala, are also activated by novel stimuli. The amygdala response is known to habituate after repetition of emotional stimuli, and it codes for novelty (Bradley et al., 1993; Kiehl, et al., 2005). The habituation of the amygdala response after repetition of novel stimuli might indicate the salience of new stimuli. In addition, it has been found that activity in the affective circuits, including the amygdala, has novelty as a pertinent driver (Weierich et al., 2010). This would mean that the results of the current study can be explained by the resection of the amygdala: without it, the novel stimuli are not properly coded or habituated, subsequently resulting in a reduced N2 for novel stimuli. Another matter to be taken into account are indications that the perirhinal cortex also plays a role in the processing of novel stimuli (e.g., Nyberg, 2005). In the current study, 10 patients who had undergone a maximal temporal resection had had their perirhinal cortex removed. This was not found to affect our results to a significant degree, but giving these factors due consideration is of major importance for the study of novelty processing.

Finally, we investigated the differences in N2 and P3 amplitudes between two age groups (younger adults; older adults), and no differences were found between younger and older adults, indicating that both the detection and processing of novel stimuli is not affected by age. This is simultaneously in line with and contradictory to existing literature on age-related differences in novelty detection and processing. There are three possible reasons why we did not find evidence to support our hypothesis regarding age-related differences in novelty detection and processing. Firstly, by dividing the participants into two consecutive age groups, the linear decrease of amplitude that we expected to find might not have come forward clearly. The older participants in the 'younger adults' group could have influenced the average amplitude in that group, while the younger participants in the 'older adults' group could have done the same, bringing the average amplitudes of both groups closer together, thus minimizing the chance of finding a significant difference between the two age groups. Secondly, in investigating the age difference only the healthy participants were taken into account, which resulted in a sample of 24 participants divided over two groups. This is a very small sample, which makes it harder to find a significant difference. Thirdly, our age range went from 19 to 64 years, which means that the oldest population group, above 64 years of age, were not included. Therefore, age-related changes in the MTL structures after 64 years were not investigated, possibly minimizing the chance of finding a significant difference between older-older adults (as they are called in Daffner et al. (2011)) and young adults. Therefore, more research is necessary to investigate differences in novelty detection and processing across the lifespan. Future research will benefit from the limitations of our current study, where we divide age in only two age groups, had a small sample size and did not include the oldest population of society. Therefore, future research

should include larger sample sizes, participants above the age of 64, and should compare three or more age ranges, or use age as a continuum or covariate.

To conclude, even though no age-related differences were found, the findings of the current study confirm that MTL structures, including the hippocampus and the amygdala, play a role in both novelty detection and the later processing of novel stimuli. This is supported by the reduced ERP novelty responses for novel stimuli in patients in comparison to the matched healthy control group. Moreover, in terms of target processing, no differences were found between the patients and the healthy control group. This indicates that target processing depends on structures outside of the MTL rather than within the MTL.

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