FINDING
A NEW BALANCE

Change in cortical activations during the lifespan

Rik J.R. van Dinteren

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Doctoral Thesis

to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. J.H.J.M. van Krieken,
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by

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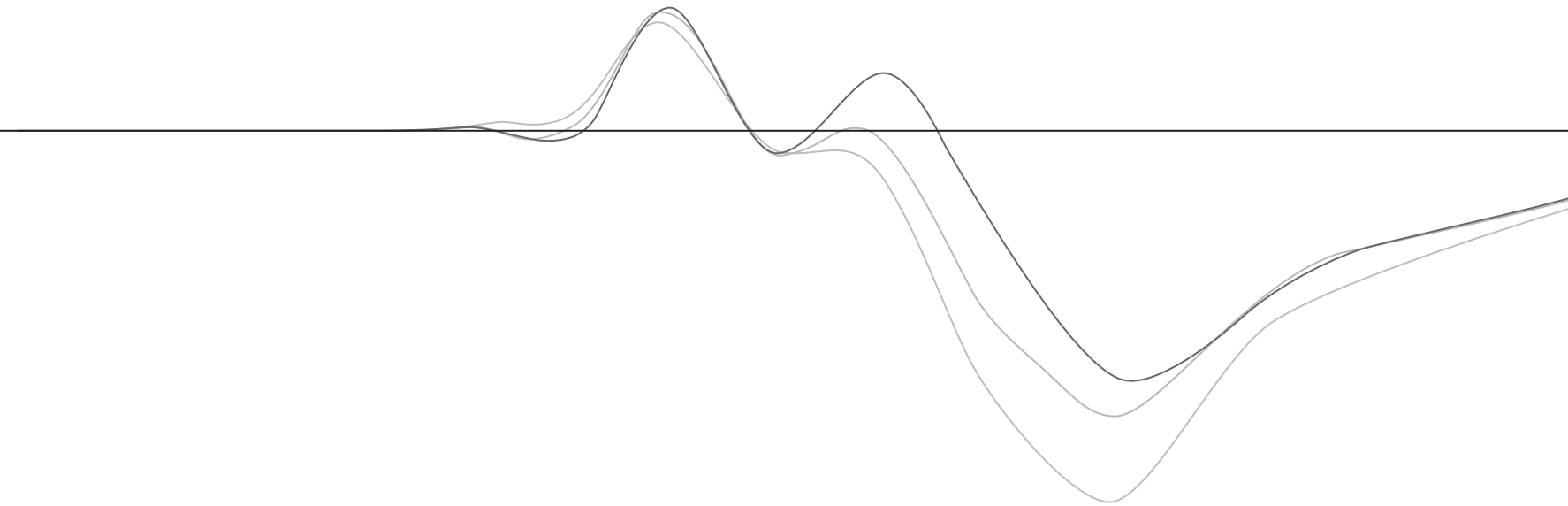
Introduction



With aging, our cognitive abilities gradually decline relative to our cognitive performance in young adulthood. For example, older adults' performance on tasks that rely on memory, reasoning, spatial visualization, and speed declines [1]. These changes are accompanied with physical changes in the brain. For instance, gray and white matter intensity decreases in frontal, anterior cingulate and temporal regions [2]. Although the decline in cognitive performance can be measured in experimental tasks, most older adults experience no or only a modest decline in daily life. In some areas – for instance vocabulary knowledge - they even outperform younger adults. This is a domain in which life experience plays a more important role than in, for example, information processing speed. Thus, the aging brain may compensate for physical shortcomings to achieve a normal behavioral performance. One hypothesis states that diminished neural activity of a brain region with difficulties can be compensated by activity in alternate connected brain networks.

In fact, during our entire lifespan, the brain is continuously optimizing the use of its resources. It does so by changing neural pathways to adjust for changes in behavior (e.g. learning) or shortcomings due to brain trauma [3]. For example, existing neural connections may need to be strengthened or other unaffected brain structures must be allocated. In addition, neural pathways that are not activated frequently enough may be pruned. An example is the extensive synaptic pruning in the young child's brain [4]. At first glance, it may seem odd that a child's developing brain eliminates nerve tracts, but this way, only functional connections will remain and the brain's efficiency is largely increased.

These different aspects of neuroplasticity have long been considered to be a characteristic exclusive to the young developing brain. Thus, the aging brain was traditionally considered to be static and only subject to a progressive deterioration of neural tissue and consequently a decline in performance. In the last decades, it has been discovered that this view is incorrect. Fortunately, the aging brain maintains its neuroplastic capacities to a large degree [3]. This gives rise to the thought that the aging brain might be capable of some form of compensation for its decline in cognitive resources.

In adults, the fully developed brain has dealt with all kinds of tasks in the past and is able to efficiently allocate its resources to reach an optimal performance. When the usual resources are scarce or insufficient, the brain may compensate for this by optimizing the activity in the existing network or by increasing activity in an alternate, connected network [5]. This way, the desired behavioral output can still be achieved. To achieve a certain goal, the brain strives to be as energy-conservative, and consequently efficient, as possible. How the brain achieves this, probably differs

from sample to sample, e.g. whether the sample exists of healthy people or certain patient groups. Even differences from individual to individual, depending on age, sex, comorbidities are a possibility.

Studying how compensatory networks are allocated in patients with (neuro) psychological disorders might open up new directions for treatment and prevention. A personalized approach in medicine appears destined to become a reality with increasing research focusing on this topic. Insight into neural network recruitment in clinical samples is an important first step. However, it is vital to first understand individual recruitment of neural (compensatory) networks in healthy older adults before we can study this in clinical samples. The issue with studying compensatory activation is that it is a phenomenon that is happening within the proverbial black box. By its nature, it is nearly impossible to study compensatory activation by only recording behavioral performance. Therefore, there is a need to investigate the source by studying the activation in the brain that underlies the behavioral output. One method to directly study brain activity is the human electroencephalogram (EEG), which has been developed and described by Hans Berger [6]. The EEG method allows a non-invasive approach to measure electrical brain potentials at the surface of the scalp.

The event-related potential (ERP) is brain activity in the EEG that is related to the neural processing of an event. Such an event can be, for example, someone calling out your name, a traffic light turning green, an off-key note in a melody, or a stimulus in an experimental paradigm. The ERP consists of several peaks and troughs that can be identified by their post-stimulus latency, baseline-related amplitude, baseline-relative polarity and order of occurrence in the ERP. The ERP to a single stimulus consists of neural activity related to the event as well as neural activity unrelated to the event, and additional artifacts and noise (unrelated to the processing of the stimulus). One way to eliminate this non-event-related activity is by presenting a multitude of stimuli and averaging all EEG segments that are phase-locked to the repeated stimuli. The averaging increases the signal to noise ratio of the signal. That is, the neural activity related to the processing of the stimulus remains, and simultaneously the spontaneous activity that is unrelated to the processing of the stimulus is reduced.

Figure 1.1 demonstrates an example of a typical (averaged) ERP and its peaks and troughs that have been related to different aspects of cognitive processing. The peaks and troughs in the ERP span a continuum ranging from exogenous to endogenous potentials. Exogenous potentials are related to responses to the physical nature of a stimulus. Endogenous potentials are related to the internal processing of the stimulus [7].

The earlier peaks and troughs are predominantly related to exogenous processes (not illustrated). For example, the amplitudes of these peaks can be manipulated by differences in stimulus loudness or tone frequency [7]. The later occurring peaks and troughs, referred to as the N1, P2, N2 and P3, are related to endogenous processing. For example, the N1 has been related to spatial orientation [8]. The N2, which occurs around 200 milliseconds post-stimulus, has been associated with attentional and mismatch processing [9]. The P3 is in general the largest and most prominent positive peak in the ERP. In young, healthy adults it occurs at approximately 300 milliseconds after stimulus presentation and is therefore also known under the moniker ‘P300’. Since the P3 is the most prominent ERP peak it has been the most extensively studied ERP component since its discovery in the early 1960s.

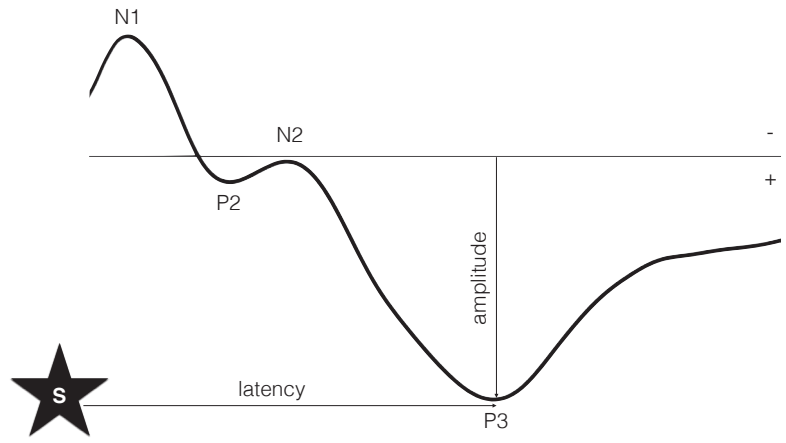


Figure 1.1 A schematic overview of the ERP. *A typical averaged event-related potential consists of several peaks and troughs named after their polarity and order of occurrence, i.e. N1, P2, N2 and P3.*

A classic ERP paradigm to elicit the P3 is known as the ‘oddball’ paradigm [10]. In the auditory form of this paradigm a participant is presented with a sequence of beeps. Intermixed within this sequence are other beeps that occur less frequent than the frequent stimuli, hence oddball stimuli, and differ for instance in pitch, loudness, or duration. The deviating oddball beeps elicit a P3 peak that is not present in the frequent stimuli. This effect is not limited to auditory stimuli though. The P3 is also elicited with deviating visual, tactile, or olfactory stimuli, or even when expected stimuli within a regular sequence are occasionally omitted, as long as the infrequent

target stimuli deviate from the frequent background stimuli. Figure 1.2 demonstrates the oddball paradigm in a schematic manner.

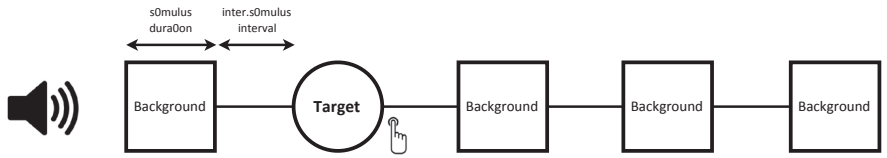


Figure 1.2 A schematic overview of the oddball paradigm.

The P3 that is elicited in this oddball paradigm is sensitive to a wide range of experimental manipulations that impact on endogenous information processing. For instance, one can decrease the probability of the infrequent target stimulus, thus manipulating the participants' expectancy to increase the P3 amplitude [11,12]. In addition to manipulating the target probability, increasing the task difficulty and thereby the mental effort a participant has to devote to the task has been positively correlated with the P3 amplitude as well [13,14]. However, uncertainty, which can be introduced by making the difference between the background and target stimulus less salient, is negatively correlated to the P3 amplitude [13]. Apart from experimental manipulations, the P3 is additionally determined and influenced by biological and physiological determinants, such as sex, circadian rhythm, fatigue, food intake or psychoactive substances [15].

The possibility to elicit the P3 by deviant stimuli has led to the conventionally accepted proposition that the P3 reflects cognitive processes that are related to detection of this deviance. Several theories have been postulated to explain what cognitive processes the P3 reflects. For instance, the stimulus-evaluation-hypothesis by Duncan-Johnson and Kopell (1981) [16] states that the P3 reflects information processing related to the evaluation of the presented stimulus. An even more influential theory is the context-updating theory by Donchin (1981) [17]. This theory states that participants, for instance in the oddball paradigm, create a mental context based on the stimuli that are presented to them. When a deviating stimulus is presented, the previously established mental context is no longer accurate and needs to be updated to account for the new information the deviating stimulus introduces. It is proposed that an increased P3 reflects the updating process. There are several alternative, yet similar, theories. For instance, the context-closure hypothesis by Verleger (1988) [18] states that participants create a meaningful mental context after stimulus presentation. However,

in this theory the P3 is thought to reflect the closing of a mental epoch when a deviating stimulus is presented to the participant.

Although all the hypotheses acknowledge the involvement of several cognitive processes, 50 years of intensive research on the P3 still cannot link this elusive wave in the ERP to one specific cognitive process. One reason is that the P3 probably reflects multiple cognitive processes (e.g., perception, attention, working memory, executive processes) that overlap in time. This is probable since the P3 encompasses such a large portion of the entire ERP duration (again see figure ERP) and often contains multiple subcomponents. Although the P3 lacks specificity, the multifariousness of the P3 makes it a suitable index of cognitive functioning in general and such a general cognitive measure can especially be valuable in studying information processing in mental aging. In addition, the P3 has other characteristics that make it a suitable measure. First, an individual's specific P3 morphology - predominantly determined by that person's physiological properties, like skull thickness and anatomical features of the corpus callosum - is a remarkably stable measure with little variation over recording sessions [19]. Second, the P3 is the most recognizable ERP component, which makes it easy to determine its amplitude and latency at the level of individual participants. Third, the paradigms used to elicit the P3 are generally short and simple and are therefore suitable for studying a wide range of participants across a large portion of the lifespan (i.e., from 5 years old onwards). Fourth, recording an ERP is a relatively affordable and quick non-invasive procedure that most people, including those of older ages, can endure with ease.

Aim and outline

This thesis aims to investigate whether the P3 is a valid index to quantify cognitive aging in both healthy and clinical populations. By doing so, it aims to capture the compensatory brain activation that might increase with aging.

After this general introduction, **Chapter 2** describes a systematic review and meta-analysis of healthy aging effects on the parietal P3 potential across the lifespan. Consequently, trajectories describing the development of the P3 (latency and amplitude) with aging are formed. Additionally, the results from the meta-analysis are validated in a large cross-sectional data set. In **Chapter 3** tears apart the developmental trajectories of the parietal P3 and compares them to the developmental trajectories of the frontal P3 in order to capture differences between both P3s' development and aspects of frontal compensation with aging, again in healthy participants. **Chapter 4** provides an overview of the role of EEG and ERPs in

predicting treatment outcome leading to **Chapter 5**, in which differences in P3s between healthy and clinical (Major Depressive Disorder) participants as well as its use in predicting treatment outcome in a large sample, are reported. Finally, in **Chapter 6** the P3 is decomposed into independent components (using independent component analysis) to capture a more accurate and localizable reflection of frontal compensation. The decomposed P3s are compared between young and old participants and are localized to a cortical source. **Chapter 7** discusses the main findings and implications of the studies and suggestions for future research.

2

A review of the age-related development of the P3

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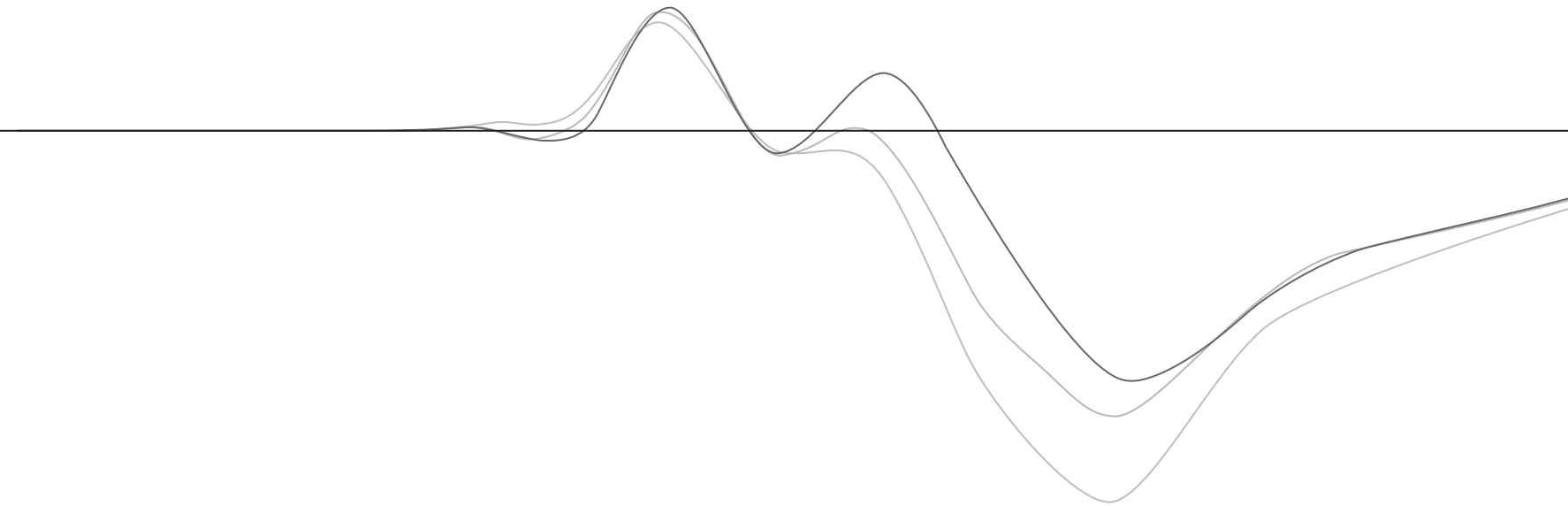


Abstract

Background: The P3 component of the event-related potential is a large positive waveform that can be extracted from the ongoing electroencephalogram using a two-stimuli oddball paradigm, and has been associated with cognitive information processing (e.g. memory, attention, executive function). This paper reviews the development of the auditory P3 across the lifespan.

Methodology/Principal findings: A systematic review and meta-analysis on the P3 was performed including 75 studies (n=2,811). Scopus was searched for studies using healthy subjects and that reported means of P3 latency and amplitude measured at Pz and mean age. These findings were validated in an independent, existing cross-sectional dataset including 1,572 participants from ages 6-87. Curve-fitting procedures were applied to obtain a model of P3 development across the lifespan. In both studies logarithmic Gaussian models fitted the latency and amplitude data best. The P3 latency and amplitude follow a maturational path from childhood to adolescence, resulting in a period that marks a plateau, after which degenerative effects begin. We were able to determine ages that mark a maximum (in P3 amplitude) or trough (in P3 latency) segregating maturational from degenerative stages. We found these point of deflection occurred at different ages.

Conclusions/Significance: It is hypothesized that latency and amplitude index different aspects of brain maturation. The P3 latency possibly indexes neural speed or brain efficiency. The P3 amplitude might index neural power or cognitive resources, which increase with maturation.

Introduction

Almost half a century ago, the group of Samuel Sutton and E.R. John first described the P3 [11], a component from the event-related potential (ERP), which has been intensively investigated since then. However, despite abundant research on this component, its developmental path across the lifespan has been relatively underexposed. The present paper will review and analyze the developmental process of the auditory P3 across the lifespan employing 1) a systematic review and meta-analysis of all studies published over the last half century and 2) an independent cross-sectional dataset including 1,572 participants. The P3 developmental process is proposed to reflect development of cognitive speed and cognitive capacity, across the lifespan.

Characteristics of the P3

The ERP is quantified by averaging activity in the electroencephalogram (EEG) time-locked to a specific event, for instance an auditory stimulus. This results in a waveform associated with the processing of that specific event. The ERPs found in such tasks have a characteristic waveform with clearly identifiable components, which are named after their polarity and approximate latency (i.e., P100, N100, P200, N200, P3). The P3 (also referred to as P3) component of the auditory ERP is a large positive waveform that reaches a maximum at approximately 300 milliseconds after stimulus onset (see figure 2.1 for an example). The amplitude is defined as the voltage difference between a pre-stimulus established baseline and the largest positive peak within a predefined latency window [14].

The P3 is commonly elicited in signal-detection tasks. A typical signal-detection paradigm is the 'oddball' paradigm that was first used by Ritter and Vaughan [10]. In the auditory version of this paradigm, participants are typically presented with two different tones that can be discriminated based on, for example, pitch or loudness. The different types of tones are presented with different probabilities (e.g., 20% vs. 80%). The frequent stimuli are designated as background stimuli, the infrequent stimuli as target or oddball stimuli to which the participant must respond, for example by counting or pressing a button [10,20,21]. See figure 2.1 for a schematic overview of the oddball.

In addition to the traditional P3 that is associated with responding to infrequent target stimuli, a slightly earlier P3 peak has been reported, which has slightly shorter latencies and a more frontally oriented topography. This component has also been labeled as *P3a* [22-25], and has primarily been linked to stimulus novelty and is not necessarily related to the generation of responses. This peak can be observed in, for

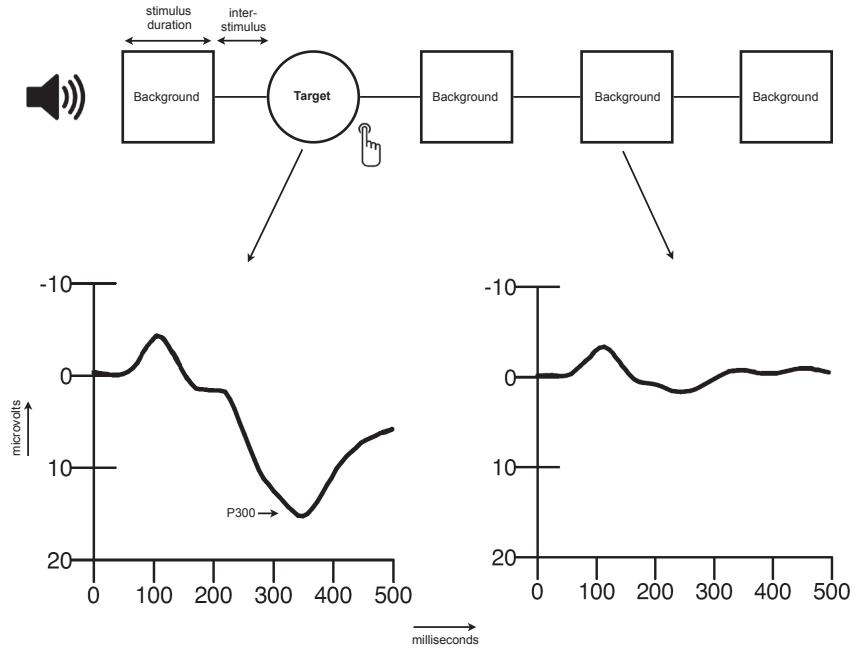


Figure 2.1 Schematic overview of the oddball paradigm and an example of an ERP.

example, a modified three-stimulus oddball paradigm including a second infrequent stimulus. Consequently, the P3 component described earlier has also been labeled *P3b*. Throughout this paper we will use the term P3 to reflect the P3b.

P3 theories

A central theme in P3 research is the exact nature of the involved cognitive processes underlying the P3, and several theories have been postulated in this respect. First, the stimulus-evaluation hypothesis states that the latency of the P3 component reflects the time needed for stimulus evaluation processes and is independent of the time needed for response processes[16]. However, this theory has been refuted in a more recent review[26,27]. A more prominent hypothesis, which has its roots in Sokolov's orienting response model and links the P3 to cognitive functioning, is the context-updating hypothesis[17,20,21]. This hypothesis states that the P3 (amplitude) represents brain activity related to updating a mental stimulus representation when deviant stimuli are presented. That is, the participant's mental model of his/her environment, or context, is evaluated and updated when a relevant and deviant stimulus is presented[14,17,21]. Finally, as an alternative to the context-updating hypothesis, the context-closure hypothesis has emerged. This hypothesis links the P3 to deactivation

processes, consequent upon the closure of a perceptual epoch. The hypothesis states that participants combine repeatedly presented stimuli in meaningful contexts. Deviating target stimuli, after a series of non-deviating background stimuli, close such a context and this closure process is reflected by the P3 [18,21,28].

Although these hypotheses recognize the involvement of various cognitive processes, still, after almost 50 years of intensive research with over 12,000 publications on the P3 it has not been possible to link the P3 to a specific cognitive process. Presumably, the P3 complex is multifarious, reflecting a culmination of multiple cognitive processes. However, there is evidence that shorter P3 latencies and larger amplitudes are associated with superior information processing [20,21,29-32]. In addition to individual differences due to trait effects, the P3 is also influenced by state variables, that is, natural and induced biological factors – like body temperature, sleep quality, exercise, food intake, drugs – which are mediated by arousal levels [15]. Thus, an interaction of cognitive processes and arousal levels determine relative changes in the P3, that is, component latencies and amplitudes. The absolute P3 morphology is predominantly determined by an individual's physiological properties, such as anatomical features of the corpus callosum [33] or skull thickness [34]. Thus despite relative changes by state variables, a person's specific P3 morphology is a remarkably stable measure that shows little variation over recording sessions or experiments [19]. In line, P3 morphology has demonstrated a high heritability of approximately 60% [35]. The main aim of the current review is to unravel the P3's development across the lifespan based on data obtained from both a meta-analysis and systematic review of existing papers and an independent large standardized dataset. First, a descriptive model of P3 development across the lifespan will be presented. This model will then be used to describe the development of information processing in terms of cognitive speed and resources.

Age effects on the P3 latency

Research on P3 development across the lifespan has been relatively scarce. However, there is clear evidence that P3 latency decreases during the first years of life [36-39], whereas in older adults the parietal P3 latency increases [40-43]. This model describing initial maturation followed by degenerative effects of aging on latency indicates that there may be a specific age range that marks a point of deflection in P3 latency development. To our knowledge, this specific trough of the P3 latency has not been described yet.

Age effects on the P3 amplitude

Findings on early developmental processes in P3 amplitude are mixed. P3 amplitudes are found to either increase during childhood or show no change [36,37,39,44]. Capacity of information processing increases rapidly during early childhood, which is expected

to enhance the P3 amplitudes. However, an opposing effect on amplitudes may result from an increase in skull thickness, as a thicker skull is related to smaller amplitudes [34]. Indeed, a study by Beauchamp et al. found an increasing brain-scalp distance as children age [45]. Thus, cranial development during childhood probably moderates early P3 amplitude development.

In adulthood, a decline of the parietal P3 amplitude with advancing age is commonly reported [40-43]. Since smaller P3 amplitudes have been associated with a decreased performance on a variety of cognitive tests indexing different aspects of information processing [21], they might thus reflect aging-related cognitive decline.

Behavioral task performance

An elegant aspect of the oddball paradigm is the possibility to quantify psychophysiological measures – i.e., the P3 latency and amplitude as described above – with their consecutive behavioral measures, such as reaction times (RTs) and errors. Speed variables – like RTs – have moderate to large associations with age during adulthood [46]. Therefore, RTs have been hypothesized to be an index of aging-related cognitive decline. In general, measures of speed tend to share 75% of the age-related variance with a variety of cognitive measures [46]. Thus, directly linking behavioral measures to the analysis of P3 latency and amplitude could result in new insights into the underlying neurocognitive mechanisms of the P3 across the lifespan.

The present review

First, a systematic review and meta-analysis will be performed, in order to model P3 developmental trajectories across the lifespan. The results of this review will be used to investigate effects of paradigm and sample characteristics on P3 latency and amplitude. Based on a literature review published by Polich (1996), besides age, an effect of stimulus saliency attributes, like stimulus intensity, stimulus duration and number of stimuli, is expected [21].

Second, based on an independent multi-site, cross-sectional dataset of 1,964 healthy participants aged 6-87 years – who all performed the same paradigm under standardized recording conditions and identical task procedures – an age-based model of the P3 across the lifespan will be estimated. In addition, the effects of within subject variables such as sex and education will be investigated further.

Finally, the estimated developmental trajectory of the P3 latency and amplitude will be compared to the developmental trajectory of behavioral measures such as reaction times and number of errors. Previous research has demonstrated that the P3 latency shows a significant positive correlation with reaction times [14].

Methods

Meta-analysis

Literature search

A systematic review was performed using Scopus with the search phrase "*P300 OR P3b AND oddball*", starting on June 18th 2012 until October 10th 2012. The search was not conducted according to a specific review protocol. All article titles and summaries were scanned for selection criteria. When the summary provided insufficient information, the methods section of the article was read. The following criteria were used to assess eligibility of articles for the meta-analysis:

a) The study had to report data on healthy participants not diagnosed with any neurological, psychiatric or other disorder which have a significant impact on the P3. When such information was not reported, a study could not be included. In studies that used a clinical population, only data from the healthy control participants were included.
b) The study had to report a mean age and a mean P3 latency and/or P3 amplitude for the healthy participants. These measures had to be reported quantitatively. Studies that reported only P3 data in graphs were excluded.
c) Studies with fewer than 15 participants in total were excluded in order to prevent Type-I errors [21,47,48].
d) Studies had to employ an auditory, active (meaning a response required from the participant on the oddball), two-stimulus (auditory stimuli differing in frequency) oddball paradigm. These criteria were based on relevant parameters mentioned in Polich (1996). The current meta-analysis focused on (binaurally) auditory paradigms since this is in accordance with the paradigm used in the cross-sectional data set.
e) P3 data for the Pz electrode site had to be available.
f) Study results had to be available in English.
g) Meta reviews and overlapping data sets (i.e., multiple papers on the same sample) were excluded.
h) Studies using the BRID database (REF: www.brainnet.net) were excluded, since data from this database were included in part 2 of this study.

The literature search resulted in a total of 1,265 studies. The literature review by Polich (1996) was checked manually for additional references that fulfilled the search selection criteria since it served as a basis for the current meta-analysis [21]. This yielded 26 additional studies resulting in a total of 1,291 studies. Figure 2.2 presents a flowchart depicting the number of studies that were excluded and the reasons for exclusion. Exclusion rationale was scored only once per study, and the main reason was noted. Therefore, some of the studies in figure 2.2 may meet multiple exclusion criteria.

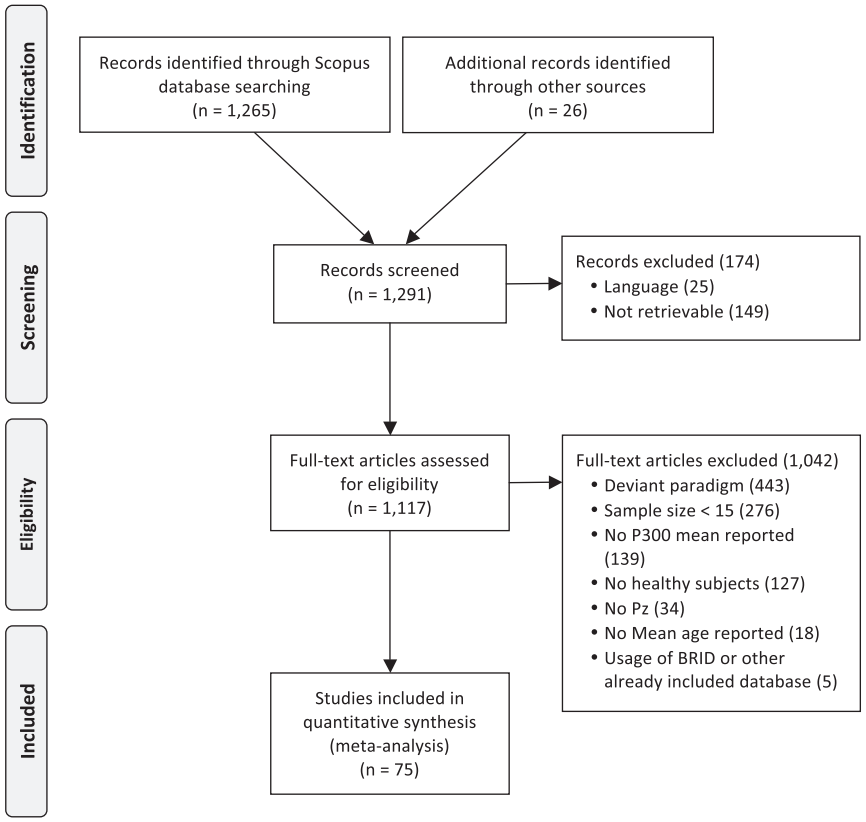


Figure 2.2 Flowchart depicting the number of exclusions per exclusion rationale in the literature selection.

Data extraction

The resulting 75 studies that were used in the meta-analysis are listed in table S1 with study details. The data entered per study are listed below:

1) *Year* was defined as the year of publication
2) C*ontinent* (if not clear, the first author's affiliation was used)
3) *Number of participants* was recorded as detailed as possible. So when data was divided over several age groups the data for each group were recorded. This applies to all data mentioned below
4) Percentage of males (if available)
5) Mean age
6) *Mean P3 latency* in milliseconds (and standard deviation if available)
7) *Mean P3 amplitude* in microvolts (and standard deviation if available)

In addition, recording parameters were also extracted. The parameter selection was based on Polich (1996) and included 1) eyes open/eyes closed if reported; 2) response type (press or count); 3) stimulus duration; 4) stimulus intensity; 5) absolute tone frequency difference between target and background. Additionally, 6) target probability; 7) total number of stimuli and 8) inter-stimulus interval were scored.

After the initial selection of appropriate studies, efforts were made to retrieve missing data by contacting the authors. All data were entered in a single spreadsheet using Microsoft Excel 2011. This spreadsheet was fully double checked for transcription errors by a second independent rater.

Outlier removal

One study reported a mean amplitude that was four standard deviations from the general mean and greatly affected average amplitude data [49]. The authors from this study mentioned several factors that may have attributed to the high amplitude scores they found, namely, the use of a low target probability, large inter-stimulus intervals, morning assessments and the use of a group of young adults [49]. Therefore, this study was considered an outlier and excluded from the analyses.

Statistical analysis

Visual inspection of the graphed latency data revealed a suspected inversed Gaussian pattern for the latency data. The latency data were transformed by inversing the scores and adding a constant (i.e., 600) in order to fit a model to the data. Transformation of the amplitude data was not necessary.

The data were entered in Graphpad Prism 6.0. Every datapoint consisted of a mean age and mean P3 latency or amplitude value. Prism has the possibility to include standard deviation and sample size in the calculations and these measures were entered when they were available. Several models were fitted to the data including a normal Gaussian, a logarithmic Gaussian and a straight line. The Gaussian models are described by three parameters; its center, width and amplitude. Center is the *x* value at the peak of the distribution; width is a measure of the width of the distribution expressed in the same units as *x;* amplitude is the height of the center of the distribution expressed in *y* units (www.graphpad.com). The model's amplitude is referred to as *height* to avoid confusion with the P3 amplitude.

In addition, one-way ANOVAs were performed to investigate the effect of *eyes open/closed* and *response type*. The other predictors were investigated using regression analysis. These predictors were entered in two blocks. The first block contained predictors based on the meta-analysis by Polich (1996) and included: *percentage of*

males, number of stimuli, and stimulus duration. The second block included: *target probability, stimulus loudness, frequency difference between target and background tone, inter-stimulus interval*. Then, the regression model was refined by entering only those predictors that showed an effect with a significance of $p < 0.10$. For the final regression model a significance level of $p < .01$ was used.

Cross-sectional dataset

Ethics Statement

All participants gave written informed consent. Local independent review board approval was obtained for all clinics.

Participants

Normative data were extracted from the Brain Resource International Database (BRID) resulting in a dataset of 1,964 healthy participants. This database contains data from multiple laboratories (New York, Rhode Island, Nijmegen, London, Adelaide, and Sydney) using standardized data acquisition techniques (identical amplifiers, standardization of other hardware, audio calibration, paradigm details, software acquisition, and task instructions). Inter-lab reliability and test-retest reliability measures are high and have been reported elsewhere [19,50,51].

Participants were aged 6 to 87 (mean = 28.38 ± 20.08). The sample consisted of 992 male and 972 female participants. Education scores varied from 1 to the maximum possible score of 18 years of education (mean = 10.89 ± 4.46). Database exclusion criteria included a personal or family history of mental illness, brain injury, neurological disorder, serious medical condition, drug/alcohol addiction, first-degree relative with bipolar disorder, schizophrenia, or genetic disorder. Participants were required to refrain from caffeine and smoking for at least 2 hours and alcohol for at least 6 hours prior to testing.

Six participants with error rates of 33% or higher on false positive errors (button press on a background stimulus) or false negative errors (no button press on a target stimulus) were considered unreliable and removed from the dataset (as an indication they have not understood the task instructions appropriately). The remaining 1,958 participants were matched for age and sex by random selection, resulting in a further exclusion of 386 participants. The resulting dataset consisted of 786 males and 786 females matched for age (mean = 27,17 ± 19.16; range = 6-87 years).

Electroencephalographic data acquisition

EEG and ERP recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Details of this procedure have been published elsewhere [19,52].

In summary, participants were seated in a sound and light attenuated room, controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Compumedics Quikcap and NuAmps amplifier; 10-20 electrode international system). Data were offline referenced to averaged mastoids with a ground at Fpz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye (bipolar). Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was <5 kOhms for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline [53]. The sampling rate of all channels was 500 Hz. A high cut-off filter at 100 Hz was employed prior to digitization. P3 latency and amplitude were quantified at Pz.

Auditory oddball

The oddball paradigm consisted of a quasi-random sequence of 280 frequent background tones (500 Hz) and 60 infrequent target (1000 Hz) tones. Two targets could not appear consecutively. All stimuli (50 ms; 5 ms rise and fall time) were presented binaurally at a volume of 75dB SPL with an inter-stimulus interval of 1000 ms. Participants were instructed to press two buttons simultaneously (one for each index finger) when they heard a target tone and to ignore the background tones. Speed and accuracy of response were both equally stressed in the instructions. Before the actual test they were presented with a brief practice run to clarify the distinction between the two tones.

Statistical analysis

Effects of age, sex and education on P3 latency and amplitude were investigated. Using Graphpad Prism 6.0, non-linear regression analyses by means of a curve fit were carried out for both latency and amplitude across the lifespan. Three different models were compared by an extra sum-of-squares F test. In addition, a one-way ANOVA was used to investigate sex effects. The significance level was set at $p < .01$ due to the large sample size. Also, separate curves were determined for males and females and were statistically compared. Education effects were investigated in a subgroup of adults using regression analysis.

Effects of age, sex and education on behavioral measures were also studied. The procedure for reaction times was identical to the latency analysis. Additionally, correlations between reaction times and P3 latency and amplitude were investigated. Lastly, correlations between the number of errors, and age, latency, amplitude and reaction time were investigated.

Results

Meta-analysis

Study characteristics

There were 75 studies selected for the meta-analysis. These were published between 1987 and 2012. All participants together (n=2,811) had a mean age of 33.3 ranging from 4 to 95 years. The overall mean P3 latency was 316.5 milliseconds (range: 290.0 - 447.5) and the overall mean P3 amplitude was 10.4 microvolts (range: 2.6 - 37.7).

Psychophysiology

Figure 2.3a shows the P3 latency across the lifespan as obtained from the meta-analysis. A logarithmic Gaussian model was the best fit when compared to a (normal) Gaussian model ($F(1,2511)=76.90$; $p<.0001$) or a linear model ($F(1,1569)=330.6$; $p<.0001$) and accounted for approximately 19% of the variance. The model reveals a trajectory in which the P3 latency decreases during childhood, reaching a trough around an age of 22 years, followed by a slow increase for the rest of the lifespan.

The P3 amplitude trajectory is shown in figure 2.3b. For amplitudes a logarithmic Gaussian model was also the best fit when compared to a (normal) Gaussian model ($F(1,2146)=121.6$; $p<.0001$) or a linear model ($F(1,2146)=24.39$; $p<.0001$). The model accounted for 9% of the variance. The maximum P3 amplitude was estimated at an age of 16 years.

Paradigm parameters and within-subject characteristics

Effects of paradigm parameters and within-subject characteristics were investigated in a subgroup in which age effects on latency and amplitude were linear so that regression analysis was possible. This subgroup was defined by the high end of the 95% confidence interval for the age center value, respectively for latency (age 25.5) and amplitude (age 22.5), until the age of 65.

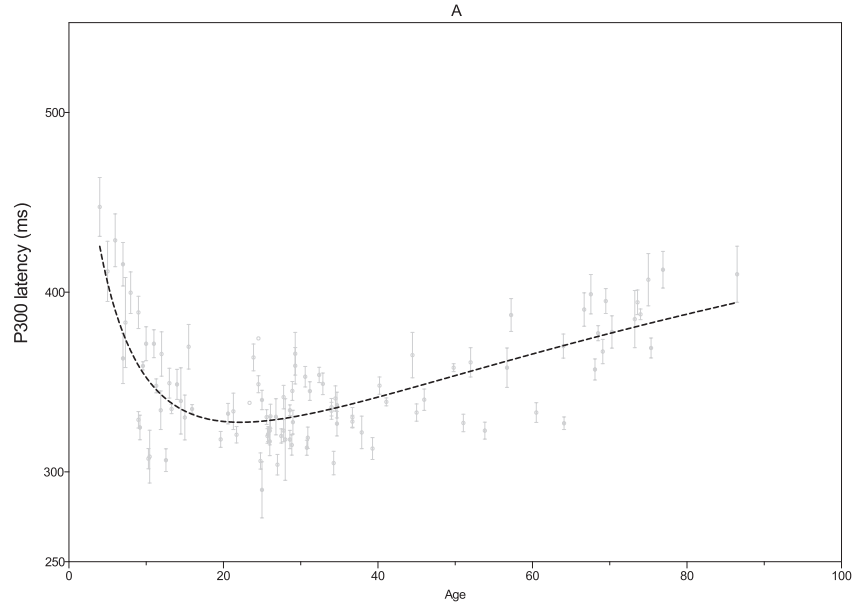


Figure 2.3 P3 latency and amplitude trajectories across the lifespan as obtained from the meta-analysis. Dots represent (subgroups from a) study. Error bars represent SEM.

For latency, one-way ANOVAs for *eyes open/closed* (F(1,18)=1.084) and *response type* (F(1,48)=2.478) were not statistically significant. These variables were therefore not included in the regression analysis. The other predictors were entered in a regression model in two blocks. Block 1 of the regression model revealed no significant predictors apart from *age*. Block 2 revealed *target probability*, *stimulus duration* and *inter-stimulus interval* as possibly significant predictors. These were entered in a final regression model that was not significant.

For amplitude, one-way ANOVAs for *eyes open/closed* (F(1,21)=2.112) and *response type* (F(1,54)=0.011) were not significant. These variables were therefore not included in the regression analysis. The same predictors as in the latency model were entered in block 1 and block 2. Block 1 of the regression analysis revealed possibly significant effects of *percentage of males* and *number of stimuli*. Block 2 revealed a possibly significant effect of *stimulus loudness*. These three predictors were entered into a final regression model. Table 2.1 lists the results. The regression model was significant for amplitude (F(3,17)=10.317; $p<.001$; $R^2=.65$). Higher numbers of (summated background and target) stimuli and louder stimuli were associated with lower P3 amplitudes.

Table 2.1 Predictors from the final regression model for P3 amplitude

	Amplitude	
	B ± SE	***β***
Constant	25.99 ± 5.85	
Male %	0.11 ± 0.06	.30
Number of stimuli	-0.02 ± 0.01	-.37[a]
Stimulus loudness	-0.16 ± 0.05	-.51[b]

$R^2 = .65$. [a]$p < .05$; [b]$p < .01$

Cross-sectional dataset

Next, the 1,964 healthy participants from the cross-sectional dataset were used to model age-related development of the P3 latency and amplitude.

Psychophysiology

In figure 2.4a the P3 latency is plotted against age. The results of the independent cross-sectional dataset demonstrated a similar trajectory compared to the meta-analysis. P3 latency decreases during childhood, reaching a minimum in

adolescence, followed by a slow increase for the rest of the lifespan. A logarithmic Gaussian model accounted for 18% of the variance and this was significantly better than a (normal) Gaussian model (F(1,1569)=179.3; $p<.0001$) or a linear model (F(1,1569)=330.6; $p<.0001$). In the cross-sectional dataset the minimum latency is estimated at approximately 25 years of age.

The P3 amplitude logarithmic Gaussian model is demonstrated in figure 2.4b. The model was able to explain 12% of the variance and this was significantly better than a (normal) Gaussian model (F(1,1569)=108.8; $p<.0001$) or a linear model (F(1,1569)=162.4; $p<.0001$). The maximum amplitude was reached at approximately 21 years of age.

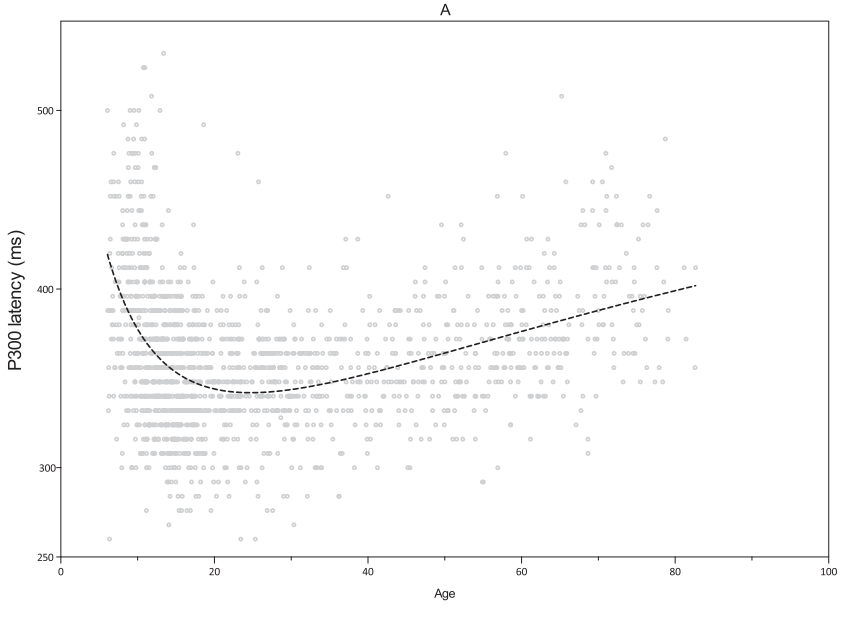
Demographics

A main effect of sex was found in one-way ANOVAs on both latency (F(1,1570)=12.606; $p<.001$; $\omega^2=.01$) and amplitude (F(1,1570)=10.499; $p=.001$; $\omega^2=.01$), albeit with small effect sizes ($\omega^{2=}.01$ is considered a small effect [54]). Separate curves for males and females demonstrated similar developmental trajectories of latency and amplitude. The curve fit statistics can be found in Table 2.2. None of the individual curve-fit parameters for the latency and amplitude models reached significance below the $p<.01$ level.

Education effects were only investigated in a subgroup. The subgroup was defined by the high end of the respective 95% confidence intervals of centers for the latency (age is 25.5) and amplitude (age is 22.5) models until the age of 65. This group was selected since at the age of 25 most individuals will have completed their educational career. The upper cut-off was chosen to minimize a possible bias due to degenerative effects at older age. An additional advantage is that in this subgroup age-related effects on latency and amplitude can be described linearly. Regression analysis revealed no effects of education on P3 latency or amplitude in the subgroup as can be seen in Table 2.3.

Table 2.2 *p*-values of differences between male and female model parameters

	Latency	Amplitude	RT
Center	.488	.032	.596
Width	.455	.306	.482
Height	.026	.053	<.001
All	.001	.001	<.001



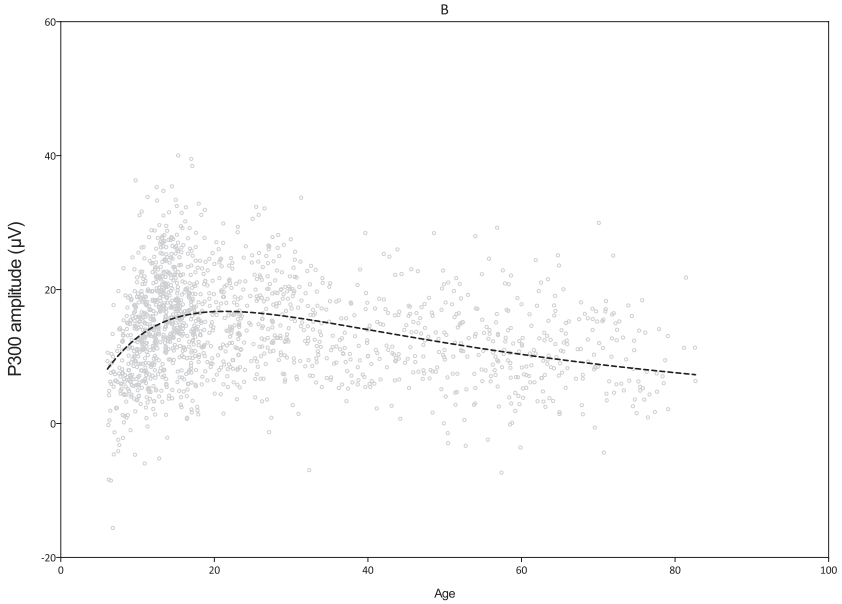


Figure 2.4 P3 latency and amplitude trajectories across the lifespan as obtained from the cross-sectional dataset. Dots represent scores from individual participants.

Table 2.3. Regression analyses on latency, amplitude and reaction times

	Latency		Amplitude		Reaction time	
	B ± SE	β	B ± SE	β	B ± SE	β
Step 1						
Constant	320.17 ± 4.77		19.45 ± 0.86		325.34 ± 16.02	
Age	0.79 ± 0.10	.33[b]	-0.15 ± 0.20	-.30[b]	0.09 ± 0.28	-.02
Sex	5.90 ± 2.54	.10[a]	1.82 ± 0.53	.138[b]	13.18 ± 5.33	.13[a]
Step 2						
Constant	316.28 ± 9.21		19.48 ±2.14		304.98 ± 23.57	
Age	0.81 ± 0.11	.33[b]	-0.16 ± 0.02	-.31[b]	-0.03 ± 0.28	-.01
Sex	5.71 ± 2.57	.09[a]	1.71 ± 0.53	.13[b]	-14.14 ± 5.39	-.14[b]
Education	0.24 ± 0.48	.02	-0.16 ± 0.10	-.06	1.14 ± 0.97	.06

Latency: $R^2 = .11$ for Step 1, $\Delta R^2 = .000$ for Step 2 (NS). Amplitude: $R^2 = .11$ for Step 1, $\Delta R^2 = .004$ for Step 2 (NS). RT: $R^2 = .02$ for Step 1, $\Delta R^2 = .004$ for Step 2 (NS). [a]$p < .05$; [b]$p < .01$

Behavioral measures

Reaction time was transformed by the same method used for P3 latency. A logarithmic Gaussian model was then fitted on the transformed reaction time data. The model accounted for 35% of the variance and this was significantly better than a (normal) Gaussian model ($F(1,1569)=830.2$; $p<.0001$). The reaction time model resembles the model for P3 latency. This is confirmed by a significant partial correlation (corrected for age) between reaction time and the P3 latency ($r=.30$; $p<.001$). Pearson's correlation coefficient indicates a medium effect size [55]. The fastest reaction times are estimated at an age of approximately 32 years of age.

A one-way ANOVA revealed a significant effect of sex ($F(1,1570)=24.26$; $p<.001$; $\omega^2=.01$), albeit with a small effect size. Separate models for male and female participants' reaction times confirm the sex effect. These models differ significantly ($F(3,1566)=12.31$; $p<.0001$) and show that males respond faster than females over all ages. There were no effects found for age and education in the subgroup, see table 2.3.

Partial correlations, correcting for age, between number of errors and P3 latencies and amplitudes were investigated. Because of the non-linear relation between age and both P3 measures the group was divided in young and older participants. Young participants were defined as all participants below the age of 20.36, which marks the

low end of the 95% confidence interval for amplitude. Older participants were defined as all participants from the age of 25.54, which marks the high end of the 95% confidence interval for latency.

In young participants, amplitude correlated significantly with false positive errors (r=-.106; p=.002; df=840) and false negative errors (r=-.163; p<.001; df=840) with small effect sizes. There were no significant correlations for latency and errors. In older participants a significant correlation was found between amplitude and false negative errors (r=-.084; p=.039; df=601) with a small effect size.

Comparison of psychophysiological and behavioral trajectories

The trajectories for reaction times, P3 latency and amplitude are presented in figure 5. The mean number of total errors per age are presented in the same figure. As can be seen the points of deflection (or center of the maxima and troughs) for reaction times, P3 latency and amplitude occur at different ages. These points of deflection, or model centers, were statistically compared. There was a significant difference between latency and amplitude (F1,3138)=8.608; p=.003), as well as between latency and reaction times (F(1,3138)=46.06; p<.0001).

General discussion

Developmental trajectories of the auditory P3 across the lifespan were examined using a systematic review and meta-analysis of all available literature and a large cross-sectional dataset. The P3 component was quantified in latency and amplitude measures. In both studies a logarithmic Gaussian model was the best fit for (inversed) latency and amplitude development across the lifespan. In children latency shortens until a minimum is reached. After the minimum, latency gradually increases with aging. Amplitude increases during childhood until a maximum is reached. For the rest of the lifespan amplitude decreases gradually. Sex effects were significant, but had only small effect sizes. The separate trajectories are broadly identical for males and females. In addition, education neither had an effect on latency nor amplitude. Therefore, it is concluded that the P3 *development* mainly is an endogenous process that is probably minimally influenced by exogenous factors.

The meta-analysis demonstrated that latency is not influenced by differences in paradigm parameters used. However, amplitude was affected by the number of stimuli presented and by the stimulus loudness. Specifically, a higher number of stimuli and louder stimuli were associated with smaller amplitudes. More familiar and more salient stimuli possibly required less cognitive resources, reflected by lower P3 amplitudes.

A remarkable finding in both parts of this review was that the P3 amplitude reached its maximum significantly earlier than the P3 latency reached its trough. Moreover, as found in the cross-sectional study, both latency and amplitude reached the centers of their respective models, earlier than reaction times. These findings are graphically summarized in figure 2.5. We therefore hypothesize that latency and amplitude index different aspects of brain maturation. The P3 latency possibly indexes neural speed or brain efficiency. The P3 amplitude might index neural power or cognitive resources, which increase with maturation.

As the brain develops it becomes more efficient at information processing. Structural organization and development leads to more efficient neural pathways and networks; Myelination increases neural speed. At older age increasing P3 latency is observed, which is in line with a “nearly linear decline from early adulthood on measures representing efficiency or effectiveness of processing” as described in a review by Salthouse (2010) on cognitive aging [1]. Therefore, the P3 latency might be an index for speed and efficiency of information processing in the brain. In a cross-sectional study using diffusion tensor MR imaging performed by Brickman et al. (2012),

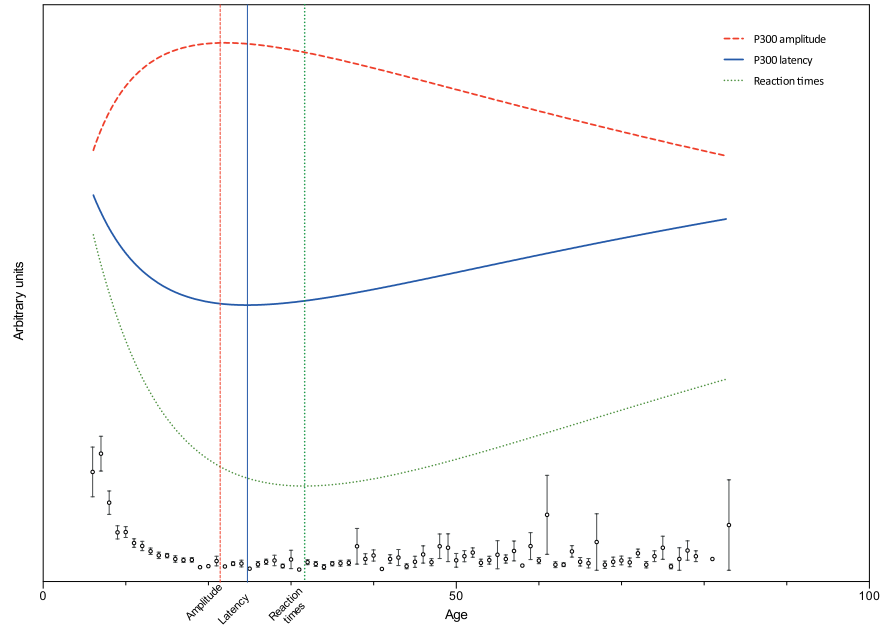


Figure 2.5 Graphical summary of the found trajectories in the cross-sectional dataset. Dots represent the number of errors. Error bars represent SEM.

age-associated differences in measures of white matter coherence were examined in participants of 7-87 years. Figure 2.6 shows fractional anisotropy (FA), a diffusion tensor imaging (DTI) measure indexing myelination and organization of white matter bundles, across age. They visually inspected the DTI data plotted as a function of age to determine an approximate point of deflection at age 30 and divided their sample into two subgroups, younger and older than 30. They found white matter fiber tracts to continue developing until they reach a brief plateau, at about age 30, after which they begin degenerating [56]. The visual resemblance of their total sample with our P3 latency data is remarkable and suggests that myelination and P3 latency may be related.

As was evident from our meta-analysis, amplitude is affected by paradigm properties. Presumably, amplitude indexes the amount of cognitive resources a participant needs to allocate, to successfully perform the task at hand. In the oddball paradigm, after a participant gets more familiar with a stimulus, because the stimulus has been presented more often, fewer resources are needed to evaluate it (which is called

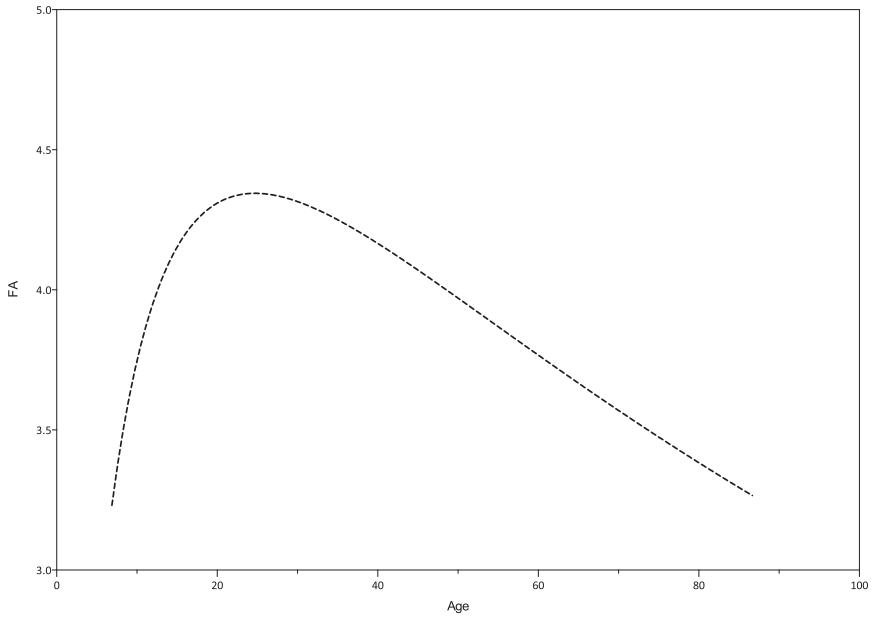


Figure 2.6 Trajectory of fractional anisotropy (FA) across the lifespan. Adapted from Brickman et al. (2012). Data points were estimated using DigitizeIt 1.6.1 and curve-fitted using Graphpad Prism 6.0.

habituation). In the same way, when a stimulus is louder, it may be easier to distinguish from the background stimuli and fewer cognitive resources are needed. As found in the cross-sectional analysis larger amplitudes are associated with fewer errors by children performing in the oddball paradigm task, reflecting more available and more allocated resources.

In the first years of life, amplitude increases when quantified using an oddball task. Although the oddball paradigm is a relatively easy task, it might still be demanding for very young children, with respect to their cognitive resources, to maintain their focus and respond accurately, which is reflected by longer reaction times and more errors. During development, children gain neural capacity and use this increased capacity to perform better on cognitive tasks. This increase in resources is quantified by an increase in amplitude until about 20 years of age.

A central question is why the P3 amplitude reaches its maximum at a younger age than the P3 latency reaches its trough? Presumably, the increase in cognitive resources and the improvement in efficiency are happening simultaneously, and the improving efficiency and neural speed might affect the model-center for P3 amplitude. A more efficient brain may not have the need to substantially recruit its cognitive capacity, if a task can be successfully performed with only a part of the available resources. Indeed, a study in adults reported that in a low demand n-back task, high performers used fewer resources by demonstrating lower P3 amplitudes in order to achieve the same performance compared to the low performers [57]. Until a certain level of efficiency is reached, a smaller proportion of cognitive resources is required to perform a given task. So, in young subjects, increasing brain efficiency and neural speed might have a moderating effect on the amplitude trajectory in which the amplitude model-center is shifted to a younger age.

As the myelination and organizational processes continue to progress after the amplitude maximum was reached and until into late adolescence, P3 latencies decline further, and task performance, quantified by shorter reaction times, improves further. The best performance is reached around the age of 30, after the optimal amplitude and latency were reached.

In older age, speed of processing is reduced [58] and behaviorally, reaction times are longer. (Subclinical) degenerative effects cause P3 latencies to increase and amplitudes to decrease. These aging-related degenerative effects are visible from neuroimaging studies as well [56,59], where changes in white matter integrity were an important factor in executive dysfunction in older people [56]. The compensation-related utilization of neural circuits hypothesis, or 'CRUNCH' model states that individuals

recruit additional neural activity as task load increases. The model also states that beyond a level of task demand, brains of older adults may reach their capacity limits leading to a decline in performance [5,57]. Because of less efficient processing older people may be required to recruit additional resources at lower cognitive load levels than younger adults to achieve the same performance [60]. These compensatory mechanisms may be mediated in the prefrontal cortices [61-65], which is in line with the anterior shift in the topography of the P3 amplitude that has been reported in older people [66-69]. Therefore, it would be interesting to investigate both frontal and parietal P3 amplitude trajectories using a more cognitively challenging paradigm. Also, a distinction in the amplitude trajectories between high and low performers may provide insights into this hypothesis.

In conclusion, our findings clearly demonstrate that the P3 follows a specific trajectory across the lifespan reflecting brain maturation in childhood and adolescence and degenerative effects in older age. Although both P3 latency and amplitude can be fitted by a logarithmic Gaussian model, there are relative differences. Specifically, the centers of both models, that mark a plateau period segregating the maturation from degenerative effects, occur at different ages. This suggests that latency and amplitude reflect different aspects of brain maturation. Specifically, the P3 amplitude might be an index for the amount of cognitive resources being used, increasing in early developmental and decreasing with further aging beyond adolescence. Higher amplitudes are related to a higher proportion of allocated cognitive resources and intra-subject to improved cognitive performance. P3 latency may be a more direct index of information-processing speed and, indirectly, cognitive performance.

As far as we know, this study is the first to investigate the developmental trajectory of the P3 across the entire lifespan in a large dataset. Using advanced curve-fitting procedures we were able to determine ages that mark a maximum or trough segregating maturational from degenerative stages. The obtained trajectories are important because they provide new ways to compare healthy age-related maturation/degeneration to that associated with certain disorders (e.g. dementia, ADHD, dyslexia, schizophrenia).

There are some limitations to the current study. First, this study describes the age-related development in a large group of healthy participants. The developmental pattern that was found for this group cannot easily be translated to individual participants. There is much variation in P3 latency and amplitude between individuals, which makes it challenging to compare the P3 of a single participant to this model (albeit, this was not the primary aim of this study). Second, in the meta-analysis, some studies could not be included because they were not available to the authors,

e.g. conference abstracts, old studies. Because the amount of studies to be scanned was extensive we chose to include only those studies that were available online or in local libraries. We believe the number of included studies is sufficient by this method, also evidenced by the similarities in results as compared to the cross-sectional sample. Although the results would have been stronger if more studies could have been included, we do not expect the results would be different from the ones presented in this paper. Third, the reported P3 latencies and amplitudes were measured using a peak-picking method. The highest peak of a component in the ERP is arbitrary since it does not represent any meaningful information about this component. Although this method is very conventional, especially in older studies, its validity can be questioned. This problem is partly solved by the large datasets that were used in our study.

3

An indication for frontal compensation

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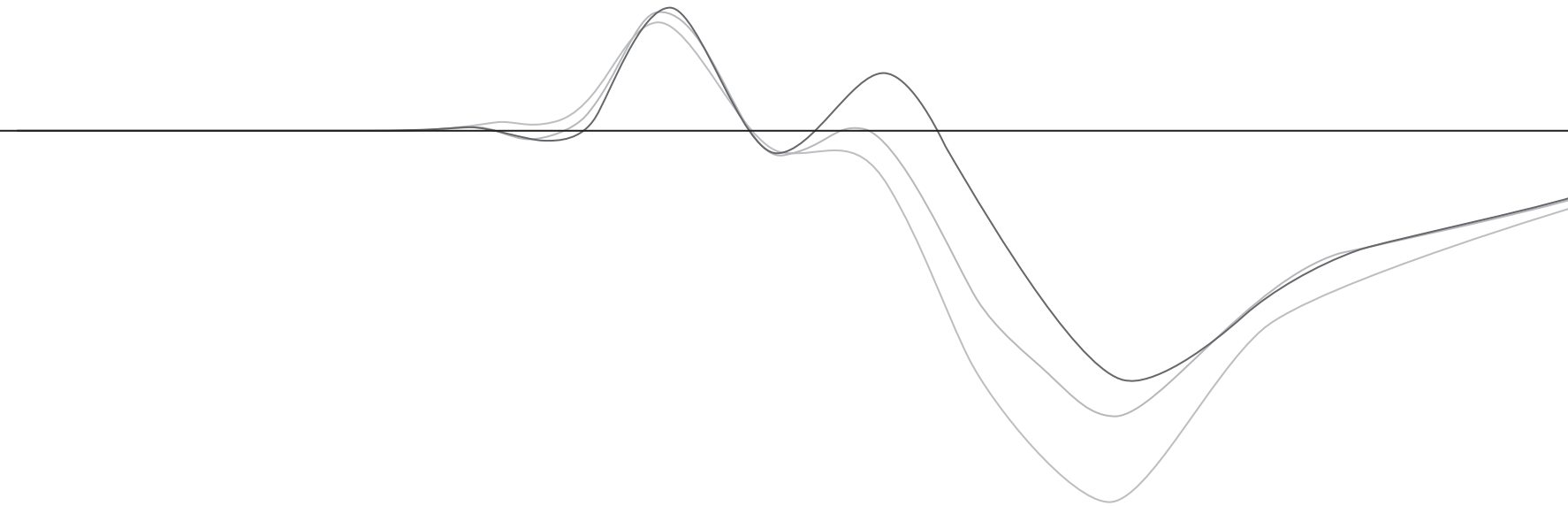

Abstract

In the present study the frontal and parietal P3, elicited in an auditory oddball paradigm were investigated in a large sample of healthy participants (N=1,572), aged 6-87. According to the concepts of the compensation-related utilization of neural circuits hypothesis (CRUNCH) it was hypothesized that the developmental trajectories of the frontal P3 would reach a maximum in amplitude at an older age than the amplitude of the parietal P3 amplitude. In addition, the amplitude of the frontal P3 was expected to increase with aging in adulthood in contrast to a decline in amplitude of the parietal P3 amplitude. Using curve-fitting methods, a comparison was made between the developmental trajectories of the amplitudes of the frontal and parietal P3. It was found that the developmental trajectories of frontal and parietal P3 amplitudes differed significantly across the lifespan. During adulthood, the amplitude of the parietal P3 declines with age, whereas both the frontal P3 amplitude and behavioral performance remain unaffected. A lifespan trajectory of combined frontal and parietal P3 amplitudes was found to closely resemble the lifespan trajectory of behavioral performance. Our results can be understood within the concepts of CRUNCH. That is, to compensate for declining neural resources, older participants recruit additional neural resources of prefrontal origin and consequently preserve a stable behavioral performance. Though, a direct relation between amplitude of the frontal P3 and compensatory mechanisms cannot yet be claimed.

Introduction

The P3 complex

The event-related potential (ERP) is a waveform that is commonly determined by averaging brain activity in the electroencephalogram (EEG) time-locked to a specific event, for instance an auditory stimulus. The ERP consists of a series of components that can be distinguished based on their latency (ms), polarity (positive/negative), amplitude (μV) and scalp distribution. The P3 complex of the ERP is a large positive waveform that reaches its peak amplitude at approximately 300 milliseconds after stimulus presentation [11]. An advantage of the P3 with respect to the other components of the ERP is its relatively large size, which makes it easy to detect. The P3 that is elicited in the auditory oddball consists of neural activity originating from presumably the prefrontal cortex, the temporoparietal junction, the primary auditory cortex and possibly more sources [70]. In the oddball paradigm a participant is presented with two (or more when distracter stimuli are included) different stimuli that have to be discriminated. The stimuli can differ for instance in pitch, loudness, or duration, and are commonly presented with two different probabilities (e.g. 20% vs. 80%). The infrequent stimulus is generally designated as the target stimulus and participants are instructed to respond to this target stimulus, e.g. by a button press or by silent counting [10,20,21]. For a schematic overview of an ERP elicited within an oddball paradigm see Figure 2.1 in the previous chapter. The oddball is a simple task that can be executed by very young children, adults and the elderly. This is an important advantage in aging studies that, like this paper, investigate a broad age range.

Besides numerous studies demonstrating the traditional parietal P3, which is associated with responding to infrequent target stimuli, another P3 peak has been reported. This peak has a slightly faster latency and a more anteriorly distributed topography, and is most pronounced in oddball paradigms that include a third infrequent non-target stimulus. This peak has been labeled P3a [22-25,71], and consequently the traditional P3 as described in the previous paragraph has also been labeled P3b. In a standard two-tone oddball paradigm the P3a cannot be identified easily and perhaps, the P3a is super-positioned on the more pronounced P3b wave – specifically in the frontal cortex - in participants that do not generate a clear P3a peak. Because in this paper the focus lies on information processing in general and a two-tone auditory oddball is used, whenever the term “P3” is used it refers to this entire P3 complex. The terms frontal and parietal are used to refer to the location where the P3 is measured.

The P3 amplitude as an index for cognitive aging

The P3 has been associated with various cognitive processes like attention, working memory, and executive function. One of the most prominent hypotheses linking the P3 amplitude to cognitive functioning is the context-updating hypothesis. This hypothesis states that the mental model a participant has of his/her current environment (context) is evaluated and updated when a relevant and deviant stimulus is introduced into the environment [17]. However, the context-updating hypothesis is only one of several hypotheses aimed at explaining the underlying cognitive mechanisms of the P3. Others are for example, the stimulus-evaluation hypothesis [16], the context-closure hypothesis [18] and the attentional resource-allocation model [14]. Recently, a robust centro-parietal positivity in an averaged ERP signal has been related to decision-making processes. This positivity showed a strong resemblance to the traditional P3 and might revitalize the idea of the P3 reflecting a decision making process [72-75]. Another recent study hypothesized that the P3 is mainly indicating activation of rare stimulus-response links. Additionally, for smaller parts the P3 also reflects components of pure stimulus-related and pure response-related processes [76]. Although the P3 remains fairly elusive with respect to the involved cognitive processes, there is broad consensus that the P3 indexes aspects of cognitive information processing. For example, the P3 amplitude can be seen as an index for the amount of cognitive resources that a participant allocates in a cognitive task [14]. Thus, with an increase in mental effort, P3 amplitude will also increase. A decline in P3 amplitude with increasing task difficulty has also been reported [77,78]. P3 amplitudes are smaller when task difficulty is manipulated by increasing the similarity between the target and background stimulus (e.g., reducing the difference in pitch), creating uncertainty whether a stimulus is a target or not. Thus, in a difficult task, P3 amplitude increases when a participant devotes more effort to it, but decreases when the participant is less certain of the stimulus category [13].

In our previous study, we modeled the developmental trajectory of the parietal P3 amplitude measured at Pz across the lifespan in a large cross-sectional sample (N=1,572). Furthermore, we performed a systematic review and meta-analysis on lifespan changes in the parietal P3 amplitude that showed similar results as were found in the cross-sectional sample. The amplitude of the parietal P3 was found to increase during childhood to reach a maximum around the age of 21, after which it gradually decreased, in line with evidence on cognitive decline from early adulthood to old age. Despite the observed decline in P3 amplitude during adulthood, behavioral performance remained relatively stable until into old age. In this earlier study we hypothesized that there might be neural processes in older age that compensate for this parietal P3 amplitude decline [79].

Compensation from prefrontal regions

Compensatory brain activity in older age has been described in several ways. One hypothesis, the Compensation-Related Utilization of Neural Circuits Hypothesis, or ”CRUNCH”, states that the aging brain recruits compensatory neural resources when solving a task in order to maintain the achieved output (i.e., the behavioral performance) at a level that is equivalent to that of a younger brain. Firstly, the aging brain may increase activity in a certain neural network to compensate for declining processing efficiency in that same network. In addition, compensation might be achieved by increased activity in other, yet connected networks. Thus, increasing the activity in a certain or alternative network may reflect compensation for reduced neural processing. Only once the limits of increased activation in a certain network and recruiting alternative neural resources are reached, task performance will decline [5,57,80].

Other relations between compensation and frontal brain activity have been found as well. Cabeza et al. (2002) compared high versus low performing old adults and demonstrated that the older low performers used neural networks similar to young participants (unilateral frontal activation), but in an inefficient manner. The old high performers compensated through a reorganization of neurocognitive networks demonstrated by bilateral frontal activation. This model was called Hemispheric Asymmetry Reduction in Old adults or HAROLD [63] (also see Berlingeri et al. (2013) for a comparison of the HAROLD model versus the CRUNCH model [81]). A posterior-to-anterior age-related shift in the recruitment of neural resources (Posterior-Anterior Shift in Aging or PASA) has been suggested to reflect compensation for age-related changes in posterior regions [65]. Recently this research group demonstrated a negative correlation between white-matter deficits and over-activation in the prefrontal cortex and medial temporal lobes in older adults that showed successful behavioral performance in executive function and memory tasks [82]. Geerligs et al. (2012) observed an increased relation between inhibition inefficiency and phase locking in the higher beta band between frontal and occipito-parietal regions. High-performing older patients showed more phase locking and they suggested that this represented a compensation mechanism leading to more effective inhibition [83]. Li et al. (2013) found that, during attention, older adults increasingly recruited neural networks that were more frontally distributed. They suggested this might be compensatory to age-related decreases in inhibition capacities [68]. A recently published study using fMRI during a working memory task, demonstrated brain activations in the left dorsolateral prefrontal cortex related to aging. The nature of this relation was dependent on task load. At low task demands, activation in this region increased with aging, whereas at higher task demands (and when participants reached their capacity limits), activation in this region decreased

with aging. In the low task demand condition increased frontal activation was related to a decrease in behavioral performance, which was not in line with the concepts of CRUNCH. Possibly, this frontal activation in this task condition may reflect inefficient neural processing or failed compensation [84].

In all, when compensatory activity is based on recruitment of alternative neural circuits, it has been proposed that these alternative neural resources are predominantly recruited from prefrontal cortices. Recruiting compensatory frontal neural circuits seems also in line with the often reported anterior shift in P3 topography with aging [66-69]. While it remains under debate whether increased frontal activation related to aging is either reflecting compensatory processes or inefficient cognitive processing [70,85], it may well be that the same neurocognitive mechanism underlies both. That is, when inhibitory abilities decrease with aging, increasing frontal activity may reflect failed or successful compensatory mechanisms in respectively low and high performing older participants. As Grady (2012) stated in a recent review, compensation may come in three forms: (1) Increased brain activation without an effect on behavioral performance (attempted compensation), (2) increased brain activity associated with improved behavioral performance (successful compensation), or (3) increased brain activity associated with a decline in behavioral performance (unsuccessful compensation).

The present study

Assuming the P3 amplitude reflects cognitive functioning in general, it might be suitable as an index for neurocognitive aging. This is supported by findings from others, for instance Walhovd and Fjell (2001), who demonstrated that the P3, measured at Cz and Pz, showed strong correlations with age. Interestingly, this correlation was not observed for the P3 amplitude measured at Fz [29]. Possibly, cognitive processing reflected by a frontal P3 might be different from the parietal P3. One of the explanations for this apparent discrepancy might lie in the concept of frontal compensatory brain activity.

Since the ERP reflects cumulative neural activation related to multiple processes involved in stimulus processing, these parallel processes (i.e. the underlying ERP components) are likely to have overlapping post-stimulus latencies [13,86]. Congruently, the P3 has been found to consist of multiple underlying independent components or sources. For instance, using independent component analysis (ICA), Onton et al. (2006) found three independent components that project to posterior cortical areas, and one projecting to the frontal cortical areas [87]. In addition, intracranial studies, lesion studies and fMRI-EEG studies (see the review by [88]) and analyses with Low Resolution Electromagnetic Tomography (LORETA) [89] point towards multiple neural

generators of the P3. Possibly, prefrontal compensatory mechanisms may weigh heavier on the P3 measured at an anterior location compared to the P3 measured at a posterior location. If the P3 measured at Fz consists of another source mix (in other words reflecting a different mixture of cognitive processes) than the P3 at Pz, and this source mix changes with aging, differences in developmental trajectories are to be expected.

In this study we aim to further test this hypothesis and firstly replicate the finding from Walhovd and Fjell (2001) that the frontal P3 does not decrease with age. Secondly, we compared the frontal and parietal P3 amplitude developmental trajectories. Thirdly, we investigated whether the combined parietal and frontal P3 lifespan trajectory is more clearly associated with the behavioral performance trajectory in an oddball task, as compared to separate frontal or parietal P3 lifespan trajectories. More precisely, it is expected that the amplitude of the frontal P3 will be lower than the amplitude of the parietal P3 in children. Since frontal brain structures mature relatively late [90,91], neural activation originating from frontal structures is lower at young age. In our earlier study, we observed a decrease in amplitude of the parietal P3 with aging [79]. Based on CRUNCH, we expect that, unlike the parietal P3, the frontal P3 will steadily increase in magnitude with advanced aging, reflecting an increase in recruitment of compensatory frontal neural circuits that predominantly weigh on the frontal P3. In short, the developmental amplitude trajectories of the frontal and parietal P3 are expected to be markedly different with aging. This would also indicate that a P3 measured only at a posterior site would be insufficient to index cognitive aging. A lifespan trajectory of combined frontal and parietal P3 amplitudes, reflecting compensated neural activity, is expected to be related more closely to behavioral performance. As the P3 latency may index information-processing speed [79,92], latencies of both the frontal and parietal P3 are expected to increase with aging reflecting an overall decline in processing speed.

Method

Participants

Data of individuals in the age range of 6-87 were extracted from the Brain Resource International Database (BRID). This database contains data from multiple laboratories (New York, Rhode Island, Nijmegen, London, Adelaide, and Sydney) that have been acquired using standardized data acquisition techniques (identical amplifiers, standardization of other hardware, audio calibration, paradigm details, software acquisition, and task instructions). Inter-lab reliability and test-retest reliability measures are high and have been reported elsewhere [19,50,51]. Database exclusion

criteria included a personal or family history of mental illness, brain injury, neurological disorder, serious medical condition, drug/alcohol addiction, first-degree relative with bipolar disorder, schizophrenia, or genetic disorder.

The sample consisted of 1,572 participants (786 males; mean age = 27.17 ± 19.16). Age distributions are listed in table 3.1. For every age (e.g., 6, 7, 8, …) sex distributions were 50/50%. Education scores varied from 1 to the maximum score of 18 years of education (mean = 11 ± 4). Participants were required to refrain from caffeine and smoking (2 hours) and alcohol (6 hours) prior to testing. All participants gave written informed consent. This sample was identical to the sample used in our previous study [79].

Table 3.1 Age distributions.

Age group	N
6 to 9	118
10 to 19	704
20 to 29	246
30 to 39	126
40 to 49	100
50 to 59	116
60 to 69	96
70 to 79	62
80 to 83	4

Electroencephalographic data acquisition

EEG and ERP recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Participants were seated in a sound and light attenuated room, controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 using a Compumedics Quick-Cap with sintered Ag/AgCl electrodes and Neuroscan NuAmps DC amplifier with a 100 Hz low-pass filter (range is DC-100 Hz). Data were offline referenced to averaged mastoids with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye (bipolar). Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin

resistance was aimed at <5 kOhms for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline [53]. The sampling rate of all channels was 500 Hz.

ERP scoring

Conventional ERP averages were obtained from Fz and Pz recording sites for target stimuli. Only stimuli with a correct target response were included in the target average. Before averaging, EEG epochs were filtered at 25 Hz with a Tukey or cosine taper to 35 Hz, above which frequency no signal was passed. For the target stimuli waveforms, the peak (amplitude and latency) of the frontal P3 was identified at Fz and of the parietal P3 at Pz. Amplitudes were defined relative to a pre-stimulus baseline average of -300 to 0 ms. The peaks were scored within a pre-determined latency window of 220-550 ms.

Experimental paradigm

The oddball paradigm (figure 2.1) consisted of a quasi-random sequence of 280 frequent background tones (500 Hz) and 60 infrequent target tones (1000 Hz). Two targets could not appear consecutively. All stimuli (50 ms; 5 ms rise and fall time) were presented binaurally (via headphones) at a volume of 75dB SPL with an inter-stimulus interval of 1000 ms. Participants were instructed to press two buttons simultaneously (one for each index finger) when they heard a target tone and to ignore the background tones. Speed and accuracy of response were both equally stressed in the instructions. Before the actual test they were presented with a brief practice run to clarify the distinction between the two tones.

Statistical analysis

Using Graphpad Prism 6.0, log Gaussian curves were fitted separately to amplitudes and (inverted) latencies of both the frontal and the parietal P3 across the lifespan. Curves are described by three parameters; a center value, a width value and an amplitude value. Center is the *x* value at the peak of the distribution; width is a measure of the width of the distribution expressed in the same units as *x;* amplitude is the height of the center of the distribution expressed in *y* units (www.graphpad.com). To avoid confusion the amplitude parameter will be referred to as the 'height' of the model. The parameters of developmental trajectory models for the frontal and parietal P3 were statistically compared against a global model (one model explaining all data) by an extra sum-of-squares F test available in Graphpad Prism 6.0. The extra-sum-of-squares F test expresses how well one model fits the data versus another simpler case of the model (i.e. the global model) by comparing the difference in sum-of-squares between the models versus the sum-of-squares that can be expected by chance. The null hypothesis in this case is that the simpler global model is correct.

Since CRUNCH is aimed at older subjects, age-effects on (1) psychophysiological measures, i.e. P3 amplitudes and latencies, and (2) behavioral performance were evaluated in a sub-group as well. *Behavioral performance* was defined as the reaction time divided by the accuracy rate (percentage of correct responses). Notice that larger values on this scale indicate a lower performance. The sub-group consisted of all participants older than 21 years. This cut-off was based on the age at which the parietal P3 reached its maximum amplitude and compensatory frontal activity is expected to start emerging. For the frontal P3 amplitude, P3 latencies (frontal and parietal) and behavioral performance an exponential growth model was tested; for the parietal P3 amplitude an exponential decay model was tested. These models were compared against a constrained linear model representing no age-related change (slope was constrained to 0). (See appendix 2 for the model equations and www.graphpad.com/guides/prism/6/curve-fitting for a description of the models.)

Next, another measure was evaluated: The *combined P3 amplitude*, defined as the mean of the amplitudes of the frontal and parietal P3 expressing the net recruited potential, was modeled by fitting a log Gaussian curve. This model's parameters (center and width) and the parameters of a log Gaussian model for behavioral performance were statistically compared against a global model by an extra sum-of-squares F test. The correlation between combined P3 amplitude and behavioral performance was calculated post-hoc.

Because each time two aging models were compared on three parameters a Bonferroni corrected alpha of .0017 (initial alpha level of .01, six tests) was employed.

Results

Developmental trajectories across the lifespan

As can be seen in Figure 3.1 the developmental trajectories of the amplitudes for the frontal and parietal P3 are markedly different. The parietal P3 amplitude increases rapidly during childhood until a maximum is reached, after which it gradually decreases. In contrast, the amplitude of the frontal P3 reaches a plateau much later (at an age of 46 years) and decreases minimally. Statistical comparison of the curve fits for both P3 amplitudes reveals that the trajectories are significantly different ($F(3,3081)=583.4$; $p<.0001$). A post-hoc analysis of the separate model parameters (i.e. the center, width and height) shows that the models differ significantly on all of these parameters, see Table 3.2.

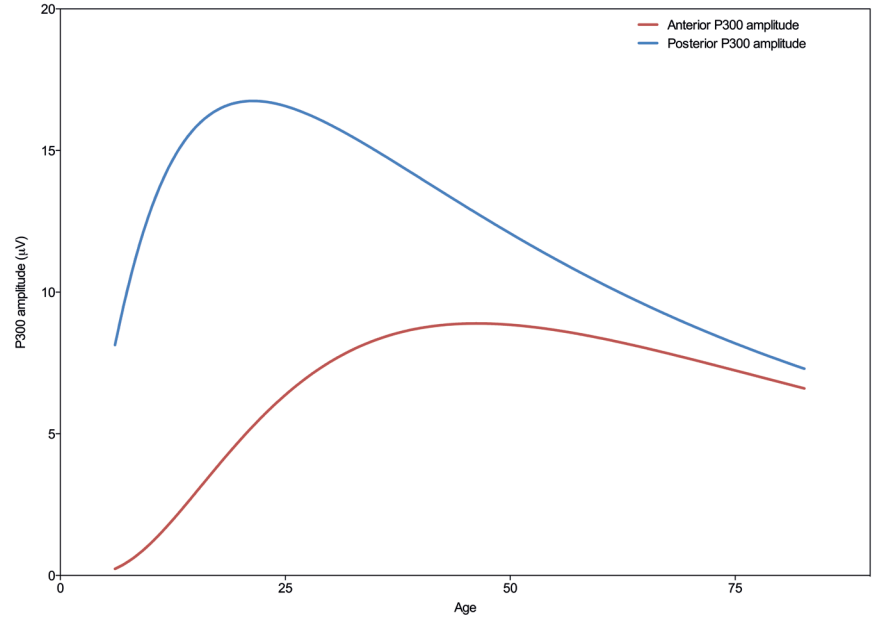

Figure 3.1 Developmental trajectories of the frontal (Fz) and parietal (Pz) P3 amplitude across the lifespan. Note the different trajectories of the frontal and parietal P3 amplitude across the lifespan, where the parietal P3 peaks around the age of 21 years and then shows a progressive decrease, and the frontal P3 peaks around the age of 46 years, showing a less pronounced decrease in amplitude with increasing age.

Table 3.2 Frontal versus parietal model parameters.

		Center (yrs.)	Width (yrs.)	Height (μV/ms)
Amplitude	Frontal	46.2	0.8	8.9
	Parietal	21.4	1.0	16.8
	p	< .0001	.0005	< .0001
Latency	Frontal	26.0	1.7	334.8
	Parietal	24.7	1.7	342.0
	p	.041	.6	.0004

As can be seen in Figure 3.2 the developmental trajectories of the latencies for the frontal and parietal P3 are parallel. Both show a decrease in latency during childhood until a minimum is reached with a center around 25 years of age, after which latency gradually increases with aging. Statistical comparison of both models reveals that the models are significantly different ($F(3,3081)=11.0$; $p<.0001$), however, this difference is driven solely by the height of the models, see Table 3.2. Thus, the latency of the frontal P3 is overall faster than the latency of the parietal P3. The trajectories in which they both develop across the lifespan are, in fact, very similar. (When height is not included in the analysis: $F(2,3081)=2.2$; $p=.115$).

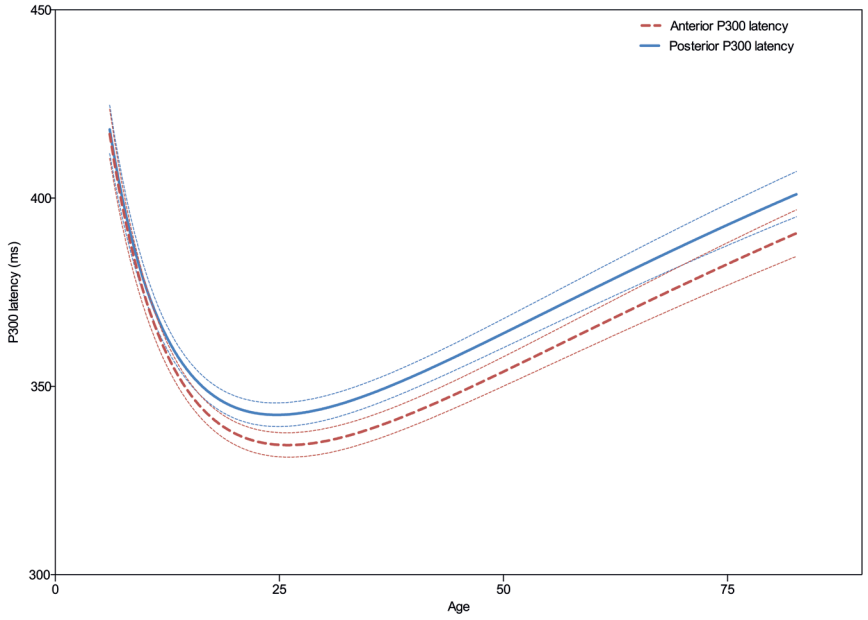

Figure 3.2 Developmental trajectories of the frontal (Fz) and parietal (Pz) P3 latency across the lifespan. Dashed lines indicate the 95% confidence interval. Note the similarity in developmental trajectories, with only an apparent overall difference in frontal and parietal latencies but not in its progression across the lifespan.

Effects of aging on psychophysiological and behavioral measures

Effects of aging on psychophysiological and behavioral measures were investigated in participants aged 21-80 years. In this sub-group, non-linear models were compared to a linear model with a slope constrained to a value of 0 (i.e., a horizontal line).

For the amplitude of the frontal P3, the exponential growth model did not significantly differ from the constrained linear model ($F(1,686)=4.7$ $p=.0313$). Post-hoc, an unconstrained linear model was compared to the constrained linear model to test whether amplitudes might actually be declining with aging. This analysis also

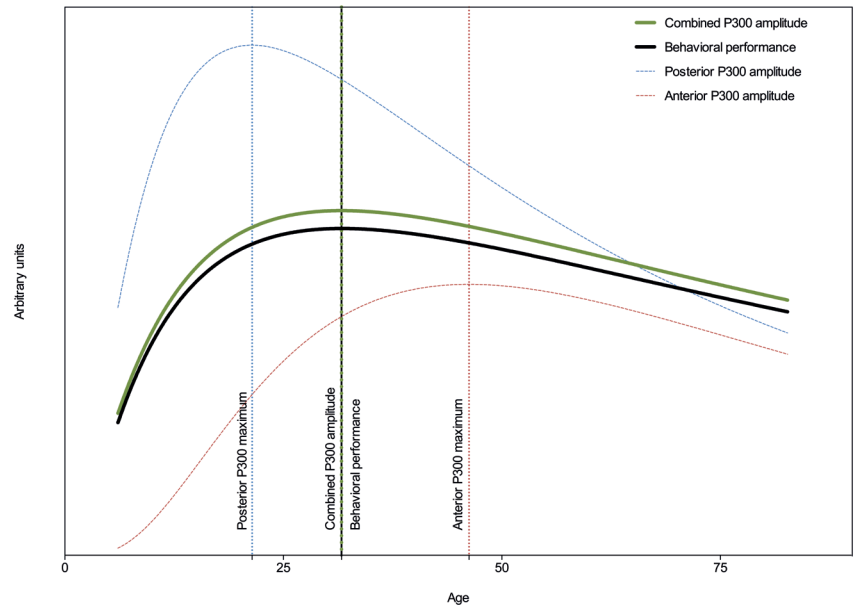

Figure 3.3 Developmental trajectories of behavioral performance, the frontal (Fz), the parietal (Pz), and the combined P3 amplitude across the lifespan. Vertical lines indicate points of deflection in these trajectories. Behavioral performance is plotted on an inverted y scale. Note the similarity between the developmental trajectories of the combined P3 amplitude and behavioral performance, suggesting that behavioral performance is best associated with frontal and parietal networks.

demonstrated no significant difference ($F(1,686)=5.2$; $p=.0226$). For the amplitude of the parietal P3, the exponential decay model explained the data significantly better than the constrained linear model did ($F(2,710)=38.8$; $p<.0001$; $R^2=.10$), suggesting an exponential decline of P3 amplitude with increasing age. Both latencies of the frontal and parietal P3 were significantly better explained by an exponential growth model than by a constrained linear model (frontal: $F(1,686)=139.3$; $p<.0001$; $R^2=.17$; parietal: $F(1,711)=183.0$; $p<.0001$; $R^2=.20$), indicating that P3 latencies increase with aging (exponentially). For behavioral performance an exponential growth model did not statistically differ from the constrained linear model ($F(1,711)=2.393$; $p=.122$) suggesting that behavioral performance remains stable across time after 21 years of age.

Figure 3.3 shows (besides the amplitude trajectories of the frontal and parietal P3 also) the combined P3 amplitude and behavioral performance across aging. An extra sum-of-squares F test of the combined P3 amplitude and behavioral performance models' parameters revealed that their centers and widths were not statistically different ($F(2,3081)=0.03$; $p=.97$) and a global model was the best fit. The global center was estimated at 31 years. A post-hoc test revealed a significant correlation between combined P3 amplitude and behavioral performance ($r=-.30$; $p<.0001$; $R^2=.09$, adjusted for age).

Figure 3.4A and 3.4B show the grand average ERPs of four age groups (i.e. 6-15, 20-30, 35-45 and 50-60 years old) measured at Fz and Pz. These figures further demonstrate that aging has different effects on frontal versus parietal ERPs in adults. The frontal P3 amplitude and latency increase with age. As can be seen in figure 3.4B, aging has a different effect on the posterior ERP. The P3 latency increases, but its amplitude decreases (in adults). It's noteworthy that it looks like the effects are not restricted to just the P3. Other components, like the P2 (only anterior) and N2, also appear to change with aging.

Discussion

The aim of the current study was to test CRUNCH by comparing the developmental trajectories of the frontal and parietal P3 elicited in an auditory oddball paradigm. It was expected that the developmental trajectories of the frontal and parietal P3 amplitudes would be markedly different, and that the combined frontal and parietal P3 would be better related to behavior as compared to either of these in isolation. No differences between developmental trajectories of the frontal and parietal P3 latencies were expected.

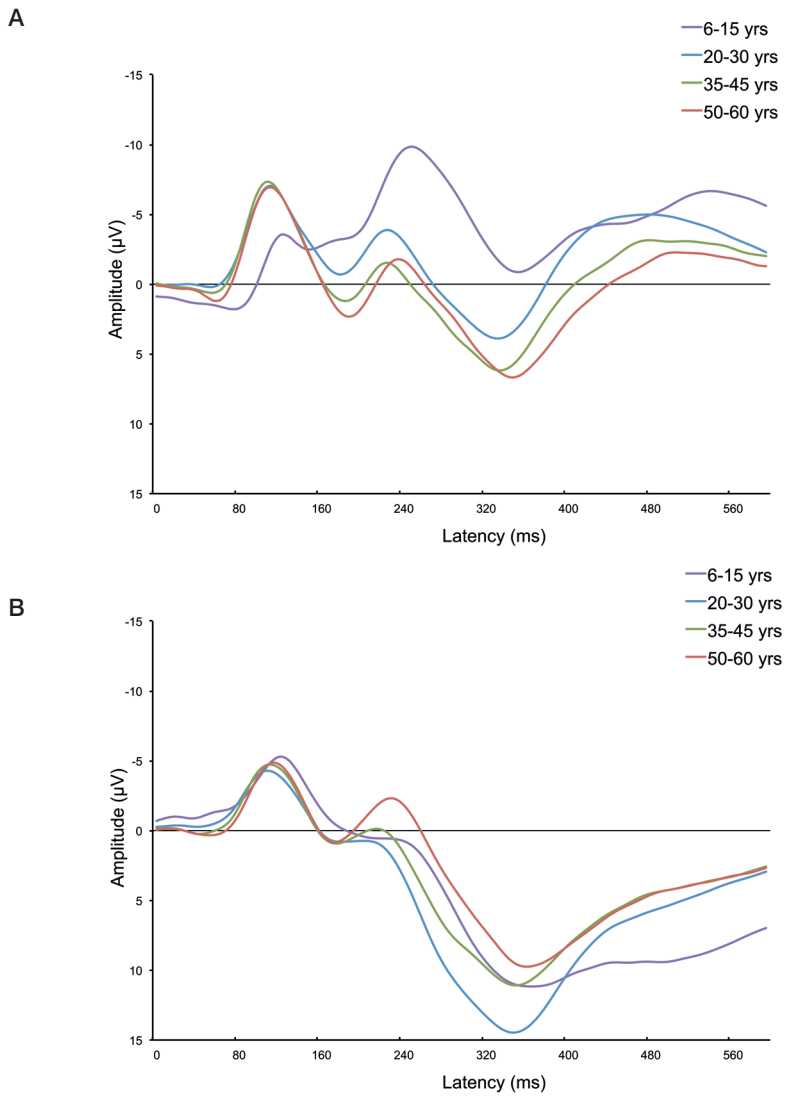

Figure 3.4 Frontal (Fz; A) and parietal (Pz; B) grand average ERPs of four age groups: 6-15, 20-30, 35-45, and 50-60 years old. This figure further visualizes the differences in how the frontal and parietal P3 are affected by increasing age. The frontal P3 amplitude increases with age, and the parietal P3 amplitude develops in a curvilinear way with age (an increase for children and a decrease for adults). Also note parallel changes on the N200 component (not investigated in this study).

As hypothesized, trajectories of the amplitudes of the frontal and parietal P3 differed significantly. While we already demonstrated [79] that the amplitude of the parietal P3 declined with aging using this sample, we here show that the amplitude of the frontal P3 did not increase with age, as would be expected from CRUNCH. Also, the frontal P3 did not *decrease* with age, as could be expected as a result of overall age-related prefrontal dysfunction. Possibly, these antagonistic effects on the frontal P3 might have cancelled each other out resulting in stable amplitudes across the lifespan. However, despite the results from the lifespan analysis, an inspection of the grand average anterior ERPs of three adult age groups indicates that frontal P3 amplitudes might subtly increase with age. The significant difference between the developmental trajectories of the frontal and parietal P3 amplitudes indicates that the frontal P3 consists of other neural sources than the parietal P3 [87-89], further confirmed by the significant difference in latency for frontal and parietal P3, which rules out volume conduction. This difference can be understood in terms of reciprocal compensation. The combined trajectory was found to be similar to the trajectory of the behavioral performance, suggesting it may reflect compensatory cognitive processes. Additionally, the correlation between the combined P3 amplitude and behavioral performance was highly significant and explained 9% of the variance in behavioral performance. Possibly, this relatively small correlation may have been due to increased variability in behavioral speed measures, such as reaction times, across the lifespan. This variability has been attributed to response-execution processes (and possibly response selection processes), but not to stimulus classification [92], and may have reduced the correlation, especially at older ages. Although latencies of the frontal P3 were in general shorter than latencies of the parietal P3, their lifespan trajectories were similar.

The results from this study are partly in line with the CRUNCH hypothesis of Reuter-Lorenz and Cappell (2008). With aging, parietal neural resources diminish and compensatory frontal mechanisms compensate for this decline, resulting in stable behavioral performance. As people grow older neuroplastic processes may result in increased, decreased, or redistributed neural resources, and compensatory cognitive mechanisms may be required to optimize behavioral performance. As a result, it is complicated to relate the P3 amplitude to specific cognitive processes. The extent to which it reflects specific cognitive functions may also vary depending on age. That is, older people might rely more on processes reflected by the frontal P3 to compensate for a loss in resources in neural networks that the parietal P3 reflects. Behavioral performance declines only when task demands require an amount of neural resources that exceeds the maximal resources older adults can achieve with neural compensation. Thus, in order to use the P3 as an index of cognitive decline not only the parietal P3 amplitude should be evaluated, but also the frontal P3 amplitude.

Adopting a lifespan approach in examining the P3 provides a unique perspective on understanding age-related changes in the brain. As was found in this study, the combination of both frontal and parietal P3 might be a good neural correlate of cognitive performance across the lifespan.

The observed results can be alternatively explained as the frontal P3 reflecting inefficient cognitive processing. As Grady (2012) stated, any (positive or negative) relation between aging and brain activity in frontal regions can be explained as compensation (successful, unsuccessful/attempted) [85]. ← deze REF verwijderen na opmaak! In order to substantiate the observed results, source analysis of the P3s at frontal and parietal regions is required. Here, different underlying sources for both of these measures are hypothesized. Another explanation for the different trajectory of the amplitude from the frontal P3 compared to that of the parietal P3 could be found in the P3a vs P3b. Unfortunately, the design of the present study does not allow for a reliable quantification of the P3a, but it would be important to investigate the developmental trajectory of its amplitude across the lifespan in future studies, especially at older ages. Possibly, the P3a plays a significant role in altering the developmental trajectory of the frontal P3 that we did not observe in the present study.

There are some limitations to this study. First, the analysis consisted of comparing age-related trajectories of P3 amplitudes and behavioral performance (cross-sectional analysis). The fact that the age-related trajectories are similar does not necessarily mean they are causally related, since for that longitudinal studies would be required. Second, we did not manipulate task load in the oddball task. It would be interesting to compare P3 amplitude trajectories for different task loads to investigate frontal compensation more directly. Third, the sample in this study was also used in our previous study [79] and the obtained results should be replicated in an independent sample. However, the sample size ensures that the obtained results are reliable. Fourth, the reported P3 amplitudes were measured by a peak-picking method. The peak amplitude of an ERP component is a somewhat arbitrary measure that may not represent meaningful information about the component. Other methods of quantifying allocated cognitive resources have been proposed, for instance by determining the area under the curve. However, there were no task manipulations to influence underlying ERP components, and thereby the P3 peak, in the used oddball paradigm. Therefore, the peak of the P3 provides a reliable approximation of allocated cognitive resources in this study.

For the purposes of indicating cognitive aging the P3 is sufficient. However, as was shown in the grand average ERPs in figure 5, the P3 seems not to be the only ERP component that changes with aging. Future studies concerning aging and ERPs should also include the P2 and N2. Furthermore, it would be interesting to compare the currently obtained developmental trajectories associated with healthy aging to those associated with pathological aging, such as seen in mild cognitive impairment or dementia. Aging-related deterioration in cognitive performance in such a clinical sample might be associated with a decline in parietal neural processes, lacking frontal compensatory processes, or both. The P3 amplitude is a solid, quick, and affordable measure that provides a more direct reflection of cognitive processing compared to behavioral measures, and that has the potential to capture these deficiencies.

4

An overview of the role of EEG/ERP in personalized medicine

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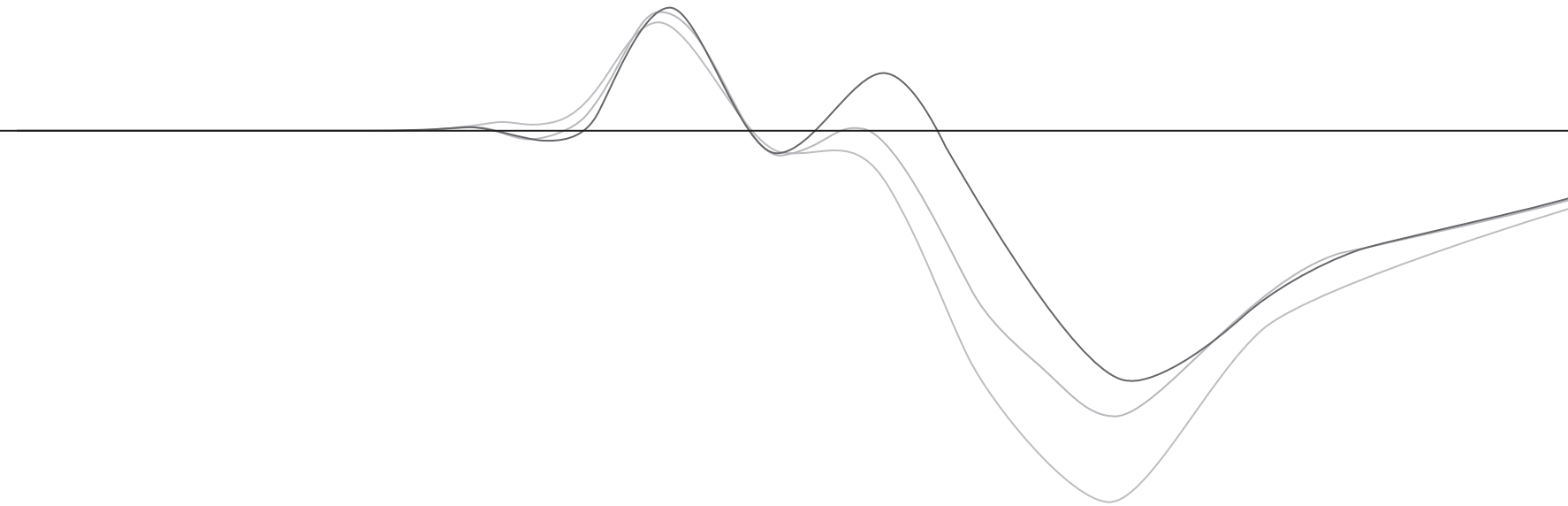

Abstract

Personalized medicine in psychiatry is in need for biomarkers that resemble CNS function at the level of neuronal activity. Electroencephalogram (EEG) during sleep or resting state condition and event-related potentials (ERP) have not only been used to discriminate patients from healthy subjects but also for the prediction of treatment outcome in various psychiatric diseases, yielding information about tailored therapy approaches for an individual. This review focuses on baseline EEG markers for two psychiatric conditions, namely major depressive disorder (MDD) and attention deficit hyperactivity disorder (ADHD). It covers potential biomarkers from EEG-sleep-research and vigilance-regulation, paroxysmal EEG patterns and epileptiform discharges, qEEG features within the EEG-main frequency bands, connectivity-markers and ERPs components that might help to identify favourable treatment outcome. Further, the various markers are discussed in the context of their potential clinical value and as research domain criteria, before giving an outline for future studies that are needed to pave the way to an electrophysiological biomarker-based personalized medicine.

Genetics, endophenotypes and biomarkers

In some fields of medicine, individualized and personalized treatment has become state of the art. Especially in oncology, the assessment of individual biological properties of the patient and the cancer cells helped to make treatment more efficient, reduce side effects and improve secondary prevention strategies [93]. The paradigm-shift from standard 'one-size-fits-all' treatment plans according to descriptive markers such as stage and locus of the cancer to individual therapy algorithms based on e.g. genetic markers is thought to be of value also for neuropsychiatric disorders and raises new hopes for tailored therapies in psychiatry. However, a mental disorder is completely different from a well observable and definable solid tumor: There is no clear organic correlate that is responsible for the symptoms, instead multidimensional and possibly very heterogeneous alterations of brain function sum up to the clinical syndrome.

Although psychiatric disorders such as major depressive disorder have an assumed high heritability of up to 37% [94], large scale genome wide association studies (GWAS) have thus far failed to link genetic variants with major depressive disorder [95]. This underpins the suggested polygenetic nature of psychiatric disorders [96] and implies the need for endophenotypes that are seen as an intermediate step between genotype and behaviour. Endophenotypes are more closely related to genotype than behaviour alone and may be a possible way to stratify a population for GWAS [97]. Although some promising findings using different sets of clinical and neuroimaging endophenotypes in major depression have been reported [98], a recent study on psychophysiological endophenotypes can be seen as a drawback to this approach since the authors were unable to replicate significant associations between endophenotypes and candidate genes [99].

Given that the link between endophenotypes and genetics might not be that strong or simple as suggested, an association between endophenotypes and disorder might still be present and could help to improve treatment and diagnostic decisions. In this context the term „biomarker" seems relevant; that is according to the National Institutes of Health (NIH) „A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [100]. The value of a personalized medicine approach is not determined by the association of a marker with genetic variants but by the improvement it yields for the diagnostic process (by making it more objective) and, probably more important, by the increased effectiveness of the treatment (i.e. a more prognostic biomarker). As Thomas Insel, director of the NIMH stated "The task is to identify the biomarker that predicts response—whether the treatment is a

medication or a psychosocial intervention." The first step towards this "precision medicine" development was the introduction of the Research Domain Criteria (RDoC) project which is aimed to transform clinical syndrome-based diagnosis into an individualized framework of psychophysiology to support the diagnostic process of mental disorders [101] and -hopefully- improve treatment. Currently several large scale studies are ongoing that should be able to shed more light on this development, such as the international Study to Predict Optimized Treatment Response (iSPOT) in 2016 patients with MDD and 672 children and adolescents with ADHD (also see: [102] for further protocol details) and the EMBARC study (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression: https://clinicaltrials.gov/ct2/show/NCT01407094).

Electroencephalogram and Biomarkers

Sparked by the discovery that the mode of function of the human central nervous system is based on electric activity [103,104], the invention of the electroencephalogram (EEG) and its first description in humans [6] provided the possibility to analyse the brain at its core functional level. Taken as a tool for assessment for biomarkers, that, according to the definition, should be assessable objectively and provide information about physiological or pathological processes or responses to treatment interventions [105], the EEG also fulfils the criteria of a cost efficient, nowadays broadly available and already established tool in the diagnostic clinical practice. Further, the EEG captures ongoing neuronal activity with a temporal resolution that surpasses any other neuroimaging modality such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Also, the EEG is not a surrogate marker of neuronal activity (such as the blood deoxygenation level dependent signal in fMRI or the glucose utilisation in PET, see [106]) but is a direct reflection of neuronal activity (post-synaptic potentials, PSP) [107]. It is therefore highly plausible that a personalized medicine approach in psychiatry could gain from electrophysiological markers.

Although electrophysiological biomarkers have been studied throughout many psychiatric disorders, the current review is dedicated to only two of them: major depressive disorder (MDD) and the attention deficit-hyperactivity disorder (ADHD). The following work describes the current state of the art of baseline EEG parameters by means of their diagnostic and predictive (prognostic) value. Treatment emergent biomarkers that yield information about changes in the early course of treatment will not be subject of the review and the interested reader is referred to Olbrich and Arns [108] or Arns and Olbrich [109] for more coverage of those.

Biomarkers

EEG-Sleep-Research

EEG biomarkers in sleep are robust and their advantage can be found in the link between clinical symptoms such as sleep initiation problems, early awakening or disrupted sleep in both, MDD and ADHD and electrophysiological assessable parameters. In MDD, the most consistently reported findings include a disturbed sleep architecture, comprising an increased rapid eye movement (REM) density [110,111], decreased rapid eye movement sleep (REM sleep) latency [112,113] and altered slow wave sleep (SWS) in MDD [114,115].

While slow wave power seems to have a discriminative value between MDD and healthy controls (HC) [114,116], a predictive value for recurrence of depressive symptoms was found for decreased SWS, decreased sleep efficiency and delayed sleep onset [117-119]. Also the slow wave activity (SWA) itself seems to be important for treatment prediction. Luthringer et al. [120] reported increased relative delta power in sleep EEG-recordings in responders to antidepressant treatment although others failed to replicate these findings [121,122]. Still, Nissen et al. [122] reported decreased SWA in responders, expressed in a high delta sleep ratio (DSR), a finding that again could not be replicated by Argyropoulos [123]. Besides classical sleep EEG parameters, also a decreased coherence within the beta, delta and theta band in sleep EEG predicted non-response in adolescents and the occurrence of depressive episodes [124].

In ADHD there is a clear lack of studies that examine EEG-derived sleep parameters, although other measures such as actigraphy and salivary melatonin measurements suggest a delayed sleep onset in a majority of children and adults with ADHD, also termed sleep onset insomnia [125-127] characterized by a delayed melatonin onset. This delayed sleep onset results in reduced sleep duration - and thus chronic sleep restriction - in ADHD, which becomes visible as the typical drowsiness patterns that can be observed in the EEG such as impaired vigilance (see "EEG-Vigilance") or excess theta (see "Frequency specific biomarkers: Theta"), for review also see [126,128].

EEG-Vigilance

Another possible EEG-biomarker that has proven its value for differentiating between patients suffering from MDD and HC is EEG-vigilance regulation. Hegerl [129] and Olbrich [130] reported that MDD is associated with an increased EEG-vigilance during rest with less and slower declines to lower vigilance stages during a 15 minute resting condition. The appeal of this marker reflecting a high tone of CNS-arousal can be found in the linkage between clinical symptoms and EEG-parameters of wakefulness regulation. A hyper stable vigilance regulation in MDD is interpreted as an electro-

physiological correlate of the often reported sleep-problems. Increased vigilance further might explain the behavioural withdrawal of patients suffering from MDD to avoid further increase of arousal [131].

The EEG-vigilance framework further suggests that a fast decline of EEG-vigilance during rest might result in increased sensation seeking and hyperactive behaviour to stabilize wakefulness regulation. Hegerl and Hensch (2014) suppose that not only manic patients [132] reveal unstable EEG-vigilance regulation patterns but also patients suffering from ADHD [128,133]. In line with this, increased theta power as a marker of drowsiness has been frequently reported in patients with ADHD [134] and as described above the majority of patients with ADHD exhibit sleep onset insomnia [125,127,128], further supporting this notion. However, a recent meta-analysis also suggested increasing levels of theta for healthy children and stable levels for ADHD children across the last 10 years [135], suggesting a possible gene X environment (sleep, circadian clock) interaction for this measure requiring further research.

Paroxysmal patterns and epileptic discharges

Unlike in neurology, there are no distinct “graphoelements” in EEG recordings that are pathognomonic for a psychiatric syndrome. However, already in 1939 it was demonstrated that during subclinical epileptiform activity patients had slower reaction times, while others did not respond at all [136], suggesting that paroxysmal activity in ‘non-epileptic patients’ can have behavioural consequences.

The occurrence of paroxysmal EEG in affective disorders has not been investigated in much detail, but previous analyses suggest a prevalence of 3-5% in depression [137] to 20-40% in affective disorders, mostly mania [138]. The 3-5% in depression is comparable to the 1-6% prevalence of paroxysmal EEG in normal populations [138-141]. On the other hand, the occurrence of paroxysmal patterns in ADHD has been estimated to be between 12-15% [142-144] to approximately 30% [145], which is relatively high, compared to normal populations. A more recent study found epileptiform discharges in 25% of children with suspected ADHD [146].

The implications for treatment in psychiatric patients with paroxysmal patterns or epileptiform discharges - but without a history of seizures - remain unclear. It is still remarkable that several studies found that ADHD patients [147-149] do respond to anticonvulsant medication, e.g. to carbamazepine [150]. Furthermore, there is some evidence that antidepressant treatment augmentation with antiepileptic drugs is effective in treatment resistant MDD [151,152] although data about the association of response and epileptiform discharges are lacking. As a further example, previous studies have demonstrated an association between paroxysmal EEG activity and

panic attacks (reviewed in [153,154]). Patients with panic disorder and epileptiform EEG-patterns have been found to clinically respond to anticonvulsants [155], thus suggesting that there could be a subgroup of psychiatric patients in whom paroxysmal/epileptiform EEG activity could be associated with their psychiatric complaints and for whom anticonvulsant treatment could be a choice for augmentation of treatment or as standalone treatment. However, this requires further controlled research.

Frequency specific biomarkers: Alpha

One of the most prominent features of a resting state EEG is the EEG-alpha activity with heritability estimates of up to 79% [35]. Alpha in adults has a mean frequency around 10Hz with a range between 7-13 Hz and has maximum amplitudes at parie-to-occipital locations in eyes closed condition.

In MDD a consistent finding is an elevated absolute [156-160] or relative alpha power [161,162] at mainly parietal and frontal [158,163] or occipital sites [164]. The reason that some studies did not find alpha power differences between patients and healthy controls [165] or found decreased (relative) alpha activity in comparison to other patient groups [166]might be related to differences of recording periods, where shorter recording periods prevent the above described [129,130] differences in vigilance regulation to occur (e.g. 6 min in [165] versus 15 min in [129,130].

In addition, there is some evidence, that EEG-alpha power can predict treatment outcome with low parieto-occipital [164,167,168] or lowered frontal alpha power [169] associated with non-response to antidepressants, although this could not be replicated in the recent multicentre iSPOT-D study in 1008 MDD patients [170]. However, for treatment with repetitive transcranial magnetic stimulation (rTMS), the opposite was reported [168,169] maybe related to higher levels of treatment resistance in these rTMS studies.

EEG-alpha asymmetry has been investigated as a biomarker for MDD with a decreased alpha power at right frontal sites relative to the left side [171-174] although many studies have failed to replicate these findings [170,175-179]. Interestingly in ADHD, Keune et al. [180] found the opposite pattern of alpha asymmetry with increased right frontal alpha power.

Two studies by the same group investigated the prognostic value of alpha asymmetry in MDD and found conflicting results [164,181], however, in the iSPOT-D study it was found that frontal alpha asymmetry (right frontal alpha dominance) was specifically related to response to the SSRI’s escitalopram and sertraline, but not to the SNRI venlafaxine

in females only [170], underscoring the importance of large samples that allow testing for gender and drug-class specific predictors of treatment outcome.

A slow background rhythm, also called a slow alpha peak frequency (APF) has been consistently found a predictor for non-response to several treatments such as stimulant medication in ADHD [52], rTMS in depression [182,183] and the antidepressants pirlindol and amitriptyline [168], for review see Arns [184].

Frequency specific biomarkers: Theta

Several studies have reported elevated slow wave activity in MDD [159,185-188], with the focus of this elevated theta-activity localized to frontal areas and often to the anterior cingulate cortex (ACC) [158,188,189], though decreased ACC activity in MDD has also been reported [190] and some studies found no differences between MDD and controls [191,192].

High frontal theta has been associated with non-response to antidepressant treatments [183,193,194] while Cook et al. [195] found no differences. Seemingly contrary to this, Spronk et al. [196] reported that low theta at the frontal midline was associated with non-response. Note that [183,193,194] all reported on widespread frontal (not midline) theta, most likely a reflection of 'drowsiness' theta as discussed above (see "EEG-Vigilance") on vigilance [128], whereas Spronk and colleagues found the opposite pattern for frontal midline theta. This suggests these two types of theta could have different implications and different origins. In line with [196] several studies have indeed shown low theta localized to the ACC, as estimated by source localization techniques, to respond worse to various antidepressant treatments [197-200]. These findings are in line with positron-emission-tomography (PET) and functional magnetic-resonance-imaging (fMRI) studies demonstrating low metabolic activity in the ACC is associated with worse treatment outcome, also see Pizzagalli [201] for an excellent review and meta-analysis on the rostral ACC and treatment outcome. Contrary to this notion, several groups have reported high perfusion in the subcallosal cingulate (SCC; in earlier work this area was also referred to as rACC) or rACC for non-responders [202,203], also reviewed in [188]. In line with this, recent results of the iSPOT-D study reported increased rACC and frontal theta to be associated with non-response, albeit with a small effect size [188]. Interestingly, these results tended to be driven mostly by treatment resistance, suggesting that future studies should also investigate the role of treatment resistance for the association of rACC / SCC perfusion and treatment outcome [188]. Conversely, Deep-Brain Stimulation (DBS) targeting the SCC in treatment resistant MDD patients has been shown to result in clinical benefits [204], positing this area, as a critical node in the depression network. However, the exact direction of these findings (high or low frontal midline theta) and exact localization (rACC vs. SCC) remains unclear from these lines of research, and future studies might shift the focus on

investigating the connectivity of this specific area with other structures rather than focusing solely on EEG theta power given the above contradictory findings.

In ADHD, excess theta compared to controls is an often-reported finding, sometimes also expressed in the Theta/Beta ratio (TBR) [134] and several reports have termed the TBR a solid biomarker to identify ADHD. These findings resulted in this measure being FDA approved as a 'diagnostic test' for ADHD (for commentary see [205]). However a recent meta-analysis could not confirm that this metric is a reliable 'diagnostic test' for ADHD [132], due to an increased TBR across the last 10 years for controls, suggesting that this marker is a non-specific marker for drowsiness, and insufficient as a diagnostic biomarker for ADHD. Apart from the diagnostic use, this metric does hold potential as a prognostic biomarker being able to predict treatment outcome. A substantial proportion (26-38%) of ADHD subjects did have a high TBR and excess theta and these subgroups have been found responders to stimulant medication [52,169,206] and neurofeedback [183,207], making this measure more likely a prognostic but not diagnostic measure [205], albeit still requiring further replication.

Frequency specific biomarkers: Beta

In MDD there is some evidence for increased beta EEG activity [186,208]. The predictive value for treatment outcome has not been investigated systematically so far.

In ADHD there is evidence for a sub-group of ADHD patients that are characterized by excess beta or beta spindles that make up 13-20% [209-211]. Several studies demonstrated that this subgroup does respond to stimulant medication [212-214]. A recent study, further demonstrated that spindling excessive beta is a result of sleep-maintenance problems and thus can indeed be considered a 'sub-vigil' beta state, and is specifically associated with impulse control problems, irrespective of diagnosis [215]. This would make the effectiveness of wakefulness promoting drugs plausible in these patients.

EEG-connectivity measures

First reports of altered connectivity in MDD in contrast to HC stem from findings of altered coherence between EEG-electrode sites [216,217]. More recent studies used a huge variety of connectivity measures like partial directed coherence, granger causality, structural synchrony index and phase synchrony index. Some found decreased EEG-connectivity in MDD [208,218-220] while others report of increased EEG-connectivity in MDD, mainly in the alpha band [221-224]. More studies are needed to disentangle the complex relationship between the different connectivity measures and their physiological interpretation and to estimate the value for treatment prediction. In this context, one study [224] found an association between increased

phase connectivity in the beta band between the subgenual prefrontal cortex and the right medial frontal cortex and treatment response. As suggested above in relation to theta, these approaches, when replicated could further shed light on the controversy between increased or decreased metabolism in the rACC/SCC.

Also in ADHD there is increasing evidence, that EEG-based measures of connectivity could be used to differentiate between patients and HC. Interestingly, most studies find increased measures of coherence especially within the beta and theta band during the resting state [225-227]. Also graph-theory network parameters seem to support an increased functional connectivity in ADHD [228]. Regarding a possible predictive value of connectivity measures, Dupuy [229] describes an association between intra-hemispheric coherence in the beta band and response to methylphenidate. These findings are promising and possibly pave the way for improved differential diagnosis and consecutive treatment.

Event-related potentials

The event-related potential (ERP) is a waveform of averaged EEG activity, time-locked to a stimulus in a cognitive task. Several components of this ERP have been studied for their predictive value in treatment outcome.

In MDD research the main focus has been on two measures, namely the P3 [11] and the loudness dependence auditory evoked potential (LDAEP), which is a derivative of the N1/P2 amplitude and its changes with increasing stimulus intensity [230]. So far, research involving the P3 has been ambiguous. Jaworska and colleagues found that responders to antidepressants have larger P3 amplitudes than non-responders [231]. A similar finding was reported by Bruder and colleagues for the P3 amplitude at occipital sites [232]. In contrast, responders to treatment with rTMS were found to have lower P3 amplitudes than non-responders, although this effect was limited to Pz and only marginally significant [183]. Regarding P3 latency, the results have been mixed as well, where some found no effect [231], while other studies found slower P3's in non-responders [233-235].

The LDAEP has proven to be a more robust predictor for antidepressant treatment response. A strong LDAEP, i.e. a steeper increase with stimulus intensity, is supposedly indicative of a low level of serotonergic activity [230,236] and is related to better outcome to an SSRI [237], whereas the effect is reversed for responders to noradrenergic antidepressants [198,238,239]. A recent study, however, failed to replicate this relation between LDAEP and treatment outcome, even though, a relation between treatment response and current source densities of the N1-LDAEP was obtained [240]. Related to this measure, Spronk and colleagues found that a larger (more negative) N1 amplitude

was related to a larger reduction of depressive symptoms after treatment with antidepressants [196].

In ADHD, ERP components have also been investigated as predictors for treatment response to stimulants. Sangal and colleagues found the topography of the P3, specifically the right fronto-central to parietal amplitude ratio, to be predictive of response to various stimulants, i.e. methylphenidate [241], atomoxetine [242] and pemoline [243]. They also reported a study in which poor responders to pemoline were treated with the antidepressant imipramine. Within this sub-group, poor responders to imipramine demonstrated slower P3 latencies [244]. Sunohara et al. could not replicate ERP P3 and N2 latencies as baseline predictors for treatment outcome in ADHD children but found some treatment emergent effects [245] which are in agreement with Winsberg et al. [246].

Summary

Sleep-EEG parameters have been found to be of discriminative and predictive value, especially in MDD. A widespread clinical use might be dampened due to the relatively large subject burden, e.g. one night at a sleep laboratory or even two to rule out first-night effects from findings [247]. In ADHD, there is a lack of studies that analyse EEG-sleep parameters although an association of the disorder with sleep-wake cycle and especially circadian alterations are evident.

EEG-vigilance measures seem to provide a less cost and effort intensive approach to assessing wakefulness-regulation during rest in contrast to polysomnography. Another advantage of EEG-vigilance based markers can be found in its association with clinical features of MDD and ADHD as outlined above. A biomarker that has a direct link to the behavioural level is more likely to be accepted in clinical routine. Still, there is a clear lack of controlled studies that demonstrate the discriminative value of EEG-vigilance parameters for response or non-response in MDD and in ADHD.

For patterns of paroxysmal or epileptiform activity it remains unclear, if treatment or augmentation with antiepileptic drugs such as valproate, or some specific antidepressants increase response rates in these MDD or ADHD subgroups. Some evidence exists that non-responders to first line treatment may benefit. Studies that analyse treatment of MDD or ADHD with antiepileptic drugs should report on subgroups based on the occurrence of pathological but subclinical EEG patterns in the future.

Several qEEG markers, especially within the alpha and theta range, revealed a discriminative value regarding treatment outcome. However, findings in this field are often contrary to what might be explainable by the variance of studied patient groups (treatment resistant or not) and not at last by the different treatment approaches that have been studied. Further, methodological and interpretation aspects need to be clarified as it is the case with the difference between diffuse frontal theta vs frontal-midline theta in MDD. Based on the existing findings, qEEG measures of the alpha, alpha asymmetry and theta frequencies deserve to be in the main focus in future studies of treatment prediction.

EEG-connectivity analysis has seen a revival within the past few years and first findings seem to be promising with regard to its value for treatment prediction. However, the used measures differ broadly; there is almost no study that uses the same measures for assessment of network-interaction and connectivity. Therefore the studies are hardly comparable. Further, many studies on EEG-connectivity do not make a-priori hypothesis about alterations of connectivity between brain regions, resulting in a high number of tests that analyse every possible connectivity pattern, possibly resulting in type-I errors. Identification of the most reliable and valid connectivity parameters and application on hypothesis driven, predefined networks should be among the first goals of future research in this field.

Not only spontaneous EEG activity, but also event-related potentials hold value for the improvement of treatment. However, as it is the case in many resting-state EEG markers, there are promising markers that sometimes could not be replicated in small-scale studies. Therefore, larger study groups and controlled trials are needed to estimate the full potential of ERPs.

Since the aim of a personalized medicine approach is to improve treatment of the individual, studies are needed that analyse the predictive value of CNS-arousal in patients for treatment outcome. Currently, data from the iSPOT and EMBARC trials in MDD are being analysed using this approach.

It should be noted that personalized medicine with a focus on treatment prediction is in need for addressing inter-individual variance, which is in contrast to the search for biomarkers that reflect homogeneous diagnostic groups. Therefore, the mentioned differences in findings, sometimes even contrary to one another when looking at predictive markers for treatment response, might yield important information about different treatment options: it is possible that a marker predicts response to one treatment while it also could be found in non-responders to another treatment.

The goal will be to disentangle these relationships with standardized and controlled trials, including a variety of treatment arms and by embracing heterogeneity.

Perspectives

The RDoCs provide a good framework to overcome subjective decisions in the treatment of psychiatric disorders and might help to bridge the gap to the advances made in medical treatment in other domains of medicine. In face of the myriads of available EEG-based parameters it seems obvious that there will not be one single marker that fulfils all criteria to aid in the diagnosis and even predict treatment in different neuropsychiatric disorders. It will require combining a set of neurophysiological but also clinical and other biomarkers to fulfil the promise of a personalized medicine approach. Simulations on existing datasets and probably the usage of non-linear methods such as artificial networks could help in the analysis of large data matrices to extract meaningful combinations for treatment prediction [183]. It should be noted that the goal is not a final threshold or combination of biomarkers for prediction but a matrix of meaningful parameters that should be subject to further refinements. Furthermore, one fundamental problem to be faced is that of defining clinically meaningful treatment endpoints. Several different primary outcome measures have been used ranging from the BDI-II to Hamilton Depression Inventory, and also using different criteria such as remission or response, whereas the agreement between these scales is far from perfect [248], thus making the 'ground-truth' of 'clinical response' a moving target dependent on the instruments and definitions used.

In the first place it is now necessary to initialize biomarker-guided treatment decisions that lead to increased remission rates in comparison to treatment as usual. Furthermore, in MDD one faces the huge variety of treatment options, ranging from psychotherapy with different branches, over psychopharmacological interventions with completely different modes of action to brain stimulation methods such as transcranial magnetic stimulation (TMS) or electro-convulsive therapy (ECT) but also sleep deprivation. In face of the high non-response rates a framework is urgently needed including different biomarkers that allow for an evidence based choice of the right treatment option at the right time for the right patients. Preferably markers should be taken into account that can be interpreted in the context of their physiological meaning since this will increase the acceptance of a marker by clinicians. Furthermore, as mentioned above on alpha asymmetry, large sample sizes are required to also address gender, age and drug-class specific predictors. Therefore, large multicentre studies for identification of those markers and their thresholds to predict treatment outcome have to be carried out, as is the case with the iSPOT-D and EMBARC

studies. The next step then will be to initiate prospective randomized controlled trials that compare the biomarker based treatment versus treatment based on therapist and patient preferences as it is currently good clinical practise. This way, personalized medicine could help to apply the already existing treatment options in a hopefully more effective and efficient way and thereby, decrease the individual burden of disease for patients.

5

The ERP, a predictor for treatment outcome?

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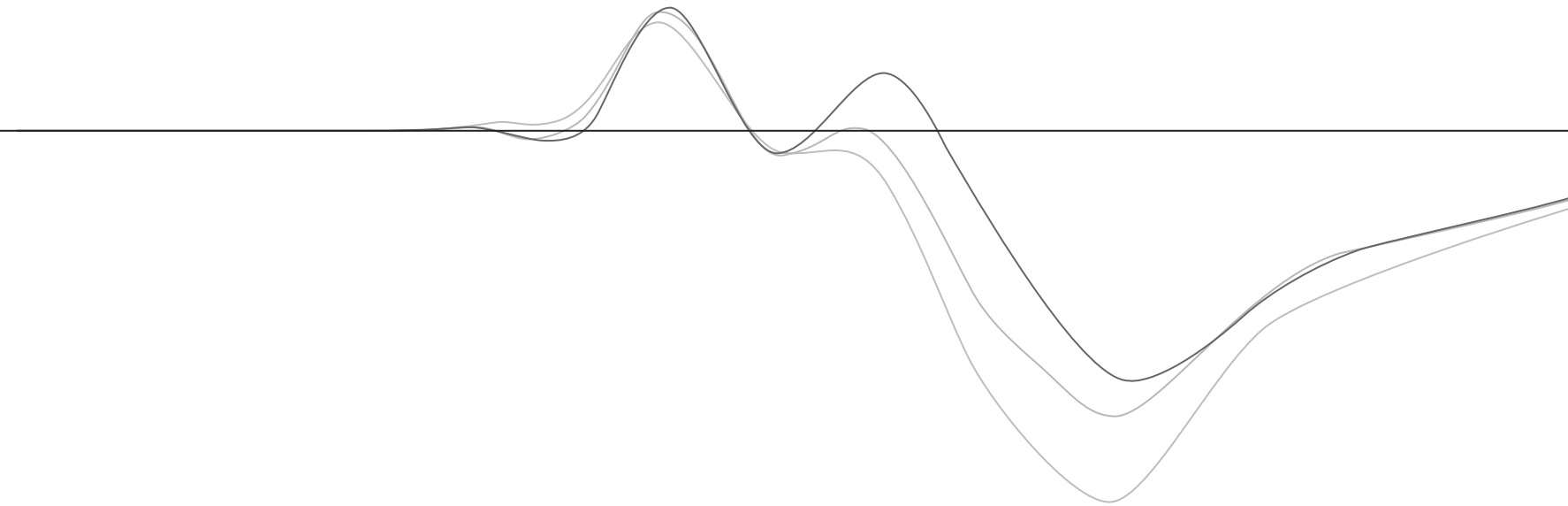


Abstract

It is essential to improve antidepressant treatment of major depressive disorder (MDD) and one way this could be achieved is by reducing the number of treatment steps by employing biomarkers that can predict treatment outcome. This study investigated differences between MDD patients and healthy controls in the P3 and N1 component from the event-related potential (ERP) generated in a standard two-tone oddball paradigm. Furthermore, the P3 and N1 are investigated as predictors for treatment outcome to three different antidepressants.

In the international Study to Predict Optimized Treatment Response in Depression (iSPOT-D) - a multi-center, international, randomized, prospective practical trial - 1008 MDD participants were randomized to escitalopram, sertraline or venlafaxine-XR. The study also recruited 336 healthy controls. Treatment response and remission were established after eight weeks using the 17-item Hamilton Rating Scale for Depression. P3 and N1 latencies and amplitudes were analysed using a peak-picking approach and further replicated by using exact low resolution tomography (eLORETA). A reduced P3 was found in MDD patients compared to controls by a peak-picking analysis. This was validated in a temporal global field power analysis. Source density analysis revealed that the difference in cortical activity originated from the posterior cingulate and parahippocampal gyrus. Male non-responders to venlafaxine-XR had significantly smaller N1 amplitudes than responders. This was demonstrated by both analytical methods. Male non-responders to venlafaxine-XR had less activity originating from the left insular cortex.

The observed results are discussed from a neural network viewpoint.

Introduction

The World Health Organization (WHO) has ranked major depressive disorder (MDD) as the leading cause of disability worldwide [249]. Individual responses to antidepressants vary which often leads to the need to try different types of medication using a 'trial-and-error' approach. The STAR*D trial [250,251] demonstrated that this stepwise approach left one third of patients resistant to treatment after being randomized to three different treatments, also with different modes of action. This is not sufficiently effective and it is essential to improve antidepressant treatment response in MDD. One way this could be achieved is by reducing the number of treatment steps and guiding the right patients to the right treatment using biomarkers. This is referred to as 'personalized medicine' or 'precision medicine'.

Treatment prediction employing event-related potentials

A potential predictor for treatment outcome lies in MDD patients' electrophysiological properties. The event-related potential (ERP) is a waveform in brain activity that is time-locked to an event, for instance an auditory stimulus. Some of the ERPs' components have been studied for their predictive value in antidepressant treatment response, where most research has been focused on the P3 (P3) and N100 (N1) (for review see: [108,109]).

The P3 consists of neural activity originating from several origins, including presumably the prefrontal cortex, the temporoparietal junction, the primary auditory cortex and possibly other sources [70]. The P3 can be measured across the scalp, but he P3 measured at a frontal electrode site does not necessarily reflect the same cortical activation as the P3 measured at a posterior site. For older participants, compensatory activation from frontal regions may be involved which may be represented by the frontal P3 and not the parietal P3 [79].

Most studies, but not all, have found lower P3 amplitudes in MDD patients compared to healthy controls. Some studies reported only non-significant trends of reduced P3 amplitudes in MDD patients [252].

So far, research on antidepressant treatment response involving the P3 has been ambiguous. There are studies that found responders to antidepressants having larger P3 amplitudes than non-responders [231,232]. In contrast, responders to treatment with repetitive Transcranial Magnetic Stimulation (rTMS) were found to have lower P3 amplitudes than non-responders, although only marginally significant [183]. Regarding P3 latency, the results have been mixed as well. Some found no effect of P3 latency [231], while other studies found slower P3's in non-responders to antidepressants [233-235].

Spronk and colleagues found that a larger N1 amplitude at baseline (assessed in an oddball paradigm) was associated with better antidepressant treatment outcome [196], suggesting that maybe the oddball N1 amplitude could serve as a predictor to treatment outcome, possibly in line with earlier research implicating the N1 component of the Loudness Dependent Auditory Evoked Potential (LDAEP) in prediction of treatment outcome (see [108,253] for review).

In this study we used data from the multi-center, randomized, prospective open-label international Study to Predict Optimized Treatment Response in Depression (iSPOT-D) (see Williams et al. [102] for details). The aim of this study was to investigate differences between MDD patients and healthy controls in the P3 and N1 component from the ERP generated in a standard two-tone oddball paradigm. Furthermore, the P3 and N1 were investigated for their predictive power of antidepressant treatment response. In addition, we tested if P3 and N1 measures can aid in differential prediction to the three medication types. We expected to find (1) reduced P3 amplitudes in MDD patients, (2) larger P3 amplitudes in treatment responders compared to non-responders and (3) larger N1 amplitudes in treatment responders compared to non-responders. In our analysis we have first used a traditional peak-picking method to quantify the ERP components and also obtain latencies for all components. In addition, we have applied a time-based analysis using eLORETA to replicate the findings obtained from the peak-picking method and to also obtain localizations of the observed effects.

This study is among one of several planned iSPOT-D studies that were approved by the iSPOT-D publication committee. Other planned analyses on EEG metrics are reported in separate manuscript such as for example Arns et al. (2015) in this journal, for an investigation of the role of frontal and rostral anterior cingulate theta EEG power in antidepressant treatment prediction.

Experimental procedures

Design

Data from this study come from the iSPOT-D study, which is an international multi-center, randomized, prospective open-label phase IV clinical trial. MDD patients were randomized to escitalopram, sertraline or venlafaxine-XR in a 1:1:1 ratio. The study was designed to approximate real-life treatment of MDD and therefore no placebo condition was included. A complete description of the study has been published earlier [102].

Participants and treatment

There were 1008 MDD patients and 336 healthy controls (HC) included in this study. All participants were aged 18-65 years. MDD patients were treatment-naïve or medication was washed-out (5 half-lives). At baseline, a primary diagnosis of unipolar, non-psychotic MDD was confirmed by administration of the Mini-International Neuropsychiatric Interview [254] according DSM-IV criteria and a score ≥16 on the Hamilton Rating Scale for Depression ($HRSD_{17}$). The visit consisted of questionnaires, an EEG assessment, a neuropsychological battery and a blood draw. After the baseline visit, MDD patients were randomized to one of the three antidepressants and a follow-up visit was scheduled after eight weeks. All baseline tests, except for the blood draw and the diagnostics, were repeated at the follow-up visit. Although this study only includes data from the baseline and week 8 visits, participants were in fact followed-up for one year in total.

This study was approved by the institutional or ethics review boards at all of the participating sites. This trial was registered with ClinicalTrials.gov. Registration Number: NCT00693849; URL: http://clinicaltrials.gov/ct2/show/NCT00693849.

Electroencephalographic data acquisition

EEG recordings were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Details of this procedure have been published elsewhere [52,102] and details of the reliability and across-site consistency of this EEG procedure have been published[19,50]. In summary, participants were seated in a sound and light attenuated room that was controlled at an ambient temperature of 22°C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quikcap with sintered Ag/AgCl electrodes; Neuroscan NuAmps DC amplifier; extended 10-20 electrode international system). Data were offline re-referenced to averaged mastoids with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1.5cm below the middle of the left bottom eyelid. Skin resistance was aimed at <5 KOhms for all electrodes. A continuous acquisition system was employed and EEG data were electrooculogram (EOG)-corrected offline [53]. The sampling rate of all channels was 500 Hz. A low pass filter with an attenuation of 40dB per decade above 100 Hz was employed prior to digitization.

The oddball paradigm consisted of a quasi-random sequence of 280 frequent background tones (500 Hz) and 60 infrequent target (1000 Hz) tones. Two targets could not appear consecutively. All stimuli (50 ms; 5 ms rise and fall time) were

presented binaurally at a volume of 75dB SPL with an inter-stimulus interval of 1000 ms. Participants were instructed to press two buttons simultaneously (one for each index finger to counterbalance motor effects) when they heard a target tone and to ignore the background tones. Speed and accuracy of response were both equally stressed in the instructions. Before the actual test they were presented with a brief practice run to clarify the distinction between the two tones.

ERP scoring

Conventional ERP averages were generated at all electrode sites for target stimuli. Only stimuli with a correct response were included in the average. Before averaging each single trial ERP was filtered with a Tukey (tapered cosine) window. No signal was passed above 35 Hz. For the target stimuli waveforms, the peaks (amplitude and latency) of the N1, P2, N2 and P3 ERP components were identified, relative to a 300 ms pre-stimulus baseline, at Fz and Pz (to capture possible compensatory effects). Using pre-determined latency windows, peaks were semi-automatically scored by BrainVision Analyzer 2: N1 (70-120 ms) and P3b (220-550 ms) and manually corrected by the first author (RvD). All scoring was checked by a second rater, and disagreements in scoring (<5%) were settled by the second author (MA).

Current source density analysis

eLORETA software and statistical nonparametric mapping method (SnPM) [255-258] were used (1) to replicate obtained results from the ERP peak-picking analysis by using a time-based analysis, and (2) to localize differences in brain activity between groups to cortical sources. This was done by analyzing time frames of averaged group ERPs with a t-test [259]. Those timeframes that significantly differ in global field power were entered in a t-test on log-transformed current source density data in order to obtain the cortical sources responsible for the group difference in brain activity [260]. eLORETA has been validated in multiple studies and the standard 10/20 EEG system employing electrode montages with for example 25 electrodes has been proven sufficient for source localization [261]. Statistics from both methods are corrected for multiple comparisons by means of a randomization procedure.

Statistics

Response was defined as a >50% decrease in $HRSD_{17}$ score from baseline to week 8. In this analysis, we primarily assessed responders vs. non-responders. Differences in age and sex were tested using a t-test or non-parametric tests (sex). In case of group differences in one of these measures, these variables were added as a covariate.

For comparison of MDD vs. healthy controls as well as investigating treatment prediction a repeated measures ANOVA was conducted for P3 and N1 amplitude and latencies with within-subject factors Site (Fz or Pz), between-subject factors group (MDD vs. Controls or Response vs. Non-Response), treatment arm (For response analyses only: ESC, SER and VEN), Age (Young vs. Old) and sex. When significant interactions were found, univariate analyses were performed. The cut-off for young and old participants was set at 46 years based on age-related development of P3 amplitude as reported in our previous studies [79,262].

A partial correlation (correcting for age) was run between the percentage improvement on the $HRSD_{17}$ between baseline and week 8, $HRSD_{17}$ at intake and $HRSD_{17}$ at week 8 and the significant ERP components obtained.

All statistics for treatment prediction were performed on data from MDD participants who completed 8 weeks of treatment per protocol: participants who were dosed with their randomized medication for a minimum of 6 weeks and who returned for their week 8 visit and were still receiving their randomized medication at this visit ('per protocol' grouping). Significance level was set at $p \leq 0.05$ and effect sizes (ES) of main effects are reported in Cohen's *d*.

Results

For the comparison between MDD and healthy controls, 1008 MDD patients were compared to 336 HC. For treatment prediction the 'per protocol' grouping consisted of 655 MDD participants. See table 5.1 for demographic information and remission and response rates for the whole MDD group and the separate treatment groups used for treatment prediction. The overall remission and response rates in this MDD sample were respectively 46% and 64%. Treatment was randomized as follows: Escitalopram (N=217), Sertraline (N=234) and Venlafaxine-XR (N=204). The treatment groups did not differ regarding age, sex, baseline MDD severity ($HRSD_{17}$), anxiety severity ($HRSD_{17}$), remission or response rates.

MDD Participants vs. Controls

There was no significant difference regarding age between MDD participants (M=37.84, SD=12.57) and HC (M=36.99, SD=13.08); t(1342)=-1.06, p=.29. Also, there were no significant differences regarding sex between the two groups (χ^2(1,1344)=.004, p=.949).

Table 5.1 Demographic features of MDD patients and controls and treatment outcomes for patients who completed treatment per protocol.

	Whole sample		Per protocol completers				Early drop-outs		
	MDD	Controls	Escitalopram	Sertraline	Venlafaxine-XR		Escitalopram	Sertraline	Venlafaxine-XR
N	1008	336	217	234	204	N	119	102	132
Females	571	191	119	139	120	Females	59	52	82
Average Age (years)	37.84 (12.57)	36.99 (13.08)	38.85 (12.47)	38.34 (12.42)	38.46 (12.87)	Average Age (years)	37.28 (12.93)	36.77 (11.85)	35.68 (12.65)
$HRSD_{17}$ Baseline	21.88 (4.12)	1.15 (1.63)	21.75 (3.98)	21.95 (4.17)	21.50 (3.89)	$HRSD_{17}$ Baseline	21.77 (4.27)	21.89 (4.18)	22.66 (4.41)
$HRSD_{17}$ Week 8	9.67 (6.43)	1.06 (1.43)	9.29 (6.60)	9.41 (6.08)	9.71 (6.22)	$HRSD_{17}$ Week 8	-	-	-
$HRSD_{17}$ Anxiety*	6.16 (1.99)	0.57 (0.97)	6.18 (1.95)	6.27 (1.96)	6.14 (1.85)	$HRSD_{17}$ Anxiety*	6.04 (2.19)	5.86 (2.19)	6.08 (2.11)
% Remission ($HRSD_{17}$)			48	47	44	% Remission ($HRSD_{17}$)	-	-	-
% Response ($HRSD_{17}$)			60	67	63	% Response ($HRSD_{17}$)	-	-	-

Abbreviations: $HRSD_{17}$, 17-item Hamilton rating scale for depression; MDD, Major depressive disorder; XR, Extended release. * measured at baseline

P3 amplitude

Repeated-measures ANOVA, yielded the following results for P3 amplitude: An effect of Site ($F(1,1087)=695.37$, $p<.001$), Sex ($F(1,1087)=29.06$, $p<.001$), a Group X Site interaction ($F(1,1087)=6.19$, $p=.013$) and a main effect of Group ($F(1,1087)=14.61$, $p<.001$).

The significant Group x Site interaction was further analyzed. Separate univariate analyses for Fz and Pz demonstrated a main effect for Group (Fz: $F(1,1091)=4.74$, $p=.03$; Pz: $F(1,1104)=18.14$, $p<.001$). MDD participants had significantly lower P3 amplitudes compared to HC at Fz ($M=3.90 \pm 5.48$ vs. $M=4.76 \pm 6.41$; $d=0.14$) and Pz ($M=9.51 \pm 5.93$ vs. $M=11.73 \pm 7.31$; $d=0.33$).

A significant correlation between P3 amplitude at Pz and depression severity at baseline ($HRSD_{17}$) was obtained within the group of MDD patients ($r=-.069$, $df=803$, $p=.024$). There were no significant correlations between P3 amplitude at Fz and baseline $HRSD_{17}$ in MDD patients nor a correlation for P3 at Pz and Fz and baseline $HRSD_{17}$ in healthy controls.

P3 latency

Repeated-measures ANOVA, yielded the following results for P3 latency: An effect of Site ($F(1,1087)=98.420$, $p<.001$), Sex ($F(1,1087)=16.21$, $p<.001$), Age ($F(1,1087)=39.592$, $p<.001$), a Group X Sex X Age interaction ($F(1,1087)=5.487$, $p=.019$) and no effect of Group ($p=.167$).

The interaction effect of Group x Sex x Age was further investigated. Separate repeated measures analyses revealed that only young females with MDD had slower P3 latencies than young female healthy controls ($F(1,433)=8.70$, $p=.003$, $d_{Fz}=-0.29$, $d_{Pz}=-0.28$). There were no effects of Group in older females, or young and old males.

N1 amplitude

Repeated-measures ANOVA, yielded the following results for N1 amplitude: An effect of Site ($F(1,1115)=551.479$, $p<.001$), Sex ($F(1,1115)=11.499$, $p<.001$), Age ($F(1,1115)=6.198$, $p=.013$), a Group X Sex X Age X Site interaction ($F(1,1115)=4.835$, $p=.028$) and an effect of Group ($F(1,1115)=11.423$, $p<.001$).

The Group x Sex x Age x Site interaction effect was further investigated by univariate analyses for both electrode sites per sub-group. The Group effect was found to be limited to young women on both electrode sites (Fz: $F(1,444)=17.08$, $p<.001$, $d=-0.42$; Pz: $F(1,444)=14.16$, $p<.001$, $d=-0.40$) and young men (only on Pz: $F(1,335)=5.56$, $p=.019$, $d=-0.29$), where MDD patients had smaller N1 amplitudes as compared to HC.

N1 latency

Repeated-measures ANOVA, yielded the following results for N1 latency: An effect of Site ($F(1,1115)=5.993$, $p=.015$), Age ($F(1,1115)=7.883$, $p=.005$) and no effect of Group ($p=.300$).

Responders vs. Non-responders ($HRSD_{17}$)

Responders did not differ from non-responders regarding sex, baseline MDD severity, baseline anxiety severity or type of treatment. However, responders were significantly younger than non-responders (M=37.42 ± 12.20 vs. M=40.51 ± 12.95; t(653)=3.05, p=.002). Since Age group was included as a between-subject factor, interactions with age group are included in the following analysis.

P3 amplitude and P3 latency

There were no effects nor interactions involving Response Type on the P3 amplitude (Group effect: p=.980) and P3 latency (Group effect: p=.296), suggesting no role of these measures in predicting antidepressant response.

N1 amplitude

Repeated-measures ANOVA, yielded the following results for N1 amplitude: An effect of Site (F(1,527)=272.271, p<.001), Sex (F(1,527)=4.747, p=.030), a Response Type X Sex interaction (F(1,527)=5.750, p=.017), a Response Type X Sex X Treatment arm interaction (F(2,527)=3.052, p=.048) and a trend effect for Response Type (p=.054). The Response Type x Sex X Treatment Arm interaction effect was further investigated by separate RM ANOVAs by sex.

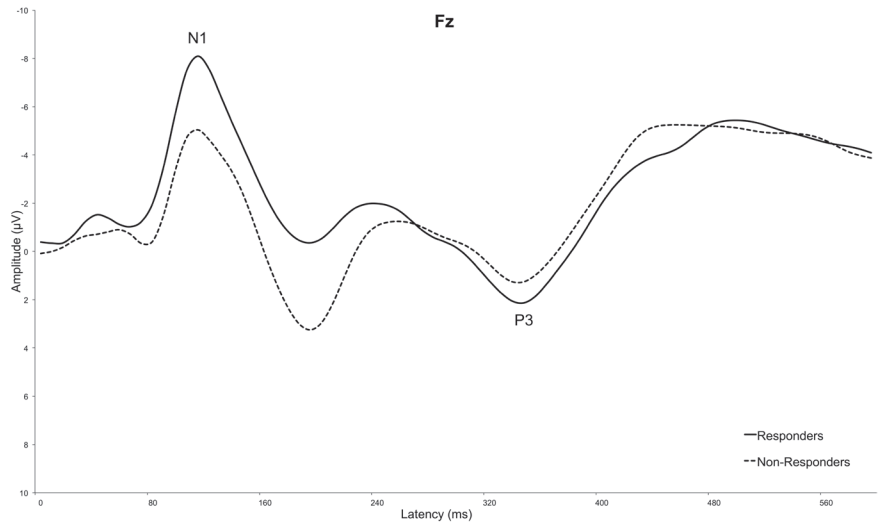


Figure 5.1 Averaged ERP measured at Fz of male responders and non-responders to venlafaxine-XR.

In males, main effects of Response Type (F1,222)=8.94, p=.003, d_{Fz}=0.41, d_{Pz}=0.24), and Site were obtained. Furthermore, there were interaction effects of Response Type X Treatment Arm (F(2,222)=5.43, p=.005) and Response Type X Site (F1,222)=4.012, p=.046) in males. Separate RM analyses per treatment arm revealed no effects of Response Type with escitalopram or sertraline. However, with venlafaxine-XR there was an effect of Response Type with large effect sizes (F(1,68)=14.45, p<.001, d_{Fz}=0.89, d_{Pz}=0.73), Site (F(1,68)=49.01, p<.001) and an interaction effect of Response Type X Site (F(1,68)=5.04, p=.028). Separating this analysis into two univariate analyses for each site demonstrated a main effect of Response Type on both sites (Fz: F(1,71)=14.02, p<.001, d=0.89; Pz: F(1,71)=11.12, p=.01, d=0.73). Male responders to venlafaxine-XR have larger N1 amplitudes than non-responders, see figure 5.1 and 5.2.

In females, a main effect of Site (F(1,305)=143.38, p<.001) and an interaction effect of Site X Age X Treatment Arm X Response Type (F(2,305)=3.75, p=.025) were obtained. In all possible subgroups (young/old using escitalopram/sertraline/venlafaxine-XR) there was no effect of Response Type on the frontal or parietal N1 amplitude in females.

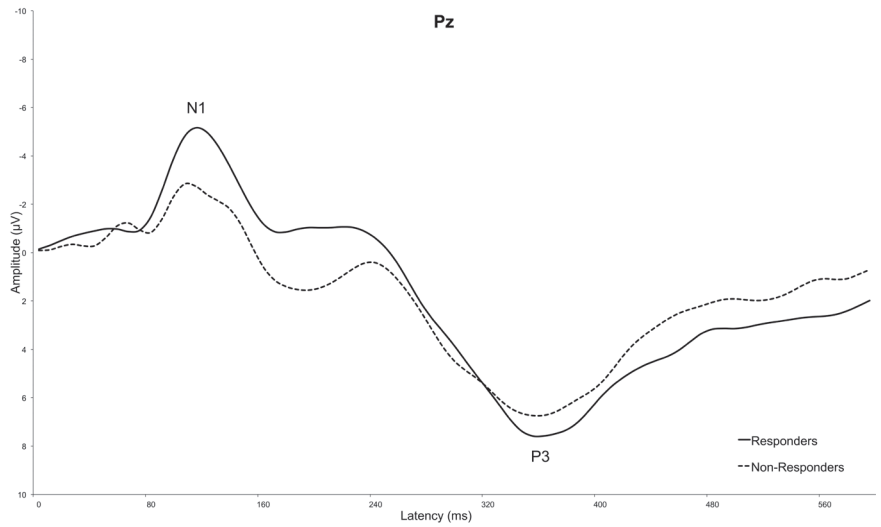


Figure 5.2 Averaged ERP measured at Pz of male responders and non-responders to venlafaxine-XR.

Within this group of males treated with venlafaxine-XR, N1 amplitude did not correlate with baseline $HRSD_{17}$ for both Fz and Pz (p>.770), however N1 amplitude at Fz did correlate significantly with $HRSD_{17}$ at week 8 (p=.043; r=.241; DF=69) and percentage improvement on $HRSD_{17}$ (p=.030; r=.258; DF=69).

Splitting the Response Type X Treatment Arm interaction into separate RM ANOVAs per treatment arm ultimately led to the same conclusions.

N1 latency

Repeated-measures ANOVA, yielded the following results for N1 latency: An effect of Site ($F(1,527)=14.981$, $p<.001$) and a Response Type X Age group X Sex X Treatment arm interaction ($F(2,527)=3.358$, $p=.036$) and no effect for Response Type ($p=.835$). The Response Type X Age group X Sex X Treatment arm interaction effect was further investigated. Of all possible sub-groups (young/old males/females using escitalopram/sertraline/venlafaxine-XR) there was no significant effect of Response Type.

Post-hoc analysis of behavioral data

In a recent study on the same iSPOT-D study, cognitively impaired patients were found to have poorer treatment outcome [263]. Therefore, post-hoc analyses including the cognitive impairment grouping factor (intact/impaired) from that study data were run. Inclusion of cognitive impairment as a factor did not alter the earlier results. In short, cognitive impairment did not refine earlier obtained results.

Post-hoc logistic regression analysis

In a subgroup of males that used venlafaxine-XR, a logistic regression analysis was performed with Response Type as dependent variable. Age (continuous), N1 amplitude (Fz) and N1 amplitude (Pz) were simultaneously entered as predictors. Age (continuous) and N1 amplitude (Pz) did not contribute significantly to the model and were removed. The logistic regression model with one predictor, N1 amplitude (Fz) predicted 68% of Response Type. There were 58% of the non-responders and 76% of the responders predicted correctly. The odds ratio for N1 amplitude (Fz) indicates that smaller values (i.e. *higher* negative amplitudes) increase the probability of being a responder, see table 5.2.

eLORETA analyses

The observed effects obtained with the peak-picking method were replicated using eLORETA analyses. In addition the eLORETA analyses provided cortical source localization of the observed P3 and N1 differences.

Table 5.2 Results of a logistic regression model with N1 amplitude at Fz as a predictor for Response Type.

			95% confidence interval for odds ratio		
	B(SE)	***p***	**Lower**	**Odds Ratio**	**Upper**
Constant	-1.493				
N1 amplitude (Fz)	-0.275 (0.087)	.002	0.640	0.759	0.901

Note: R^2=.14 (Hosmer & Lemeshow), .18 (Cox & Snell), .24 (Nagelkerke). Model $\chi^2(1)=13.95$, $p<.001$.

MDD vs HC

The eLORETA software was applied to ERP data of MDD patients and healthy controls to find time points in the EEG where they significantly differed (t>3.878, $p<.05$). This was located at 344-384 ms post-stimulus which corresponds to the P3 interval. Between-group comparisons of the averaged current density distributions for this time segment were performed using a t-test on the log-transformed current density values. MDD patients' P3s consist of less activity originating from the posterior cingulate and parahippocampal gyrus (BA31, t>3.498, $p<.05$, 2-tailed test), see figure 3.

Temporal source analysis with eLORETA localized the difference regarding the N1 between MDD patients and healthy controls at 104-120 ms post-stimulus. However, between-group comparison of averaged current density distributions within this timeframe yielded no significant differences in source space.

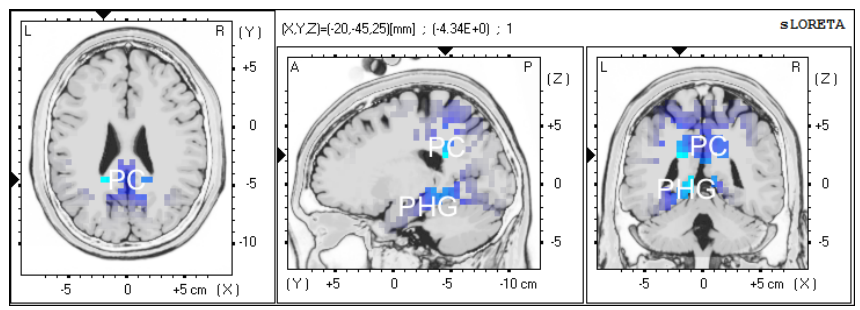


Figure 5.3 MDD patients' P3s consist of significantly less activity originating from the posterior cingulate (PC) and parahippocampal gyrus (PHG).

Male responders to venlafaxine-XR vs. non-responders

Based on the peak-picking results, the same analysis was conducted for male responders vs. non-responders to venlafaxine-XR within the N1 interval (70-120 ms). The EEGs of male responders to venlafaxine-XR differed significantly from male non-responders to venlafaxine-XR at 88-104 ms post-stimulus ($t>3.38$, $p<.05$). Between-group comparisons of the averaged current density distributions of the time segment 88-104 ms were performed using a t-test on the log-transformed current density values. Male non-responders to venlafaxine-XR had significantly less activity originating from the left insula cortex, BA13 ($t=-3.72$, $p=.048$), see figure 5.4.

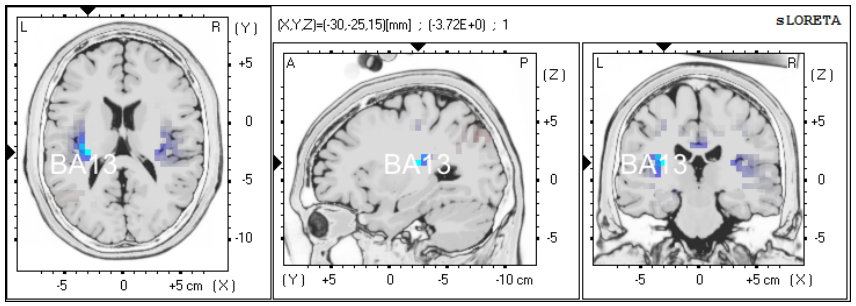


Figure 5.4 Male non-responders to venlafaxine-XR have significantly less activity originating from the left insular cortex (BA13) at 88-104 ms post-stimulus (the N1 time frame).

Discussion

In this study differences between MDD patients' and healthy controls' P3 and N1 components of the auditory oddball ERP were investigated. Furthermore, these components were investigated for their value in predicting antidepressant treatment response. For validation purposes, two different analytic methods were used and both methods confirmed the main results. Additionally, CSD analyses were used to localize cortical sources of differences in brain activity between groups.

MDD and P3

The P3 amplitude was smaller in MDD patients compared to healthy controls, with small effect sizes ($d_{Fz}=0.14$; $d_{Pz}=0.33$), and within the MDD sample P3 amplitude at Pz also correlated with MDD severity. A temporal global field power analysis confirmed this finding by significant global field power differences between the groups in a time

interval that corresponded to the P3. Using the largest sample size to date, this study confirms other findings of low P3 amplitudes in MDD patients [264-267]. In addition, we were able to localize the difference in P3 amplitude between the groups to specific cortical structures, namely the posterior cingulate and the parahippocampal gyrus (PHG). The posterior cingulate is a large posterior hub in the default mode network (DMN) that has consistently been found to be abnormal in MDD [268]. In this view, the PHG serves as a central hub within a sub-network that links the DMN to the hippocampus and thereby facilitates in memory [269]. Cognitive problems associated with MDD (attention, working memory) might be related to inefficient information processing originating from suboptimal connections between the PHG sub-network and the DMN. The P3 amplitude might be a biomarker for indexing the neural interaction between the DMN and the PHG sub-network. This is highly speculative and requires further replication, but it would impose a new interesting view on the P3.

For the N1 it was found that MDD patients had low N1 amplitude, and this was specifically found for young subjects (age <46 yrs). This is in agreement with [270], albeit other studies have not found differences in N1 amplitude [232,266,271,272]. The effect was validated by significant differences in global field power between the groups at a time point that corresponds to the time window of the N1, however, no significant differences in cortical current source densities between young MDD patients and young healthy controls at this N1 time window were found.

Treatment prediction

For antidepressant response prediction, we could not replicate earlier reports of differences in P3 amplitude between responders and non-responders to antidepressant treatment [231,232]. Although, it has to be noted that these earlier reports used paradigms that were cognitively more challenging that the standard oddball paradigm from this study. Such paradigms might be more sensitive to predicting treatment response. Furthermore, the treatments that were investigated in these studies differed from our study. However, we did find male responders to venlafaxine-XR demonstrating larger (more negative) pre-treatment N1 amplitudes than non-responders, with large effect sizes ($d_{Fz}=0.89$, $d_{Pz}=0.73$) and N1 amplitudes at Fz correlated significantly with percentage improvement on $HRSD_{17}$. Furthermore, this finding replicates our earlier study in 25 MDD patients using identical methods and the exact same oddball paradigm where this same effect was found for the whole group, including males and females [196]. The source of this difference in N1 amplitude was localized to the insular cortex.

The insula has been associated with MDD and with antidepressant treatment response in other studies. In PET studies, hypometabolism of the anterior insula, among other

regions, was associated with response to fluoxetine [273], while increased metabolism of the insula was associated to remission after treatment with escitalopram [274]. Using fMRI, increasing activation of the insula as venlafaxine treatment progressed was observed in MDD patients [275]. In another fMRI study where unmedicated MDD patients performed a task requiring attention to bodily senses, insula activity was negatively correlated with depression severity [276]. A role of the insula in MDD and treatment response seems evident, but it may come in different forms. For instance, four different functional regions of the insula were identified in a meta-analysis: activation in the anterior-ventral region was related to the social-emotional neural network; the mid-posterior region was activated in sensorimotor tasks; the central insula was activated in smell and taste; cognitive tasks activated the anterior-dorsal insula [277].

Since, the present study utilizes the oddball task, the insula region mapping to a cognitive brain network is plausible to be involved. Activation of the insula makes sense in a paradigm in which salience, attention and working memory are relevant. Indeed, the insula, together with the anterior cingulate, has been described as a hub in a salience network. Herein, it is involved in bottom-up detection of salient stimuli and facilitation of attention and working memory resources by switching between neural networks when a salient stimulus is perceived [278].

Another explanation is that the effect that we found for the N1 amplitude is partly a reflection of the known relation between the LDAEP and treatment response (for instance [198,237].

Why the prediction holds for only male responders to venlafaxine-XR needs further testing. Sex-specific and treatment-specific effects have been observed in earlier iSPOT-D reports though. For instance, it was found that, in women only, pre-treatment alpha-asymmetry predicted treatment response for escitalopram and sertraline, but not for venlafaxine-XR [170]. And in another study it was found that low frontal and low anterior cingulate cortex theta activity were associated with treatment response. Further post-hoc analysis revealed that the effect was mainly driven by one treatment, venlafaxine-XR [188]. So, in sum, sex certainly seems to have an effect in predicting treatment response by EEG measures in, and furthermore, the effect may depend on the type of medication. The size of the iSPOT-D sample allows to observe these nuances.

The study had several strengths and weaknesses. The multi-center nature of the study along with the large sample size, are strong aspects of the study. Furthermore, the use of two different analysis (peak-picking and eLORETA) methods that resulted

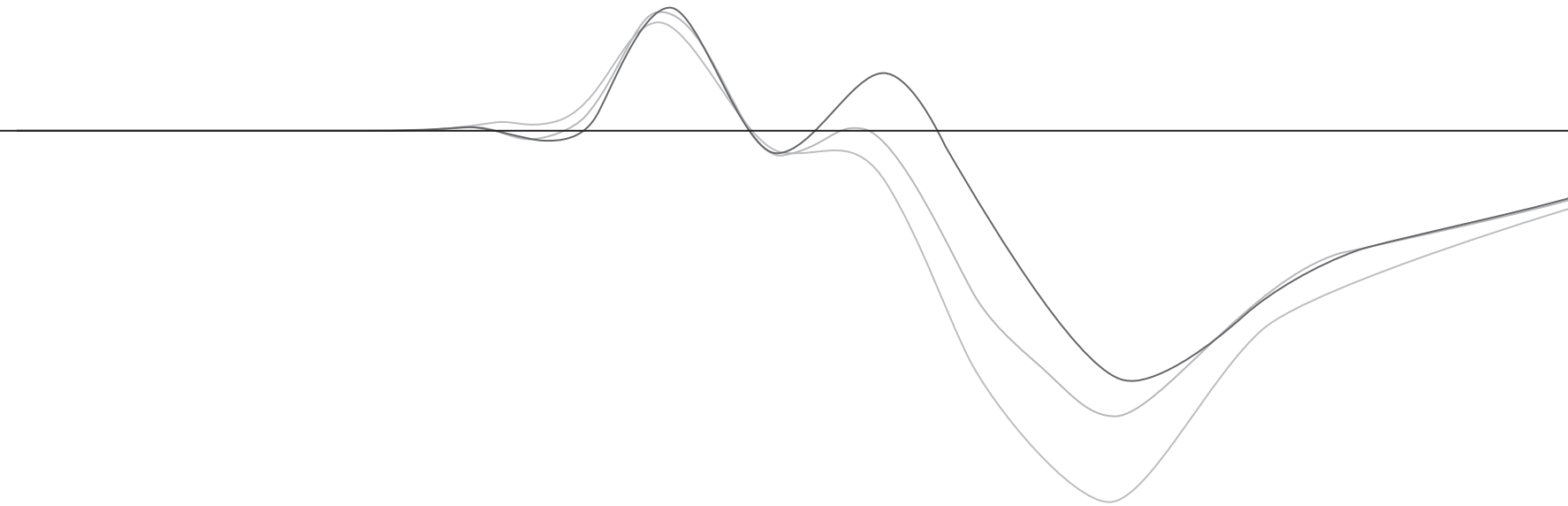
in the same findings for P3 and N1 is a strength. A weakness is the already mentioned low spatial resolution of eLORETA (as implicated by the name: Low Resolution Tomography). It localizes brain activity exactly, but it does so on an approximate head model. Therefore, observed brain regions to which group differences in current source densities were located should be interpreted with caution. The analyses were also run for Remission, but this yielded no effects of N1 or P3 latencies/amplitudes (data not shown).

In conclusion, MDD patients compared to HC have low P3 amplitude with a small ES, unlikely to be of diagnostic utility. Furthermore, the N1 component from the ERP is a potential predictor for antidepressant treatment response to venlafaxine-XR, specifically in male MDD patients and with large effect sizes. Both main results also replicate results from previous small-scale studies, and the prediction results add emphasis on sex differences and localize differences to the insula. Regarding prediction of treatment outcome the observed results have limited clinical value. However, from an integrative perspective the N1 amplitude can provide more clinical value when it will be included in a sophisticated algorithm of multiple metrics such as EEG and neuropsychology [188,263]. Future studies should investigate whether these markers, integrated with other markers, can improve prediction of treatment outcome. Furthermore, future treatment prediction studies in MDD should focus on sex as an important factor in analyses, and consider a priori stratification by sex.

6

A decomposition of the P3

In preparation:
van Dinteren, R., Hüster, R.J., Jongsma, M.L.A., Kessels R.P.C, & Arns, M.
Differences in cortical sources of the event-related P3 potential between young and old participants indicate frontal compensation.



Abstract

The event-related P3 potential as elicited in auditory signal detection tasks originates from neural activity of multiple cortical structures and presumably reflects an overlap of several cognitive processes. The fact that the P3 is affected by aging, makes it a potential metric for age-related cognitive change. The P3 in older participants is thought to encompass frontal compensatory activity in addition to task-related processes. The current study investigates this by decomposing the P3 using group independent component analysis (ICA). Independent components (IC) of young and old participants were compared in order to investigate the effects of aging. Furthermore, exact low-resolution tomography analysis (eLORETA) was used to compare current source densities between young and old participants for the P3-ICs to localize differences in cortical source activity for every IC. One of the P3-related IC's reflected a different constellation of cortical generators in older participants compared to younger participants, suggesting that this P3-IC reflects shifts in neural activations and compensatory processes with aging. This P3-IC was localized to the orbitofrontal/temporal, and the medioparietal regions. For this IC, older participants showed more frontal activation and less parietal activation. The differences in cortical sources was localized in the precentral gyrus and the parahippocampal gyrus. This finding might reflect compensatory activity recruited from these cortical sources during a signal detection task.

Introduction

The P3 (or P300) is a positive-going event-related potential recorded in the electroencephalogram that peaks at approximately 300 milliseconds after stimulus presentation [11]. The P3 that is elicited in an auditory signal detection task, i.e. the oddball paradigm [10], presumably reflects overlapping activity of several cognitive processes. It is generated by neural activity of multiple cortical structures [70].

The aging P3

The multifariousness of the P3 and the fact that it is affected by age-related changes in cognitive capacities, suggests it as a sensitive metric for cognitive performance [21,79]. In an earlier study the developmental trajectories of the P3 amplitude across the lifespan were compared between frontal and parietal electrode sites. It was demonstrated that the age-related changes were remarkably different between these locations. The parietal P3 amplitude increased in childhood to reach its peak in adolescence, then declined for the rest of the lifespan. In contrast, the frontal P3 amplitude reached its peak at a much older age, 46 years, after which it remained constant for the rest of the lifespan. It was concluded that the P3 wave reflects different mixes of cortical activation depending on the location of measurement and the age of the participant, among other probable factors. The frontal P3 amplitude might reflect compensating activity from frontal regions that becomes more prominent as people age [262].

This compensatory activity is possibly originating from the prefrontal cortex (PFC) that is related to higher order cognitive processes that are involved in regulating attention, working memory, and problem solving. These processes can be lateralized and it has been demonstrated that in older participants this lateralization reduces (this model is referred to as HAROLD, Hemispheric Asymmetry Reduction in Old Adults [279]). This phenomenon might reflect changes in cognitive strategies used by older adults and/or neuroplastic reorganization in the aging brain [63]. Similarly, the Compensation-related Utilization of Neural Circuits Hypothesis (CRUNCH) by Reuter-Lorenz and Cappell (2008) [5] posits that the aging brain, facing a decline in cognitive performance, can compensate to some degree by increasing activity in alternative connected neural networks [57,80]. The P3 potential has a relatively long duration and consists of multiple overlapping slow potentials that reflect the several cognitive processes that are devoted to the task at hand. In line with this thought, there are many neural generators identified for the P3, e.g. the PFC, the temporo-parietal junction, primary auditory cortex, and other sources [70]. The P3 might be exceptionally sensitive to pick up subtle changes in the relative contribution of the different cognitive processes that give rise to it. Therefore, it is a likely candidate for

capturing compensating activity that is increasingly allocated as people age. A simple comparison of P3 potentials between older and younger adults would be a first step. However, one has to extract and separate the various underlying sources of information that altogether give rise to the P3 potential in order to compare both age groups thoroughly.

Besides the often reported anterior shift in topography of the P3 in aging [66-69], Frodl et al. (2000) observed two subcomponents of the P3 by dipole source analysis with BESA that were differently affected by aging. The temporo-parietal P3 subcomponent was smaller in older adults whereas the frontal P3 subcomponent remained unchanged. These findings seem to explain the noted topographical change of the P3 with aging [280]. Furthermore, there are reports of differences between younger and older adults in activation of the cortical regions that contribute to the P3 wave. For instance, it has been reported that P3s of older adults consist of more activation in prefrontal [69] and temporal regions compared to younger adults [69,281].

The decomposed P3

Because the spatio-temporal overlap of activity patterns from different neural sources inherent to scalp EEG recordings, methods for the decomposition have been brought forward to recover the activity patterns of sources that are otherwise mixed and hidden in multichannel EEG data. Independent component analysis (ICA) or principal component analysis (PCA), as applied to data of single as well as multiple subjects, have become prominent tools to recover neural source patterns from various measurement modalities (e.g., Eichele, et al., 2011; Huster et al., 2015). ICA achieves this by decomposing the original recordings such that the resulting sources (usually referred to as components) exhibit maximal statistical independence; PCA, on the other hand, results in merely uncorrelated component activity patterns PCA for EEG has a somewhat longer tradition, whereas studies applying ICA for the dissociations of P3 subcomponents is still somewhat scarce. Nonetheless, multiple studies have found independent components of the ERP using ICA that are physiologically plausible. Debener et al. (2005) decomposed concatenated single-trial ERP data from a novelty oddball paradigm and found two independent component clusters that respectively accounted for the novelty P3 and P3b responses [282]. Brown et al. (2015) found a similar dissociation using PCA, and further reported a differential susceptibility of the two P3 subcomponents to drug exposure [283]. Others also reported a dissociation of the frontal and parietal P3s from the succeeding slow wave activity that often appears as prolonged activity associated with the P3 peak (e.g.,[284,285]). Makeig et al. (1999) identified three IC's in the ERP; a frontoparietal component, a longer-latency parietal component, post-motor potential and a left frontocentral potential [286].

Aim

This study aims at unraveling aging effects on cognitive processes that are involved in signal detection tasks by identifying the independent sources that contribute to the P3 wave as observed in the recorded ERP. ICs derived from the complete sample of healthy participants will be reconstructed into single-subject EEG responses for each component. The acquired single-trial EEGs will be compared between younger and older individuals in the sample. Based on our earlier work [79], it is expected that one or more P3-ICs will emerge that differ between age groups, potentially reflecting compensatory brain activation (i.e. ICs with a more anterior topography). Further P3-ICs are expected that do not differ between age-groups (i.e. ICs with a more posterior topography) and rather reflect general task-related activation. Furthermore, exact low-resolution tomography analysis (eLORETA) [255] is used to compare current source densities between younger and older participants for the P3-ICs to localize differences in cortical activity for every IC. The differences in cortical activity are expected to mainly originate from anterior regions, reflecting compensatory activation. Older participants are expected to demonstrate more activation within relevant frontal regions. Also, differences to a lesser degree are expected in posterior regions.

Methods

Participants

The sample consisted of 99 healthy participants, aged 18 to 82 years all recruited and tested at the same location (Research Institute Brainclinics, Nijmegen, The Netherlands). All participants voluntarily gave written informed consent. Local IRB approval was obtained for all clinics. These data are a subset of the data reported in previous papers [79,262,287]. Exclusion criteria were a personal or family history of psychiatric disorder, neurological disorder, brain injury, addiction or serious medical condition. Participants were required to refrain from caffeine, alcohol and nicotine for at least 2 hours prior to electroencephalographic data acquisition. The data collection was approved by the local IRB (CMO Region Arnhem Nijmegen; #2002/008).

Table 6.1. Demographics of the used sample.

	N	Mean age (SD)	Males/Females
Young	50	23 (3.5)	19 / 30
Old	49	59 (9.6)	23 / 27
Total	99	41 (19.5)	42 / 57

The sample was divided in a young and an old group with a cut-off at 46 years [262]. Sample demographics are shown in table 6.1. The percentage of male/female participants did not significantly differ for the age-groups ($X^2(1,99)=0.529$, $p=.30$). Additionally, post-hoc analysis of differences in global field power by sex by age-group revealed no significant differences in the ERPs at any frame.

Experimental paradigm

The oddball paradigm consisted of a quasi-random sequence of 280 frequent background tones (500 Hz) and 60 infrequent target tones (1000 Hz). Two targets could not appear consecutively. All stimuli (50 ms; 5 ms rise and fall time) were presented binaurally (via headphones) at a volume of 75dB SPL with an inter-stimulus interval of 1000 ms. Participants were instructed to press two buttons simultaneously (one for each index finger to counterbalance motor effects) when they heard a target tone and to ignore the background tones. Speed and accuracy of responses were both equally stressed in the instructions. Before the actual test participants were presented with a brief practice run to clarify the distinction between the two tones.

Electroencephalographic data acquisition

EEG acquisition was performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Participants were seated in a sound and light-attenuated room, controlled at an ambient temperature of 22 °C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Compumedics Quick-Cap and NuAmps amplifier; 10-20 electrode international system) with a ground at AFz. Data were offline referenced to averaged mastoids. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye (bipolar). Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was <5 kOhms for all electrodes. A continuous acquisition system was employed and the sampling rate of all channels was 500 Hz. A high cut-off filter at 100 Hz was employed prior to digitization.

ERP scoring

Conventional ERP averages were computed relative to the target and background stimuli for all EEG channels per participant using Brain Vision Analyzer (Brainproducts, Germany). Only segments with a correct target response were included in the target average. Before averaging, the EEG epochs were filtered with a high-pass IIR filter of 0.16 Hz (12dB/Oct) and a low-pass filter of 40 Hz (24 dB/Oct). Vertical and horizontal ocular correction was applied according to the Gratton algorithm [53]. The segments

ranged from -200 to 800 ms around stimulus presentation. Segments were DC detrended and baseline corrected for the pre-stimulus interval of -200 to 0 ms. Segments were considered to contain artifacts when there was a difference of 20 μV or more between two subsequent data points, when the difference between the highest and lowest voltage within a 100 ms epoch exceeded 150 μV, when the maximum or minimum amplitude respectively exceeded 100 or -100 μV within -200 to 300 ms, or when activity was measured below 0.5 μV in 50 ms. Rejected segments were not included in the calculation of the target average. Right before averaging baseline correction was done again.

Independent component extraction

To decompose the P3 into its constituent components, a group ICA on the multi-subject EEG data was set up [288,289]. Hence, after preprocessing of the EEG an adjusted number of background and target trials was randomly selected from each subject's available data. Note that the number of trials has to be the same for each subject in order to compute a group ICA. The number of background trials for further processing was restricted such that the average noise level of the condition-specific single-subject ERPs, computed as root mean squares of the baseline periods, did not differ between the background and target conditions. This procedure was implemented not to bias the group ICA towards background-related brain responses. These constraints led to a selection of 250 trials (200 background and 50 target trials) from each of the 99 participants that entered the analysis.

Group ICA extracts statistically independent components consistently expressed across participants. In short, each single-subject dataset first undergoes an individual principal component analysis (PCA), thereby extracting most relevant and orthogonal time courses. These first-level principal components then are used as variables in a second, group-level PCA, now estimating most-relevant and orthogonal principal component time courses capturing activity patterns correlated across subjects. Ultimately, these undergo ICA that finally computes the statistically independent component time courses. Importantly, this nested procedure is capable of capturing some of the topographical variability we usually see with EEG events found in each of the single-subject datasets of a multi-subject study. Please refer to [288,289], for a more detailed description of the algorithm.

A total of ten independent components were extracted using group ICA, because two procedures suggested this to correspond to the intrinsic dimensionality of the data. First, the inspection of the single-subject PCAs revealed that on average ten components explained about 95% of the variance of the scalp EEG data. Second, the ICASSO software package was used to assess the reliability and stability of the ICA

solutions of 100 runs [290]. This combination of group ICA and ICASSO was used for evaluating models with 9, 10, and 11 components, and the ten-component solution revealed sufficient reliability and stability. Correspondingly, at each level of this analysis, including single-subject PCAs, group PCA, and group ICA, ten components were extracted. The ten resulting group components are characterized by their topographies and time courses, with estimations aiming at a maximal statistical independence of the latter, and naturally lead to a characterization of the latent data structure at the group level.

To statistically analyze the differences between younger and older participants and to assess the brain sources underlying each independent component, the scalp EEG corresponding to each component was reconstructed for every single subject. Hence, for every subject the matrices estimated during the data reduction and group ICA steps were extracted and applied to the single-subject EEG. By means of these individual demixing matrices, the subject-specific component time courses and topographies were reconstructed that directly relate to the group-level components. Then, the subject-specific EEG for each component was reconstructed by multiplying each single component time course with its corresponding coefficients of the subject-specific mixing matrix. The subject-specific EEG patterns corresponding to certain independent components formed the basis for our statistical analyses. Group independent components as well as the subject-specific mixing and demixing matrices were computed using self-written MATLAB scripts that followed the procedures described in Eichele et al. (2011).

Independent component group analysis

The subject-specific EEG/ERPs were reconstructed for every independent component and then compared between younger and older subjects. The data was entered in the eLORETA software [256,257] that can analyze global field power of both groups at every time frame and produce a *t*-value for each time frame. Those time frames where the *t*-value exceeds the significance level ($p<.01$) comprise the ERP segments where the groups differ significantly from each other. These time frames were used in a spatial analysis.

The validated [291] eLORETA software yields images of current source density differences with exact localization, albeit that the spatial resolution is low. Current source density is calculated by squaring the weighed sum of scalp potentials for each voxel (A/m2). The computations are made in a realistic head model [292], using the MNI152 template [293] with standard electrode positions displayed on the scalp [294,295]. The three-dimensional solution space is restricted to cortical gray matter, as determined by the probabilistic Talairach atlas [296].

The eLORETA software solves the inverse problem under the assumption that the smoothest of all possible solutions (meaning that neighboring voxels should demonstrate maximally similar activation) is the most plausible one. This comes at the cost of low resolution. Averaged current source density values for the two age groups were log-transformed and statistically compared. The software compares the groups on a voxel basis and identifies those voxels with t values that exceed a significance level. Additionally, the software corrects for multiple testing by means of a randomization procedure.

Results

ERP time frames

In figure 6.1 the grand average ERPs for younger and older participants at midline sites are shown. Figure 6.2 shows the head maps corresponding to the 200-520 ms post-stimulus time interval. The time frames where the difference in global field power between averaged group ERPs exceeded the significance level were at 54-74 ms and 182-580 ms ($t>4.953$, $p<.01$).

Independent Components

ICs are ordered according to their contribution to the signal. The first four ICs revealed by ICA largely explained the signal. In figure 6.3 and 6.4, these ICs are displayed for the complete sample. Using eLORETA the current source densities were calculated for localization purposes. IC1 was localized to an orbitofrontal/temporal region and a medioparietal region; IC2 was localized to the precuneus/cingulate gyrus area; IC3 was localized to an area around the precuneus of the right parietal lobe, see figure 6.4.

IC group comparisons

The ICs were subjected to a time-domain analysis using t-tests to compare the two groups. For IC1, groups differed significantly from each other at 276-492 ms post-stimulus ($t>4.282$, $p<.01$). For IC2, the groups differed significantly from each other at 208-250 ms post-stimulus ($t>4.266$, $p<.01$). For IC3, the groups differed significantly from each other at 238-316 ms post-stimulus ($t>4.190$, $p<.01$).

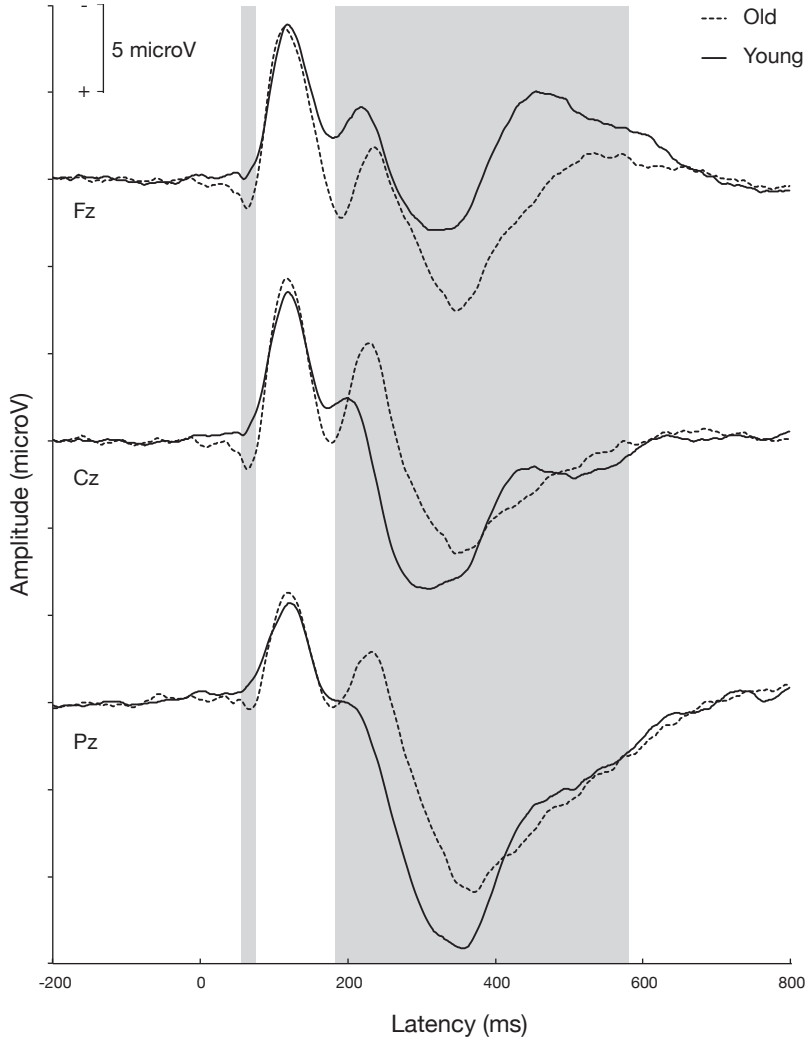


Figure 6.1 Grand average ERPs for younger and older participants at midline sites. Greyshading indicates significant group differences in global field power just after stimulus presentation and during the P3 interval ($p<.01$).

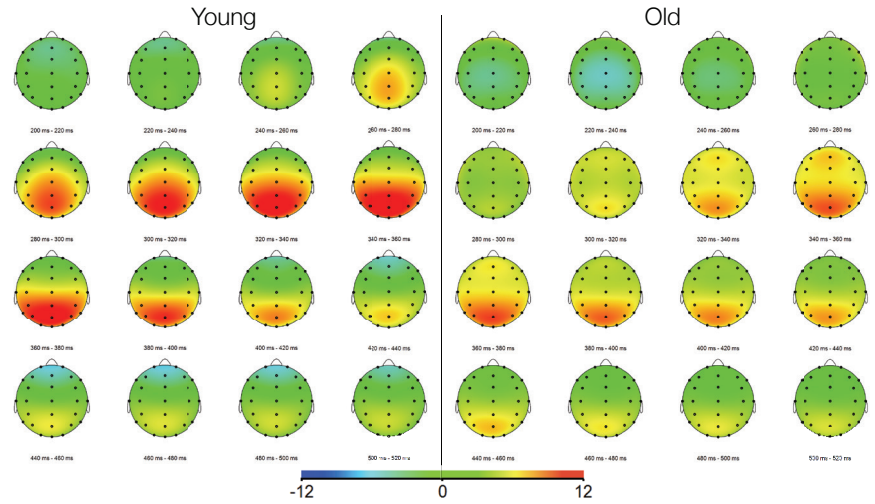


Figure 6.2 Head maps corresponding to the P3 time interval of 200-520 ms post-stimulus of younger and older participants. Notice the reduced parietal activity over parietal electrodes, the higher activity over frontal electrodes, and the delayed onset in old participants compared to young participants.

The significant time frames were segmented into 20 ms epochs in order to reduce the number of tests that were run per analysis. For every IC separately, segments were analyzed for group differences in cortical source localization by voxel-by-voxel *t*-tests. For IC1, old participants had significantly more activation in the precentral gyrus and the parahippocampal gyrus (PHG). This was true for the early part of IC1, i.e. 276-296 ms ($t>3.364$, $p<.01$), 298-316 ms ($t>3.351$, $p<.01$) and 318-338 ms ($t>3.499$, $p<.01$). In the 318-338 ms epoch there were differences in cortical activations, besides the precentral gyrus and PHG, localized to the insula, cingulate gyrus, uncus, subcallosal gyrus, inferior parietal lobule and post-central gyrus. Figure 6.5 shows the back-constructed ERPs of IC1 for both groups at Fz, Cz and Pz. It can be seen that IC1 has a higher frontal peak amplitude and a lower parietal peak amplitude in older participants. In figure 6.6 the differences between both groups in cortical activations for IC1 are demonstrated. For IC2, IC3 and IC4, there were no significant differences between younger and older participants regarding current source densities.

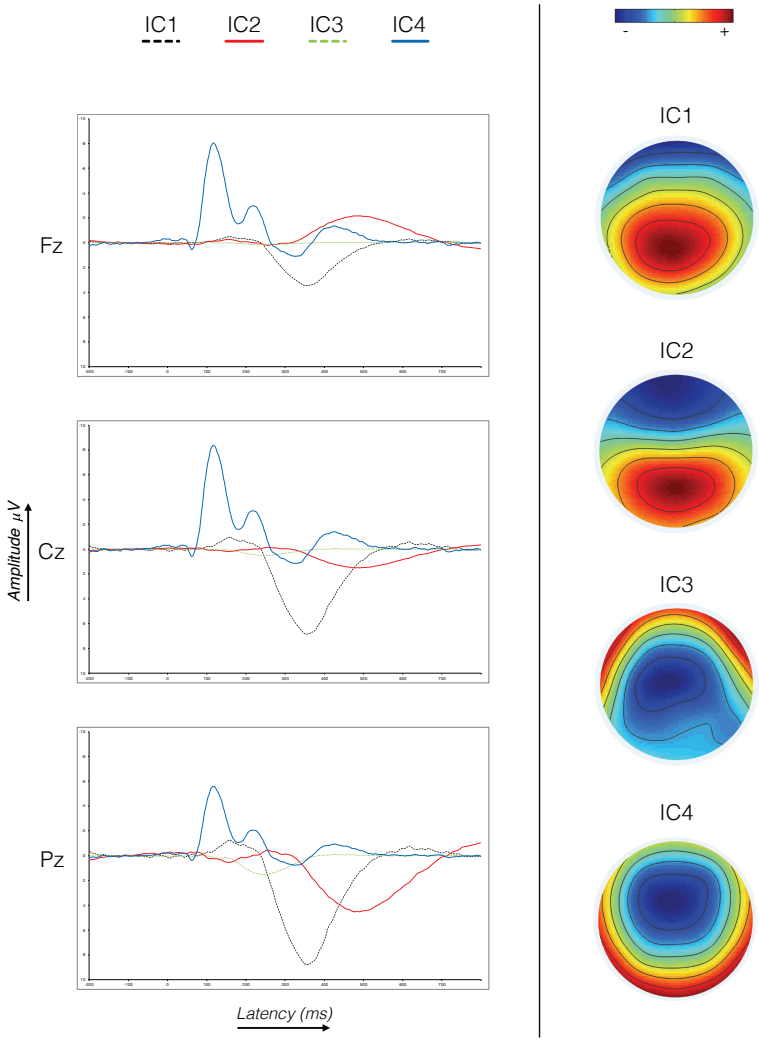


Figure 6.3 The left half of the figure shows ERPs of IC1, IC2, IC3 and IC4 at Fz, Cz and Pz. The right half of the figure shows the topographies of these four independent components.

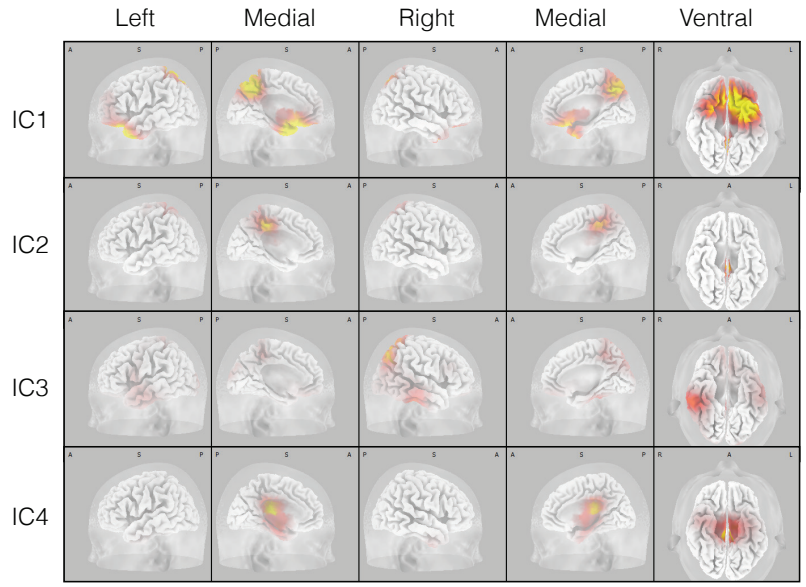


Figure 6.4 Different views of cortical sources of the four independent components (IC) that were derived from the P3 potentials of the complete sample.

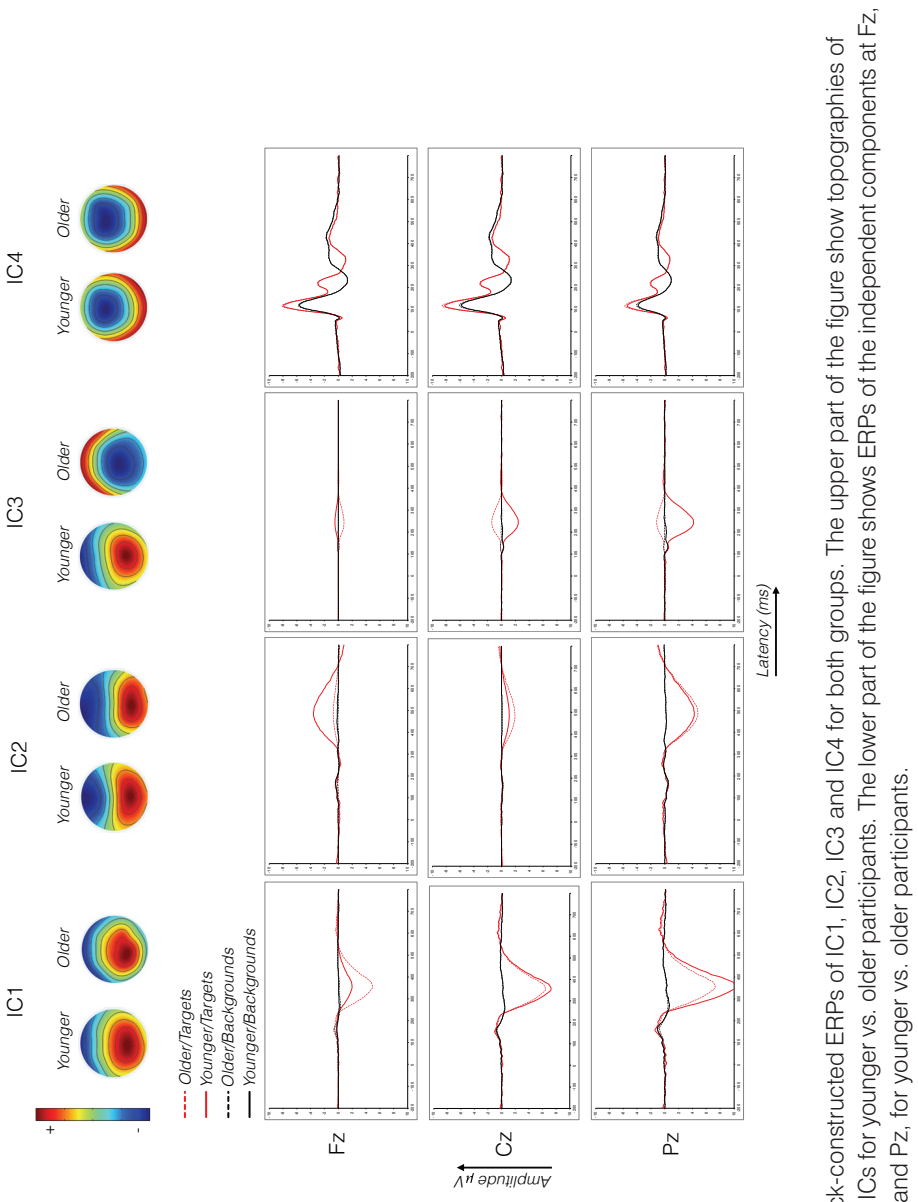


Figure 6.5 Back-constructed ERPs of IC1, IC2, IC3 and IC4 for both groups. The upper part of the figure show topographies of the ICs for younger vs. older participants. The lower part of the figure shows ERPs of the independent components at Fz, Cz and Pz, for younger vs. older participants.

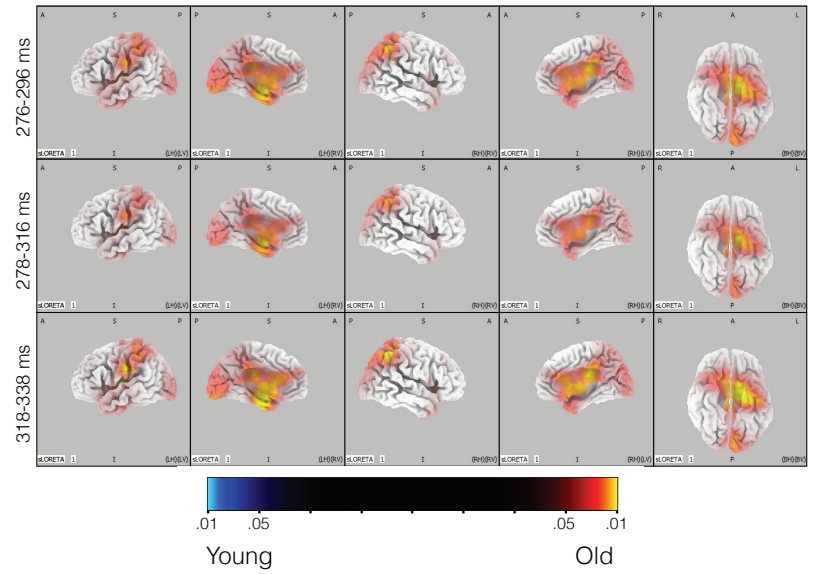


Figure 6.6 For IC1, older participants had significantly more activation than younger participants in the precentral gyrus and the parahippocampal gyrus. Difference in activation is depicted on a scale of p-values. Voxels with more activation in older participants have a red color scheme. Voxels with more activation in younger participants have a blue color scheme (there are none).

Discussion

The aim of the present study was to unravel aging effects on oddball ERPs, and especially focusing on the P3 elicited in an auditory oddball paradigm. This was attempted by identifying the independent sources that contribute to the P3 and comparing these P3-ICs between younger and older participants. Furthermore, current source densities of the P3-ICs were compared between both groups to study differences in cortical activity. It was expected that some ICs reflect compensatory activation whereas others reflect general task-related processes.

The ERPs of younger and older participants differed significantly in global field power regarding all of the ERPs components, except the N1. There were three ICs identified as sources of the P3 wave (IC1, IC2 and IC3). For the whole group, IC1 was localized

to an orbitofrontal/temporal and a medioparietal region; IC2 was localized to the precuneus/cingulate gyrus region; and IC3 was localized to a region around the right precuneus, see figure 6.4. Our results are partly in line with the results reported by Makeig et al. (1999) who also found a fronto-parietal component and a second longer-latency parietal component among two other components [286].

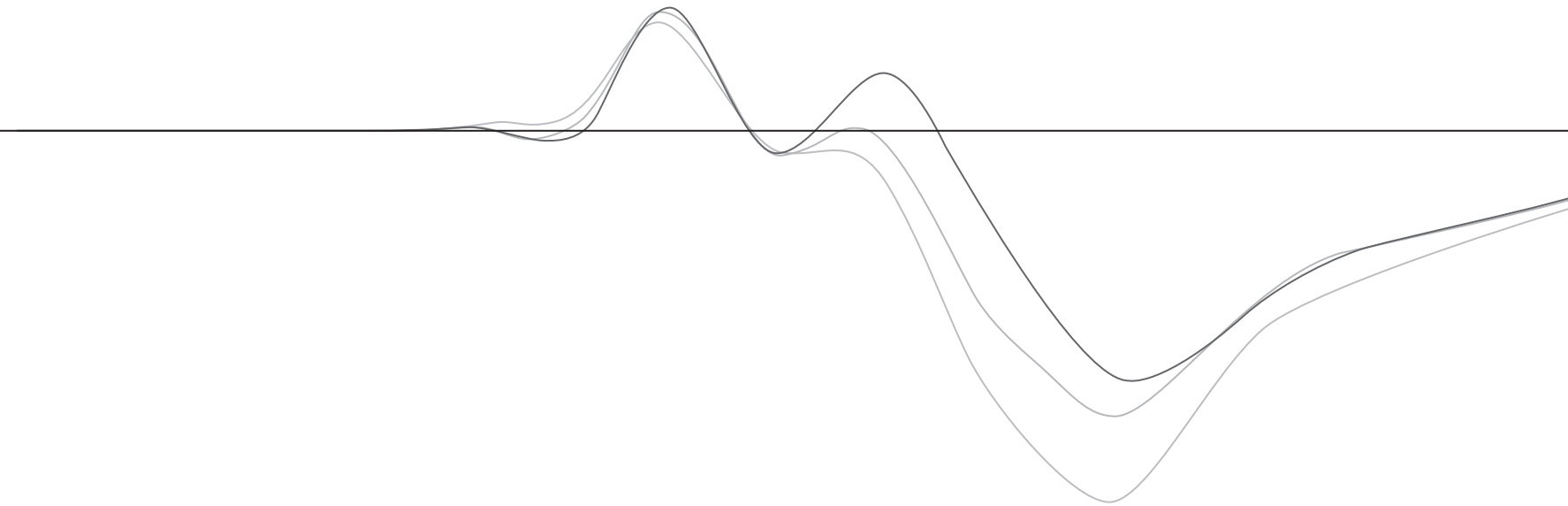
Individual ERPs were back-reconstructed based on the ICs. The three IC-ERPs of the two age groups differed significantly in the time domain. In the source domain, only IC1 showed significant differences in cortical source activity between older and younger participants. With IC1, older participants had more activation than younger participants in mainly the precentral gyrus and the parahippocampal gyrus. For the latter part of the P3 wave other cortical structures, i.e. the insula, cingulate gyrus, uncus, subcallosal gyrus, post-central gyrus and inferior parietal lobule, demonstrated significant differences in activation as well.

In sum, older participants use their available brain capacity differently from younger participants when they are performing the same oddball task. IC1 reflects a different mix of cortical sources in older participants compared to younger participants and therefore, this IC seems to be the most obvious P3-IC that partly might be reflecting compensatory processes in old age (i.e. the frontal P3 component we described earlier in Van Dinteren et al. (2014)). Differences in cortical activations were spread over multiple sources indicating there are possibly multiple neural networks involved. IC1 was localized to orbitofrontal and medial regions in the whole sample, which partly corresponds to the idea that compensatory activation comes from frontal regions.

Concluding, the P3 can be separated into three clear independent components. All of these components differ in activity between younger and older participants. Despite the significant differences found in the time-domain the effects were not present in the source localisation for all IC's. The cortical sources of only one component differ between younger and older participants. In the back-reconstructed ERPs based on this IC it was seen that it had more frontal activation and lesser parietal activation in older participants compared to younger participants. This IC possibly reflects compensatory brain activation that is increasingly recruited as people age. In favour of CRUNCH, as people age the sources of IC1 are shifting whereby frontal contributions are increasing and parietal contributions are declining.

7

Summary and discussion



Summary

The aim of the present thesis was to examine the validity of an ERP index that is suitable for quantifying and indexing cognitive aging in both healthy and clinical populations. It has been hypothesized that older participants increasingly recruit brain activity originating from frontal regions of the cortex that compensate for age-related decline in other, task-related, cognitive resources [5,64,80]. Therefore, a valid ERP index has to capture task-related cortical activity and compensatory cortical activity that is increasingly recruited with aging. A possible candidate lies within the P3 component. The ERP P3 is a wave of brain activation that is elicited in response to the presentation of an event, e.g., a stimulus during a specific task, and it is representative of cognitive processes related to the processing of such an event [14,17]. Due to its clear link to several cognitive processes involved in information processing, the P3, was the main focus of this thesis.

The P3 is an interesting potential because it reflects the amount of cognitive resources that a participant allocates in a certain cognitive task [14]. It is a large wave with a relatively long duration and therefore possibly reflects multiple cognitive processes. Because of the latter, it is especially suitable as an index for cognition in general. Additionally, it is a very robust and stable measure that has been investigated intensively during the past decades. Furthermore, the paradigms that are used to elicit the P3 are generally easy to understand and acquisition of the P3 can be done with relatively little discomfort for study participants. Both are important when the intention is to test participants in a wide age range, ranging from childhood to late adulthood.

In *chapter 2*, the literature on the P3 was reviewed and analyzed, specifically findings of the effect of age on the latency and amplitude of the P3. In this chapter a meta-analysis was performed on available data from the existing literature in order to obtain a concept of the age-related changes in the P3 across the entire lifespan. Developmental trajectories were created to observe the manner in which P3 latency and P3 amplitude change during the lifespan. Then, the models based on the literature were validated by data from a large cross-sectional dataset containing participants aged 6 to 87 years. In both datasets a logarithmic Gaussian model was the best fit for (inversed) P3 latency and amplitude development across the lifespan. In children the P3 latency shortens until a minimum is reached at the age of 22 years. After the minimum, the P3 latency gradually increases with aging for the rest of the lifespan. The P3 amplitude increases during childhood until a maximum is reached at 16 years of age. For the remaining part of the lifespan the P3 amplitude decreases gradually. Concluding, the P3 follows a specific developmental trajectory across the

lifespan that is reflecting brain maturation and degeneration in respectively younger and older participants. Although the combined amplitude and latency describe the same P3 component, these two dependent variables demonstrate different developmental trajectories. This suggests that they reflect different aspects of age-related change. The P3 latency is possibly an index for brain efficiency and information processing speed whereas the P3 amplitude is understood to index allocated cognitive resources in a certain cognitive task.

Chapter 3 investigated whether the aging-related development of the P3 differed between frontal and posterior brain regions in the same cross-sectional dataset that was used in the preceding chapter. The preceding chapter already appreciated the role of compensatory brain activation that is increasingly recruited with aging. The best-fit models of age-related change in P3 latency and P3 amplitude were fitted again, but this time separately for the frontal and parietal cortex. When these models were compared, it was clear that P3 latency developed similarly across frontal and parietal positions. However, different best-fit models of age-related change in P3 amplitudes for both sites were observed. The P3 amplitude measured at a frontal site developed slower, reaching its peak at a later age (46 years) and then remained approximately constant for the remainder of the lifespan. A lifespan trajectory of combined frontal and parietal P3 amplitudes was found to closely resemble the lifespan trajectory of behavioral performance. The results were interpreted within the concepts of the compensation-related utilization of neural circuits hypothesis (CRUNCH) by Reuter-Lorenz and Cappell (2008). This hypothesis states that to compensate for declining neural resources, older participants recruit additional neural resources of prefrontal origin and consequently preserve a stable behavioral performance. Indeed, it was observed that behavioral performance on the task in this study did not decline with age in adults. Following the results of chapters 2 and 3 the P3 across the scalp appears to be an excellent index for (compensated) cognitive resource allocation in healthy participants. It will be interesting how the P3 might be of value as an index for cognitive performance in clinical samples.

In *chapter 4* the role of EEG and ERPs in predicting treatment outcome was reviewed. Based on prior ERP literature we hypothesized a potential role of the P3 in predicting treatment outcome. There have been observations of relations between P3 (latency and amplitude) and treatment prediction, but the results are ambiguous [297]. Although the main focus was on the P3, the N1 was also investigated. The N1 is interesting because of its relation to the loudness dependence auditory evoked potential (LDAEP), which is a derivative of the N1/P2 amplitude difference and how it changes with increasing stimulus intensity [236,237]. The LDAEP and the N1 have been linked to antidepressant treatment response [196,198,237-239].

Chapter 5 investigated the use of the P3 ERP component in treatment prediction further. This was done within the international Study to Predict Optimized Treatment in Depression (SPOT-D) project that provided 1008 MDD patients. The iSPOT-D study is a large multicenter randomized clinical trial including MDD patients that were randomized to one of three frequently prescribed antidepressants (Sertraline, scitalopram, Venlafaxine-XR). The P3 amplitude was found to be reduced in MDD patients compared to controls. Using source localization techniques this difference between the groups in neural activity could be localized to specific cortical regions, that is, the posterior cingulate and the parahippocampal gyrus. Unfortunately, the P3 was not able to dissociate those who responded well to antidepressant treatment from those that did not respond. However, the N1 amplitude could indeed dissociate responders from non-responders to treatment although this effect was limited to a sub-group of males that were randomized to the SNRI Venlafaxine-XR. The N1 amplitude might therefore be of value when included in a sophisticated algorithm of multiple additional metrics, such as EEG/ERP, genetics, neuropsychological measures and demographic variables.

That the P3 could not dissociate responders from non-responders to treatment was disappointing. The lack of predictive power might have been related to the fact that the P3 encompasses several cognitive processes and is therefore not specific enough. So, in *chapter* 6, the P3 signal was decomposed into separate independent components using independent component analysis to capture a more accurate and localizable reflection of frontal compensatory brain activation. The decomposed P3s were compared between young and old participants and localized to a cortical region. It was observed that one of the independent components reflected a different mix of cortical activity in old and young participants. This suggests that this specific independent component reflects shifts in neural activations related to increasing frontal compensatory activation in older participants. Using source localization, the cortical activity of this independent component was determined to be originating from the orbitofrontal/temporal region and the medial-parietal region of the cortex. The difference in cortical activation of this independent component between younger and older participants was localized to the precentral gyrus and the parahippocampal gyrus.

Discussion and Conclusion

Although ideally one would use a longitudinal sample to investigate effects of aging, this would require decades of research time if one wants to cover the whole adult lifespan, which is not feasible for many research questions. The next best thing is a

cross-sectional dataset. The large collection of data that was gathered from the existing literature and the size of the cross-sectional dataset that was used for the empirical studies are two strong feats in this thesis. The fact that similar results are yielded from both samples is another strength. Additionally, there are some important benefits that come with the classic oddball paradigm that was used in the experiments. First, it is a paradigm that is easy to understand and can be utilized with people of all ages, from the very young to the oldest of the old. Second, it is a reliable and valid paradigm that has proven itself repeatedly over the past decades in many experiments.

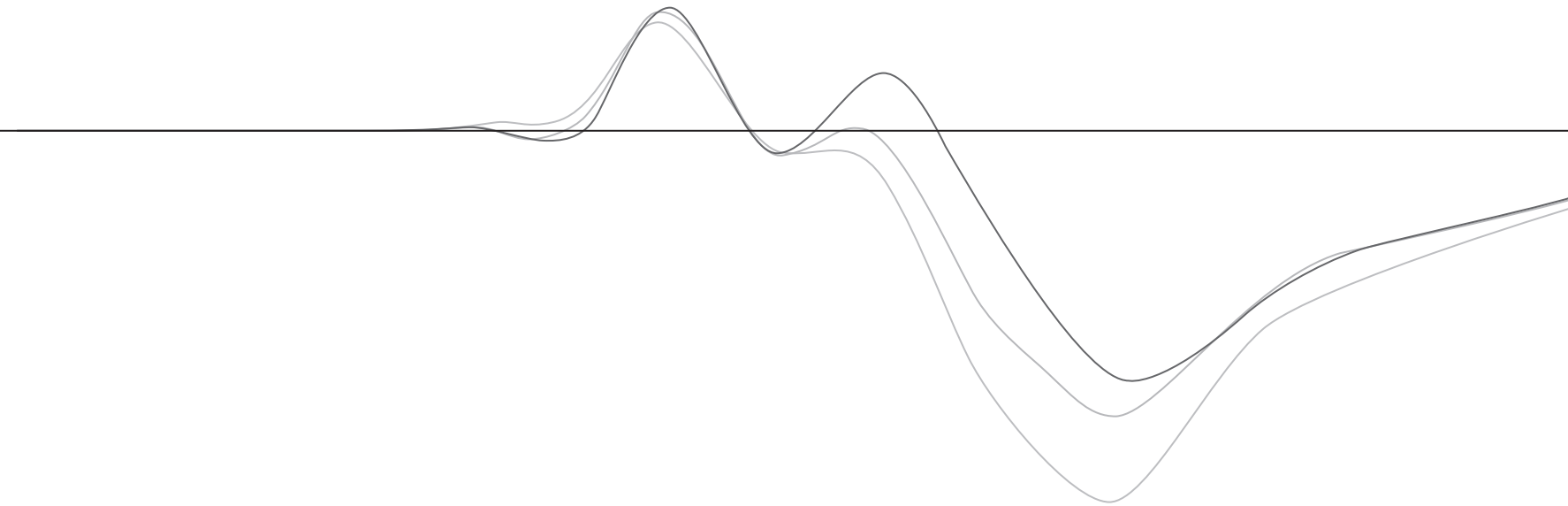
However, the strengths described in the above paragraph at the same time introduce limitations to the study. All the participants performed in the standard oddball paradigm only. For more intensive research of compensatory brain activity, the standard oddball paradigm might not be challenging enough in every age group. A paradigm that allows for manipulation of the task load would be a valuable addition in future research. Another limitation is that the results that were observed are not applicable to individual subjects because the P3 varies highly inter-individually. In other words, the P3 can be a valuable index for compensated cognitive functioning, but one cannot make a reliable assessment of someone's cognitive performance based on solely his or her P3 at a certain time. The aim of the chapter 6 was to acquire more insight in the independent components that contribute to the P3 and to define an independent component that reflects compensatory processes in older age. Although, there was such an independent component observed, it did not reflect purely the frontal compensatory processes, but the general parietal processes as well. In that sense, the analytical method was unsuccessful.

In all, the results of the studies of this thesis clearly show that the P3 amplitude and latency change across age. Generally, P3 latency and amplitude optimize in childhood until adolescence. Then, a peak is reached and they decline for the rest of the lifespan. Remarkably, the peaks of the developmental trajectories of the P3 latency and P3 amplitude do not align. Both are measures that describe the same ERP component, but apparently do reflect different aspects of brain development or brain maturation. The P3 latency, expressing the temporal aspects of the P3, presumably reflects brain efficiency that is affected by neural speed of organization and utilization of cortical regions. The P3 amplitude, expressing the magnitude of the P3, presumably reflects neural capacity that is allocated in a certain cognitive task. However, it should be stressed that averaged P3 amplitudes are affected by variability in P3 latencies. For example, when single-trial ERP peaks show large variability in latencies, the P3 amplitude of the averaged ERP will be decreased as a result.

Although a decline in P3 amplitude in older participants was observed at a parietal region, no obvious decline in behavioral performance was noticeable. Possibly, this is due to older participants recruiting other cortical regions and thus being able to successfully compensate for the loss in neural capacity. In this view, compensatory activation is proposed to be originating from frontal cortical regions. Indeed, when the P3 amplitude trajectories across the lifespan measured at a frontal and a parietal site were compared, clear differences became apparent. Additionally, a trajectory of combined frontal and parietal P3 amplitudes aligned perfectly with behavioral performance. Furthermore, it was observed that the underlying sources that compose the P3 differed between younger and older participants. Older participants had increased contributions originating from the precentral gyrus and the parahippocampal gyrus (PHG). The PHG is an interesting structure that was already found to be of importance in differentiating MDD patients from healthy participants. The PHG might serve as an important hub facilitating in information processing. The P3 might reflect changes in this structure's function that lead to inefficient information processing in aging or clinical disorders.

To conclude, older participants use their available brain capacity differently from younger participants when performing the same behavioral task. By doing so, they are able to achieve a similar behavioral performance. There is a limitation to this compensatory process, however. As cognitive tasks get more complex, older participants might reach their capacity limits earlier than younger participants. This may not occur that often in many day-to-day tasks, making frontal compensation an effective and successful strategy in everyday life. Therefore, future studies should investigate the level of effectiveness of compensatory strategies by using increasingly complex experimental cognitive tasks. Also, inclusion of other imaging methods to measure recruited brain activity is valuable. For example, a (f)MRI can be combined with EEG or MEG to provide more spatial resolution and at the same time maintain a high temporal resolution. Other research directions may involve neuromodulation techniques such as transcranial direct current stimulation (tDCS) or transcranial magnetic stimulation (TMS) that can directly manipulate brain regions directly during the execution of a cognitive task in order to investigate the effects on task performance between younger and older participants. Finally, in a more qualitative approach, it would be interesting to investigate whether the age-related change in cortical activations is indicative of age-related change in cognitive strategies.

Appendix 1



APPENDIX 1

Study	N	Percentage men	Mean age (years)	Age range (years)	Continent	Target probability (%)	Eyes open / closed	Reponse type	Total number of stimuli	Stimulus duration (ms)	Stimulus loudness (dB SPL)
298*	55	49	49.8	15-89	Australia	15	-	count	400	50	80
299*	12	-	56.6	28-81	North America	20	open	press	300	50	72
300	32	88	20.6	18-24	Asia	20	-	count	-	90	75
301*	63	43	42.9	22-78	Asia	15	-	press	-	-	75
302	21	-	34.0	22-55	Europe	20	-	press	-	40	64
303*	154	-	9.7	4-15	Asia	20	closed	press	160	120	60
304	20	-	64.1	43-80	Europe	33	-	count	200	20	-
305	20	50	39.3	25-59	Asia	25	closed	press	160	100	75
306	16	69	31.9	-	Europe	20	closed	count	150	40	97
30	28	64	31.2	-	Europe	15	-	count	-	40	75
307	29	100	11.5	-	North America	10	closed	count	264	50	64.5
308	78	40	28.6	-	Asia	20	-	press	-	-	-
309	19	84	28.6	-	Europe	20	closed	press	500	40	80
310*	72	50	10.1	6-8	Europe	20	closed	press	-	50	60
311*	18	-	29.3	-	Europe	20	closed	count	150	40	97
312	36	61	27.5	-	Europe	15	-	count	130	50	-
313	41	100	24.5	20-33	North America	12.5	open	press	-	60	60
314	21	62	28.9	-	Europe	20	-	press	-	-	-
315	23	65	30.6	-	North America	20	open	press	-	50	60
316	15	73	43.7	28-70	North America	15	-	press	600	40	-
317	29	62	66.7	46-79	Europe	20	open	press	-	100	-
318	19	37	26.8	-	Europe	20	-	press	200	100	65
319	40	73	36.7	20-54	Australia	15	open	press	287	50	60
320	39	46	68.5	60-77	Asia	20	-	press	-	50	70
321	28	100	29.0	18-45	Europe	20	open	press	-	120	-
322	55	52	60.5	40-79	Asia	20	-	count	400	50	-
323	15	100	27.0	-	Asia	20	open	press	-	120	-
324*	32	56	31.0	10-68	Europe	20	closed	count	100	120	60
325*	72	50	57.6	22-95	Europe	20	-	count	240	80	-
326	18	67	15.5	-	Asia	20	closed	press	200	200	90
327	17	35	37.9	-	Australia	15	open	press	287	50	60
328	22	45	41.4	-	Europe	15	-	press	-	100	-
329*	80	68	28.2	14-51	Australia	15	open	press	287	50	60

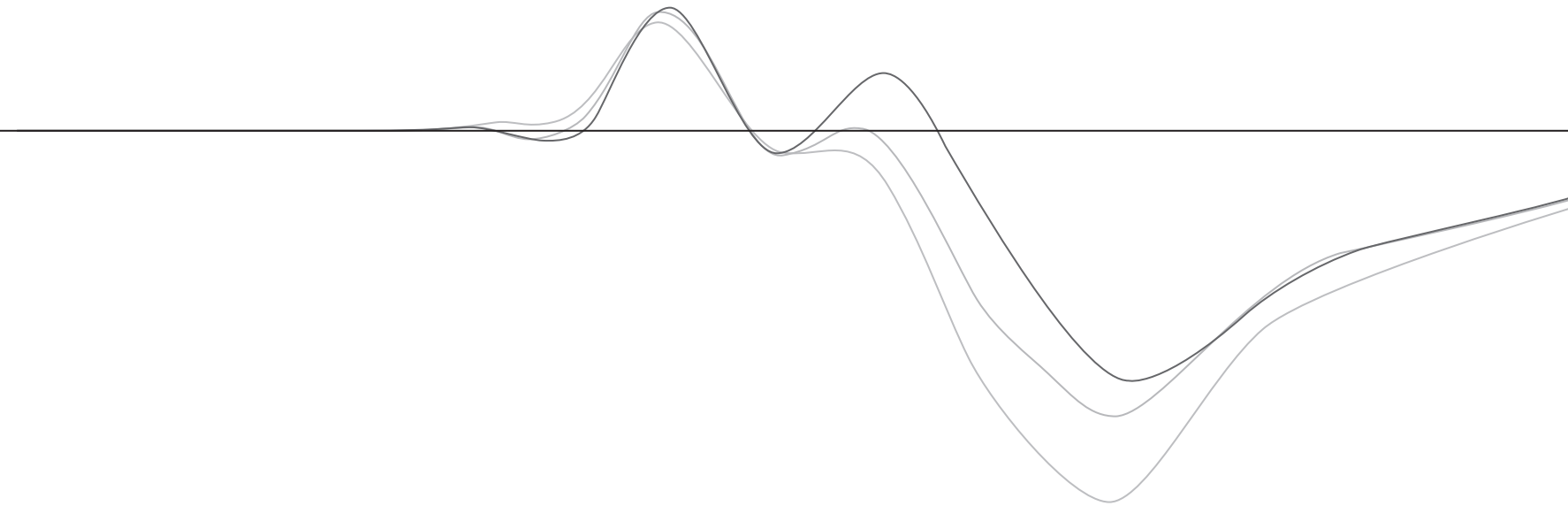
APPENDIX 1

Study	N	Percentage men	Mean age (years)	Age range (years)	Continent	Target probability (%)	Eyes open / closed	Reponse type	Total number of stimuli	Stimulus duration (ms)	Stimulus loudness (dB SPL)
330*	59	47	56.1	22-92	Europe	20	-	count	-	80	80
331	33	45	27.8	-	Asia	15	-	press	270	50	75
332	25	64	28.9	-	Asia	15	-	count	400	200	-
333	36	58	25.8	20-37	Asia	20	-	press	-	100	70
31	18	56	26.0	22-34	Europe	20	-	count	240	80	80
334	28	79	24.0	18-47	North America	15	-	press	200	50	97
335	23	100	9.2	7-12	Europe	20	closed	count	-	-	-
336	16	56	11.9	10-13	Europe	20	open	count	-	100	-
337	20	50	25.0	19-31	Europe	20	-	press	400	60	-
338*	16	50	26.5	20-34	Europe	20	-	press	-	-	-
339	21	52	7.0	-	Europe	20	closed	press	238	400	-
340	15	53	34.7	23-55	Europe	20	-	count	-	50	-
341	53	62	73.6	-	Europe	20	closed	press	100	100	80
342*	40	45	64.6	39-89	North America	15	-	count	-	50	80
343	16	81	67.6	-	Europe	20	-	count	-	100	75
344	40	55	25.7	20-36	Asia	20	closed	press	-	100	70
345*	192	-	46.0	20-65	Europe	25	closed	count	512	50	70
49	35	69	29.3	-	Europe	14	-	press	-	50	-
346	15	100	21.3	16-25	Asia	20	closed	press	-	50	-
347	36	42	17.2	14-21	Europe	15	open	press	300	50	-
348	42	48	40.2	18-60	Europe	20	-	press	400	20	-
349	57	42	24.5	19-35	Europe	20	open	press	400	-	-
350	26	0	30.9	-	Asia	20	closed	press	-	100	-
351*	68	50	50.0	20-80	Europe	20	-	press	400	50	110
352	15	47	34.3	-	North America	15	closed	count	385	-	110
353	16	44	74.0	60-92	Europe	20	closed	press	200	80	75
354	28	82	21.7	17-27	Europe	20	-	press	300	100	75
355	40	60	25.7	18-39	Europe	10	closed	press	384	500	-
356	20	60	69.5		Europe	15	-	press	213	100	-
357	32	38	23.4	19-34	Europe	20	-	count	-	50	65
358	38	100	49.0	25-58	Asia	20	closed	count	250	120	-
38*	57	47	13.0	7-18	Asia	20	closed	count	100	50	-
77	17	53	23.9	-	Asia	25	open	press	-	70	-

APPENDIX 1

Study	N	Percentage men	Mean age (years)	Age range (years)	Continent	Target probability (%)	Eyes open / closed	Reponse type	Total number of stimuli	Stimulus duration (ms)	Stimulus loudness (dB SPL)
359	25	48	32.9	17-52	Asia	20	-	press	250	50	80
360	110	33	11.3	10.2-12.9	North America	20	open	press	400	50	-
361	17	71	57.2	27-81	Europe	-	open	count	240	400	-
362	40	38	25.6	18-45	Asia	16.7	-	count	-	50	-
363	17	65	20.1	-	Europe	20	open	unknown / subjects choice	300	100	-
364	23	57	10.3	-	Europe	20	closed	count	-	-	-
365	33	61	32.4	-	Asia	15	-	press	400	100	85
366	27	59	51.1	20-72	Europe	20	-	press	-	60	-
367	51	78	9.0	6-13	Asia	20	closed	unknown / subjects choice	200	-	-

Appendix 2



The model equations that were used are listed below. Descriptions of the models can be found on the Graphpad Prism website (www.graphpad.com/guides/prism/6/curve-fitting).

Log Gaussian model

Center is the *x* value of the peak of the distribution; *Width* expresses the width of the distribution in the same units as *x*. *Height* is the peak of the distribution expressed in *y* units.

$$y = Height * \exp(-0.5 * \left(\frac{\ln\left(\frac{x}{Center}\right)}{Width}\right)^2)$$

Exponential growth model

The *y* value when *x* is zero defines *y(0)*. The rate constant, *k*, is expressed in reciprocal of *x* values.

$$y = y(0) * \exp(k * x)$$

Exponential decay model

The *y* value when *x* is zero defines *y(0)*. The rate constant, *k*, is expressed in reciprocal of *x* values. *Plateau* is the *y* value when *x* is infinite.

$$y = (y(0) - Plateau) * \exp(-K * x) + Plateau$$

Constrained linear model

$$y = 0$$

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Nederlandse samenvatting

Van kind tot adolescent, van volwassene tot oudere; gedurende de gehele levensloop ondergaat het menselijk lichaam vele veranderingen. Dat geldt niet in de minste plaats voor het brein. In ons leven worden de mogelijkheden die ons brein ons biedt continu geoptimaliseerd. Zo heeft het brein van een jong kind bijvoorbeeld veel neuronen en synaptische verbindingen. (De synaps is de contactplaats waar informatie-overdracht van de ene naar de andere zenuwcel plaatsvindt.) Op weg naar volwassenheid wordt een groot deel van de overtollige neuronen en synaptische verbindingen 'weggesnoeid' (de Engelse benaming is *synaptic pruning*). De synaptische verbindingen die nauwelijks worden gebruikt zijn degene die worden weggesnoeid. De verbindingen die veel worden gebruikt worden daarentegen steeds sterker. Kortom, het brein leert. Met veroudering wordt er een nieuwe uitdaging aan het brein gesteld. Cognitieve vaardigheden zoals geheugen, informatieverwerking, aandacht en concentratie, gaan achteruit naarmate we ouder worden, een proces dat al rond het 30e levensjaar begint. De verminderde cognitieve vermogens bij oudere volwassenen gaan gepaard met fysieke veranderingen in het brein. Zo neemt bijvoorbeeld de hoeveelheid zenuwcellen in de frontale en temporale hersenkwabben af met veroudering. Toch merken de ouderen zelf in het dagelijks leven geen of slechts een geringe achteruitgang in hun cognitieve functioneren. Het gaat hier namelijk om een subtiele afname in cognitieve vermogens die alleen zichtbaar is tijdens experimentele taken. Op andere vaardigheden, zoals woordenschat, presteren ouderen juist beter dan jonge volwassenen. Woordenschat is namelijk een vaardigheid waarbij ervaring een belangrijkere rol speelt dan bijvoorbeeld informatieverwerkingssnelheid. Die levens-ervaring speelt wellicht ook een rol in hoe het brein omgaat met de cognitieve uitdagingen die we veelvuldig aan moeten gaan. Het verouderende brein compenseert mogelijk voor fysieke tekortkomingen om zodoende een eindresultaat te behalen dat vergelijkbaar is met dat van een jonger brein. Reuter-Lorenz en Cappell publiceerden in 2008 een wetenschappelijk artikel waarin een model werd gepostuleerd met het acroniem CRUNCH. Deze vijf letters staan voor 'compensation-related utilization of neural circuits hypothesis' en dit model houdt in dat wanneer mensen een moeilijke taak moeten uitvoeren, zij compensatoire hersenactiviteit kunnen inzetten om zodoende alsnog een goede gedragsmatige prestatie te behalen. Deze additionele activiteit zou bij ouderen voornamelijk vanuit de prefrontale regionen van het brein afkomstig zijn.

Het bestuderen van compensatoire netwerken in het brein - en hoe deze worden ingezet op individueel niveau door patiënten met (neuro)psychologische aandoeningen - kan mogelijk leiden tot nieuwe inzichten voor behandelingen en preventie van degeneratieve aandoeningen zoals dementie. Een dergelijke gepersonaliseerde behandelwijze lijkt de toekomst te hebben voor meerdere stoornissen. Het verkrijgen van inzicht in hoe neurale netwerken worden ingezet in patiënten kan belangrijke

informatie over de werking van het brein opleveren. Het is echter essentieel om eerst te begrijpen hoe neurale (compensatoire) netwerken een rol spelen in het brein van gezonde volwassenen. Om dit doel te behalen is het van belang dat niet alleen de prestaties op cognitieve taken worden onderzocht maar dat eveneens de processen die in het brein plaatsvinden gedurende die taak in kaart worden gebracht. Een methode om hersenactiviteit in kaart te brengen is het elektro-encefalogram, beter bekend onder het acroniem EEG, of hersenfilmpje. De eerste EEG-metingen bij mensen werden in het begin van de 20e eeuw door Hans Berger beschreven. Deze techniek maakt het mogelijk om hersenactiviteit te meten middels sensoren die op de buitenkant van het hoofd worden geplaatst en die de elektrische activiteit van het brein registreren.

Wanneer er tijdens een experimentele taak een stimulus wordt aangeboden, bijvoorbeeld een pieptoon of een object op een beeldscherm waarop de proefpersoon dient te reageren, vinden er verschillende processen plaats in het brein. De hersenactiviteit die optreedt na het aanbieden van de stimulus is een representatie van de cognitieve processen die worden ingezet om de gevraagde taak uit te voeren. Het stukje taak-gerelateerde hersenactiviteit dat we zien in het EEG wordt een *event-related potential* of ERP genoemd. Kortgezegd is de ERP niets anders dan de taak-gerelateerde hersenactiviteit. De ERP kan gevisualiseerd worden als een golvende lijn bestaande uit een aantal pieken en dalen zoals te zien is in Figuur 1.1 in het eerste hoofdstuk. Wetenschappers hebben de pieken en dalen van het ERP genoemd naar hun polariteit, positief of negatief, en de volgorde waarin ze optreden. De derde positieve piek, de P3, is over het algemeen de grootste en meest opvallende piek in de ERP. Bij jonge, gezonde volwassenen treedt deze piek zo'n 300 milliseconden nadat een stimulus is aangeboden op. Daarom wordt de P3 ook vaak aangeduid als de P300. De P3 is al onderwerp van onderzoek sinds het begin van de jaren '60.

Een klassieke taak om deze P3 op te wekken is het zogenaamde 'oddball' paradigma. In deze taak krijgen proefpersonen een reeks van tonen te horen die bijna allemaal dezelfde toonhoogte hebben, met af en toe een toon ertussen die een andere toonhoogte heeft. Aan proefpersonen wordt gevraagd om de afwijkende toon – de vreemde eend in de bijt, ofwel de 'oddball' - te ontdekken. Er wordt aan de proefpersonen gevraagd om zodra zij deze afwijkende toon horen te reageren, bijvoorbeeld door een knop in te drukken. De ERP na zo'n afwijkende toon bevat een duidelijke P3 golf. Die P3 golf ontbreekt in de ERP's die gerelateerd zijn aan de reguliere tonen in de taak. Een schematische weergave van de 'oddball' taak is weergegeven in Figuur 1.2 in hoofdstuk 1.
Eén van de meest gangbare manieren om de P3 te kwantificeren is door het bepalen van de latentietijd (in milliseconde) en de amplitude (in microvolt) van deze golf in de

ERP. Hiervoor wordt eerst bepaald op welk punt de P3 maximaal is. Vervolgens wordt de latentietijd bepaald door te meten hoeveel milliseconden het duurt na het aanbieden van een stimulus, zoals een toon in het 'oddball' paradigma, tot de P3 het maximum heeft bereikt. De amplitude wordt bepaald door het verschil in microvolt tussen dit maximum en het potentiaalniveau voordat de stimulus wordt aangeboden te bepalen. In Figuur 1.1 in hoofdstuk 1 zijn de latentietijd en amplitude ter verduidelijking weergegeven.

Nu kan de P3 worden beïnvloed door bepaalde aspecten van de experimentele taak te veranderen. Bijvoorbeeld, door de afwijkende tonen minder frequent aan te bieden vallen deze meer op. Dit leidt tot een hogere P3 amplitude. Het feit dat de P3 kan worden opgewekt door middel van onder andere de bovengenoemde experimentele taak is reden om aan te nemen dat de P3 bepaalde denkprocessen reflecteert. Een invloedrijke theorie van Emanuel Donchin beschrijft dat proefpersonen een mentale representatie creëren van hun omgeving. De omgeving is in het geval van de 'oddball' taak een serie van tonen van een gelijke toonhoogte. Wanneer een toon met een afwijkende toonhoogte wordt gepresenteerd, is die mentale representatie niet langer correct en dient te worden geüpdatet. Binnen deze theorie zou de P3 een reflectie zijn van dit update-proces. Hierdoor is de P3 een geschikte maat om subtiele veranderingen in het cognitief functioneren in kaart te kunnen brengen. Op deze wijze hebben wij het cognitief functioneren gedurende de gehele levensloop in kaart gebracht. Daarnaast heeft het 'oddball' paradigma als voordeel dat het een eenvoudige taak is die uit te voeren is door zowel jonge kinderen, volwassenen en ouderen.

In dit proefstuk hebben we allereerst een literatuuronderzoek uitgevoerd (hoofdstuk 2) waarin het effect van leeftijd op de P3 latentietijd en amplitude wordt onderzocht. Hiervoor zijn gegevens uit reeds eerder gepubliceerde onderzoeken verzameld en samengebracht om te analyseren. Het betreft hier uitsluitend gegevens van gezonde mensen van uiteenlopende leeftijden en bij wie middels een EEG een P3 is gemeten. Met behulp van deze data is een model opgesteld dat de verandering van de P3 latentietijd en amplitude beschrijft gedurende de levensloop. Omdat er eveneens een eigen dataset beschikbaar was die gegevens bevat van ruim 1500 mensen van 6 tot 87 jaar oud die een oddball paradigma hebben uitgevoerd, was het mogelijk het model op basis van de literatuur te toetsen tegen de resultaten van onze eigen dataset. Hieruit werd geconcludeerd dat naarmate kinderen ouder worden hun P3 latentietijd afneemt en hun P3 amplitude toeneemt. Dit proces zet zich voort tot in de adolescentie waarna er een omslagpunt wordt bereikt. Na het omslagpunt is het proces omgekeerd voor de rest van de levensduur. De P3 volgt een ontwikkelingstraject gedurende de levensloop dat de ontwikkeling van het brein bij jonge mensen, en de degeneratie van het brein bij oudere mensen, reflecteert. De omslagpunten

van de P3 latentietijd en amplitude liggen echter niet op dezelfde leeftijd. De P3 latentietijd is het kortst zo rond de 22 jaar oud terwijl de P3 amplitude maximaal is zo rond de 16 jaar oud. In hoofdstuk 2 is dit in Figuur 2.3, 2.4 en 2.5 visueel weergegeven. Hoewel beide maten dezelfde P3 golf beschrijven, reflecteren ze verschillende aspecten van veranderingen in het brein die gerelateerd zijn aan veroudering. Mogelijk is de P3 latentietijd een indicatie van de efficiëntie van het brein, terwijl de P3 amplitude een indicatie is van de mentale inspanning die wordt geleverd bij een bepaalde taak.

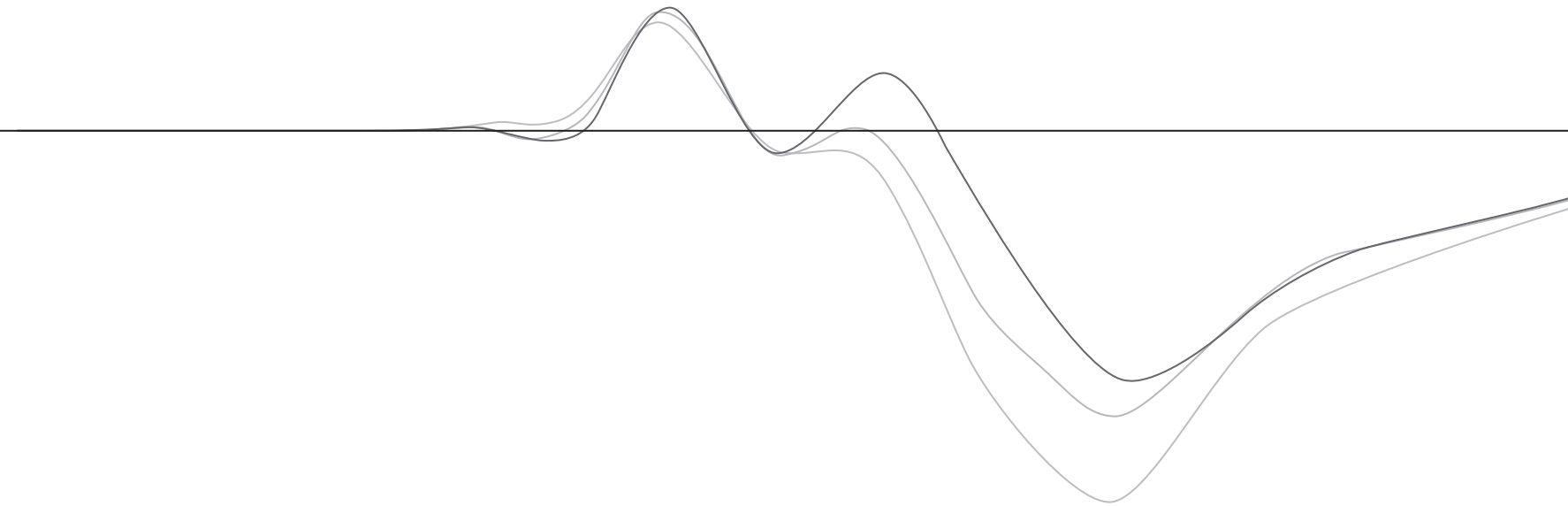
In het derde hoofdstuk werd onderzocht of de ontwikkeling van de P3 gedurende de levensloop verschilt, afhankelijk van de locatie waar de P3 wordt gemeten: namelijk boven het voorste, frontale gedeelte van het brein, of boven het meer naar achter gelegen pariëtale gebied. Toen deze metingen werden vergeleken viel op dat de ontwikkeling van de frontale P3 anders verliep dan die van de pariëtale P3. Zo bereikte de frontale P3 amplitude pas een maximum rond de 46 jaar oud. Bij de pariëtale P3 lag dit maximum rond de 16 jaar oud. Een ander verschil was dat de frontale P3 amplitude nadat het maximum was bereikt nauwelijks meer afnam voor de rest van de levensduur terwijl de pariëtale P3 amplitude dat wel deed. We hadden het vermoeden dat de frontale P3 een reflectie zou kunnen zijn van de compensatoire processen in het brein die worden beschreven door CRUNCH. We maakten daarom een derde model dat de ontwikkeling beschreef van de gemiddelde amplitude van de frontale en pariëtale P3. We dachten zo een weergave te hebben van de cognitieve processen die worden ingezet tijdens de oddball taak inclusief eventuele compensatoire processen vanuit het frontale deel van het brein. Het ontwikkelingsmodel van deze gecombineerde P3 amplitude bleek een goede weergave te zijn van de gedragsmatige prestaties op de oddball taak.

Het vierde hoofdstuk is een beschrijving van de literatuur over de rol van het EEG en de ERP's in het voorspellen van het succes van behandelingen in patiënten. Hiermee is het een opmaat naar het vijfde hoofdstuk waarin we hebben gekeken of we met behulp van de P3 konden voorspellen welke patiënten met een depressie baat hebben bij een behandeling met antidepressieve medicatie. De P3 amplitude was lager bij depressieve patiënten dan bij gezonde mensen. Helaas bleek de P3 geen onderscheid te kunnen maken tussen patiënten die goed reageerden op medicatie en patiënten die geen baat hadden bij de medicatie.

Dat de P3 geen geschikte voorspeller was voor therapiesucces bij depressieve patiënten heeft wellicht te maken met het feit dat de P3 een te algemene representatie is van meerdere opgetelde cognitieve processen in het brein. Men moet bedenken dat er veel hersenactiviteit plaatsvindt wanneer een cognitieve taak wordt uitgevoerd en dat de origine van deze hersenactiviteit een verscheidenheid aan hersenstructuren kent. Met andere woorden, verschillende hersenstructuren zijn actief, maar deze gedifferentieerde informatie gaat verloren bij de EEG-meting. We meten dan enkel het gecombineerde signaal dat al deze structuren samen tot stand brengen. In het zesde hoofdstuk wilden we de verschillende hersenstructuren die betrokken zijn bij het genereren van de P3 beter in kaart brengen. Middels analyses die ontworpen zijn om het opgetelde EEG-signaal uit te splitsen naar de verschillende onderliggende signalen kwamen we tot vier signalen die ten grondslag liggen aan de P3. Met andere analyses konden we onderzoeken of de hersenstructuren vanwaar deze vier signalen ontstonden verschilden tussen jongeren en oudere mensen. Inderdaad bleek dat een van de vier signalen bij oudere mensen een andere bijdrage van hersenschorsactiviteit bevatte dan bij jonge mensen. Dit kan betekenen dat dit specifieke signaal, dat een onderdeel is van de P3, een verschuiving weergeeft in de hersenstructuren die worden ingezet om een cognitieve taak uit te voeren, wanneer mensen ouder worden. We hebben eveneens onderzocht waar het verschil in deze hersenschorsactiviteit gelokaliseerd is in het brein. De analyses leidden ons naar de precentrale hersenwinding en de parahippocampale hersenwinding. Oudere mensen hadden meer hersenactiviteit vanuit deze structuren in het brein dan jonge mensen. De parahippocampale hersenwinding is een belangrijk schakelstation, of 'telefooncentrale', in het verwerken van informatie. De P3 reflecteert mogelijk veranderingen in de werking van dit schakelstation wat leidt tot een andere manier waarop informatie in het brein wordt verwerkt.

Kortom, oudere mensen zetten hun beschikbare cognitieve capaciteit op een andere manier in dan jonge mensen wanneer ze eenzelfde cognitieve taak moeten uitvoeren. Op deze manier behalen ze een gedragsmatige prestatie die vergelijkbaar is met die van jonge mensen. Het brein van oudere mensen compenseert op deze wijze voor de effecten van veroudering en behaalt zodoende toch het gewenste gedragsmatige eindresultaat. Er zijn echter wel grenzen aan deze compensatietechniek. Als cognitieve taken te complex worden, bereiken oudere mensen hun capaciteitslimiet sneller dan jonge mensen. In het dagelijks leven zal dit echter niet vaak voorkomen en is frontale compensatie een effectieve strategie.

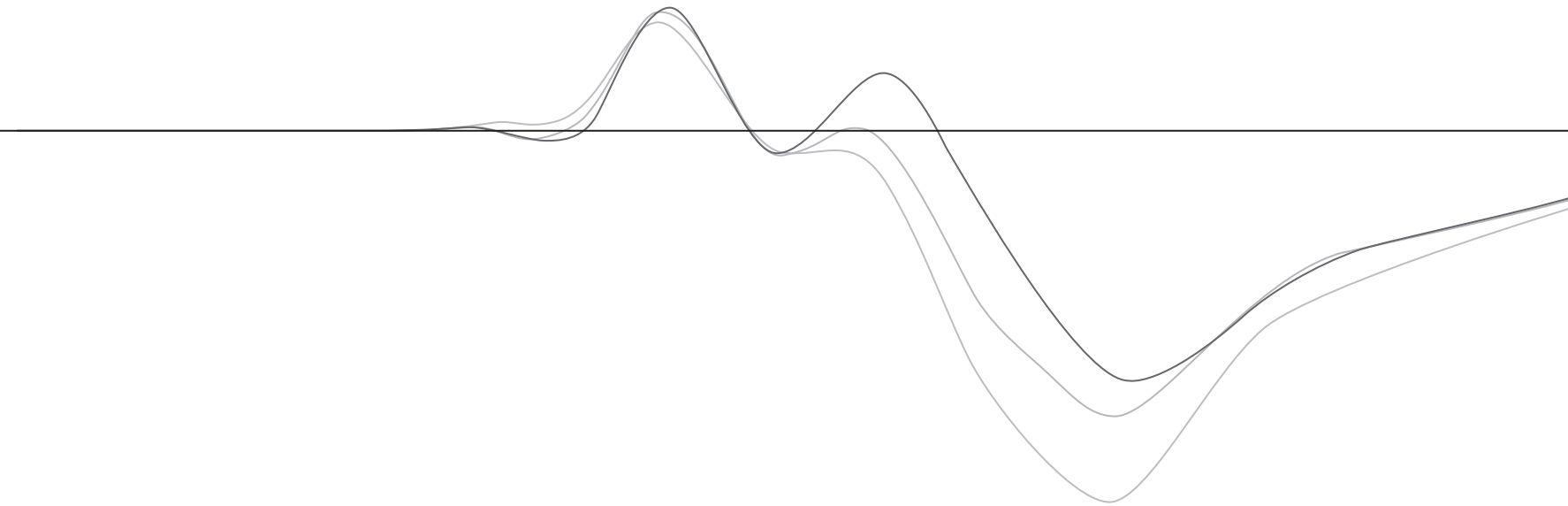
Dankwoord



Tijdens het schrijven van dit proefschrift kregen mijn vrouw en ik twee prachtige meisjes. In de eerste magische maanden viel er veel te leren voor ons. Dit was in het begin niet makkelijk, maar naarmate de tijd verstreek ontdekten we efficiëntere wijzen om de dagelijks terugkerende handelingen aan te pakken en merkten we dat het ons relatief wat makkelijker afging. Er waren echter momenten waarop de meiden besloten om ons volle potentieel te testen. Op die momenten ging onze prestatie merkbaar achteruit op de taak die ons was toebedeeld, namelijk het opvoeden van een tweeling. Gelukkig konden onze eigen ouders hulp bieden en op die manier compenseren voor onze eigen tekortkomingen op die momenten. Op een bepaalde manier is het omgaan met een uitdagende taak zoals hierboven beschreven analoog aan hoe het verouderende brein het voor elkaar krijgt om een uitdagende cognitieve taak goed te volbrengen.

Mijn dank gaat uit naar mijn promotor en copromotors voor hun constructieve bijdragen, mijn mooie vrouw voor haar onvoorwaardelijke steun en onze beider ouders voor hun bereidwillige hulp met de kinderen. Zonder hen was dit boek niet mogelijk geweest.

Curriculum Vitae



Rik van Dinteren was born on July 22nd, 1981 in Nijmegen, the Netherlands. After graduating from secondary school (VWO, Maaswaalcollege, Wijchen) in 2000 and a one-year intermezzo of studying design and technology in Enschede, he started a study psychology majoring in neuropsychology and rehabilitation psychology at the Radboud University in Nijmegen. He did his master internship at the Canisius Wilhelmina hospital in Nijmegen with a thesis on rule shifting in Parkinson's disease patients. In 2007 he obtained his master diploma.

After graduating, he started working as a psychologist in a small practice. He was quickly drawn to research and found a job as junior researcher and study coordinator at the Research Institute Brainclinics in Nijmegen. There he coordinated two large international randomized controlled trials. In September 2012 he combined this function with working as an external PhD candidate, with Roy Kessels as promotor. In his research he focused on age-related changes in event-related potentials in healthy and clinical participants.

Since October 2015 he started working as a trainee at a clinical research organization, Julius Clinical in Zeist. Here he aims to work as a clinical research associate in the future.

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