

Becoming conscious of that which we are apparently ignoring: How the detection of acoustic change can result in a forced intrusion into consciousness.

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Abstract

We live in a busy and complex world, so the ability to focus our attention on relevant information at the expense of the irrelevant is essential in allowing us to avoid distraction. However, it is also important that our attention be captured by external stimuli that, although irrelevant to the task at hand, may nevertheless provide information about important changes to our immediate environment. This capture/orienting of attention is an involuntary, fundamental, and biological mechanism necessary for survival. The present thesis employed event-related potentials (ERPs), the minute responses of the brains electrical activity, to examine how changes in the acoustic environment can lead to the capture of attention.

Study 1 examined an ERP component, the P3a, which is associated with the processes that lead to the forced capture of attention by external stimuli. This intrusion into consciousness can be studied using an auditory sequence, the oddball paradigm, which consists of a frequently occurring and homogenous ‘standard’ stimulus. At times, a feature of the standard is changed to form a rarely occurring ‘deviant’. If the extent of change between standard and deviant is large enough, processes associated with attention capture may be activated. Study 1 of this thesis employed a more time-efficient multi-feature optimal paradigm, which allows for the presentation of numerous deviants in one auditory sequence. The standard stimulus was a pure tone. Four of the six deviants were created by changing a single feature of the standard (frequency, duration, increase and decrease in intensity), while the remaining two deviants varied on more than one feature from the standard (environmental sounds, white noise). Results revealed that only the

environmental sounds (i.e. animal sounds, human voices, musical instruments) and white noise bursts, elicited the P3a, while the other four deviants did not.

Studies 2 and 3 determined whether the attention capture processes associated with the P3a could be observed during the sleep onset and sleep periods, where awareness of the external environment is diminished. For sleep to be of benefit it needs to remain as undisturbed as possible, without constant awakenings by irrelevant external input, however, the sleeping organism must still have the ability to become conscious of possibly relevant input that requires immediate action. In Study 2, a P3a was elicited again following only the environmental sound and white noise deviants across wakefulness and the sleep onset period. Surprisingly, during definitive sleep, the environmental sounds continued to elicit a P3a suggesting that attention capture processes may still remain active during sleep. Nonetheless, only the first 30 minutes of sleep were examined. Study 3 was then conducted to examine the P3a across the entire night. Results revealed that the environmental sounds did, in fact, elicit a P3a during both NREM and REM sleep. The present thesis demonstrates that attention capture mechanisms, observed during wakefulness, are also active during sleep onset and sleep when awareness of the external environment is diminished. This is especially critical because the sleeping organism may be vulnerable to external danger, requiring the immediate ability to orient attention to incoming information, leading to awaking and conscious awareness.

Table of Contents

ABSTRACT	II
LIST OF TABLES	VII
LIST OF FIGURES.....	VIII
CHAPTER 1: GENERAL INTRODUCTION.....	1
1. THE ERP TECHNIQUE.....	4
2. AUDITORY PROCESSING.....	15
3. CLINICAL APPLICATIONS.....	32
4. PROBLEMS WITH THE ODDBALL PARADIGM	33
5. THE MULTI-FEATURE OPTIMAL PARADIGM	34
6. THE PRESENT THESIS.....	41
REFERENCES	44
CHAPTER 2	57
1. INTRODUCTION.....	60
2. EXPERIMENT 1	71
2.1. Results	71
2.1.1. Deviant-Related Negativity	72
2.1.2. P3a	73
2.2. Discussion.....	74
3. EXPERIMENT 2	75
3.1. Results	75
3.1.1. Standard ERP	75
3.1.2. DRN	77
3.1.3. P3a	82
3.2. Discussion.....	84
3.2.1. DRN	85
3.2.2. P3a	85
4. EXPERIMENT 3	88
4.1 Results	88
4.2 Discussion.....	88
5. GENERAL DISCUSSION.....	89
6. EXPERIMENTAL PROCEDURES	95
6.1 Experimental Procedure for Experiment 1.....	95
6.1.1 Subjects.....	95
6.1.2 Procedure and Stimuli	96
6.1.3. EEG/ERP Recording.....	97
6.1.4. Quantification and Statistical Analyses	98
6.2. Experimental Procedure for Experiment 2.....	100
6.2.1. Subjects.....	100
6.2.2. Procedure and Stimuli	100
6.2.3. ERP/EEG Recording.....	101
6.2.4. Quantification and Statistical Analyses	102
6.3. Experimental Procedure for Experiment 3.....	102
6.3.1. Subjects.....	102
6.3.2. Procedure and Stimuli	103
REFERENCES	104
CHAPTER 3	112
1. INTRODUCTION.....	114
1.1 ERPs.....	117

1.1.2 Processing of Acoustic Change	118
1.2 Sleep Onset	120
1.2.1 DRN and P3a during sleep onset and sleep	123
1.3 The optimal paradigm	124
1.4 Present Study.....	125
2. METHODS	126
2.1 Subjects	126
2.2 Neurophysiological recording	126
2.3 Procedure and stimuli	127
2.4 Sleep stage scoring	129
2.5 ERP analysis.....	130
2.6 Quantification and statistical analyses	131
3. RESULTS	133
3.1 DRN.....	133
3.2 P3a	135
4. DISCUSSION	139
4.1 The DRN during sleep onset.....	140
4.2 The P3a during sleep onset.....	141
4.3 Disassociation of the DRN and P3a	147
4.4 Consciousness and the P3a.....	147
5. CONCLUSIONS	150
REFERENCES	152
CHAPTER 4	161
1. INTRODUCTION.....	164
1.1 Auditory ERPs and information processing.....	165
1.2 DRN during sleep.....	168
1.3 P3a during sleep	169
1.4 Optimal paradigm.....	169
1.5 Present Study.....	171
2. METHODS	171
2.1 Subjects	171
2.2 Physiological Recordings	172
2.3 Procedure and stimuli	172
2.4 Sleep stage scoring	174
2.5 ERP analyses.....	174
2.6 Quantification and statistical analyses	175
3. RESULTS	177
3.1 DRN.....	177
3.1.1. Waking State	177
3.1.2 DRN during sleep	178
3.2 P3a	179
3.2.1 Waking State	179
3.2.2 P3a during sleep.....	180
3.3 Late positivity during REM.....	185
4. DISCUSSION	187
4.1 DRN in wakefulness and sleep	187
4.2 P3a during wakefulness.....	189
4.3 P3a during sleep	190
4.4 Late positivity during REM.....	193
4.5 Disassociation of the DRN and P3a	194

5. CONCLUDING REMARKS.....	195
REFERENCES	198
CHAPTER 5: SUMMARY AND CONCLUSIONS.....	206
5.1 IMPLICATIONS.....	210
5.1.1 The Environmental Sounds.....	210
5.1.2 Altered States of Consciousness.....	212
5.2 THE P3A AS A MEASURE OF CONSCIOUS AWARENESS?	214
5.3 CONCLUDING REMARKS	216
APPENDIX 1.....	219
APPENDIX 2.....	244
APPENDIX 3.....	268

List of Tables

	Page
 Chapter 2	
Table 1 - Experiment 1 mean amplitudes (SD in parentheses) and 95% confidence intervals at the Fz electrode site for difference waves at the time interval of the DRN.....	72
Table 2 - Experiment 1 mean amplitudes (SD in parentheses) and 95% confidence intervals at the Cz electrode site for difference waves at the time interval of the P3a	73
Table 3 - Experiment 2 mean amplitudes (SD in parentheses) and 95% confidence intervals at the Fz electrode site for difference waves at the time interval of the DRN	78
Table 4 - Experiment 2 mean amplitudes (SD in parentheses) at midline electrodes for difference waves at the time interval of the P3a. Confidence intervals (95%) are also reported for the Cz electrode site	83
Table 5 - Mean (SD in parentheses) accuracy and reaction time (RT) during the behavioural detection task	88
 Chapter 3	
Table 1 - The intensity, frequency, duration, and probability of the standard stimulus and the six deviant stimuli	129
Table 2 - Mean amplitudes (SD in parentheses) at the Cz electrode site for the difference waves at the time interval of the P3a. Confidence intervals (95%) are also reported for the Cz electrode site	137
 Chapter 4	
Table 1 - Mean amplitudes (SD in parentheses) at the Cz electrode site for the difference waves at the time interval of the P3a. Confidence intervals (95%) are also reported for the Cz electrode site	180

List of Figures

	Page
 Chapter 1	
Figure 1 – Theory of signal averaging	11
Figure 2 - An example of “raw” event-related potentials elicited by standard and deviant stimuli and the associated deviant-minus-standard difference waveform	28
 Chapter 2	
Figure 1 – Multi-feature optimal sequence.....	70
Figure 2 - Grand average ERP waveforms to the standard stimulus and six deviant stimuli in Experiment 1.....	71
Figure 3 - Grand average ERP waveforms to the standard stimulus across the optimal and four oddball conditions in Experiment	77
Figure 4 - Grand average difference waves in the optimal condition	79
Figure 5 - Grand average difference waves in the oddball condition	80
Figure 6 – Spline maps of the DRN for both oddball and optimal conditions...	81
Figure 7 – Spline maps of the P3a for both oddball and optimal conditions.....	84
 Chapter 3	
Figure 1 – FFT analysis of both early and late stage N1	130
Figure 2 - Grand average difference waveforms of the 6 deviants at the Fz, Cz, and Pz electrode sites.....	135
Figure 3 – Spline maps of the P3a.....	138
Figure 4 – Spline map of the P2 component to the increment deviant during stage N2	139
 Chapter 4	
Figure 1 - Grand average difference waveforms of the 6 deviants at the Fz and Cz electrode sites.....	178

Figure 2 - Grand average difference waveform for the environmental sounds at multiple scalp sites	182
Figure 3 - Grand average difference waveform for the white noise deviant at multiple scalp sites	183
Figure 4 - Grand average difference waveform for the increment deviant at multiple scalp sites.....	185
Figure 5 - Grand average difference waveform for the duration deviant at multiple scalp sites	186

Chapter 1: General Introduction

The brain's ability to become aware (or "conscious") of the external world relies, in part, on how it processes stimuli within attended and unattended channels. Selective attention allows the observer to become conscious of what is deemed to be relevant, while also inhibiting the processing of irrelevant information, allowing it to be "ignored". The observer should thus not become conscious of that which is to-be-ignored. Selective attention requires the active participation of the subject and is thus also called "active" attention. Importantly, the subject chooses to attend to what they deem to be relevant and thus become conscious of this input. Highly relevant stimulus input might nevertheless occur in another sensory modality that is currently being ignored. For purposes of survival, the observer must be able to become aware of this highly relevant but unattended stimulus input. This detection of potentially relevant external input is carried out rapidly and automatically, without the need for active, selective attention. If it is determined that an incoming stimulus is indeed highly relevant, ongoing cognitive activity controlled by the central executive will be interrupted. The central executive is located in the frontal lobes and is responsible for the allocation of attentional and cognitive resources to incoming input. Once the central executive is interrupted, attention may then be switched from on-going tasks to the auditory channel and the contents of sensory memory will be probed, allowing for the conscious perception of the auditory experience. This allows for an evaluation of the relevance of this input, allowing the individual to become aware (or conscious) of its features and subsequently to take appropriate action. William James (1890) called this process "passive" attention or "attention capture". In the case of passive attention, the individual does not choose to

become aware of the stimulus input. Rather, the input may be so relevant that it “intrudes” into conscious awareness. This intrusion must be able to occur regardless of the extent of ongoing cognitive activities (e.g. what the subject is doing) or even if the intent of the observer is to not become aware of this input. The auditory system is especially useful for detecting unattended, but highly relevant information, as the observer has the ability to detect input from every direction. This is not the case for other sensory modalities. Our somatosensory sense is also, however, exquisitely sensitive to touch, often leading to startle as a result of unexpected input. In terms of survival, this system is poorly adaptive for warning of imminent danger and is obviously only effective when possible predators are dangerously near. The brain is thus equipped with highly sensitive mechanisms capable of rapidly detecting different elements of acoustic change. The visual modality is not well suited for attention capture. The observer cannot perceive visual stimuli occurring beside or behind him/her. The present thesis focuses on passive attention or attention capture processes in the auditory modality.

The attention capture processes are implicated in the development of many day-to-day appliances and systems. The majority of alarm systems and emergency response systems are developed based on their ability to alert individuals, forcing them to become conscious of their external auditory environment. For example, most alarm systems use the presentation of a very intense auditory stimulus to capture the attention of the individual to a potential intruder. Additionally, emergency response teams (e.g. fire trucks, ambulances) also rely on intense auditory stimuli to alert individuals of their presence. These systems often also incorporate auditory change into the alarm systems. Thus, the auditory stimulus changes. Auditory change from a homogenous past also

signals relevance. Acoustic change that signals an increase in intensity is more relevant for survival than other types of acoustical change. An increase in stimulus intensity is experienced as approaching or “looming” and elicits a fear response in animals, whereas a decrease in stimulus intensity is experienced as retreating or “fading” and does not elicit the same fear response (Bach, Schachinger, Neuhoff, Esposito, Salle, Lehmann, et al., 2007; Freiberg, Tually, & Crassini, 2001; Maier & Ghazanfar, 2007)

In many studies of cognitive psychology, models of information processing have traditionally been developed on the basis of behavioural performance. The subject’s overt response (subjective self-report; accuracy of detection; reaction time) is used to infer the extent to which a stimulus has been processed. When stimuli are not attended and in the absence of an overt response, knowing the extent of processing of the to-be-ignored channel is methodologically very difficult. A major problem with studying cognitive processes occurring outside the current focus of attention is that the researcher does not have direct access to the subject’s mental state. At one extreme, if information in the unattended channel were processed completely automatically (i.e., independent of attention), the observer would be aware of its entire contents. At the other extreme, if awareness of the contents requires strong attention, it is possible that the observer would not be aware of any of the contents of the unattended channel. The absence of a response is thus ambiguous. The paradigm could be changed by requiring a response to a relevant stimulus occurring in the unattended ear. This, however, would also result in attention being directed to the unattended channel. Awareness of the relevant stimulus would then be a result of selective, active attention and rather than passive attention capture. Event-

related potentials (ERPs), on the other hand, provide an exquisite means to monitor processing of the unattended stimulus with millisecond precision.

1. The ERP Technique

ERPs are the changes in the electrical activity of the brain (the electroencephalogram or EEG) that are elicited by a physical stimulus or an internal, psychological event (Picton, Lins, & Scherg, 1995). They reflect the synchronous firing of post-synaptic potentials in large groups of neurons in the cortex. A major advantage of ERPs is that they provide a measure of ongoing information processing unavailable with traditional performance measures such as the speed and accuracy of behavioural responding. This permits an in depth analysis of the “stages” of processing affected by a given experimental manipulation (Luck, Woodman, & Vogel, 2000). Secondly, ERPs can be used to study cognitive processes with very high temporal resolution (millisecond precision) often not feasible with other neuroimaging techniques such as functional magnetic resonance imaging (fMRI).

1.1 Historical Review. Hans Berger first reported the discovery that human electrical brain signals could be recorded by placing electrodes on the scalp in 1929. From then, the electroencephalogram (EEG) became a promising tool for both scientific research and clinical applications. Nonetheless, the EEG signal provided a summation of electrical signals from hundreds of different neural sources representing sensory, cognitive, and motor processes. In the 1930s, the first ERP recordings were performed by Davis, Davis, Loomis, Harvey, and Hobart, (1939) allowing scientists to observe electrophysiological changes in the EEG in response to stimulus input. The changes that occurred however were very small and often very difficult to observe. A major

breakthrough came with the use of signal averaging techniques in the 1950s (Dawson, 1954; see section 1.2).

Initially in the 1950s and 1960s, researchers were mainly interested in so-called “sensory” evoked potentials. These evoked potentials varied as a function of stimulus features. It was not until the remarkable studies of Sutton and colleagues (Sutton, Tueting, Zubin, & John, 1967) that researchers noted that some of the evoked potentials were influenced more by internal, psychological events than strictly the psychical features of the stimulus. They employed the now frequently used “oddball” task in which a frequently presented and homogenous “standard” stimulus was presented. At rare or “odd” times, a feature of the standard was changed and referred to as the “target”. Subjects were asked to detect (often, keeping a running mental count) the occurrences of these rare, target stimuli. The target elicited a positive ERP component occurring around 300 ms, often labelled the “P3” or “P300”. This was not observed following the standard stimulus. It was not, however, the physical feature of the target that elicited the P3. Rather it was the rareness of occurrence of the target and the fact that it needed to be detected. Thus, if the researcher switched the physical features of the standard and the target (the standard now became a rare target and the target became the frequently occurring standard), a P3 would now be elicited by the former standard. To further emphasize that the P3 was now a result of the actual physical stimulus, the P3 could be elicited by any rare stimulus in any modality, for example a rare auditory or a rare visual stimulus. If the subject ignored the stimulus train, the rare stimulus no longer elicited the P3.

Researchers began to distinguish between sensory and cognitive evoked potentials, often dividing certain responses, or components, into those that are mainly affected by sensory factors (the physical stimulus) and those mainly affected by the more psychological or cognitive factors. Cognitive evoked potentials then gained widespread use in a number of psychophysiology laboratories. Traditional cognitive psychology relied strictly on behavioural measures such as the accuracy of a response to a stimulus or the reaction time (RT) to it. The researcher then inferred the cognitive processes that led to the response and what the consequences would be. Such inferring of the nature of the cognitive processes has been vehemently criticized as being mentalistic and unscientific. Cognitive processes have a past, a present and a future. Many researchers employ cognitive evoked potentials to provide a real-time measure of the various stages of information processing. They are especially useful when subjects are asked to ignore a stimulus channel and for which a behavioural response is not made. They thus offer an exquisite means to monitor the extent of these so-called automatic, “pre-attentive” or “pre-conscious” processes. As an example, the search of semantic memory is thought by many researchers to occur automatically. Thus, if an observer is presented with the word “dog”, words related to it such as “cat” and “bark” are also automatically searched in semantic memory. An ERP labeled as “N400” (a negative deflection occurring at about 400 ms) is often used to study semantic processing. When the word “dog” is followed by a semantically congruent word such as “cat”, an N400 is not elicited. However, if dog is subsequently followed by a word that is semantically incongruent such as “leaf”, a large amplitude N400 is elicited (see Tavakoli et al., 2015c in Appendix 1). ERPs can also be used to study cognitive processes during unconscious states such as natural sleep

(Campbell & Colrain, 2002; Colrain & Campbell, 2007), general anesthesia (Van Hooff, De Beer, Brunia, Cluitmans, & Korsten, 1997), and coma (Harrison & Connolly, 2013; Morlet & Fischer, 2014).

Rather than dividing evoked potentials into two categories, sensory and cognitive evoked potentials; the term “event-related potentials” came to be employed in the 1960s. Some researchers still however refer to evoked potentials as those that originate in pre-cortical regions of the brain, for example the brainstem auditory evoked potential while referring to ERPs as those that originate in cortical regions and are influenced by cognitive processes.

1.2 Theory of Signal Averaging. A major limitation of the use of ERPs is that their amplitude is very small relative to the amplitude of the continuous “raw” EEG. Because of this, ERPs are usually not visible within continuous EEG. In most cases, ERP components can vary in amplitude from less than 1 μV to about 20 μV . Nevertheless, the amplitude of the continuous waking EEG varies anywhere from about 25 μV to 150 μV . During natural sleep, the amplitude of the ongoing EEG can be more than 200 μV . The ERP “signal” (the actual response to the stimulus or psychological event) is therefore buried in the much larger background EEG “noise” (Picton, 1995). Several methods exist for extracting the ERP signal from the background EEG noise. The most powerful means to do so is through the use of signal averaging (Dawson, 1954). Initially the ongoing, continuous EEG is sampled. In cognitive experiments, the EEG is often sampled every 1 or 2 ms (i.e., at a 1000 or 500 Hz sampling rate, respectively). Cognitive events rarely occur as often as every 2 ms. Different EEG epochs (also known as “sweeps” or “segments”) are identified for each of the EEG channels and stimulus/response events.

Each single EEG epoch corresponding to the same stimulus or response event is stored in computer memory. A single trial epoch often begins prior to the onset of the stimulus to provide an indication of random pre-stimulus activity and then continues for a fixed time after its onset. An epoch might thus begin 100 ms prior to stimulus onset and continue for 800 ms following it. The actual length of the epoch should obviously include all ERP components of interest. If a researcher were mainly interested in the “P3” component, occurring anywhere between 300-500 ms after stimulus onset, the epoch might continue then to at least 800 ms in order to ensure that the entire component is present within the epoch. These single trial epochs are then aligned and the voltages from all these EEG epochs at each time point are averaged together. This is equivalent to summing the single-trial EEG waveforms and then dividing by the number of trials.

Signal averaging is a procedure whereby a constant signal (the ERP component of interest) emerges from the random, ongoing background EEG (or noise) within these trials. Researchers typically refer to this as the signal-to-noise ratio (S/N ratio); the amplitude of the signal divided by the amplitude of the noise. For example, if the signal of interest is a 10 μV P3 component, and the EEG noise on a typical single trial is 50 μV , then the S/N ratio is 10:50, or 0.2. It is assumed that the amplitude of the signal (the P3) is constant. Thus in this example, the average of the P3 component would be 10 μV , just as the average of 10+10+10+10+...10 μV is 10 μV . The amplitude of the random noise is assumed to be unrelated to the time-locking event (e.g. the stimulus or the response). Its amplitude across numerous trials is thus random. It may be positive-going on some trials and negative-going on others. Its amplitude might be high or low. The average of a random event over a sufficiently large number of trials should tend towards zero. As a

result, with a sufficiently large number of stimulus repetitions, the average of the background noise should be reduced towards zero while the signal of interest remains constant and begins to emerge. The amplitude of the random EEG noise decreases as a function of the square root of the number of trials. Thus, after 4 stimulus presentations, the amplitude of the background EEG is reduced by 2 (i.e., it is now 1/2 of its single trial amplitude). Therefore, if the researcher wishes to halve the amplitude of the noise (thus doubling the S/N ratio), the number of trials must increase 4 times (note, not 2 times; the relationship is not linear). If after 16 trials, the S/N is not sufficient to allow the signal to emerge and the researchers needs to double it (make the signal twice as large as the noise), 64 trial presentations will now be needed. And, if that is still not sufficient, 256 trials will be needed to again double the S/N ratio. Tavakoli & Campbell (2015a; 2015b) provide an in depth explanation of the stimulus presentation, data acquisition, and signal processing steps required to conduct ERP experiments (see Appendix 2 & 3).

The Computer of Averaged Transients (CAT; Clynes, 1962) provided a method to average numerous EEG trials together. The EEG following the onset of a single stimulus could be stored. The EEG following the next stimulus was then summed to that existing in memory and this summed activity replaced what was in memory. Thus with each stimulus presentation, the summation was updated. Of course, a problem with early computational systems was processor speed and memory limitations. Each single EEG trial (or epoch) following stimulus presentation needed to be sorted and stored for each of the EEG channels and for each different type of stimulus. Initially, the continuous EEG was stored on FM tape and then tediously played back, for each stimulus at a time. It was not until the advent of modern microcomputers with relatively large RAM memory and

large hard disks was it possible to store the very large amount of data that are collected in typical EEG studies. It was also possible to collect data from many different EEG channels, allowing for a map of the scalp distribution of the response, displaying the distribution of the voltage variation across the scalp.

Figure 1 (taken from Tavakoli & Campbell, 2015b) illustrates the averaging procedure. The upper left portion of the figure illustrates 4 un-averaged superimposed single (or “raw”) trials. These single trials contain both background noise and the signal of interest. Immediately below the single trials, the average of the 4 trials is presented. A positive component at about 200 ms is beginning to emerge. Again, to double the S/N ratio of the average, 4 times the number of trials (i.e., 16 trials) must be presented. The upper middle portion superimposes 4 averages of 4 trials each. The average of these 16 trials is presented below the superimposed averages. Now, both the negative and positive components are beginning to emerge from the background noise. To double this S/N ratio, 64 trials must be presented. The upper right hand portion superimposes again 4 averages, but each trace is now the average of 16 trials. On the bottom right portion of the Figure, the average of the 64 trials has been computed. The ERP components of interest can be viewed much more clearly here; a negative-going peak at about 100 ms and a positive peak at about 200 ms. Compare this average to the upper left portion of the Figure in which 4 single trials are superimposed in which the ERPs of interest are embedded in the much higher amplitude background noise.

Theory of Signal Averaging

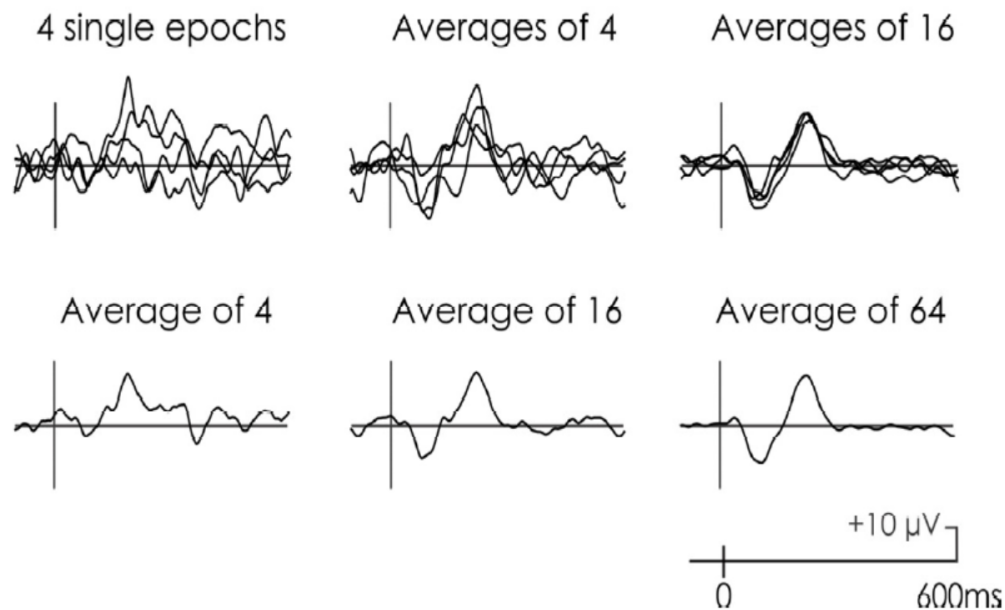


Figure 1. Theory of signal averaging. A 700 ms epoch is illustrated beginning 100 ms prior to stimulus onset. The upper left portion superimposes 4 unaveraged (i.e., single trial) epochs. Immediately below, the average of the 4 trials is presented. A small amplitude negativity at about 100 ms and a larger positive component at about 200 ms are beginning to emerge from the noise. The upper middle portion superimposes 4 averages of 4 trials each. The average of these 16 trials is presented immediately below this. The upper right hand portion superimposes again 4 averages, but each trace is now the average of 16 trials. On the bottom right portion of the Figure, the average of the 64 trials has been computed. The ERP waveform is now clearly apparent against what is now only small amplitude noise.

1.3 ERP Labeling and Classification. The ERP waveform consists of a series of deflections, representing the summation of several functionally and structurally distinct “components”. Two definitions of an ERP component are used. Näätänen and Picton (1987) define it as “[...] the contribution to the recorded waveform of a particular generator process, such as the activation of a localized area of cerebral cortex by a specific pattern of input.” What the researcher observes and measures from the scalp-recorded response are “deflections”. They then point out that “the components contributing to these peaks can usually be inferred only from the results of the

experimental manipulation” (Näätänen and Picton, 1987, p.376). Donchin, Ritter, & McCallum (1978) emphasize the independence of experimental manipulation, “Functionally different aggregates need not be anatomically distinct neuronal populations. But it is assumed that neuronal aggregates whose activity will be represented by an ERP component have been distinctly affected by one or more experimental variables” (Donchin et al., 1978, p.353).

ERP components can be classified as being either “exogenous” (exo=outside) when the ERP is mainly affected by the physical properties of the stimulus, or “endogenous” (endo=inside) when it is mainly affected by the more psychological properties such as attention, decision-making, memory search, and meaningfulness (Sutton et al., 1967). Exogenous components are not affected by ongoing cognitive activities of the subject and can thus be elicited in the absence of attention and conscious awareness.

The Sutton et al. (1967) experiment can be used as a classic example of exogenous and endogenous processes. Subjects might be presented with two different auditory stimuli, one that occurs frequently and one that occurs rarely. The frequently occurring stimulus is an 80 dB SPL auditory tone while the rarely occurring stimulus is a less intense 70 dB SPL auditory tone. The exogenous ERPs will typically be larger to the 80 dB standard stimulus because it is more intense. The subject is, however, asked to keep a mental count of the rarely occurring stimuli. The rarely presented but less intense 70 dB target will elicit a large P300. The P300 is often considered to be a classic endogenous component. This P300 will be elicited not because of the change in the physical features to a less intense stimulus but because of the relevance of the stimulus to

the subject (instructions to keep a mental count). Again, if the frequently and rarely occurring stimuli are swapped, then the now more intense 80 dB stimulus will elicit the P300 and the less intense 70 dB stimulus that had elicited the P300 previously, will now no longer do so.

In the Näätänen and Picton (1987) definition, ERP components represent the intracranial sources of voltage fluctuations that reflect specific neurocognitive processes. Hence, it is presumed that different ERP components reflect different stages of information processing. In general, ERPs that mainly reflect sensory processing occur earlier while those that reflect mainly psychological events occur later. Some researchers thus classify ERPs according to their time of occurrence (or latency) as early, middle and late components. The early components are much affected by the physical features of the stimulus. Thus, the early latency components of auditory, visual and somatosensory ERPs will be much different. Within the auditory modality, early, components can be observed to occur within the first 10 ms following auditory stimulus onset. They originate from auditory brainstem pathways and hence are often referred to as brainstem auditory evoked potentials (BAEPs). BAEPs are very useful for their clinical and applied applications in assessing auditory pathologies, especially in infants and in the study of neurological disorders. Following these, mid-latency auditory evoked potentials can be found, peaking from 10 to 50 ms following auditory stimulus onset. They are thought to originate in part from the medial geniculate nucleus of the thalamus and the primary auditory cortex. Mid-latency evoked potentials are often difficult to record and interpret as they are very susceptible to muscle artifact. These components are followed by long-latency auditory evoked potentials, or late auditory evoked potentials (LAEPs), which

occur anywhere from 50 to about 800 ms following stimulus onset. LAEPs are mainly affected by cognitive and psychological processes. They will be the main focus of the present thesis.

ERP components are often labeled in relation to their polarity (e.g. whether they are positive- or negative-going deflections), their latency (the amount of time between stimulus onset and the peak amplitude of the component), and/or their sequential order (how many other components have occurred between it and stimulus onset). Different methods of nomenclature exist for labeling the ERP components, and unfortunately each involves a compromise. The first commonly used method refers to ERPs by their polarity and latency. For example, the previously mentioned late positivity, P3, has also been labeled “P300” because it is a positive-going peak occurring at about 300 ms following stimulus onset when a target is very easy to detect. One issue with this method is that the latency of a component can vary dramatically based on subject populations and how difficult the target is to detect. For example, if subjects were presented with a linguistic study in which the frequent stimulus was a verb in the present tense and the target was a verb in the past tense, the late positivity might occur at 600 ms. Should the label “P300” now be changed to “P600” even though both refer to the same cognitive process?

Another method that overcomes this ambiguity is to refer to ERP components by their polarity and their sequential order in the ERP waveform. For example, P1, P2, and P3 are three different positive-going ERP components that might be elicited in sequence by an auditory target stimulus. P1 is the initial component occurring at about 50 ms (also referred to as P50), while P2 (“P200”) and P3 (“P300”) are the second and third positive components within the waveform. One downfall of this method is that it makes the

labeling of numerous small deflections within a larger component (sub-components) or the observation of a new component difficult (Picton, 1995). For example, following the identification of the P3, researchers discovered that in certain instances it could be subdivided into two separate components with distinct latencies and scalp distributions (the distribution of the components voltage across the cortex). These were subsequently labeled as the P3a and the P3b to reflect the earlier (P3a) and later (P3b) subcomponents of the overall P300 component that may at certain times overlap temporally but represent two distinct cognitive processes (for a review, see Polich & Criado, 2006). In another example, the auditory N1 component has been labeled, the N1a, N1b and N1c (Näätänen & Picton, 1987).

A third method of nomenclature that has also been employed involves the naming of a component based on the cognitive process that it reflects or its functional significance (Picton, 1995). For example, the mismatch negativity (MMN) is a component that will be discussed within this thesis. This component is thought to reflect the pre-conscious detection of change within the auditory modality. The MMN, as its name implies, is a negative component that detects a “mismatch” between the features of the current incoming auditory input and those of the preceding auditory stimuli stored in sensory memory (Näätänen, Gaillard, & Mantysalo, 1978; Näätänen, 1990).

2. Auditory Processing

Näätänen (1990; 1992) proposed three modes by which external auditory stimuli can be “experienced”. The term “experience” is poorly defined but appears to be similar to what is equally controversial, “consciousness”. In this context, consciousness is

describing “awareness”. The observer is aware that a stimulus has been presented, but does not necessarily know what the stimulus is.

A single mode describes the selective or active attention process. This thesis is mainly concerned with passive rather than active attention processes. The active attention process will therefore only be briefly described. The features of all incoming stimuli are extracted automatically, without the need for attention. This is thus a pre-attentive or pre-conscious process. These features are then stored, again automatically, in a brief-lasting sensory memory. The purpose of active attention is to permit attention to be focussed on what the observer deems to be relevant and then to eventually become conscious of this input. That which is deemed to be irrelevant should be inhibited from further processing and thus not attain consciousness. Many different models surrounding active, selective processing have been proposed. Importantly, how does the observer distinguish between what is relevant and what is irrelevant? In the Näätänen model, the features of the relevant stimulus are determined by the central executive and stored in working memory. Working memory is maintained by active, effortful attention and its capacity is very limited. One cannot therefore be aware of all stimuli bombarding the sensory receptors. The features of all input are compared to that which exists in working memory. If they match and thus are deemed to be relevant, additional processing is warranted, perhaps leading to awareness of this input. If they fail to match and are thus deemed to be irrelevant, additional processing can now be inhibited and the observer will not be conscious of this input.

In nature, however, certain input that is not being actively attended might be critical for survival or for mating purposes. A “passive” means must therefore exist which

will allow this highly relevant, but unattended input, to forcefully enter or to “intrude” into consciousness, regardless of the current cognitive demands (regardless of “what the observer is doing”). This process is also called attention capture (James, 1890). Näätänen proposes two modes by which attention capture can occur. Importantly, the processing in each mode occurs automatically, without the need for active attention.

2.1 Transient Detector System. The first mode, the transient detector system, as its name implies, detects change in the transient energy (typically, stimulus onsets and offsets) of the auditory stimulus. The output of the transient detector system varies in direct proportion to the energy (typically, its intensity) of the stimulus. In other words, a more intense auditory stimulus would result in an increase in output, while a less intense stimulus would result in a decrease in output. The output of the transient detector system can be monitored by a negative-going auditory ERP component, N1, (for an elaborate review, see Näätänen & Picton, 1987). N1 peaks at about 100 ms after stimulus onset and its amplitude is maximum over fronto-central areas of the scalp. The amplitude of N1 varies directly with the intensity of the auditory stimulus, with more intense stimuli eliciting a larger amplitude N1. Rate of stimulus presentation also affects its amplitude, with infrequently presented stimuli eliciting larger N1s. The N1 is said to be an obligatory ERP component, elicited by any auditory stimulus regardless of the subject’s direction and level of attention. It is, therefore, largely an exogenous ERP component reflecting pre-attentive, pre-conscious processing in the transient detector system. As such, at the time of N1 the observer would not be conscious of the occurrence of the auditory stimulus.

The transient detector system sends an interrupt signal, proportional to its output, to the central executive controlling attention and conscious awareness. If this output is sufficiently high, ongoing processing of the central executive will be interrupted and attention will be switched to processing the potentially much more relevant auditory input. This series of events may then lead to a probe of sensory memory allowing its contents to become available to consciousness. The operations of the transient detector system explains why alarm systems employ high intensity stimuli to alert individuals and force them to cease what they are doing to pay attention to the acoustic stimulus. Even though these individuals were not actively paying attention for possible alarms, they will now passively become aware of it.

2.2 Change Detector System. Näätänen indicates that it is not only high intensity stimuli that can result in attention capture. A second mode, the change detector system, involves the detection of change in any feature of the stimulus, including (but not limited to) pitch, location, duration, and/or intensity. The change detector system is somewhat more complex than the transient detector system because it involves a memory comparison system. Recall that the features of the incoming stimulus are extracted and stored in a brief-lasting “sensory” memory. If the features of the next incoming stimulus match those stored in sensory memory, memory is improved and additional processing ceases. If, however, those features fail to match, change is detected and further processing is warranted. The output of the change detector system varies also with the extent of change. Detection of change is associated with a different ERP negativity, the mismatch negativity (MMN), peaking at about 100-200 ms after stimulus onset. It is largest over fronto-central areas of the scalp and inverts in polarity at the mastoids, when

a nose reference is used (see Tavakoli & Campbell, 2015a for a review of the differential effects of referencing sites). This scalp distribution has been explained by generator sources in and around the auditory cortex, although frontal contributions have also been suggested (for reviews, see Alho, 1995; Näätänen, Paavilainen, Rinne, & Alho, 2007).

The MMN is often recorded in a passive oddball paradigm in which the subject is presented with a string of frequently occurring, homogenous “standard” stimuli and rarely occurring “deviant” stimuli. The subject is typically however engaged in a secondary task and not actively attending to the auditory stimuli. The operations of the change detector system, like those of the transient detector system take place independent of attention. What the subject is doing is therefore incidental. The change from the standard to the deviant elicits the MMN. A more recent model maintains that the MMN is elicited by a mismatch between the auditory input and the predictions formed on the basis of the trends or rules that are automatically detected in the recent auditory stimulation (Näätänen, Kujala & Winkler, 2011; Paavilainen, 2013; Winkler, 2007; Winkler, Denham, & Nelken, 2009). The repeating, homogenous standard stimulus thus represents a special case of acoustic regularity and pattern. A rule is established that a standard is followed by a standard. The presentation of the deviant violates this rule. The amplitude of the MMN varies directly with the extent of stimulus change. It is enhanced as the difference between the deviant and the standard stimuli is increased. A larger extent of change between deviant and standard also results in increased behavioural detection accuracy and decreased reaction times (Lang, Nelson, & Collins, 1990; Sams, Paavilainen, Alho, & Näätänen, 1985; Tiitinen, May, Reinikainen, & NÄ, 1994).

Therefore, the MMN is regarded as an index of auditory discrimination accuracy (Novak, Ritter, Vaughan, & Wiznitzer, 1990; Näätänen, 1992; Tiitinen, May, & Näätänen, 1997).

The output of the change detector system varies with the extent of change. Again, this output is forwarded to the central executive controlling allocation of attentional resources. Processes leading to a switching of attention and an intrusion into consciousness may follow. Thus, any large change to a frequently occurring homogenous acoustic stimulus might result in a forceful interrupt of the central executive. Even a decrease in intensity can trigger the interrupt of the central executive, providing the decrease in intensity is large enough.

There are, however, confounds when the extent of auditory change is large or when change is caused by an increase in intensity. Highly novel deviants or those deviants are more intense than the standard will elicit a larger N1. The deviants will also elicit an MMN while the standard will not. The N1 and the MMN occur at approximately the same time (100-150 ms) and they both show a fronto-central maximum scalp distribution. Thus, in the deviant ERP waveform a larger negativity will be apparent from 100 to 150 ms compared to that of the standard ERP waveform. This is, however, a composite N1 and MMN. This increase in negativity after the occurrence of the deviant is thus often called a deviant-related negativity (DRN) because it represents a composite negativity, the spatial and temporal summation of the N1 and MMN (Jacobsen & Schröger, 2003; May & Tiitinen, 2010).

2.2.1 Automaticity of the MMN. Because the detection of either an increase in acoustic intensity or acoustical change, in general, is essential for survival, it must occur rapidly, and without the need for active attention being directly towards the auditory

channel. Näätänen insists that both the functions of the transient and change detector systems operate automatically, independent of attention and consciousness. The MMN and N1 thus occur passively and prior to the conscious awareness that an auditory stimulus has been presented, or “pre-consciously” (Näätänen, 1990). A large body of literature has examined the extent to which these systems operate independent of attention (see, Wiens, Szychowska, & Nilsson, 2016). Early studies asked subjects attend to the auditory oddball sequence and detect the rare deviant. In other conditions, the auditory channel was to-be-ignored. Some studies indicated that while the MMN was elicited in the “ignore” condition, it was larger when the auditory stimuli were attended (Woldorff, Hackley, & Hillyard, 1991; Woldorff, Hillyard, Gallen, Hampson, & Bloom, 1998; Arnott & Alain, 2002; Trejo, Ryan-Jones, & Kramer, 1995). Thus, contrary to the Näätänen position, the MMN was affected by attention and was not elicited automatically. This was, however, countered by the fact that active detection of the deviant also elicits another negativity occurring at about the time of the MMN. This is the N2b (initially, the MMN was also labelled as the N2a). Attention to the auditory channel caused an increase in the amplitude of the N2b rather than the MMN per se (Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993). Studies needed to be designed in which attention is never directed to the auditory channel containing the deviant so that the overlapping N2b is not elicited. Another series of studies asked subjects to attend to visual tasks while the irrelevant auditory oddball sequence was played in the background. The visual tasks could be very easy or very difficult, with the reasoning being that an easy visual task would allow subjects to sample (or “eavesdrop) on the auditory channel. On the other hand, a difficult visual task would not allow a sampling of the auditory

channel. A large number of studies indicated that the MMN was either unaffected or only slightly affected by these task demands (Alho, Woods, Algazi, & Näätänen, 1992; Harmony et al., 2000; Kathmann, Frodl-Bauch, & Hegerl, 1999; Muller-Gass, Stelmack, & Campbell, 2006; Muller-Gass, Macdonald, Schröger, Sculthorpe, & Campbell, 2007; Otten, Alain, & Picton, 2000; Sculthorpe, Collin, & Campbell, 2008; Zhang, Chen, Yuan, Zhang, & He, 2006).

Unfortunately, during the waking state, the subject is almost never completely unaware of their external environment. If asked, the subject will almost always report at least partial awareness of the auditory channel and more importantly, awareness of the occurrence of the deviant. Thus, in spite of the very clever designs of these studies in the waking state, none are able to prevent at least partial awareness of information in the unattended channel. It is possible that only “partial” awareness of the deviant is sufficient to drive the MMN change detector system. To truly examine the pre-conscious nature of the MMN requires a period of time during which conscious awareness of the external deviant stimulus is near zero. This may only be possible during unconscious states such as natural sleep, coma, and general anesthesia. A major difference between sleep and other unconscious states is that sleep is natural and rapidly reversible. The present thesis will therefore focus on sleep as a measure of consciousness. Sleep is not a uniform state, however. It consists of different stages, often divided into non-NREM (NREM) and REM sleep. NREM sleep is further divided into sub-stages, N1, N2 and N3 reflecting different “depths” of sleep. Stage N1 represents the transition from waking to definitive stage N2 sleep.

Results from studies examining the MMN during sleep have not always been consistent. When an oddball paradigm is used, most studies have failed to observe a distinct MMN during NREM sleep (Loewy, Campbell, & Bastien, 1996; Loewy, Campbell, de Lugt, Elton, & Kok, 2000; Macdonald, Jamshidi, & Campbell, 2008; Nashida et al., 2000; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994; Nordby, Hugdahl, Stickgold, Bronnick, & Hobson, 1996; Paavilainen et al., 1987; Winter, Kok, Kenernans, & Elton, 1995). Some studies have examined the predictive coding capabilities of the MMN during sleep to violations of an acoustic pattern. These studies have also noted the absence of an MMN-like response during stage NREM sleep (Sculthorpe, Ouellet, & Campbell, 2009; Strauss et al., 2015). Nevertheless, few studies have reported the presence of an MMN during NREM sleep when using an oddball paradigm (Ruby, Caclin, Boulet, Delpuech, & Morlet, 2008; Sabri, De Lugt, & Campbell, 2000; Sabri, Labelle, Gosselin, & Campbell, 2003; Sabri & Campbell, 2005).

During REM sleep, some studies have reported the presence of both an attenuated N1 and MMN (Atienza, Cantero, & Gomez, 1997, 2000; Atienza & Cantero, 2001; Loewy et al., 1996; Macdonald et al., 2008; Nashida et al., 2000; Ruby et al., 2008). Other studies, on the other hand, have been unable to elicit an MMN during REM sleep (Loewy et al., 2000; Sallinen, Kaartinen, & Lyytinen, 1996). The duration of the sensory memory appears to be shorter in REM sleep compared to the waking state (Atienza et al., 2000). Studies that have reported an MMN during REM sleep have presented stimuli relatively rapidly (about every 500 ms). In comparison, when stimuli are presented at slower rates (every 1 or 2 seconds), the MMN cannot be elicited even by similar deviant

stimuli (Niiyama et al., 1994; Nordby et al., 1996). Several different types of deviants have been used when studying the MMN during sleep (i.e. changes in frequency, intensity, duration). It is, therefore, possible that the type of deviant used and the extent of change between standard and deviant will affect the likelihood of elicited an MMN during sleep.

2.3 Intrusions into Consciousness. When the output of the transient or change detector system reaches a certain variable threshold, an interrupt is sent to the central executive, controlling the allocation of attentional resources. This could then results in a switch of attention, in which the contents of sensory memory will be probed allowing them to become available to consciousness. This “intrusion into consciousness” is thought to be indexed by a different ERP component, the P3a. The P3a, peaking at about 200-300 ms following stimulus onset, is a positive component with peak amplitudes over centro-frontal areas of the scalp (Escera, Alho, Winkler, & Näätänen, 1998). The centro-frontal topography of the P3a may reflect the interruption of the frontally located central executive that controls the allocation of attentional resources (Escera, Alho, Schröger, & Winkler, 2000). It seems to be generated by a complex network of regions, the prefrontal, cingulate, and hippocampal cortices (Halgren et al., 1995), consistent with the attention-controlling role of the frontal central executive. In a study by Escera et al. (1998), the P3a to novel environmental sounds had two distinct subcomponents. The early portion of the P3a, peaking at around 230 ms, had a centrally dominant scalp distribution with a polarity reversal at posterior and lateral regions. The late portion of the P3a, on the other hand, peaked at around 330 ms and displayed a frontally maximum scalp distribution. The scalp

distributions of these proposed P3a subcomponents are in line with studies indicating multiple generator sources of the P3a.

The P3a was thought to reflect “passive” processes, providing the observer with a means to become conscious of otherwise unattended stimulus input. A problem with this interpretation is that an independent measure of the switching of attention and consciousness could not be provided with a passive paradigm. The evidence for an intrusion into consciousness was the P3a. What cognitive process did the P3a signify? An intrusion into consciousness. A now classic Schröger and Wolff (1998) study provided an independent behavioral measure of this process. They required subjects to actively attend to the auditory sequence and presented them with equally probable short- and long-duration auditory stimuli. The subject's task was to actively listen to the auditory stimuli and signal the duration of the stimuli by pressing an appropriate mouse key. At rare and unpredictable times, the frequency of the stimulus was slightly changed. This frequency deviant was however irrelevant to the duration discrimination task. The small frequency change did nevertheless elicit an MMN and a P3a. Critically, its presentation resulted in deterioration in performance on the duration task. Accuracy of detection decreased and reaction time increased following presentation of the deviant. Based on this deterioration in performance, the authors inferred that the presentation of the deviant must have resulted in a switch of attention from the processing of the relevant feature of the stimulus (its duration) and toward the processing of an irrelevant feature (its frequency).

A large series of studies over the past 15 years have now examined this “distraction” effect and the extent to which P3a does indeed reflect the switching of attention and the subsequent attention capture (and consciousness) process (for a review,

see Parmentier, 2014). It was hypothesized that if the P3a reflected an actual switching of attention, its amplitude should be highly correlated to the extent of deterioration in performance. A large P3a, reflecting a larger switching of attention away from the task at hand should result in larger deterioration in performance. Initial studies did indeed show this effect (Berti & Schroger, 2001; Escera et al., 1998; Escera, Yago, & Alho, 2001). More recent studies have not always found the deterioration in performance to be related to the amplitude of the P3a (Berti, 2012; Horvath, Czigler, Birkas, Winkler, & Gervai, 2009; Parmentier, Elsley, & Ljungberg, 2010; Wetzel, Schröger, & Widmann, 2013). Some have reported an improvement in performance following the presentation of a deviant that elicits a P3a (SanMiguel, Morgan, Klein, Linden, & Escera, 2010); while others have noted that a deviant can result in a deterioration in performance, yet not elicit a P3a (Rinne, Sarkka, Degerman, Schroger, & Alho, 2006). There is thus some debate about whether the P3a reflects the actual switching of attention or simply part of the process that leads to this switch (for a review, see Wetzel et al., 2013).

Wetzel et al. (2013) had subjects engage in a visual task in which they were asked to sort target stimuli based on whether they were animal or clothes via button press. Concurrently, an irrelevant “to-be-ignored” auditory oddball sequence was presented in the background. In one condition, the timing between the presentation of auditory and visual stimuli was synchronized such that the irrelevant auditory stimuli were always followed by presentation of the to-be-attended visual targets. The auditory stimuli, therefore, could act as an informative warning signal for the subsequent presentation of the visual task stimuli. In a second condition the time between the auditory and visual stimuli was random. Moreover, the visual targets only followed the auditory stimuli on

50% of trials. The auditory stimuli could not be used as cues for timing the onset of the visual stimulus in this second condition. In both conditions, the auditory deviants elicited a P3a. In the first condition, reaction times were slower on trials in which an auditory deviant was presented compared to trials in which the standard was presented, providing evidence that attention was diverted to the irrelevant auditory channel, distracting attention away from the relevant visual task. The presentation of the auditory deviants did not have an effect on performance in the second condition even though it did elicit a P3a. The authors interpreted these findings as indicating that the processes indexed by the P3a do not reflect the actual switching of attention (attention capture) per se, given that the behavioural distraction effect and the physiological P3a appeared separable. They suggested that the P3a might reflect a precursory process that occurs prior to the actual switch of attention. Further, they posited that distraction might be more likely to occur in cases in which distracting stimuli provide information relevant to the ongoing task. More recently, Parmentier (2016) has indicated that deviant stimuli yield distraction irrespective of the sounds' informational value. Horváth et al. (2008) also suggest that P3a might reflect higher-level detection processing, including the evaluation of events as significant, rather than the actual switch of attention itself. Hoelig and Berti (2010) also present evidence that the P3a might reflect the initiation of the switch as opposed to the actual switch of attention. Although the exact nature of the P3a is a subject of debate, there is general agreement that the P3a does reflect processes associated with the overall capture and switch of attention.

2.3.1 Difference Waves. The MMN and P3a are best observed in a difference wave constructed by subtracting, point-by-point, the ERPs elicited by the standard

stimulus from those elicited by the deviant stimulus. The subtraction process is illustrated in Figure 2. This subtraction process removes common processing received by both the standard and the deviant. This is usually the obligatory, exogenous processing that is common to both the standard and deviant (e.g., the N1-P2 complex). Thus, when the features of the standard and deviant are very similar, the obligatory, exogenous components of the two ERPs will be very similar. This will be removed in the subtraction process, leaving only processing unique to the deviant (e.g. the MMN and possible subsequent P3a).

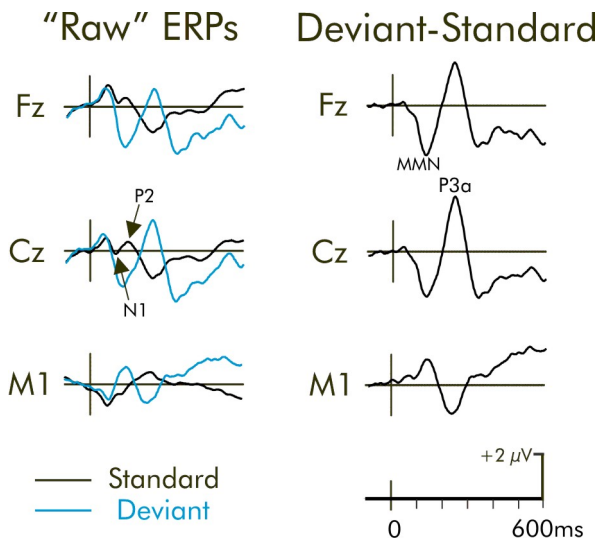


Figure 2. Computing the difference wave. In this example, the subject was presented with a frequently occurring standard stimulus, a 1000 Hz pure tone. In the left column, the standard waveform is illustrated. The standard elicited an N1 (at about 100 ms) and a later P2, at about 180 ms. On 8% of trials, a white noise deviant was presented. This deviant stimulus elicits an additional negativity that overlaps with the N1 and P2 (apparent in the "Raw ERPs" column). This is the MMN. The MMN is however best observed in the deviant-standard waveform (right column). The subtraction process removes processing that is common to both the standard and the deviant. The MMN is maximum over fronto-central areas of the scalp but inverts in polarity (recorded as a positive potential) at the mastoid (M1). In this example, the later positivity, the P3a, is also apparent following presentation of the deviant. It peaks at about 250 ms and is largest over centro-frontal areas of scalp.

2.3.2 Factors Affecting the P3a. In the Näätänen model, attention capture and the associated P3a can result from sufficient activation of either the transient or change detector systems. While any perceptible stimulus change will elicit an MMN, only a small number of these stimuli will also elicit a P3a. In general, the probability of eliciting a P3a increases with the extent of stimulus change. Different types of deviant stimuli have been used to examine the P3a. These include pure tones, novel environmental sounds, white noise stimuli, and complex speech sounds.

Oddball studies using pure tone deviants have demonstrated that frequency (Berti & Schröger, 2001; Deacon, Nousak, Pilotti, Ritter, & Yang, 1998; Escera et al., 2001; Jankowiak & Berti, 2007; Pakarinen, Takegata, Rinne, Huotilainen, Näätänen, 2007; Schröger & Wolff, 1998; Wetzel & Schröger, 2007), duration (Jaramillo, Alku, Paavilainen, 1999; Pakarinen et al., 2007) and decrement deviants (Deacon et al., 1998; Macdonald et al., 2008; Muller-Gass et al., 2006; Muller-Gass et al., 2007; Rinne et al., 2006) will elicit a relatively small amplitude or sometimes absent P3a. An increment deviant has consistently been shown to elicit a P3a (Macdonald et al., 2008; Muller-Gass et al., 2007; Rinne et al., 2006). This is probably because a deviant created by increasing the intensity of the standard (i.e., an increment deviant) results in greater activation of both the transient and the change detector systems.

Environmental sounds (such as human voices, animal sounds, car noises, musical instrument, etc...) and white noise deviants vary widely from pure tone standards in terms of spectral content and intensity. As a result, environmental sounds (Combs & Polich, 2006; Escera et al., 2001; Frank, Yee, & Polich, 2012; Wetzel, Berti, Widmann, & Schröger, 2004; Wetzel & Schröger, 2007) and white noise deviants (Combs & Polich,

2006; Frank et al., 2012) have been shown to elicit particularly large amplitude P3as compared to pure tone deviants.

2.3.3 Automaticity of the P3a. Some studies have found that the P3a is elicited regardless of task demands (Harmony et al., 2000; Muller-Gass et al., 2006; Munka and Berti, 2006; Yucel, Petty, McCarthy, & Belger, 2005) or goal-related information (Wetzel et al., 2013). Nevertheless, in these studies both auditory and visual stimuli were presented discretely (sequentially). It might have been possible for subjects to have also attended to the auditory channel between presentations of the visual stimuli even though they were instructed to ignore it. This concept of attentional slippage (Lachter, Forster, & Ruthruff, 2004) assumes that the elicitation of the P3a may be attributed to brief shifts of attention to the auditory channel, especially when discrete visual stimuli are used. To overcome this issue, Muller-Gass et al. (2007) used a continuous multiple object-tracking task (MOT) in which multiple objects moved in random directions over a computer monitor, half of which were target to-be-tracked and the other half, non-targets, to be-ignored. The difficulty of the task was manipulated by varying the number of targets and non-targets. Their results indicated that the deviant stimuli elicited a significant P3a even during the most difficult version of the MOT task, where it would have been very unlikely for subjects to also attend to the auditory stimuli. The amplitude of the P3a did not differ between the easy and difficult conditions. This finding suggests that the elicitation of the P3a does not require available central resource capacity, and confirms the automatic nature of the processes underlying it.

Nevertheless, similar to the MMN, it is difficult to truly examine the automatic nature of the P3a during the waking state. During the waking state, the subject is almost

never completely unaware of their external environment. Therefore, the presence of the P3a during the difficult visual tasks could be a result of partial awareness to the auditory channel. As a result, examining the P3a when consciousness levels are near zero would provide a more realistic evaluation of its automatic nature.

2.3.4 P3a in Sleep. A problem with the study of ERPs during sleep is that ERPs will be markedly altered compared to the waking state. The auditory N1 may be absent during NREM sleep. On the other hand, the amplitude of P2 may drastically increase (for a review, see Crowley & Colrain, 2004) during NREM sleep. The P2 occurs somewhat earlier (around 180-200 ms) than the P3a (200-300 ms). Distinguishing between the P2 and P3a may however be very difficult. The few studies that have investigated the MMN during sleep have not reported a P3a. Ruby et al. (2008), however, reported a positivity in NREM sleep at the time of the P3a in response to a deviant stimulus. The positivity they detected was centrally maximum, occurring around 250 ms in wakefulness, stage N1, stage N2, and REM. During stage N2, this positivity had a reduced amplitude compared to the waking P3a. The authors noted that this long-lasting positivity had an earlier frontal component (228 ms) and a later parietal component (246 ms). The topographies of these stage N2 components resembled that of the P3a and P3b (the classic P300) elicited in an active paradigm in the waking state. Nevertheless, the early latency of the second positivity (246 ms) would be much earlier than the classic P300.

Some studies have reported the presence of a positivity in REM sleep occurring at the time of the waking P3a (Bastuji, Garcia-Larrea, Franc, & Mauguire, 1995; Cote, Etienne, & Campbell, 2001; Perrin, Garcia-Larrea, Mauguire, & Bastuji, 1999; Pratt, Berlad, & Lavie, 1999; Sallinen et al., 1996; Niiyama et al., 1994). Cote and Campbell

(1999) found a frontal positivity in REM sleep to deviants that represented an increase in intensity from the standard. Macdonald et al. (2008) found that during REM sleep, only the +10 dB increase in intensity seemed to elicit a P3a while the -20 dB decrease in intensity did not. Ruby et al. (2008) however used duration deviants and observed P3a-like and P3b-like components following the MMN during REM sleep. There is thus some evidence that during REM sleep, rarely occurring but potentially highly relevant auditory input might interrupt the central executive allowing the sleeper to possibly become conscious of the external environment.

3. Clinical Applications

Due to the passive nature of both the MMN and P3a, they serve as excellent tools in both clinical and applied fields in which the ability of patients or other groups (e.g. children, the elderly) to sustain attention to more traditional behavioural tasks cannot be maintained. Thus, the recording of ERPs during passive auditory oddball paradigms provides a means of examining information processing when attention is not required. Even though the level of attention paid to the task may vary between patient groups and controls, this varying level of attention should not affect the amplitude of the MMN and P3a. The actual extent of processing might however be abnormally low or abnormally high. This is because attention-capture and the associated switching of attention have both positive and negative consequences. It does provide a means of becoming aware of a highly relevant stimulus input that occurs outside of the present focus of attention. Such detection is critical for survival. If an automobile driver fails to detect the sound of a horn from another driver, they risk a serious vehicle accident. On the other hand, the vast majority of the potentially relevant stimuli turn out, in fact, to be irrelevant. Processing of

the irrelevant auditory input may thus distract attention away from other more relevant ongoing cognitive activities. An abnormally low threshold for the switching of attention may therefore lead to frequent, but needless, interruptions of these ongoing cognitive activities. On the other hand, an abnormally high threshold for the switching of attention may not result in the switch of attention, when in fact this switch is necessary. A wide variety of patient groups have been studied including, attention deficit hyperactivity disorder (Gumenyuk et al., 2005), schizophrenia (Atkinson, Michie, & Schall, 2012; Hermens et al., 2010; Nagai et al., 2013), depression (Lepistö et al., 2004), Parkinson's (Solís-Vivanco et al., 2015; Yamaguchi, Yamagata, & Kobayashi, 2000), and alcoholism (Polo et al., 2003). Applied, developmental studies have reported a P3a-like positivity in infants (Háden et al., 2009; Kushnerenko et al., 2007), toddlers (Putkinen, Niinikuru, Lipsanen, Tervaniemi, & Huotilainen, 2012), children and adolescents (Shestakova et al., 2002; Wetzel & Schröger, 2007). The MMN and P3a have also been studied during partial and complete unconscious states, as well as in patients with head trauma, concussions, or in coma (Blain-Moraes et al., 2016; Fischer, Dailler, & Morlet, 2008; Fischer, Luaute, & Morlet, 2010; Schnakers et al., 2008). Current evidence suggests that they provide an excellent means to predict emergence from comatose states (for reviews, see Chennu & Bekinschtein, 2012; Harrison & Connolly, 2013; Morlet & Fischer, 2014). Patients who do not display a P3a have been demonstrated to remain in an unresponsive state for a longer period of time. In the cases in which a P3a is elicited, authors have tentatively suggested that the unresponsive patients may show possible signs of recovery (Fischer et al., 2008; 2010).

4. Problems with the Oddball Paradigm

Not all deviants will elicit a P3a. If a P3a is not observed in a patient, it could be because of an audiological, neurological, or psychiatric abnormality or because the deviant was not sufficiently large to elicit a P3a. Many different deviants might need to be presented in order to determine which are more likely to elicit a P3a. A major limitation with the use of the oddball paradigm is that the time required to present a sufficiently large number of standard and deviant stimuli to allow the background EEG to be sufficiently attenuated can be very long. The amplitude of the MMN and P3a can be quite small (1-2 μ V), and as a result, several thousands of stimulus repetitions would be required in order to allow the MMN and P3a to emerge from the background EEG. The deviant stimulus is also presented very rarely within the oddball paradigm. If it is presented on 10% of trials, only 100 deviants will be presented after 1000 trials. When the researcher needs to determine which types of deviants are most likely to elicit a P3a, because the threshold for eliciting it may be very low for some subject populations but very high for others, a separate oddball sequence would need to be run for each type of deviant. Each oddball sequence often lasts approximately 10–15 min. The data will then need to be replicated (run a second time) to collect an adequate number of deviant trials. In clinical populations, children, or the elderly, the signal-to-noise ratio may be poorer and the incidence of artifact greater than in controls, requiring considerably more stimulus repetitions. Thus, if several different oddball sequences are to be presented, testing time may be very long indeed, often exceeding two hours.

5. The Multi-Feature Optimal Paradigm

5.1 The Optimal Paradigm and the MMN. Näätänen, Pakarinen, Rinne, and Takegata (2004) have developed a multi-feature “optimal” paradigm to greatly reduce

testing times for the recording of the MMN. In their optimal paradigm, 5 different deviant stimuli were presented in the same sound sequence such that the standards and deviants alternated. Thus, the probability of occurrence of the standards and deviants is 0.5.

However, five different deviants are presented. Thus the probability of occurrence of a specific deviant is 0.1. A sequence of 10 stimuli is presented (i.e., 5 alternating standards and deviants) but the occurrence of a specific deviant is randomized. Another sequence of 10 alternating standards and deviants is then presented, but again with a different random order for the specific deviants. Each of the deviants was created by varying a different feature of the standard (thus, a multi-feature sequence). The assumption was that the MMNs can be independently elicited for the different auditory attributes, and that the other deviant tones strengthen the memory trace of the standard with respect to the stimulus attributes they have in common. In the optimal paradigm, the total number of stimuli presented in a single sequence lasting about 10 minutes would be the same as in an oddball sequence. However, the large advantage to the optimal sequence is that 5 different deviants (in this example) have been presented. If an oddball paradigm is used, a single deviant would be presented. Thus, 5 different oddball sequences would need to be presented to compare the effects of the different deviants. Although some studies include perhaps two deviants in an oddball sequence, the time that is saved by using the optimal paradigm is apparent. In order for the optimal paradigm to be effective, the MMNs recorded to the various deviants within it need to be similar to those recorded when single deviants are presented in multiple repetitions of the oddball paradigm. This was indeed what Nääätänen et al. (2004) found. No difference was found in the MMNs recorded using

the new optimal paradigm and those obtained in multiple repetitions of the traditional oddball paradigm.

Researchers have also examined the MMN to modified versions of the optimal paradigm. Jankowiak and Berti (2007) and Grimm et al. (2008), both merged a three-deviant version of the multi-feature paradigm with the classic Schröger–Wolff distraction paradigm (Schröger & Wolff, 1998). The distraction paradigm does however require attention to be paid to a different feature (duration discrimination in the case of Jankowiak & Berti (2007) and phonetic discrimination in the case of Grimm et al. (2008)) and the features of the different deviants are irrelevant. Jankowiak and Berti (2007) found a robust MMN to frequency, intensity, and location deviants, while Grimm et al. (2008) found robust MMNs to their frequency location, and duration deviants. Other modified versions of the optimal paradigm have also been employed (Pakarinen et al., 2007; Pakarinen, Lovio, Huotilainen, Alku, Näätänen, Kujala, 2009; Pakarinen et al., 2013; Pakarinen, Sokka, Leinikka, Henelius, Korpela, Huotilainen, 2014). Pakarinen et al. (2009; 2013) used another modified optimal paradigm to examine the MMN to phonetic and acoustic changes in speech sounds. All sound changes elicited statistically significant MMNs, with the MMN amplitudes increasing as the extent of deviance increased. They noted that this modified optimal paradigm can be useful for studying speech and language disorders, language development, and the evolution of phoneme categorization during development and during native or second language learning. In a separate study, Pakarinen et al., (2014) further modified the optimal paradigm by decreasing presentation of the standard so it was presented with equal probability to the nine linguistic deviants. They also observed significant MMNs to all deviants.

In an oddball paradigm, it has been well established that the amplitude of the MMN varies inversely with the probability of occurrence of the deviant (Deacon et al., 1998; Sabri & Campbell, 2001). Fisher, Grant, Smith, & Knott (2011a) demonstrated that deviant probability within an optimal paradigm also affects the amplitude of the MMN. In their study, they compared a 5-deviant optimal paradigm in which deviant probability was $p=0.1$ (for each deviant) to a 3-deviant optimal paradigm in which deviant probability was increased to $p=0.17$ (for each deviant). They noted significant MMN amplitude attenuations for the 3-deviant optimal paradigm.

Given its advantage over the traditional oddball paradigm, the multi-feature paradigm has been employed in clinical research to rapidly examine the effects of different deviants on the MMN (Chang et al., 2015; Fisher et al., 2011b; Kujala, Lovio, Lepistö, Laasonen, & Näätänen, 2006; Lepistö et al., 2004; Thönnessen et al., 2008). Similar time-saving optimal sequences have been employed using complex musical and speech sounds as deviants in adults (Grimm et al., 2008; Pakarinen et al., 2009; 2014; Sokka et al., 2014; Vuust et al., 2011) and children (Lovio et al., 2009; Partanen, Torppa, Pykäläinen, Kujala, & Huotilainen, 2013).

The optimal paradigm has also been used to study manipulations of a single feature. Thus, the extent of deviance of a single feature might be very small or very large compared to the standard. Pakarinen et al. (2007) altered the original optimal paradigm by presenting 4 deviants at 6 different magnitudes of change from the standard. Remarkably, overall 24 deviants ($p=.02$) were presented within the sequence. They found that all 24 sound changes elicited significant MMNs. The MMN amplitude increased and latency decreased with increasing magnitude of sound change. They did not however

compare their results to those obtained with multiple repetitions of oddball sequences. Tavakoli and Campbell (submitted) have carried out this crucial study. They presented different optimal paradigms in which a single feature of the standard was manipulated. Note that the optimal paradigm was designed to manipulate different features of the standard. The Tavakoli study was not a multi-feature paradigm (only a single feature was manipulated). In separate experiments, they manipulated the extent of deviance of the frequency and intensity of the standard. In each experiment, 6 different magnitudes of change were presented. The MMNs elicited by the multiple deviants presented within a single optimal sequence were then compared to single deviants presented within an oddball sequence, one for each deviant. Again, the MMNs were very similar within the optimal and oddball paradigms.

5.2 The Optimal Paradigm and the P3a. The purpose of the present thesis is to determine whether the multi-feature optimal paradigm can also be used for the study of the P3a. Far fewer studies have employed an optimal paradigm for this purpose. This might be because the multi-feature optimal paradigm, while appropriate for the use with the MMN, may be inappropriate for the use with the P3a. It has been postulated that the P3a is associated with the evaluation of deviants for relevance and significance in order to interrupt the central executive and cause a switch of attention. The alternating pattern of standards and deviants within the multi-feature paradigm may make the evaluation of these deviants for significance less likely.

Jankowiak and Berti (2007) did employ an active multi-feature paradigm with frequency, intensity, and location deviants paired with a duration discrimination task. Three different conditions were compared in which one, two, or three standard stimuli

separated the deviants. The authors noted that small frequency, intensity, and location deviants could elicit a P3a as long as at least two standard stimuli occurred between deviants. This, however, could be due to the fact that only three deviants were used; hence, when each alternating trial is a standard stimulus, the probability of each deviant occurrence is rather high. Additionally, they noted that a P3a was not typically elicited when a passive multi-feature paradigm was employed, but they did not describe these findings extensively.

Other researchers have used versions of the multi-feature optimal paradigm with more complex speech sounds (Pakarinen et al. 2014; Sokka et al., 2014) and constant-vowel syllables (Grimm et al., 2008; Sorokin, Alku, & Kujala, 2010). Sorokin et al. (2010) used the multi-feature paradigm to study changes in constant-vowel syllables in speech and non-speech sounds. All deviants elicited significant MMN amplitudes; however, only the frequency change and the human and non-human novel sounds elicited significant P3a amplitudes. As such, the authors concluded that the optimal paradigm might not be well suited for the elicitation of the P3a. They stated that constant variation in optimal paradigm may lower the importance of changes in terms of the orienting response and prohibits the evaluation of attention shifting mechanisms. When introducing rare, notably different novel sounds into the stream of standards and deviants, the evaluation of the attention shifting mechanisms and the elicitation of the P3a is more likely (Sorokin et al., 2010). The authors did not, however, compare their results to deviants presented within separate oddball sequences. Grimm et al. (2008) asked subjects to perform phonetic discrimination on consonant–vowel syllables. The standard stimuli were two different consonant–vowel (CV) syllables (ka and pa). Stimulus characteristics

of the standards occasionally deviated either in frequency, location or duration. The extent of change from the standard was relatively small. Both active (subjects performed the phonetic discrimination task) and passive (subjects ignored auditory stimuli and engaged in a visual task) paradigms were run. In the passive paradigm, when the subjects ignored the auditory optimal sequence, the authors reported that the different deviants did elicit a significant P3a. It could be questioned, however, whether the positivity observed by Grimm et al. was a “true” P3a. Its amplitude was very small (less than 0.5 μ V) and it peaked very late (about 500 ms) compared to the usual much larger and earlier 250–300 ms P3a observed in most oddball studies.

In the Pakarinen et al. (2014) study, the standard was a pseudoword “ta-ta”. The deviants differed from the standard in spectral density, frequency, intensity, sound-source location (left/right), noise level, consonant duration, omission (“ta-“), vowel change (“ta-to”), or the vowel duration. Three additional emotional utterances (happy, angry, sad) of the standard were also included as deviants. The authors reported significant P3a amplitudes to the three emotional deviants. The authors did not quantify P3a amplitudes for the 9 linguistic deviants, although their Figure (Figure 1) does reveal a positivity of about 3–4 μ V at about 400 ms following the presentation of a deviant reflecting an increase in noise level and change in spectral density deviants. Similarly, Sokka et al. (2014) used the same modified optimal paradigm as Pakarinen et al. (2014) to assess the switching of attention in individuals with job burnout. The authors reported significant P3a amplitudes to the emotional stimuli. Similar to Pakarinen et al., the authors did not report any P3a results to the linguistically changed stimuli, although there seems to be evidence of a P3a-like positivity to a number of the deviant stimuli. Because the subjects’

attention was diverted away from the auditory sequence, it is possible that the extent of change from the standard was not large enough to elicit a P3a to all of the deviants in the above-mentioned studies, and as a result, only the deviants that varied widely from the standard elicited a P3a. Additionally, the probability of occurrence of the standard was equated to the deviants, therefore, it is possible that the memory trace for the standard is not strengthened enough in order to elicit a P3a to deviants whose features do not vary widely from the standard. Neither Pakarinen et al. (2014) or Sokka et al. (2014) compared the P3a elicited by their deviants within multi-feature paradigm to deviants presented within separate oddball paradigms. Therefore, it is difficult to determine whether similar results would be obtained when using the traditional oddball paradigm.

6. The Present Thesis

The P3a is thought to reflect processes associated with an interrupt of the central executive and subsequent switching of attention and to allow the observer to become aware of potentially highly relevant stimulus input occurring outside of the current focus of attention. P3a studies have used both active and passive paradigms. In the active paradigm, the subject is asked to attend to a train of auditory stimuli and make a decision about one of its features (for example, its duration). A rarely occurring deviant, representing a change in an irrelevant feature (for example, its frequency) is presented within the train. This deviant elicits a large P3a. The majority of studies have employed oddball sequences. An active, multi-feature optimal paradigm would be more difficult to employ as deviants occur on 50% of trials. Subjects might then have difficulty determining the features of the auditory stimuli that should be attended to. Moreover, using an active paradigm in a clinical or applied setting would require attention to be

sustained for a very long period of time and this may not be possible for a large number of groups. The MMN has been examined in more than a thousand different studies (for a review, see Näätänen et al., 2012) using passive oddball paradigms. One reason for this is that almost all deviant stimuli that can be perceived will passively elicit an MMN. This is not the case for the P3a. Only some deviants will do so. To determine which deviants will elicit P3a and if so, how its amplitude will vary with manipulation of deviant features will require several different deviants to be presented. This would require many oddball sequences to be run if a clinical or applied population is to be tested. In general, this may not be feasible.

The principle question addressed by this thesis is whether a multi-feature optimal paradigm can be used to elicit the P3a. This initial study (Study 1) consisted of three different experiments. A second study (Study 2) was run to determine how the gradual loss of consciousness during the sleep onset period affects the waking P3a. Many argue that the sleep onset period is not sleep at all. Subjects are still conscious of their external environment and might still be able to sample the auditory channel containing the deviants. A third study (Study 3) was thus run to determine how definitive sleep and the different stages of sleep affect the P3a process.

The general questions asked in this thesis are:

Study 1:

- What types of auditory deviant stimuli are most likely to interrupt the central executive and elicit a P3a during the waking state?

- Can a time-efficient multi-feature optimal paradigm also elicit P3a? Will the results be comparable to those obtained with the traditional oddball paradigm?

Study 2:

- Do processes associated with the P3a remain active during the sleep onset period, marking the transition from a conscious to an unconscious state?
- Is the likelihood of certain deviants eliciting a P3a differentially affected by the loss of consciousness during sleep onset?

Study 3:

- Some researchers question whether the sleep onset period (stage N1 sleep) is truly a sleep period. Subjects may still be conscious of the external environment. Definitive sleep is defined as an unconscious state with minimal awareness of the external environment. How do the different stages of sleep affect the interrupt of the central executive and P3a?
- Are the same deviants that elicit a P3a during waking also likely to elicit a P3a during NREM and REM sleep?

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Chapter 2

Study 1: Can an auditory multi-feature optimal paradigm be used for the study of processes associated with attention capture in passive listeners?

Overview: ERP methods provide a means to measure the extent of processing when subjects are not actively attending to the stimulus sequence. Moreover, it can do so with millisecond precision, a temporal resolution not available to other cognitive neuroscience methods. The initial study examines how auditory stimulus change can result in an interrupt in the central executive in spite of the fact that these stimuli are not part of the current focus of attention. If these stimuli are deemed to be relevant enough, they may be forced into consciousness and result in a switch of attention away from current cognitive processing and toward the potentially more relevant auditory input. Such stimuli may elicit a large amplitude, positive-going ERP component, the P3a. Only a few stimuli will, however, result in the process associated with a forced intrusion into consciousness. Traditionally, an oddball paradigm is employed. Some deviants will elicit P3a but most will not. To determine which stimuli are likely to do so would require several oddball sequences to be presented, one for each type of deviant. This was done in Study 1. A considerable amount of time is however required for each oddball sequence to be presented. Since the deviants occur very rarely, numerous repetitions are required for the small amplitude P3a to emerge from the background EEG noise in which it is embedded. A very time-efficient “multi-feature” optimal paradigm can reduce testing time considerably by presenting several deviants in a single sequence. It remains to be determined if the P3a that is elicited in the single optimal paradigm is comparable to that elicited in the oddball paradigm. Indeed, some authors have indicated that the optimal paradigm may not be suitable for use of the P3a. A major problem in these studies is that the authors did not directly compare the optimal P3a results to those obtained with the traditional oddball paradigm. The P3a may be absent or attenuated by some deviants

employed in the optimal paradigm compared to a perhaps the robust P3a that may be elicited by the same deviants within the traditional oddball paradigm. The purpose of Study 1 is to determine whether this is in fact the case.

Six different auditory deviant stimuli were used in the optimal paradigm and four of these were run separately using separate oddball paradigms. The present study employs deviants that are commonly used in applied and clinical settings. The different deviants that were selected have in previous passive paradigms been demonstrated to either not elicit a P3a or elicit a P3a that varies in amplitude.

Study 1 consists of 3 separate experiments. The purpose of Experiment 1 was to determine whether the multi-feature optimal sequence in which commonly used deviants are employed could, in fact, elicit both a DRN and P3a. Experiment 2 then examined the DRN and P3a elicited by the deviants within the optimal paradigm to those elicited in separate oddball paradigms. Some deviants did elicit a P3a of varying amplitude. Other did not elicit a P3a. A third experiment was therefore run to determine if the perceptibility of the various deviants could explain this variation in P3a amplitude.

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1. Introduction

For purposes of survival, the observer must become conscious of highly relevant stimuli that occur outside of the focus of current, active attention. Such stimuli may trigger an interrupt in the central executive controlling the allocation of attention and cognitive resources, causing a switch of attention from the task-at-hand and refocused on the potentially more relevant stimulus. Such stimulus-driven control of attentional resources is called attention capture or passive (involuntary) attention (James, 1890).

A large amount of the processing of stimulus input takes place automatically, independent of attention and consciousness. The study of automaticity in information processing is facilitated by the recording of event-related potentials (ERPs), as they provide a means of determining the extent to which to-be-ignored stimuli are processed. ERPs are the minute changes in the electrical activity of the brain that are elicited by a physical stimulus or an internal, psychological event. The involuntary capturing of attention and switching of attention to the processing of the potentially highly relevant input has traditionally been associated with a positive-going ERP component, labelled the P3a, peaking at about 250-300 ms following stimulus onset (Escera et al., 1998). More recently, researchers have questioned whether the P3a reflects the actual switching of attention or is better viewed as part of a process that leads to this switch (see Wetzels et al., 2013; Parmentier, 2014 for reviews).

Because of its association with the processes leading to attention capture, there is increasing interest in the P3a in clinical and applied settings. A major reason for this is because attention capture and the associated switching of attention have both positive and negative consequences. It does provide a means of becoming aware of a highly relevant,

stimulus input that occurs outside of the present focus of attention. On the other hand, the vast majority of the potentially relevant stimuli turn out, in fact, to be irrelevant.

Processing of the irrelevant auditory input may thus “distract” attention away from other more relevant ongoing cognitive activities. An abnormally low threshold for the switching of attention may therefore lead to frequent, but needless, interruptions of these ongoing cognitive activities resulting in a number of clinical syndromes. On the other hand, an abnormally high threshold for the switching of attention is associated with other clinical syndromes. A wide variety of patient groups have been studied including, attention deficit hyperactivity disorder (Gumenyuk et al., 2005), schizophrenia (Atkinson et al., 2012; Hermens et al., 2010; Nagai et al., 2013), depression (Lepistö et al., 2004), Parkinson’s (Solis-Vivanco et al., 2015; Yamaguchi et al., 2000), and alcoholism (Polo et al., 2003). Applied, developmental studies have reported a P3a-like positivity in infants (Háden et al., 2009; Kushnerenko et al., 2007), toddlers (Putkinen et al., 2012), children and adolescents (Shestakova et al., 2002; Wetzel et al., 2007). P3a has also been studied during partial and complete unconscious states in patients with head trauma, concussions, or in coma (Kaipio et al., 2000; Morlet and Fischer, 2014), and during natural sleep in young adults (Macdonald et al., 2008; Ruby et al., 2008).

Recording ERPs in clinical and applied settings presents many problems. Many patient groups are unable to tolerate long testing sessions. The recording procedure thus needs to be as brief as possible. In many situations, the ERPs need to be recorded passively, without the requirement for sustained attention. If active attention to a task is required, whatever ERP differences emerge between the group of interest and controls might be attributed to an inability to remain vigilant and to sustain attention. In some

cases, such as studies with the demented, infants and young children, and studies examining the effects of unconscious states, active tasks can obviously not be used.

The present study examines the results of a so-called multi-feature optimal paradigm that allows the recording of a P3a to six different types of auditory “deviants” in a single sequence. Data can therefore be collected relatively rapidly. We shall also demonstrate that this paradigm can be used to record a robust P3a to certain stimuli even though the subject is not actively attending to the auditory sequence.

The oddball paradigm. The P3a is typically elicited using the so-called auditory oddball paradigm. The oddball sequence consists of a frequently occurring homogeneous “standard” stimulus. At rare and unpredictable (or “odd”) times, a feature of the standard is changed to form a “deviant”. The subject is often asked to focus attention on a visual task (for example, reading a book or watching a silent video) and to ignore the auditory sequence. Because attention is not directed toward the auditory stimuli, the ERPs are thus elicited passively by these stimuli. In the classic Näätänen model (1990; 1992), attention capture is triggered by two distinct mechanisms by which a task-irrelevant auditory stimulus may eventually be consciously perceived. In this model, stimulus onsets (a change from the absence of a stimulus) and offsets (a change from the presence of a stimulus) activate a transient-detector system, reflected in the auditory modality by the “N1” ERP component, peaking at about 100 ms. Both the standard and deviant therefore elicit an N1. The output of this system varies directly with acoustic energy and the rarity of stimulus presentation. Thus, a rarely occurring deviant that signals an increase in intensity will elicit a larger N1 than a less intense, more frequent standard. A stimulus does not however need to be intense to capture attention. A second mechanism, the

change detector system, as the name implies, detects change in *any* feature of the stimulus, including its pitch, location, duration, and/or intensity. The output of the change detector system is reflected by a different negativity, the mismatch negativity (MMN), peaking at about 100-200 ms after stimulus onset. A more recent model maintains that the MMN is elicited by a mismatch between the current auditory input and the predictions formed on the basis of the trends or rules that are automatically detected in recent auditory stimulation (Näätänen et al., 2011; Paavilainen, 2013; Winkler, 2007; Winkler et al., 2009), the repeating, homogenous standard stimulus in the oddball paradigm thus being a special case of acoustic regularity. Highly novel deviants might elicit both a larger N1 than the standard, and also an MMN. This increase in negativity after the occurrence of the deviant is often called a deviant-related negativity (DRN) because it represents a composite negativity, the spatial and temporal summation of the N1 and MMN.

If the output of the transient or change detector system is sufficiently high, a trigger is sent to the central executive resulting in a switch of attention away from ongoing, attended cognitive tasks and toward the interrupting stimulus event. P3a is thought to reflect at least part of these processes that lead to and cumulate in the capturing and switching of attention. Thus, while any perceptible stimulus change will elicit an MMN/DRN, only a small number of these stimuli will also elicit a P3a. In general, the probability of eliciting a P3a increases with the extent of stimulus change.

Stimuli whose features vary widely from pure tone standards, such as novel environmental sounds (e.g., musical instruments, animal sounds, novel sounds) and white noise, have been demonstrated to elicit a large amplitude P3a in passive paradigms (Cahn

et al., 2009; Kushnerenko et al., 2007). A change in a single feature of the standard stimulus can also elicit a large P3a particularly if this change represents about a 10 dB increase in intensity, but even a very large 20 dB decrement in intensity can elicit a small amplitude P3a (Macdonald et al., 2008; Muller-Gass et al., 2006) although a small decrement will not (Rinne et al., 2006). Many studies have employed small frequency and duration deviants but these elicit only a small amplitude or absent P3a.

Active attention. The P3a has also often been elicited in very attention-demanding (or “active”) intra- and inter- modality studies. In a now classic study, Schröger and Wolff (1998) presented subjects with equally probable short- and long-duration auditory stimuli. The subject’s task was to actively listen to and signal the duration of the stimuli by pressing an appropriate key. At rare and unpredictable times, the frequency of the stimulus was slightly changed. This frequency deviant was however irrelevant to the duration detection task. The small frequency change did nevertheless elicit a P3a. Importantly, its presentation resulted in deterioration of performance on the duration detection task. The behavioural deterioration in performance thus provides an independent measure of the switching of attention; presumably the presentation of the deviant resulted in a switch of attention from the processing of the relevant feature of the stimulus (its duration) and toward the processing of an irrelevant feature (its frequency). Another advantage of the use of the active paradigm is that the P3a can be elicited by deviants that represent a small extent of change from the standard. In passive paradigms, a large extent of change appears to be required. Unfortunately, as mentioned above, in many applied and clinical settings, studies requiring active, sustained attention cannot be employed. Moreover, Grimm et al. (2008) have noted that the DRN increases

dramatically in amplitude when attention is directed to the auditory sequence compared to when it is ignored. The authors note that this might be because of a very large increase in the amplitude of another overlapping negativity, the N2b, which summates with the DRN. Distinguishing between the DRN and the N2b can however be extremely difficult. Many applied researchers are interested in differences associated with the DRN/MMN. Again, as mentioned previously, when a task requires active attention, whatever ERP differences emerge might reflect an inability to focus attention rather than an ability to detect change.

The optimal paradigm. The MMN/DRN has often been used in a very large number of applied and clinical studies of the detection of change and sensory memory (see reviews by Bartha-Doering et al., 2015; Näätänen et al., 2012). The amplitudes of the MMN/DRN and possible subsequent P3a are typically much smaller than the ongoing, background EEG. Through the use of averaging procedures, the amplitude of the background EEG can be reduced allowing the small amplitude ERP signal to emerge. The averaging process does however require the repetition of many stimulus presentations. In spite of the use of the oddball paradigm in applied settings, a major limitation is that the time required to present a sufficiently large number of standard and deviant stimuli to allow the background EEG to be sufficiently attenuated can be very long. This is especially the case when the researcher needs to determine which deviants are most likely to elicit a P3a because the threshold for eliciting it may be very low for some patient groups but very high for others. A separate oddball sequence would thus need to be run for each type of deviant. Each oddball sequence often lasts approximately 10-15 minutes. If the data are to be replicated, the sequence will need to be repeated a

second time. In clinical populations, the signal-to-noise ratio may be poorer and the incidence of artifact greater than in controls, requiring considerably more stimulus repetitions. Thus, if several different oddball sequences are to be presented, testing time may be very long indeed, often exceeding 2 hours.

Näätänen et al. (2004) have developed a multi-feature “optimal” paradigm to greatly reduce testing times for the recording of the MMN. In this optimal paradigm, several different deviant stimuli are presented in a single auditory sequence. In their initial study, 5 different deviant stimuli were presented in a sequence, every other stimulus being a standard (thus with a probability of occurrence of 0.5) and the alternating stimulus being one of the five equally probable types of deviants (i.e., each with a probability of occurrence of 0.1). Each of the deviants was created by varying a different feature of the standard. The authors then compared the MMN that was elicited by the different deviants in the optimal paradigm to those which were elicited by the deviants when they were presented in separate oddball sequences. The MMNs elicited by the 5 deviants in the multi-feature optimal paradigm were quite similar to those elicited in the 5 separate oddball sequences. In both oddball and optimal sequences, “large” deviants will elicit a larger MMN than “small” deviants (Pakarinen et al., 2007; Sams et al., 1985). In an oddball sequence, it has been well established that the amplitude of the MMN varies inversely with the probability of occurrence of the deviant (Deacon et al., 1998; Näätänen et al., 1980; Sabri & Campbell, 2001). Fisher et al. (2011b) demonstrated that deviant probability within an optimal paradigm also affects the amplitude of the MMN. It was larger in a 5-deviant than in a 3-deviant optimal sequence. The multi-feature optimal paradigm has also been employed in clinical studies to rapidly examine the effects of

different deviants on the MMN (Fisher et al., 2011a; 2012; Kujala et al., 2006; Thönnessen et al., 2008). Similar time-saving optimal sequences have been employed using complex musical and speech sounds as deviants (Pakarinen et al., 2009; Vuust et al., 2011).

Can an optimal paradigm be used to elicit a P3a to different deviants? The focus of most studies employing a multi-feature optimal paradigm has been on the MMN. Few have reported the presence of a P3a. Jankowiak & Berti (2007) did employ an active multi-feature oddball paradigm and noted that small frequency, intensity and location deviants could elicit a P3a. However, a P3a is not typically elicited when a passive multi-feature paradigm is employed. This could be because the extent of deviance in these passive paradigms may not have been large enough for the P3a to be elicited. It is also possible that the multi-feature optimal paradigm is poorly suited to do so. Sorokin et al. (2010), for example, questioned whether the constant alternating standard-deviant pattern precluded its use for the evaluation of attention switching mechanisms and the P3a. In their study, an optimal paradigm was used to examine the processing of consonant-vowel syllables (in speech and non-speech sounds) as deviants compared to a syllable used as a standard stimulus. All deviants elicited an MMN/DRN. However, only a large frequency deviant elicited a significant P3a. Pakarinen et al. (2014) employed a modified multi-feature paradigm also presenting speech-like sounds (bisyllabic pseudowords) as stimuli. The authors did change the usual alternating standard-deviant pattern, employing 9 different deviants but equated the probability of occurrence of the standard and the deviants ($p=.09$ for all 10 stimuli; 9 deviants and 1 standard). In addition, 3 rarely occurring variants of the standard with strong emotional prosody – happy, angry, and sad

– were included in the sequence in addition to the deviants (each, however, with a probability of .02). Again, all the deviants and the emotional speech sound stimuli elicited an MMN/DRN. Only the emotional sounds elicited a P3a. The authors acknowledged that their “emotional” spoken stimuli were highly complex, deviating from the standards in terms of their features and saliency. It is possible, for example, that increases in the intensity and/or abruptness of the stimuli may have been the critical factor for eliciting the P3a rather than their emotional salience. Sokka et al. (2014) used the Pakarinen et al. (2014) modified optimal paradigm to assess possible attentional alterations in individuals with mild to severe symptoms of job burnout. Again, the three emotional stimuli elicited a P3a, for both controls and job burnouts. Neither Pakarinen et al. nor Sokka et al. presented P3a results for the non-emotional speech sounds. Grimm et al. (2008) also employed complex speech sounds, consonant-vowel (CV) syllables as standards. Their frequency, duration and location deviants represented a relatively small extent of change. In spite of this relatively small extent of change, when subjects ignored the optimal auditory sequence, the authors reported that the different deviants did elicit a significant P3a. This seemed to contradict the Sorokin et al. (2010) claim that the nature of optimal paradigm precluded its use for the study of the P3a. It could be questioned whether the positivity observed by Grimm et al. was a “true” P3a. Its amplitude was very small (less than 0.5 μ V) and it peaked very late (about 500 ms) compared to the usual much larger and earlier 250-300 ms P3a observed in most oddball studies.

The present study. The present study employs deviants that are used much more commonly in applied and clinical settings. A passive multi-feature optimal paradigm will be used during which subjects are asked to ignore the auditory stimuli while engaged in a

visual task. The different deviants that were selected have in previous passive paradigms been demonstrated to either not elicit a P3a or elicit a P3a that varied in amplitude.

Oddball studies have demonstrated that frequency (Berti & Schroger, 2001; Deacon et al., 1998; Escera et al., 2001; Jankowiak & Berti, 2007; Pakarinen et al., 2007; Schröger & Wolff, 1998; Wetzel & Schröger, 2007), duration (Jaramillo et al., 1999; Pakarinen et al., 2007) and decrement deviants (Deacon et al., 1998; Macdonald et al., 2008; Muller-Gass et al., 2006; Muller-Gass et al., 2007; Rinne et al., 2006) will elicit a relatively small amplitude or absent P3a. An increment deviant has consistently been shown to elicit a P3a (Macdonald et al., 2008; Muller-Gass et al., 2007; Rinne et al., 2006). Environmental sounds (Combs et al., 2006; Escera et al., 2001; Frank et al., 2012; Wetzel et al., 2004; Wetzel & Schröger, 2007) and white noise deviants (Combs et al., 2006; Frank et al., 2012) appear to elicit a large amplitude P3a.

Previous studies using a multi-feature passive optimal paradigm have consistently demonstrated that almost all deviant stimuli will elicit an MMN/DRN. The passive optimal paradigm might however be poorly suited for attention capture (Sorokin et al., 2010); it is not clear if commonly used deviants can elicit a P3a in a passive optimal sequence even though they may do so when subjects actively attend to the sequence (Jankowiak & Berti, 2007). Three different experiments were run. The purpose of the initial study was to determine whether a multi-feature optimal sequence in which commonly used deviants can, in fact, elicit both a DRN and P3a.

For this purpose, only a small number of subjects needed to run. The optimal sequence consisted of a single standard pure tone and 6 different deviants. Three of the deviants, environmental sounds, white noise, and increments, have consistently elicited a

large P3a in previous passive oddball studies. Frequency, duration, and decrement deviants, on the other hand, have less consistently been shown to elicit a P3a in the passive studies and were thus also included as the other three deviants.

The general stimulus procedure is illustrated in Figure 1. It consisted of a sequence in which every other stimulus was a standard pure tone (thus, $p=0.5$) and the alternating stimulus was one of the 6 different deviants (each with a $p=0.083$). Subjects were asked to ignore these auditory stimuli while watching a silent video.

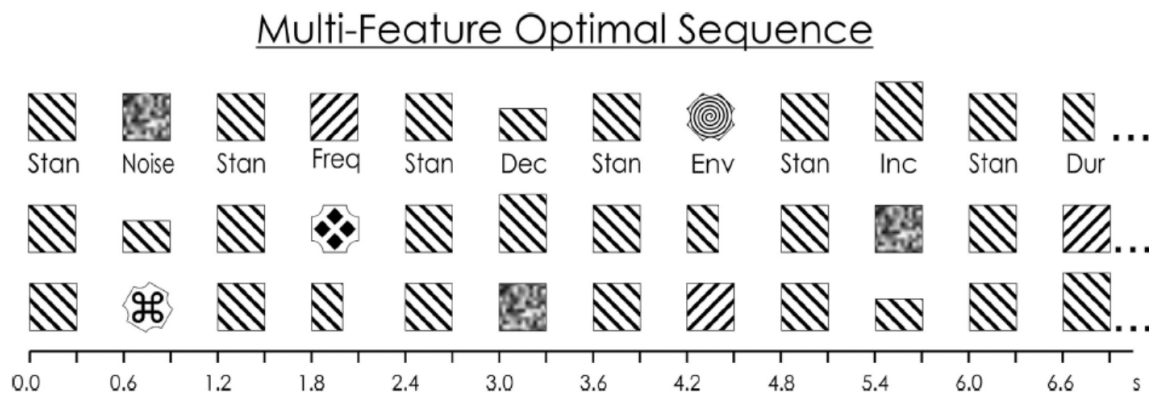


Figure 1. Multi-feature optimal sequence. A stimulus is presented every 600 ms. Every other stimulus is a standard, lasting 200 ms. The standard alternates with a deviant. The deviant was created by changing a single feature or multiple features of the standard. In the example, in the first line, 12 stimuli are presented in an array. The sequence begins with a standard (“Stan”) and then alternating with the standards: a white noise (“Noise”) deviant, a frequency (“Freq”) deviant, a decrement (“Dec”) deviant, an environmental sound (“Env”) deviant, an increment (“Inc”) deviant, and a duration (“Dur”) deviant. Each of the six different deviants was presented in the array. In the second line, the 6 deviants are presented again but in a different randomized order. Note that a different environmental sound was presented throughout the sequence.

2. Experiment 1

2.1. Results

The ERPs elicited by the auditory standard and deviant stimuli are presented in Figure 2. As may be observed, the ERPs to the auditory standard (left portion of Figure) consisted of a small amplitude negativity, N1, peaking at approximately 100 ms and a positivity, P2, at approximately 170 ms after stimulus onset.

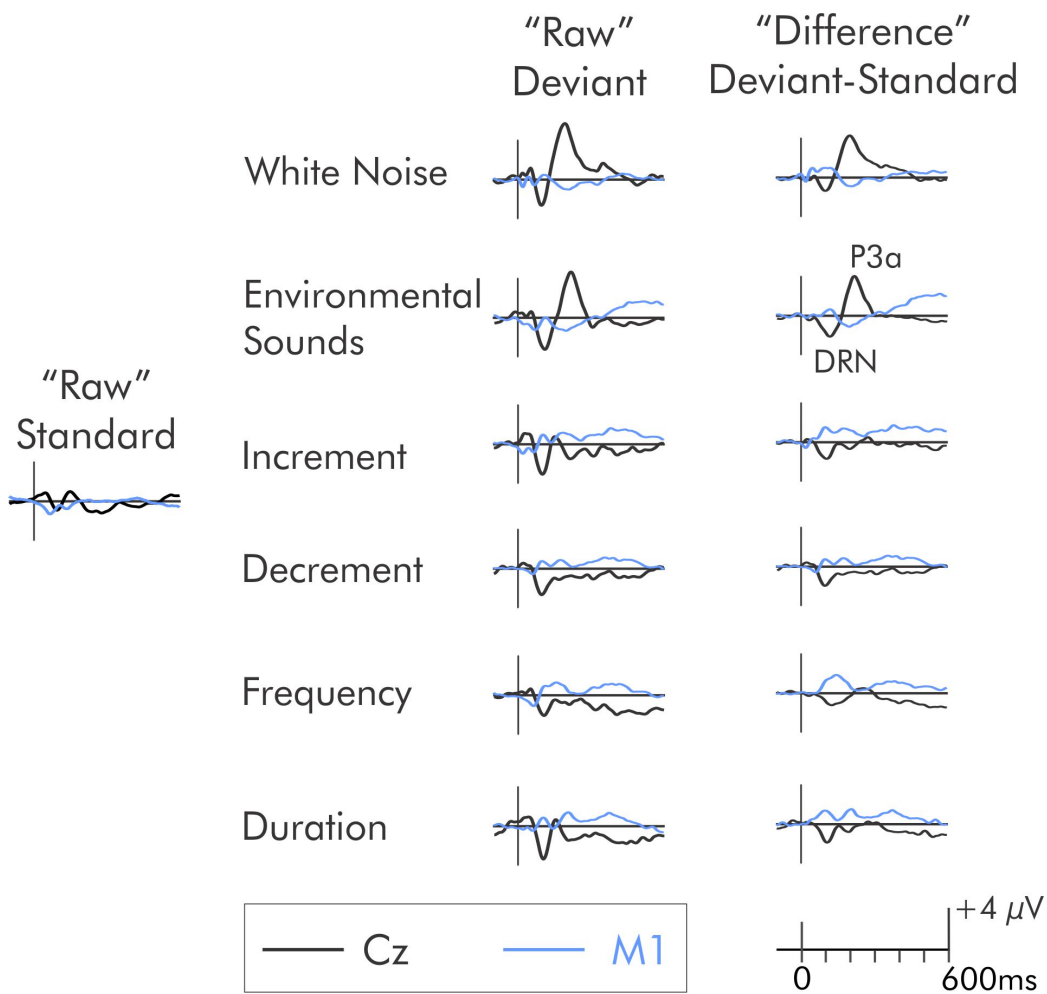


Figure 2. Grand average ERP waveforms in Experiment 1. The left column illustrates the grand average ERP waveform to the standard stimulus. The middle portion illustrates the raw ERP for the six different deviants at Cz and the left mastoid. The right portion

provides the deviant-standard difference waves for the six deviants. As may be observed, a DRN is apparent for each of the deviants. However, a P3a was elicited only by the white noise and environmental sounds. All other deviants failed to elicit a significant P3a.

2.1.1. Deviant-Related Negativity

The “raw” ERPs for each of the 6 deviants are illustrated in the middle portion of Figure 2. A large negativity at about 120-150 ms is apparent for all deviants. This is the DRN. It is best observed in the right portion of the Figure representing the deviant-standard difference waves. The DRN was maximum over fronto-central areas of the scalp and inverted in polarity at the mastoids. Confidence interval testing (Table 1) revealed that the amplitude of the DRN differed significantly from the zero-voltage baseline for all 6 deviants ($p < .03$ in all cases). A two-way ANOVA with repeated-measures on deviant type (white noise, environmental sounds, intensity increment, intensity decrement, frequency, and duration deviants) and electrode site (Fz and Cz) was conducted. There was no main effect of deviant type, $F(5,40)=0.66$, $MSE=2.71$, $p < .66$, $\eta^2_p=.08$. Similarly, the main effect of electrode site was not significant $F(1,8)=0.30$, $MSE=1.46$, $p < .60$, $\eta^2_p=.03$. The deviant type x electrode site interaction was also not significant $F(5,40)=0.5$, $MSE=0.22$, $p < .77$, $\eta^2_p=.05$.

Deviant type	Amplitude (μV)	95% CI
White noise	-1.29 (1.58)	[- 2.51, -0.07]
Environmental sounds	-2.26 (1.57)	[- 3.48, -1.05]
Increment	-1.97 (1.52)	[- 3.13, -0.80]
Decrement	-1.96 (1.88)	[- 3.41, -0.51]
Frequency	-1.94 (1.61)	[- 3.18, -0.71]
Duration	-1.95 (1.63)	[- 3.21, -0.51]

Table 1. Experiment 1 mean amplitudes (SD in parentheses) and 95% confidence intervals at the Fz electrode site for difference waves at the time interval of the DRN.

2.1.2. P3a

A later positivity, P3a, peaking from 180 to 240 ms after stimulus onset, was observed in the difference wave for some of the deviants. Confidence interval testing (Table 2) revealed that the amplitude of the P3a differed significantly from the zero-voltage baseline for only the white noise and environmental sound deviants ($p < .001$ in both cases). P3a recorded to the four other deviants failed to reach significance. As a result, only the white noise and environmental sounds were included in the analysis of variance. A two-way ANOVA with repeated measures on deviant type (white noise, environmental sounds) and electrode site (Fz and Cz) was conducted. There was no main effect of deviant type, $F(1,8)=0.80$, $MSE=2.31$, $p < .40$, $\eta^2_p=0.91$. There was a main effect of electrode site, $F(1,8)=8.15$, $MSE=1.37$, $p < .02$, $\eta^2_p=0.50$. The P3a was significantly larger at Cz than at Fz. The deviant type $\times$ electrode site interaction was not significant, $F(1,8)=0.09$, $MSE=0.42$, $p < .77$, $\eta^2_p=0.01$.

Deviant type	Amplitude (μV)	95% CI
White noise	5.05 (1.75)	[3.70, 6.40]
Environmental sounds	4.53 (1.41)	[3.45, 5.62]
Increment	0.38 (2.47)	[−1.51, 2.28]
Decrement	0.11 (2.24)	[−1.61, 1.83]
Frequency	0.47 (1.18)	[−0.43, 1.39]
Duration	0.17 (1.38)	[−0.88, 1.24]

Table 2. Experiment 1 mean amplitudes (SD in parentheses) and 95% confidence intervals at the Cz electrode site for difference waves at the time interval of the P3a.

2.2. Discussion

All deviants employed in this study did elicit significant DRNs. The DRN showed a scalp topography typical of that observed in oddball studies; it was larger over fronto-central sites of the scalp and inverted in polarity at the mastoids. These results are thus consistent with the original Näätänen et al. (2004) study, revealing a multi-feature optimal paradigm can be used to record an MMN/DRN to a wide variety of deviants. Only the white noise and environmental sound deviants elicited a significant P3a. This is consistent with oddball studies in which these deviants consistently elicit a large P3a. Moreover, the P3a that was elicited in the present study did have the usual centro-frontal maximum scalp topography. The failure to observe a P3a following the presentation of either the frequency or duration deviant is also consistent with many passive oddball studies. It was surprising that the intensity deviants failed to elicit a P3a. Large 9-10 dB increment deviants, similar to the one used in the present study, have often been reported to elicit a P3a in oddball studies (Macdonald et al., 2008; Muller-Gass et al., 2007; Rinne et al., 2006). While small decrements may not elicit a P3a in oddball paradigms (Rinne et al., 2006), larger 20 dB decrements often have also been observed to do so (Macdonald et al., 2008; Muller-Gass et al., 2007).

The present findings are reminiscent of those of Sorokin et al. (2010) who suggested that while the optimal paradigm might be used for the study of the MMN, it may not be well-suited for the passive study of the P3a. In the oddball paradigm, the memory trace for the standard is assumed to be strengthened with each repetition of the standard. In the multi-feature optimal paradigm, when the deviants vary from the standards on only a single dimension, it is assumed that the deviants also strengthen the

memory trace for the standard for the stimulus features they have in common. It is thus possible that only complex deviants, with more than a single feature differing from the standard can elicit a P3a when a multi-feature optimal paradigm is used. They are acoustically widely different from the repeating standard sound and typically cover a wider range of frequencies and intensities than a pure sinusoidal tone. Thus, even though large increments and decrements may elicit a P3a in an oddball sequence, they may fail to do so in a multi-feature optimal sequence.

To resolve these issues requires a direct comparison of the DRN and P3a elicited by deviants within a multi-feature optimal paradigm to those elicited in separate oddball sequences. Unfortunately, neither Sorokin et al. (2010) nor Pakarinen et al. (2014) did so. This was the purpose of Experiment 2. The white noise and environmental sound deviants were presented in both optimal and oddball sequences. The increment and decrement deviants were also presented in both sequences because previous oddball studies have indicated they might elicit a P3a. On the other hand, the frequency and duration deviants were not run in an oddball sequence because previous studies have indicated they elicit a small or absent P3a. They were however included in the optimal sequence to assure that deviant probability remained constant between Experiments 1 and 2. In addition, the sample size was increased in order to improve the probability of finding statistically significant differences among the various comparisons.

3. Experiment 2

3.1. Results

3.1.1. Standard ERP

Because the DRN and P3a were measured in a difference wave, an assumption is made that the processing of the standards is constant across all conditions. Any differences observed in the difference wave could therefore only be attributed to the additional processing of the deviant. This assumption was tested. Figure 3 depicts the ERPs elicited by the standard auditory stimuli during the optimal and 4 oddball sequences. The amplitude of N1 and P2 were very small because of the fast rate of stimulus presentation. The ERP waveforms elicited by the standards in the 4 different oddball conditions were very similar. As a result, the standard data in the separate oddball sequences were collapsed to compare them directly to those elicited in the optimal condition. For this purpose, a t-test was run at Cz to determine the effects of type of paradigm on the amplitudes of the standard N1 and P2. Their amplitude did not significantly differ between the optimal and oddball conditions ($t < 1$ in both cases). An additional negativity at about 200 ms was also observed in the ERPs following the standard stimulus. This later negativity was about 0.6 μV larger in the oddball than in the optimal condition. The difference in amplitude between the optimal and oddball conditions was significant when measured at Cz, $t(17) = 4.46$, $p < .001$.

Standard ERPs

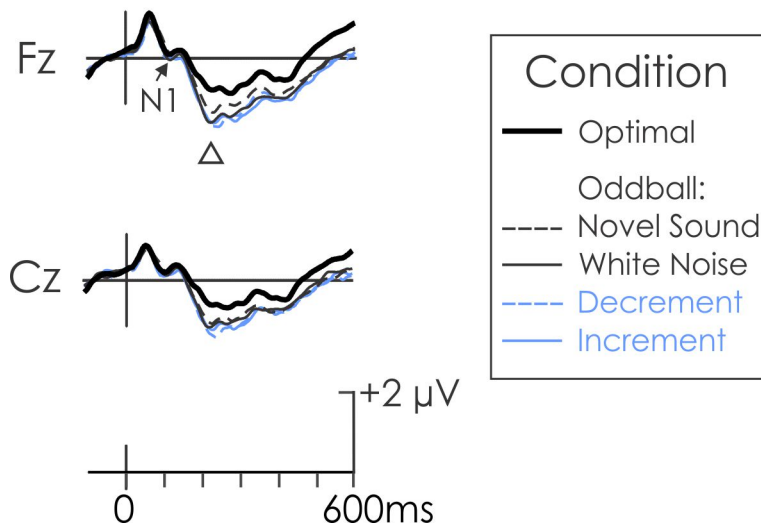


Figure 3. Grand average ERP waveforms to the standard stimulus. Experiment 2 grand average ERPs to the standard stimuli in the optimal (thick line) and oddball (thin lines) conditions. The ERPs elicited in the 4 oddball conditions were very similar and therefore collapsed for further analyses. The amplitude of the N1 and P2 components were not significantly different across optimal and oddball conditions. The amplitude of a later negativity around 200 ms (open arrow) was, however, significantly reduced in the optimal condition.

3.1.2. DRN

The difference waves for the various deviants in the optimal and oddball conditions are illustrated in Figures 4 and 5, respectively. In both conditions, all deviants elicited a DRN maximum over fronto-central regions, peaking at about 100-150 ms after stimulus onset, and inverting in polarity at the mastoids. Confidence interval testing (Table 3) in the optimal and oddball conditions revealed that all deviants in both the sequences elicited a significant DRN ($p < .01$ in all cases). The four-way ANOVA with

repeated-measures on condition (optimal, oddball), deviant type (white noise, environmental sounds, intensity increment, intensity decrement), frontality (frontal, fronto-central, central), and laterality (left, midline, right) was conducted. There was an overall main effect of condition, $F(1,17)=5.68$, $MSE=6.54$, $p<.03$, $\eta^2_p=0.25$; the DRN being slightly reduced in amplitude in the optimal compared to the oddball condition. There was also a main effect of deviant type, $F(3,51)=3.30$, $MSE=15.87$, $p<.03$, $\eta^2_p=0.16$. The DRN amplitude was largest overall to the increment deviant and smallest to the decrement deviant. Importantly, the condition x deviant type interaction was not significant, $F(3,51)=0.54$, $MSE=5.78$, $p<.65$, $\eta^2_p=0.03$. The DRN was largest over frontal sites, $F(2,34)=3.46$, $MSE=0.85$, $p<.04$, $\eta^2_p=0.37$. Additionally, there was a main effect of laterality, with slightly larger amplitudes over the left electrode sites, $F(2,34)=7.11$, $MSE=0.99$, $p<.002$, $\eta^2_p=0.35$. All interactions involving electrode site failed to reach significance ($F<1$, in all cases).

Deviant type	Condition	Amplitude (μV)	95% CI
White noise	Opt ^a	-1.41 (1.80)	[-2.31, -0.52]
	Odd ^b	-1.60 (2.41)	[-2.81, -0.40]
Environmental sounds	Opt	-1.53 (1.62)	[-2.34, -0.72]
	Odd	-1.97 (1.54)	[-2.74, -1.20]
Increment	Opt	-1.70 (1.57)	[-2.48, -0.92]
	Odd	-2.13 (2.12)	[-3.18, -1.07]
Decrement	Opt	-1.21 (0.98)	[-1.69, -0.72]
	Odd	-1.83 (1.85)	[-2.75, -.091]

^a Optimal Paradigm.

^b Oddball Paradigm.

Table 3. Experiment 2 mean amplitudes (SD in parentheses) and 95% confidence intervals at the Fz electrode site for difference waves at the time interval of the DRN.

Optimal Deviant-Standard Difference

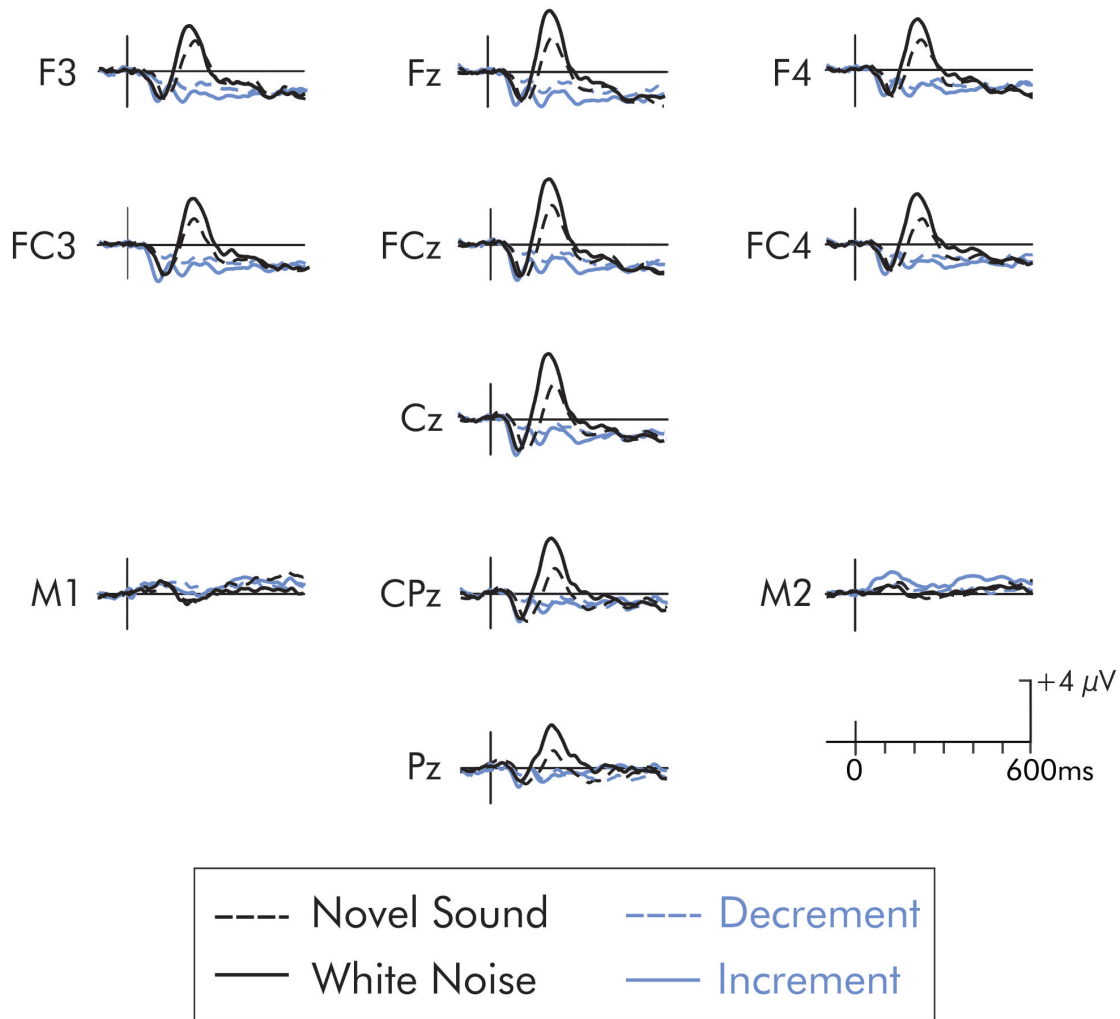


Figure 4. Grand average difference waves in the optimal condition. ERPs to the white noise, environmental sounds, increment, and decrement deviants superimposed. All deviants elicited a DRN. Again however only the white noise and environmental sounds elicited a large amplitude P3a. The increment and decrement deviants failed to elicit a

significant P3a. The P3a was largest over centro-frontal electrode sites, decreasing in amplitude over posterior and inferior regions.

Oddball Deviant-Standard Difference

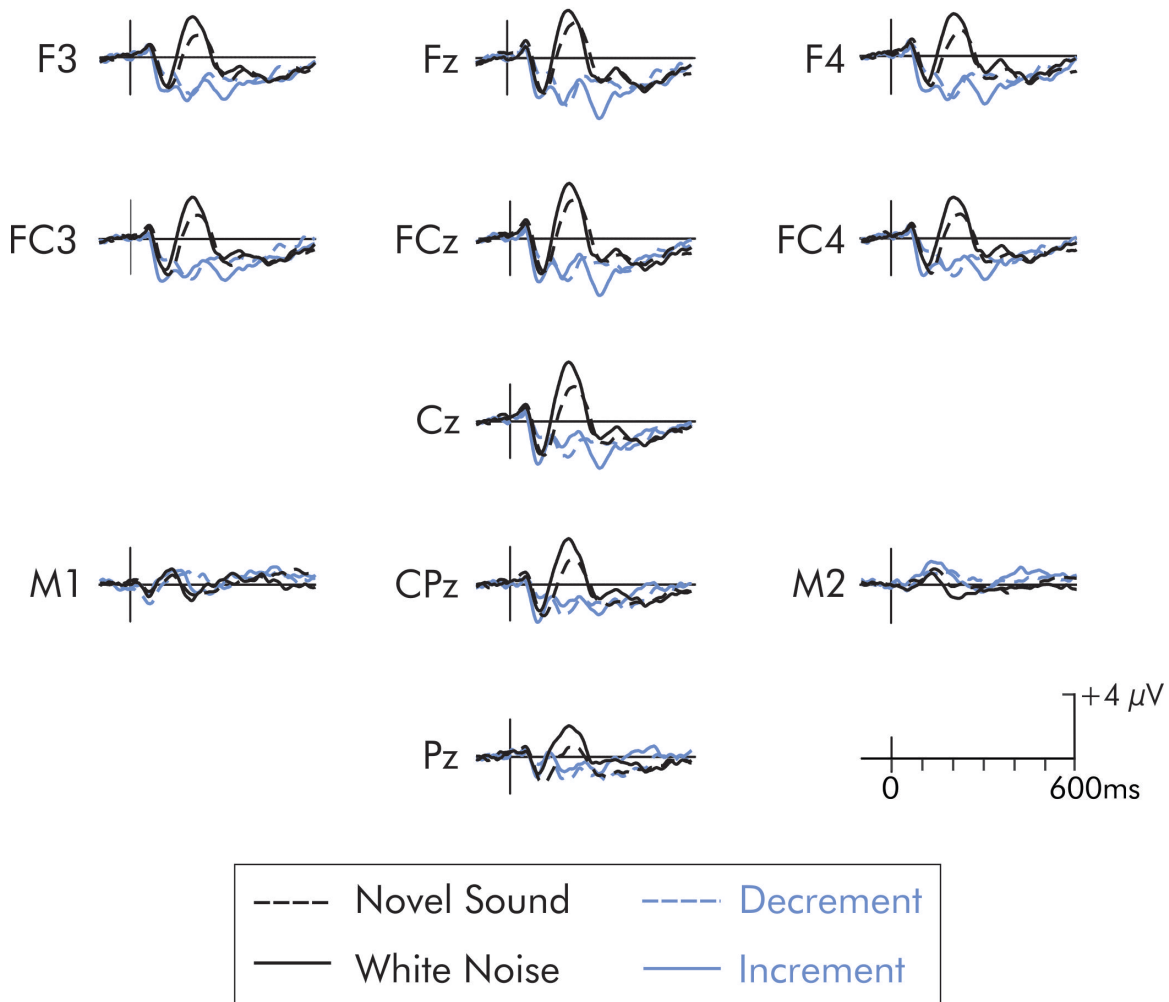


Figure 5. Grand average difference waves in the oddball condition. All deviants elicited a DRN that was significantly larger than in the optimal condition. Only, the white noise and environmental sounds elicited a P3a. The P3a was also larger in the oddball than the optimal condition. The increment and decrement deviants failed to elicit a significant P3a.

Spline scalp distribution maps (Perrin et al., 1989) of the DRN were also computed for each of the four deviant types for both optimal and oddball conditions (Figure 6). As can be observed, the DRN had a fronto-central scalp distribution, with a polarity reversal at the mastoids regardless of the type of deviant and whether the deviant was presented in the oddball or optimal paradigm.

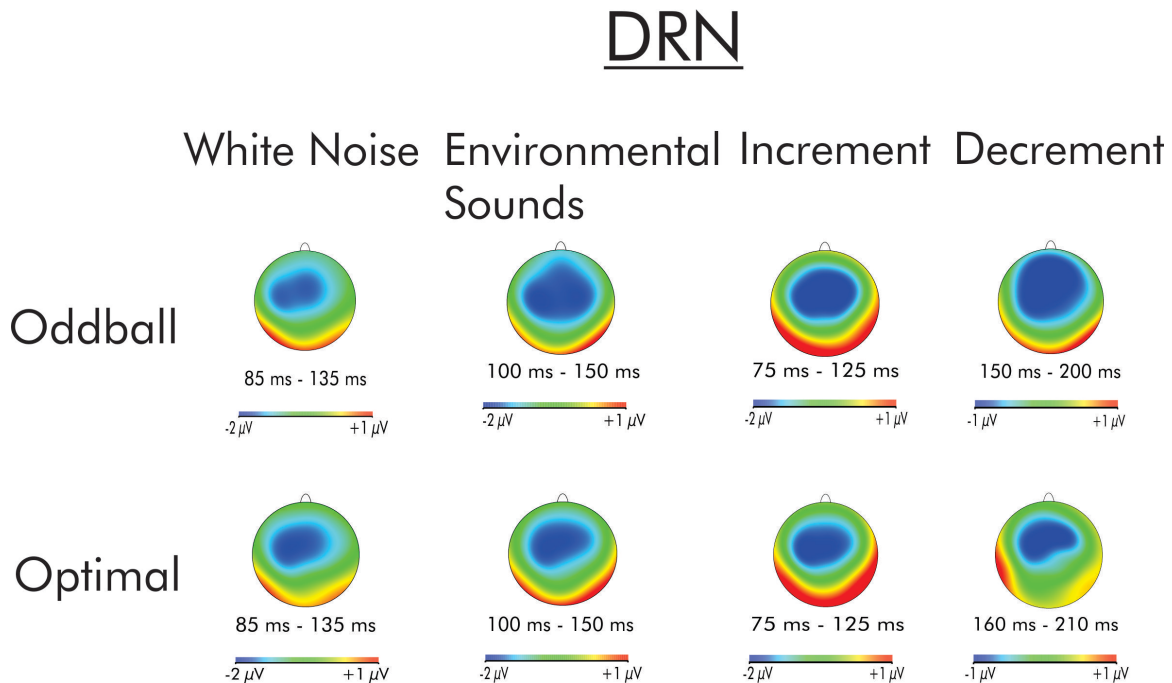


Figure 6. Spline maps of the DRN. The scalp distribution maps of the DRN for the 4 deviants in the optimal and oddball conditions. The scalp distribution of the DRN was very similar across both conditions regardless of the type of deviant. It was largest over fronto-central areas of the scalp and inverted in polarity at the mastoids. Note: because the amplitude of the DRN to the decrement deviant was small, the maximum and minimum scaling range for this deviant was adjusted.

3.1.3. P3a

Table 4 presents the mean amplitudes of the P3a for the various deviants in the optimal and oddball conditions. Confidence interval testing (Table 4) again revealed that only the white noise and environmental sounds elicited a significant P3a in both the optimal and oddball conditions ($p < .002$ in all cases). Neither the increment nor the decrement deviant elicited a significant P3a in either sequence. A four-way ANOVA with repeated-measures on condition (optimal, oddball), deviant type (white noise, environmental sounds), frontality (frontal, fronto-central, central), and laterality (left, midline, right) was run. There was no main effect of condition, $F(1,17)=3.24$, $MSE=15.19$, $p < .09$, $\eta^2_p=.16$. A significant main effect of deviant type was found, $F(1,17)=14.06$, $MSE=18.08$, $p < .002$, $\eta^2_p=.45$. The white noise deviant elicited the largest amplitude P3a (Mean=3.12, SD =0.53 μV) compared to the environmental sound deviants in both the optimal and oddball conditions. Importantly, the condition x deviant type interaction was not significant, $F(1,17)=0.90$, $MSE=4.84$, $p < .35$, $\eta^2_p=.05$. The main effect of frontality was not significant, $F(2,34)=2.03$, $MSE=1.49$, $p < .14$, $\eta^2_p=.11$. There was a main effect of laterality, $F(2,34)=14.22$, $MSE=3.01$, $p < .0001$, $\eta^2_p=.45$. All interactions involving electrode site failed to reach significance ($F < 1$ in all cases).

Spline maps were also computed for the two deviants for both optimal and oddball conditions (Figure 7). The maps were very similar for the white noise and environmental sound deviants independent of the sequence in which they were elicited.

Correlations were also computed for all four deviants in each condition. Bonferroni correction for multiple comparisons was applied with an adjusted p-value of .0125. P3a amplitude to white noise, environmental sounds and decrement deviants were

significantly ($p < .001$) correlated across the two conditions ($r = .81, .79$ and $.73$, respectively). The correlation for the increment deviant was small and not significant ($r = .37, p < .13$).

Deviant type	Electrode	Condition	Amplitude (μV)	95% CI
White Noise	Fz	Opt ^a	3.43 (2.66)	
		Odd ^b	3.84 (3.09)	
	Cz	Opt	3.67 (2.42)	[2.46, 4.87]
		Odd	4.02 (3.21)	[2.42, 5.61]
Environmental sounds	Fz	Opt	1.84 (2.03)	
		Odd	2.95 (2.45)	
	Cz	Opt	1.79 (2.09)	[0.75, 2.84]
		Odd	2.70 (2.68)	[1.37, 4.04]
Increment	Fz	Opt	-1.40 (1.56)	
		Odd	-0.19 (1.63)	
	Cz	Opt	-1.73 (1.42)	[-1.44, 0.16]
		Odd	0.64 (1.61)	[-0.60, 1.15]
Decrement	Fz	Opt	-0.79 (1.34)	
		Odd	-0.01 (1.77)	
	Cz	Opt	-0.41 (1.33)	[-1.08, 0.24]
		Odd	-0.04 (1.37)	[-0.39, 0.56]

^a Optimal Paradigm.
^b Oddball Paradigm.

Table 4. Experiment 2 mean amplitudes (SD in parentheses) at midline electrodes for difference waves at the time interval of the P3a. Confidence intervals (95%) are also reported for the Cz electrode site.

P3a

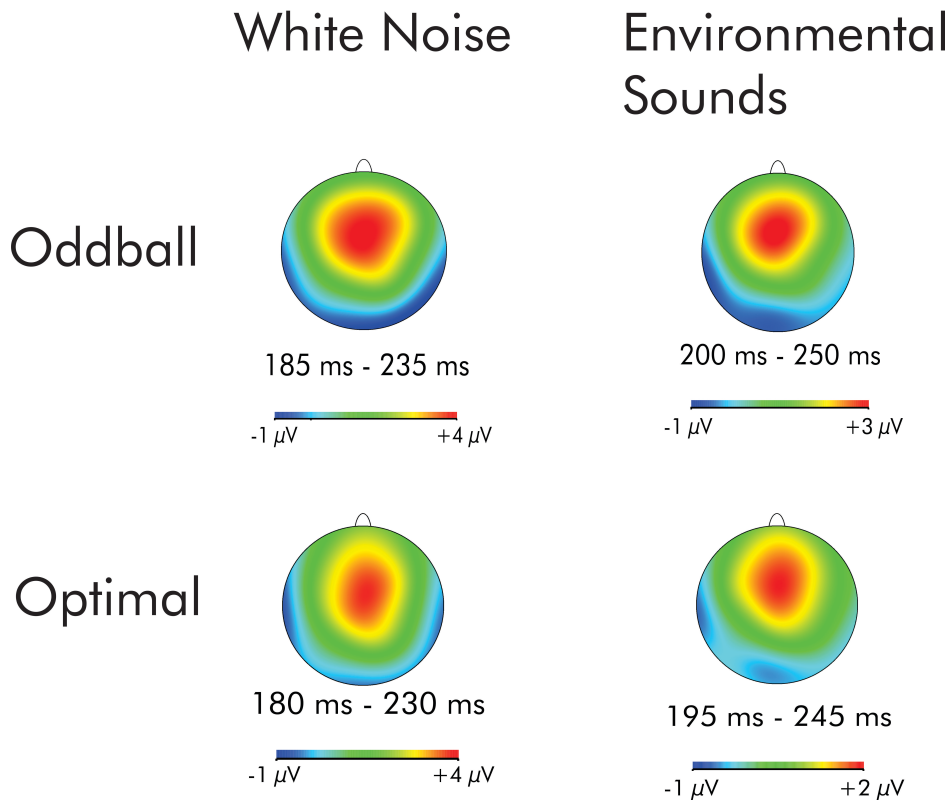


Figure 7. Spline maps of the P3a. Only maps for the P3a elicited by the white noise and environmental sound deviants in the optimal and oddball conditions are illustrated. The scalp distribution of the P3a was very similar across optimal and oddball conditions. The P3a was largest over centro-frontal areas of the scalp and declined in amplitude over lateral and inferior regions. Again, the maximum and minimum scaling range were adjusted between deviants and conditions.

3.2. Discussion

The results of Experiment 1 indicated that a large P3a could be elicited by white noise and environmental sound deviants using a multi-feature optimal paradigm. Previous oddball studies indicated that large increment and decrement deviants also consistently

elicit a P3a. In the initial study, the increment and decrement deviants surprisingly did not elicit a P3a when an optimal paradigm was used. Experiment 2 thus included a direct comparison to separate oddball sequences.

3.2.1. DRN

The results indicated that the multi-feature optimal sequence was successful in replicating effects observed when the very time-consuming separate oddball conditions were run. All deviants again elicited a significant DRN. In Experiment 2, the amplitude of the DRN did significantly vary among the different deviants, regardless of whether they were presented in an optimal or oddball sequence. Importantly, there was no interaction between the type of deviant and oddball-optimal conditions. Thus for both oddball and optimal conditions, the DRN was largest following presentation of the increment and smallest following the presentation of the decrement. Similarly, the scalp distribution maps of the deviants were very similar across optimal-oddball conditions. These findings thus replicate the original Näätänen et al. (2004) findings indicating different types of deviants will affect the MMN similarly in oddball and optimal paradigms. The present study did however observe that the DRN was slightly, but significantly, attenuated in the optimal condition.

3.2.2. P3a

Again, only the white noise and environmental sounds elicited a large P3a when the optimal paradigm was used. This was also the case when the deviants were presented in separate oddball sequences. The P3a tended to be larger in the oddball condition, although the difference did not attain significance. A main effect of deviant type was found for the P3a. It was significantly larger for the white noise deviant. Again, the

critical interaction between deviant type and condition was not significant. Similarly, there was no significant interaction involving condition and electrode site. The P3a topographic maps were very similar for the two types of deviants during the oddball and optimal conditions. There is thus little reason to suspect that the intracranial sources of the P3a observed in optimal and oddball paradigms were different.

The correlations between the amplitude of the P3a observed for the white noise and environmental sound deviants in the optimal and oddball conditions were very high. Thus, even at the individual subject level, subjects who had a large amplitude P3a in the oddball condition also had a high amplitude P3a in the optimal condition. Similarly, those who had a small P3a in one condition also tended to have a small P3a in the other condition.

Experiment 2 thus presents convincing evidence that a single multi-feature optimal sequence can produce results very similar to those obtained in very long and time-consuming separate oddball sequences both at the group and individual level. There is nevertheless a small cost in the use of the optimal paradigm. Both the amplitude of the overall DRN and the P3a were slightly attenuated compared when separate oddball sequences were run. It should also be noted that the processing of the standard stimulus did appear to differ in the two paradigms. The amplitude of the small N1 did not vary between the two. On the other hand, a late 200 ms negativity was significantly larger in the oddball conditions. This may reflect an N1-off response occurring at the time of the offset of the stimuli (Näätänen & Picton, 1987). Its occurrence did overlap both temporally and spatially with the P3a. In the difference wave, the overall P3a would thus have been somewhat reduced, perhaps slightly more for the oddball than the optimal

deviants. Regardless, the relative difference in the amplitudes of the DRN and P3a elicited by the various deviants in the oddball and optimal conditions was dependably preserved.

The 10 dB increment and 20 dB decrement again failed to elicit a P3a when the optimal paradigm was run. The present study does nevertheless convincingly demonstrate that it is not the alternating standard-deviant sequence within optimal paradigm that accounts for the absence of the P3a (Sorokin et al., 2010). When the increment and decrement were presented in separate oddball sequences in Experiment 2, they still failed to elicit a P3a.

The variation in the amplitude of the P3a may be related to the concept of perceptibility of the deviant. It is possible that only the white noise and environmental sound stimuli were readily perceptible and the increment and decrement much less so relative to the standard. This is however unlikely. The perceptibility of a deviant does directly affect the amplitude of the MMN recorded both in the traditional oddball and optimal paradigms (Näätänen, 1992; Näätänen et al., 1993; Novak et al., 1990; Pakarinen et al., 2007; Tiitinen et al., 1997). The DRN in Experiment 2 was largest to the increment deviant, even though a P3a was not subsequently elicited. Still, to determine the perceptibility of the various deviants requires an independent behavioural study. In Experiment 3, subjects were therefore asked to attend to the different oddball sequences and signal their detection of the deviants.

4. Experiment 3

4.1 Results

Table 5 presents the mean accuracy of detection and RT as a function of deviant type. Accuracy of detection was high for all 4 deviants and did not significantly vary, $F(5, 45)=1.03$, $MSE=0.0008$, $p<.41$, $\eta^2_p=.10$. RTs, on the other hand, were significantly affected by deviant type, $F(5, 45)=6.10$, $MSE=1058$, $p<.001$, $\eta^2_p=.40$. Mean RT was fastest for the increment and slowest for the decrement deviant.

Deviant type	Accuracy	RT (ms)
White noise	.98 (.04)	340 (38)
Environmental sounds	.98 (.03)	374 (55)
Increment	.99 (.01)	334 (34)
Decrement	.97 (.03)	394 (40)

Table 5. Mean (SD in parentheses) accuracy and reaction time (RT) during the behavioural detection task.

4.2 Discussion

The final experiment was designed to determine the perceptibility of the deviants employed in these studies. Subjects detected the four deviants with high accuracy. On the other hand, RTs were significantly affected by the type of deviant. The slowest RT was observed to occur with the decrement deviant, and indeed the P3a to this deviant was absent in Experiments 1 and 2. Similarly, the DRN recorded in Experiment 2 was much attenuated for this deviant. The fastest RTs occurred following the presentation of the increment. Consistent with the behavioural data, the increment also elicited the largest DRN. Still, this deviant failed to elicit a significant P3a in either Experiment 1 or 2. Both the white noise and environmental sound deviants elicited a large P3a in Experiment 2

but RTs to these deviants were however slightly slower and the DRN (Experiment 2) attenuated compared to what was observed for the increment.

The behavioural study did employ different oddball sequences for each deviant stimulus. Although similar methodologies have been used in many ERP studies to study perceptibility of the deviant, there are limitations. Such paradigms assume that perceptibility of deviance can be measured by the accuracy and speed of voluntary (conscious) responding following presentation of these deviants. The subject was not asked to respond to the standard and thus the discriminability of the deviant from the standard was not directly tested.

Nevertheless, in spite of these limitations, the behavioural results of the final experiment do indicate that the perceptibility of the deviants is closely associated with the amplitude of the DRN. Their perceptibility do not however appear to be strongly associated with attention capture and the P3a. Berti (2013) also noted that the amplitude of the P3a may not necessarily be affected by the extent of stimulus change.

5. General Discussion

The original Näätänen et al. (2004) multi-feature optimal paradigm was designed to provide a rapid means of recording the series of events associated with the detection of stimulus change and/or violation of acoustic regularity. Their original study indicated that the MMN elicited by varying differences within a single optimal sequence was quite similar to that when the deviants were presented in separate oddball sequences. The primary aim of the present study was to determine if a passive optimal sequence could also be reliably used for the study of the subsequent P3a. The different deviants were selected on the basis of their likelihood of eliciting a P3a based on previous oddball

studies. This was also successful. While some deviants, the white noise and environmental sounds, elicited a large P3a, others, the frequency, duration, increment and decrement deviants failed to do so. When the same deviants were presented in separate oddball conditions, the same pattern of P3a results were again apparent. The scalp distributions of the P3a elicited within the optimal and oddball sequences also did not significantly differ and the maps of the P3a were very similar. The present study also indicated that the amplitudes of the DRN elicited by the different deviants in an optimal sequence were very similar to those elicited in the oddball sequence. Moreover, individual subject variation in the amplitude of the P3a was consistent across both types of sequences. Its amplitude elicited by the white noise and environmental sound deviants within the multi-feature optimal sequence was highly correlated to that elicited by the same deviants within the oddball sequences. The results thus offer very strong evidence that the multi-feature optimal paradigm provides a remarkably rapid means to collect DRN and P3a data very similar to that obtained with separate, tedious oddball paradigms. When 6 different deviants are employed, testing times can be reduced from more than 2 hours to about 20 minutes! Still, some caution may need to be heeded. There was a small cost for the use of the optimal paradigm. The DRN was slightly, but significantly reduced and when a P3a was elicited, its amplitude was slightly attenuated compared to that observed in the oddball paradigm. This might be a function of the alternating standard-deviant pattern in the optimal sequence. Näätänen et al. (2004) indicate that the presentation of pure tone deviants strengthens the memory trace of the standard for those features that both stimuli have in common. However, the presentation of the white noise and environmental sound deviants will only weakly strengthen the memory trace of the

standard because few features are shared. As such, the amplitude of the overall MMN/DRN for all deviants may be smaller.

Although the multi-feature optimal paradigm can be used for the rapid collection of data to study the effects of different deviants on both the MMN/DRN and the P3a, it was somewhat surprising that only the white noise and environmental sound deviants were able to elicit a P3a. A number of previous studies have indicated that large increases in the intensity of the standard will elicit a P3a (Macdonald et al., 2008; Muller-Gass et al., 2007; Rinne et al., 2006). This was not because the optimal paradigm is poorly suited for the study of the P3a (Sorokin et al., 2010). A P3a could not be elicited even when the increment was used as a deviant in an oddball sequence. Also, it was not because the increment was less easily perceived than either the white noise or environmental sound deviants. The increment deviant used in the present series of studies elicited the largest DRN. When subjects were asked to overtly detect the increment deviant occurring in an oddball sequence, behavioural responses to it were more rapid compared to other deviants.

The 200 ms stimulus duration used in the present studies was unusually long. Previous studies that have reported a large P3a to the increment employed brief 50-100 ms duration stimuli. It has been known for some time that perceived intensity of a stimulus is affected by stimulus duration, a relationship called “temporal integration” (Stevens and Hall, 1966; Zwislocki, 1960). Therefore, the perceived intensity of a stimulus increases as the duration of the stimulus is increased. Temporal integration would also affect the perceived intensity of both the standards and deviants and as such

might therefore have affected the likelihood of the increment deviant resulting in attention capture (cf, Schröger, 1996).

The purpose of this study was not to determine why only the white noise and environmental sound deviants were able to elicit a large amplitude P3a. This has however been the subject of recent discussion. Common to these deviants is the fact that their spectral content, of course, varied widely from the standards (Berti, 2012). Because the frequency spectrum of these deviants is very wide, stimulus energy (intensity) will at times be greater than for the standards. It is thus possible that with passive paradigms, only ecologically valid stimuli (those that signal threat) will elicit a P3a. An increase in the intensity of auditory input signals the potentially critical approach of an organism within the environment and is experienced as “looming”, and may elicit a fear response in animals. A decrease in intensity by contrast is experienced as “fading” or retreating (Bach, Schachinger, Neuhoff, Esposito, Salle, Lehmann, et al., 2007; Freiberg, Tually, & Crassini, 2001; Maier & Ghazanfar, 2007). If a P3a can only be elicited by such ecologically valid stimuli, it is of course puzzling why the intensity increment did not do so. Also countering this proposal is the fact that a large decrement in intensity can also elicit a P3a. It is also possible that those deviants that failed to elicit a P3a (all pure tone stimuli) represented only a change in a single feature of the standard.

The scalp distribution of the P3a may consist of an early and later positive peak having distinctive scalp distributions (Escera et al., 1998). Berti (2013) suggests that the early positivity might be a reflection of an overlap between and summation of the P2 and P3a components as a result of sufficient output of both the N1-P2 transient detector system (because of the higher intensity of the deviant at the non-specific standard

frequencies) and the MMN-change detector system (because the deviant reflects change). The rare environmental sound would thus elicit a large P2 at about 200 ms, overlapping with the P3a process. This same reasoning would also apply to the white noise deviant because its intensity also varied from the standard and it also signals change. In the present study, the amplitude of the white noise-elicited P3a was significantly larger than that for the environmental sounds, replicating the findings of Frank et al. (2012). Wetzel et al. (2013) however failed to observe differences in the amplitude of the P3a elicited by environmental sound and white noise deviants. They also reported that the scalp topography of the respective P3a varied, being more fronto-central when elicited by environmental sounds and more central when elicited by white noise. It is possible that wide differences in the experimental protocol could account for these differences. A disadvantage of the use of environmental sound stimuli in the applied context is that the frequency spectrum, intensity and identifiability of such sounds will vary from trial-to-trial because each stimulus is different (Debener et al., 2005). The features of the white noise stimulus can remain constant (as was the case in the present study) and yet elicit a P3a whose morphology is very similar to that elicited by environmental sounds (Frank et al., 2012).

The present study was also not designed to determine the functional significance of the P3a. Again, this has been a topic of recent debate. Undoubtedly, the classic notion that it reflects a switching of attention from the current task-at-hand to a potentially more relevant stimulus input (Escera et al., 1998) no longer seems to be tenable. In studies in which subjects actively attend to the channel containing the auditory stimuli, a number of early studies by Schröger and colleagues did indicate that P3a was closely associated

with behavioural measures of distraction (Berti et al., 2004; Schröger and Wolff, 1998). Thus, performance on a primary task would deteriorate following the presentation of an irrelevant auditory deviant stimulus presumably because processing of the potentially much more relevant deviant (associated with the MMN-P3a process) would automatically divert (or result in a switching of) attentional resources away from the task-at-hand. Fewer resources would thus be available for the processing of this task. More recent studies now indicate that the association between P3a and behavioural measures of distraction is not always this consistent (see discussions by Berti, 2013; Parmentier, 2014; Wetzel et al., 2013). Some studies have reported a low correlation between the amplitude of the P3a and deterioration of performance across groups and different types of deviants. Thus, while a large variation in P3a might be observed, a concomitant variation in performance may not be observed (Berti, 2012; Horvath et al., 2009). Others have found that a deviant might elicit a large P3a and thus should result in a large deterioration in performance, but fails to do so (Parmentier et al., 2010; Wetzel et al., 2013). Others have reported an improvement in performance following the presentation of a deviant that elicits a P3a (SanMiquel et al., 2010). And, others have noted that a deviant can result in a deterioration in performance, yet not elicit a P3a (Rinne et al., 2006). Various explanations for whether the elicitation of a P3a will be associated with behavioral measures of distraction have been offered (see Parmentier, 2014 for an elaborate review). These include the nature of the task (intra-modal or cross-modal), whether the deviant also activates the transient detector system and whether it is predictable. The informational value of the deviant with respect to a target stimulus has also been claimed to have an effect on the P3a and resulting effects on performance, although this

relationship has been recently questioned (Parmentier, 2016). Horvath et al. (2008) suggest that P3a might reflect higher-level detection processing, including the evaluation of events as significant, rather than the actual switch of attention itself. Hoelig and Berti (2010) present evidence that the P3a might reflect the initiation of the switch. The actual switch of attention is dependent on other factors. Wetzel et al. (2013) also support the notion that the P3a reflects a precursory process that occurs prior to the actual switch of attention.

5.1 Conclusion

The purpose of the present set of experiments was to determine whether a multi-feature optimal paradigm could reliably be employed for the study of the P3a, an ERP component associated with attention capture. Of the 6 deviants that were presented, only white noise and environmental sounds were able to elicit a P3a. When separate oddball sequences were run, a P3a was again only elicited in those sequences in which white noise or environmental sounds acted as deviants. The scalp distribution maps of the P3a elicited in the optimal and oddball paradigms were also very similar. The P3a that was elicited in the optimal paradigm was nevertheless somewhat reduced. The optimal sequence does therefore provide a time-saving and highly reliable paradigm to study DRN and P3a processes resulting in a very large reduction in testing time compared to the alternative, separate presentation of several oddball sequences.

6. Experimental Procedures

6.1 Experimental Procedure for Experiment 1

6.1.1 Subjects

Nine subjects (6 females) between the ages of 20 and 30 years ($M = 23.8$, $SD = 3.1$ years) volunteered to participate in this study. None had any reported history of neurological, psychiatric, or hearing disorders. This study was approved by the University of Ottawa Research Ethics Board following the guidelines of the Canadian Tri-Council (Medical, Natural and Social Sciences) on ethical conduct involving human subjects. These guidelines are similar to those used by the Declaration of Helsinki. In accordance with these guidelines, all subjects gave written consent and the nature of the experiment was explained to them. All subjects received an honorarium for their participation.

6.1.2 Procedure and Stimuli

Auditory stimuli were presented monaurally to the right ear through EAR 3A insert earphones while the subject sat in a sound-attenuated room watching a silent, subtitled video. Subjects were asked to ignore the auditory stimuli. Ear of presentation has however little effect on the P3a (Grimm et al., 2008).

The auditory multi-feature optimal paradigm consisted of an alternating standard and deviant sequence. However, 6 different deviants were presented. Thus, the standard occurred on 50% of trials while a specific deviant occurred on 8.33% of trials (i.e., the probability of overall deviant occurrence was also .50). The standard auditory stimulus was an 80 dB SPL 1000 Hz pure tone.. Deviants in the optimal sequence included (a) a 90 dB SPL 1000 Hz increment tone, (b) a 60 dB SPL 1000 Hz decrement tone, (c) a higher frequency 1100 Hz 80 dB SPL tone, (d) a shorter duration 100 ms, 80 dB SPL 1000 Hz tone (e) an 80 dB peak SPL white noise burst, and (f) environmental sounds (with an average intensity of 80 dB SPL). A different environmental sound was presented

on each trial so that none of the environmental sounds were repeated. All stimuli had a duration of 200 ms (with the exception of the duration deviant) and a rise-and-fall time of 5 ms. The deviants were pseudo-randomized so that in an array of 6 deviants, each of the different deviants was presented once. In different arrays, the order of presentation of the six deviants was randomized. The last deviant in an array could not also appear as the first deviant in the subsequent array. The first 15 tones in the sequence consisted entirely of standards. The SOA (onset-to-onset) was 600 ms. In total, 932 stimuli were presented in a sequence lasting about 9.5 min. The sequence was presented a second time with a short break between presentations.

6.1.3. EEG/ERP Recording

The EEG activity was recorded from 29 scalp sites across frontal, central, temporal, parietal, and occipital areas of the scalp using silver-silver chloride passive electrodes embedded in an electrode cap. Two additional electrodes were placed on the left and right mastoids (M1 and M2). Vertical eye movements and blink artifacts were recorded from an electrode placed on the infra-orbital ridge of the left eye (lower EOG). The nose served as a reference for all channels, including the EOG. Inter-electrode impedances were kept below 5 k Ω . The physiological data were digitized continuously at a 500 Hz sampling rate and stored on hard disk for later analyses. The time constant was 2 s.

Offline, the data were reconstructed using Brain Products' Analyzer2 software. The continuous EEG data was digitally filtered using a low-pass filter set at 20 Hz. The EEG was visually inspected for channels containing high levels of noise. These channels were replaced by interpolating the data of the surrounding electrode sites (Perrin et al.,

1989). A vertical EOG channel was computed by subtracting activity recorded at FP1 from that of the lower EOG. A horizontal EOG channel was computed by subtracting FT9 activity from that of FT10. Independent Component Analysis (Chaumon et al., 2015; Makeig et al., 1996) was subsequently used to identify eye movements and blink artifacts that were statistically independent of the EEG activity. This algorithm was trained to recognize each subject's blink signature, and this factor was then partialled out of the EEG traces. The continuous data were subsequently reconstructed into single, discrete 700 ms epochs, beginning 100 ms before stimulus onset. The average of the activity in the 100 ms pre-stimulus period served as a zero voltage baseline. Drifts in voltage from the baseline were then corrected for each epoch. Epochs in which EEG activity exceeded $\pm 100 \mu\text{V}$ were excluded from further analyses. The single epochs were then sorted and averaged on the basis of stimulus type (standard, different types of deviants) and electrode site.

6.1.4. Quantification and Statistical Analyses

The auditory deviant stimuli elicited a series of deflections not apparent for the standard, including an early DRN and for some deviants, a P3a. These additional deflections are best observed in a difference wave computed by subtracting point-by-point the average of the standard from that of the deviant. The subtraction process removes processing that is common to both the standard and the deviant. The DRN and P3a were initially identified in the grand average (average of all subjects' averages) difference wave. In individual subjects, the DRN and P3a were quantified as the mean of all data points within ± 25 ms of the peak amplitude identified in the grand average.

Significant differences among the deviants for either the DRN or P3a would usually be determined through the use of an ANOVA statistical procedure. A purpose of this initial study was to determine if any of the different deviants could elicit a P3a. The observation of a significant difference in the amplitude of the P3a among the deviants cannot be used as evidence that all deviants, in fact, elicited the component. To avoid this ambiguity, it is first necessary to demonstrate that significant DRN and P3a components were elicited by each deviant. Confidence intervals were therefore computed for the amplitude of the DRN and P3a in the difference wave for each deviant. This procedure determined the probability that amplitude values fell within an upper and lower range relative to the zero voltage pre-stimulus baseline level. Thus, in the case of DRN, when the upper limit of a confidence interval was significantly less than 0 μV , (i.e., was negative-going), the interval was considered to contain a significant negativity. In the case of P3a, when the lower limit of a confidence interval was significantly more than 0 μV , (i.e., was positive-going), the interval was considered to contain a significant positivity. This procedure is equivalent to computing a t-test between the standard and deviant waveforms (Winer et al., 1971). This procedure was run on the Fz data for the DRN and for the Cz data for the P3a, where they tend to be maximum in amplitude. Because a negative directionality was predicted in the case of the DRN and a positive directionality was predicted in the case of the P3a, one-tailed tests of significance ($p < 0.05$) were applied to the confidence intervals. To restrict the likelihood of chance findings, the DRN had to conform its usual latency (100–250 ms) and scalp distribution (fronto-central maximum and an inversion in polarity at the mastoids) while the P3a also had to conform its usual latency (180–350 ms) and scalp distribution (centro-frontal

maximum). Only those deviants that elicited a significant DRN or P3a were later compared using the ANOVA procedure. Post-hoc testing (Fisher's LSD) was applied to significant main effects of the ANOVA procedures.

6.2. Experimental Procedure for Experiment 2

The methods employed in Experiment 2 were quite similar to those in Experiment 1.

Only differences between the two experiments will be described.

6.2.1. Subjects

A larger sample size was tested in this experiment. Eighteen subjects (16 females) between the ages of 20 and 32 years (Mean = 23.6, SD=3.6) volunteered to participate in this experiment. All had self-reported normal hearing with no history of neurological or psychiatric disorders. None of the subjects had participated in the previous described Experiment 1. Again, this study was approved by and conducted according to the guidelines of the Canadian Tri-Council on ethical conduct involving human subjects.

6.2.2. Procedure and Stimuli

The subject's task was again to watch a silent video. The auditory stimuli were thus to-be-ignored.

6.2.2.1. Optimal Sequence. The same auditory optimal sequence used in Experiment 1 was again run. Stimuli thus included a standard 80 dB SPL 1000 Hz tone and 6 different deviants, including the frequency, duration, increment, decrement, white noise and environmental sounds.

6.2.2.2. Oddball Sequences. Four separate auditory oddball sequences were also run. Each sequence consisted of a frequently occurring "standard" ($p=0.92$) and rarely

occurring “deviant” ($p=0.08$) stimuli. In each sequence, the standard was an 80 dB SPL 1000 Hz tone. The same standard was thus used in the oddball and optimal sequences. In different conditions, different features of the standard were changed to form the deviant, (a) a 90 dB SPL 1000 Hz increment, (b) a 60 dB SPL 1000 Hz decrement, (c) an 80 dB peak SPL white noise burst, or (d) different environmental sounds having an average intensity of 80 dB SPL. The frequency and duration deviants were not run in separate oddball sequences. The deviants occurred pseudo-randomly with the restriction that at least 3 standards followed the occurrence of a deviant. In addition, both the optimal and oddball sequences began with the presentation of 15 standards allowing a brief-lasting sensory memory for the standard to be well established. As in Experiment 1, all stimuli had a duration of 200 ms with a rise-and-fall time of 10 ms. The SOA (onset-to-onset) was again 600 ms. A total of 932 stimuli were presented in a block lasting about 9.5 minutes. The optimal and each oddball condition were presented two times. The order of presentation of the different oddball and optimal sequences was randomized. A 2-3 minute break was given between sequences.

6.2.3. ERP/EEG Recording

The EEG activity was recorded from additional electrode sites to increase spatial sampling. The EEG was recorded from 61 sites across frontal, central, temporal, parietal, and occipital areas of the scalp using silver-silver chloride electrodes embedded in an electrode cap (Brain Products, GmbH, Munich, Germany). Two additional electrodes were placed on the left and right mastoids (M1 and M2). Similar to Experiment 1, the nose served as a reference for all channels. All other ERP/EEG recording and analysis parameters were identical to Experiment 1 (see section 2.1.3.).

6.2.4. Quantification and Statistical Analyses

As in Experiment 1, the DRN and P3a responses were isolated in a difference wave. The peak of the DRN and P3a components were again identified in the grand average and quantified in individual subjects as the mean of all data points in the ± 25 ms interval surrounding the peak. Confidence interval testing was initially conducted to determine whether the component of interest was significantly different from the zero-voltage baseline. Only those deviants that elicited a significant DRN or P3a were considered for additional statistical analyses. These additional analyses also included a region of interest (ROI) factor to compare fronto-central electrode sites (F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4) because the DRN and P3a responses are largest over these scalp sites. For both the DRN and P3a, a four-way analysis of variance was conducted with repeated-measures on condition (optimal, oddball), deviant type (white noise, environmental sounds, increment, decrement), frontality (frontal, fronto-central, central), and laterality (left, midline, right). In addition, correlation analyses were conducted on the individual subjects' P3a amplitudes for the four deviants employed in both optimal and oddball conditions. Bonferroni correction for multiple comparisons were applied to these multiple correlations.

6.3. Experimental Procedure for Experiment 3

6.3.1. Subjects

Ten subjects (7 females) between the ages of 22 and 30 (Mean=24.6, SD=2.4) volunteered to participate in this experiment. All had self-reported normal hearing with no history of neurological or psychiatric disorders. None of the subjects had participated in either Experiments 1 or 2. This study was again approved by and conducted under the

guidelines of the Canadian Tri-council (Medical, Natural and Social Sciences) on ethical conduct involving human subjects.

6.3.2. Procedure and Stimuli

Subjects were presented with the four different auditory oddball sequences described in Experiment 2 (see section 6.2.2.2). They were instructed to button press upon hearing the rare deviant stimulus (i.e., a change from the frequently occurring standard). Again, the probability of the deviant was 0.08. Each oddball sequence consisted of a total of 282 stimuli, lasting approximately 4.5 minutes.

Responses occurring within 200-1200 ms after the onset of the deviant were identified as correct responses. Mean accuracy of detection and reaction times (RT) were measured for the 4 deviants. A one-way analysis of variance (ANOVA) was conducted separately for both accuracy of detection and RT.

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Chapter 3

Study 2: Highly relevant stimuli may passively elicit processes associated with consciousness during the sleep onset period.

Rational: Not all deviants will elicit a P3a in the waking state. The first study indicated that deviants that vary widely from the standard are more likely to elicit a P3a when subjects are awake and conscious. Very little is known, however, about the changes that the P3a undergoes during the transition from a waking state to a sleeping state, marked by sleep onset. Long-latency ERPs are especially affected by this transition. Some studies have required subjects to button press upon detection of the rarely occurring deviant (or “target”) stimuli during the sleep onset period. This procedure, however, requires subjects to sustain attention (and thus to remain conscious) and may obviously influence the sleep onset period. Very few studies have used passive paradigms in which the subject ignores the auditory stimuli to systematically investigate the types of deviants that may interrupt the central executive during the sleep onset period. The few studies that have examined the P3a have used oddball paradigms and have reported mixed results. Some authors have observed a small amplitude P3a while others have failed to observe a P3a during sleep onset. Differences in the type of deviants that have been employed could account for the inconsistent findings. A major problem with the use of different oddball sequences is that the sleep onset period can be very short, lasting only a few minutes in some subjects. Study 2 of this thesis uses the time-efficient multi-feature optimal paradigm employing 6 different deviants to attempt to reconcile the inconsistencies in the literature.

Study 2 has been accepted for publication in the journal *Consciousness and Cognition*, subject to revision. It is formatted based on the requirements of the journal.

Tavakoli, P., Varma, S., & Campbell, K. (under review). Highly relevant stimuli may passively elicit processes associated with consciousness during the sleep onset period. Submitted to *Consciousness and Cognition*.

1. Introduction

A number of neuroscience methods have been proposed to study the process by which individuals can become conscious of the external environment during apparently unconscious states (for reviews, see Koch et al., 2016; Laureys & Tononi, 2009; Massimini et al., 2009). In this context, consciousness can be defined as “awareness” of external environmental events. During unconscious states such as coma, general anaesthesia, and natural sleep, the individual appears to be profoundly unaware of their external environment (for reviews, see Morlet & Fischer, 2014; Sanders et al., 2012). The present study examines the sleep onset period, marking the transition from a waking, conscious state to one of sleep and unconsciousness. This type of study can also be carried out using general anaesthetics although there are many concerns. Obviously, the risk of serious injury is not incidental. Moreover, drug-induced unconsciousness is not natural and unlike sleep, cannot easily be reversed.

The present study examines the extent of processing of acoustic change during the sleep onset period, a period of time when awareness of the external environment is gradually lost. In order to study acoustic change, an unchanging homogeneous, frequently occurring auditory stimulus is presented rapidly. At times, this stimulus is changed. The brain is equipped with mechanisms capable of rapidly detecting acoustic change and taking appropriate action should the need arise. The detection of acoustic change may be critical for survival. A major difference between sleep and other unconscious states is that the sleep state is rapidly reversible. The sleeper must evaluate all incoming stimuli for potential relevance, such as biological and/or personal information (e.g. a very intense stimulus, the interruption of breathing, a baby’s cry), in order to force an awakening to

take appropriate action. Yet for sleep to be of benefit, it needs to remain as undisturbed as possible, and only interrupted when the stimulus input is potentially highly relevant.

Therefore, even during sleep, a decision must be made about whether new stimulus input is so highly relevant and critical that it requires an arousal to wakefulness, or whether it is, in fact, irrelevant allowing sleep to remain undisturbed.

Sleep is not a uniform state. It consists of a series of sub-stages. Changes in EEG frequency bands and other physiological signals, especially eye movement (EOG) and muscle (EMG) activity, are used to differentiate between these sub-stages. During wakefulness, the EEG shows low amplitude, high frequency (>15 Hz) beta activity and lower frequency (8-12 Hz) alpha activity. Non-REM (NREM) sleep can be subdivided into stages N2 and N3 and the EEG is mostly dominated by high amplitude, lower frequency theta (4-7 Hz) and delta (0.5–3 Hz) activity (for a review, see Scammell et al., 2017).

The sleep onset period, largely involving what is called stage N1 sleep, is characterized by a reduction in the relative amount of beta and alpha activity, and the appearance of slower theta waves compared to wakefulness. A number of other physiological changes are also apparent, such as rolling eye movements, changes in heart rate, respiration, muscle tonus, and temperature. Foulkes and Vogel (1965) observed the presence of dream-like mentation during the pre-sleep waking period in which the EEG was dominated by alpha activity. They suggested that the onset of the transition into sleep might precede the traditional stage N1 classification of sleep onset. Because of the changes in so many different activities, the definition of actual sleep onset is somewhat problematic. Some researchers employ a behavioural definition of sleep onset. Thus,

subjects are said to be asleep when they no longer are able to respond to external target stimuli. Subjects are still capable of overtly responding to external stimuli in what has been traditionally defined as stage N1 according to physiological criteria (Bastuji et al., 1995; Cote et al. 2002; Colrain et al. 2000; Johnson et al., 1976; Ogilvie et al., 1991), although lapses in performance and the presence of micro sleeps are often observed (Williams et al., 1962). Overt responses are rare during stage N2 sleep. For this reason, the appearance of phasic events associated with stage N2 (e.g. K-Complexes and spindles) have often been used to define onset of sleep. Other laboratories emphasize the appearance of delta slow waves to be more representative of sleep onset during the initial portion of stage N2 sleep (Marzano et al., 2013), although even in these instances there appears to be two different types of slow waves based on their rate of occurrence, amplitude, and scalp distribution (Siclari et al., 2014).

Hori et al. (1994) developed a 5-point scoring system based on characteristic EEG patterns appearing at sleep onset. According to this system, the standard sleep stage N1 is divided into three EEG stages II, III, and IV. The waking state is classified as EEG stage I while the standard stage N2 sleep is classified as EEG stage V. They found that the hypnagogic dream-like state, the period immediately prior to sleep, likely started a few minutes prior to the start of stage N1 and continued for a few minutes past the start of stage N2. Tanaka et al. (1996) further extended this by examining changes in hypnagogic EEG by using a 9-point EEG stage classification system. They observed that each EEG stage lasted on average approximately 30 seconds to 2 minutes. A difficulty with the use of these detailed classification systems is that the duration of each sub-stage is often too brief to reliably examine responses to external stimuli within each sub-stage. Colrain et

al. (2000) and Gora et al. (1999) subdivided stage N1 into early and late sub-stages based on the proportion of alpha and theta activity. Both studies showed differential brain responses to external stimuli based on whether the EEG within stage N1 was dominated by alpha or theta activity.

1.1 ERPs

A major difficulty encountered in the study of information processing during sleep is that the experimenter does not have direct access to the sleeper's mental state. For instance, the sleeping subject is usually unable to provide either a verbal or behavioral response to external stimuli or queries. Thus, even if they were conscious of the external environment, they may be unable to signal this to the experimenter. The absence of an overt response cannot be used as evidence of the absence of conscious awareness of the stimulus. It is of course possible to awaken the subject and ask them to recall their mental activity. The reliability of such subjective recall is questionable. A failure to recall events immediately prior to awakening may reflect a failure of memory storage or retrieval rather than a lack of awareness of the external stimulus.

Event-related potentials (ERPs) provide an exquisite method to examine the extent of information processing during the transition into sleep during which the subject may no longer signal awareness of an external stimulus (for reviews, see Campbell et al., 1992; Drykstra et al., 2017; Koch et al., 2016). During wakefulness, all auditory stimuli elicit an obligatory negativity at about 100 ms, ("N1") followed by a positivity at about 200 ms ("P2"). The obligatory N1 and P2 deflections are mainly affected by the physical properties of the stimulus and are especially large to loud and infrequently presented auditory stimuli.

1.1.2 Processing of Acoustic Change

Many studies employ a so-called auditory oddball paradigm to study acoustic change. The subject is presented with a rapidly presented and frequently occurring homogenous “standard” stimulus. At rare (or “odd”) times, a feature is changed to form a “deviant” stimulus. The subject is often asked to ignore the auditory sequence of stimuli while attending to another, typically visual, task. The auditory ERPs are thus elicited passively, independent of attention. Such processing is thus said to be pre-attentive, or pre-conscious. The presentation of the standard elicits the obligatory N1-P2. The deviant stimulus also elicits an obligatory N1-P2, but in addition, another later negativity, the mismatch negativity (MMN), signalling the detection of acoustic change (Näätänen, 1990; 1992).

The MMN occurs at about 100-200 ms following stimulus onset and is largest over frontal areas of the scalp, inverting in polarity at the mastoids. In the classic Näätänen model (1990; 1992), the MMN is associated with a pre-conscious memory-based comparison system in which the features of the incoming stimulus are compared against the features of the preceding stimuli (the standard) stored in sensory memory. Following presentation of another standard, the sensory memory is improved. However, when a deviant is presented, one of its features fail to match those stored in sensory memory and change is detected. A more recent model maintains that the MMN is elicited by a mismatch between the current auditory input and the predictions formed on the basis of the trends or rules that are automatically detected in recent auditory stimulation (Näätänen et al., 2011; Paavilainen, 2013; Winkler, 2007; Winkler et al., 2009), the repeating, homogenous standard thus being a special case of an acoustic pattern. The

output of the change detection system varies directly with the extent of stimulus change, the amplitude of the MMN reflecting this output. The MMN can be elicited by a change in almost any feature of the standard stimulus including its frequency, location, duration, and intensity (for reviews, see Garrido et al., 2009; Näätänen et al., 2007). In the case of a change representing an increase in stimulus intensity, the negative-going ERP that is observed is not a “true” MMN. This is because the amplitude of the N1 would be larger for the deviant than the standard. The increase in intensity also signals stimulus change and thus would also elicit an MMN. The negativity that is observed following presentation of this deviant would represent a composite N1+MMN. This composite negativity is often called a deviant-related negativity (DRN). In this article, for consistency, the negativity following deviants will be described as a DRN.

The output of the change detection system varies directly with the extent of deviance. If the output is large enough, an interrupt is sent to the central executive resulting in a sequence of events that may culminate in a switch of attention from current cognitive demands and to a probing of the auditory channel. This “capture of attention” (James, 1890) has been associated with a later 200-250 ms positivity, maximum over centro-frontal areas of the scalp, the P3a (Escera et al., 1998). There is currently some debate about whether the P3a reflects the actual switch of attention toward incoming auditory stimuli or the precursor process that leads to conscious awareness (for reviews, see Parmentier, 2014; Wetzel et al., 2014). The current understanding is that the presence of the P3a reflects at least higher-level detection processing, such as the evaluation of events as significant (Horvath et al., 2008; Holig & Berti, 2010; Wetzel et al., 2013). The central executive may then make a decision to switch attention away from current task

demands, leading to the process of involuntary capture of attention by the intruding event.

In the waking state, while any perceptible stimulus change will elicit a DRN, only a small number of these deviants will also elicit a P3a. Deviants whose features vary widely from pure tone standards, such as novel environmental sounds (e.g., musical instruments, animal sounds) have been demonstrated to elicit a large amplitude P3a in the waking state (Combs & Polich, 2006; Frank et al., 2012; Kushnerenko et al., 2007; Wetzel et al., 2013; Wetzel & Schröger, 2007). Similarly large amplitude P3as have also been observed following white noise deviants (Cahn & Polich, 2009; Combs & Polich, 2006; Frank et al., 2012). Both of these deviants vary widely in spectral content compared to pure tone standard stimuli. A change in a single feature of the standard stimulus can also elicit a large P3a especially if the change represents an increase in the intensity of the standard (Macdonald et al., 2008; Muller-Gass et al., 2007; Rinne et al., 2006). By contrast, deviants that reflect decreases in intensity or small changes in the frequency, duration or location will elicit only a small amplitude or absent P3a (Grimm et al., 2008; Macdonald et al., 2008; Muller-Gass et al., 2006; 2007; Rinne et al., 2006).

1.2 Sleep Onset

Early sleep onset studies have tended to use active rather than passive oddball paradigms. Subjects are asked to overtly signal their detection of the rare acoustic change. The behavioural response thus serves as evidence that the subject was in fact conscious of the rare “target”. Detection of the target is associated with the P3b, a positive-going component maximum over parietal regions of the scalp (Sutton, 1967). The P3b can be contrasted with the P3a; the P3b occurs later, around 300-400 ms, and

has a more centro-parietal scalp topography. Importantly, the P3b requires active detection of the rare target while the P3a can be elicited passively in the absence of attention to the auditory channel. When subjects fail to detect the target or are asked to ignore the stimulus sequence, the P3b is not elicited. Bastuji et al. (1995) employed an active oddball paradigm and showed a slight attenuation of the P3b during stage N1. However, this could be because trials in which subjects accurately detected the target and trials in which they failed to do so were averaged together, resulting in an appearance of an attenuation of the P3b. When Cote et al. (2002) sorted trials according to accuracy of target detection, the P3b remained large during stage N1 as long as subjects signalled detection of the target. The major attenuation occurred when subjects failed to signal detection of the target. Colrain et al. (2000) asked subjects to keep a running count of the rarely occurring target stimuli. They subdivided stage N1 to determine whether alpha-dominant or theta-dominant EEG would differentially affect information processing. They noted that during alpha-dominant stage N1, the P3b was similar to that recorded in wakefulness occurring at about 320 ms while during theta-dominant stage N1, a positivity was still apparent but occurred at about 400 ms. The authors suggested that this was probably a sleep-unique P450 rather than a P3b. Similarly, Strauss et al. (2015) observed a P3b during the early phases of stage N1, which they labelled as stage N1 responsive. The P3b was no longer observed during the later phases of stage N1, and thus labelled it as stage N1 non-responsive.

A critical problem with the use of active paradigms during sleep onset is that the requirement for subjects to actively attend to the auditory stimuli may in itself affect the sleep onset process. Moreover, when subjects are asked to actively attend to the auditory

channel during the sleep onset period, it is then difficult to compare these results to those of actual sleep, when subjects are obviously no longer attentive. For these reasons, more recent studies have tended to use passive paradigms, in which the subject is not attending the auditory stimuli (Chen et al., 2016; Macdonald et al., 2008; Ruby et al., 2008; Sabri et al., 2003; Strauss et al., 2015)

A problem with the recording of ERPs during sleep onset and sleep is that some waking ERP components may be absent during sleep, some may become dramatically enhanced, while others appear to be unique to sleep and cannot be recorded at all during wakefulness. During wakefulness, all auditory stimuli elicit the N1 and P2. The obligatory N1-P2 are mainly affected by the physical properties of the stimulus and are especially large to loud and infrequently presented auditory stimuli. N1 and P2 undergo dramatic changes during sleep onset (for a review, see Campbell & Colrain, 2002). N1 gradually decreases in amplitude during sleep onset until it reaches near-baseline levels during stage N2 sleep. On the other hand, P2 has been observed to increase in amplitude during sleep (Cote et al., 2001; Crowley et al., 2002; Harsh et al., 1994). During stage N2, stimuli may also elicit a large negativity at about 300 to 350 ms (“N350”). This N350 is unique to sleep and is quite similar to the often-reported vertex sharp wave, associated with sleep onset (Colrain et al., 2000b). The N350 may be followed by a positivity at about 450 ms (“P450”). A very infrequently occurring stimulus may also elicit a K-Complex during NREM sleep, which consists of an extremely large amplitude negativity (“N550”), followed by a later positivity (“P900”). By contrast, in the waking state, the amplitudes of N1 and the MMN may not exceed 1 μ V.

1.2.1 DRN and P3a during sleep onset and sleep

Results of previous studies examining the DRN during stage N2 sleep are inconsistent. Some authors observed that the DRN is much attenuated or absent (Loewy et al., 2000; Macdonald et al., 2008; Nashida et al., 2000; Nittono et al., 2001; Winter et al., 1995). During stage N1, a reduction in the amplitude of the DRN has also been shown to occur (Nashida et al., 2000; Sabri et al., 2000; 2003; Winter et al., 1995). Nittono et al. (2001) observed that when stage N1 was subdivided into early and late sub-stages, a DRN could be observed during early stage N1 but not in late stage N1. Most of these studies have used either deviants created by changing the frequency or intensity of the standard. Ruby et al. (2008) employed a duration deviant. Contrary to other studies, they found a significant DRN during wakefulness, stage N1, and stage N2 sleep.

The P3a has been studied much less often than the DRN. Most of the above-mentioned DRN studies did not report a P3a to be elicited by their frequency and/or intensity deviant stimuli, probably because the extent of deviance was not sufficiently large. Winter et al. (1995) did employ small and large deviants within a passive 3-stimulus oddball paradigm. Both deviants elicited a P3a in the waking state. However during overall stage N1, a P3a was not elicited. The authors did, however, report the presence of a large P210 (probably a P2) and a later P430, occurring following the large frequency change. Neither component, however, had the scalp distribution or latency that is typical of the waking P3a. Ruby et al. (2008) did observe a reduced P3a during overall stage N1 following the presentation of their duration deviant. It is thus possible that the effects of sleep onset will vary depending on the feature of the standard that is changed.

1.3 The optimal paradigm

As noted, in the waking state few deviants will, in fact, elicit a P3a. Differences in previous sleep onset studies might well be explained by the selection of a specific deviant type. To determine which deviants are most likely to elicit a P3a during the sleep onset process, a separate oddball paradigm would need to be run for each type of deviant. A problem with ERP methodology is that the “signal” of interest (the P3a in this case) is embedded within the much larger background EEG “noise”. Through the use of averaging procedures, the amplitude of the background EEG can be reduced allowing the small amplitude ERP signal to emerge. The averaging process does, however, require the repetition of many stimulus presentations. Each oddball sequence will often last approximately 10–15 min to permit a sufficiently large number of stimuli to be presented. If the data are to be replicated, the sequence will need to be repeated a second time. If several different oddball paradigms are to be presented, testing time may be very long indeed, often exceeding 2 h. Unfortunately, the sleep onset period can be very short, and as a result it may not be feasible to examine the effects of numerous deviants on the P3a.

A more recent time-efficient multi-feature “optimal” paradigm has been developed (Näätänen et al., 2004) to significantly reduce testing times. The optimal paradigm consists of an alternating pattern of standards and deviants presented in a single auditory sequence. Five or more deviants are often presented within the sequence. While the overall probability of standard and deviant occurrence is 0.5, the probability that a specific deviant will be presented is very low. Thus, if 5 deviants are presented, the probability of occurrence of each is 0.1. Each deviant typically represents a change in a different feature (“multi-feature”) of the standard. The optimal paradigm has been

validated for its use for recording the DRN (Fisher et al., 2011; 2012; Näätänen et al., 2004; Pakarinen et al., 2009; 2014; Sokka et al., 2014; Sorokin et al., 2010; Tavakoli & Campbell, 2016; Torppa et al., 2014; Vuust et al., 2011). Tavakoli and Campbell (2016) employed a passive multi-feature optimal paradigm to determine the association between 6 different types of deviants and the P3a amplitude. The different deviants that were selected have in previous waking-state passive paradigms been demonstrated to either not elicit a P3a or elicit a P3a that varied in amplitude (Berti and Schröger, 2001; Combs and Polich, 2006; Deacon et al., 1998; Escera et al., 2001; Frank et al., 2012; Jankowiak and Berti, 2007; Muller-Gass et al., 2006, 2007; Pakarinen et al., 2007; Rinne et al., 2006). They also ran several separate oddball paradigms using one deviant in each to compare the results to those obtained in the optimal paradigm. Only the white noise and environmental sound deviants in both the optimal and separate oddball paradigms elicited a significant P3a. The other frequency, intensity, and duration deviants did not.

1.4 Present Study

The aim of the present study was to determine the extent of processing of acoustic change in the external environment during the sleep onset period. The sleep onset process is associated with a loss of awareness of the external environment. The sleeper must, however, be able to detect and take action following the presentation of certain highly relevant external stimuli. These presumably highly relevant stimuli elicit a P3a in the waking state. Will they continue to do so during the sleep onset period?

Evidence of the detection of change is provided by the DRN. The DRN is, however, thought to reflect pre-conscious processing. Critically, some of the deviants may also elicit a P3a, associated with the evaluation of the deviant and possible

subsequent conscious awareness of the external environment. The present study employs the multi-feature optimal paradigm used by Tavakoli and Campbell (2016). Importantly, this time efficient paradigm permits the presentation of several deviant stimuli during the brief sleep onset period. The optimal paradigm was presented passively to subjects during the waking state, early and late stage N1, and the first 30 minutes of stage N2 sleep.

2. Methods

2.1 Subjects

Twelve subjects (10 females), between the ages of 20 and 30 years (mean=23.3 years, SD=3.57 years) volunteered to participate in this experiment. None had any history of hearing, neurological, or sleep disorders. Written informed consent was obtained prior to the start of the study and subjects received an honorarium for their participation.

Subjects refrained from caffeine and alcohol in the 24h prior to the start of the study. The study was conducted according to the Canadian Tri-Council guidelines (Medical, Natural, and Social Sciences) on ethical conduct involving human subjects.

2.2 Neurophysiological recording

EEG and electrooculography (EOG) activity were recorded using Grass gold-cup electrodes, filled with electrolytic paste, and affixed to the skin by surgical tape and to the scalp by gauze. Brain Products BrainAmp amplifiers and Recorder software were used for the recording of the physiological signals. The EEG was recorded from 18 electrodes across frontal, central, and parietal, occipital sites (Fp1, Fp2, FT9, FT10, F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4, O1, O2) according to the 10/10 system of electrode placement. Two additional electrodes were placed on the left and right mastoids (M1 and M2). Vertical EOG was recorded from electrodes placed at the supra-orbital and infra-

orbital ridges of the left eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. The nose served as a reference for all channels, including the EOG channels. Inter-electrode impedances were kept below 5 k Ω . The high-frequency filter was set at 75 Hz and the time constant was set at 2 s. The physiological data were digitized continuously at a 500 Hz sampling rate and stored on hard disk for later analyses.

2.3 Procedure and stimuli

The waking data were collected between 22:30 and 23:15 while subjects were seated in a sound-attenuated room and asked to watch a silent, subtitled movie of their choice and ignore the auditory stimuli.

Auditory stimuli were presented monaurally to the right ear using EAR 3A insert earphones. A multi-feature auditory optimal paradigm was presented. It consisted of six deviant stimuli presented in the same sequence so that every other tone was a 80 dB SPL 1000 Hz “standard” tone burst ($p=0.5$) and every other was one of 6 deviants (each with a $p=0.08$). Deviants in the optimal sequence included (a) a 90 dB SPL increment pure tone, (b) a 60 dB SPL decrement pure tone, (c) an 80 dB peak SPL white noise burst, (d) different environmental sounds (with an average intensity of 80 dB SPL), (e) a higher frequency, 1100 Hz, pure tone, and (f) a shorter duration, 100 ms, pure tone. Table 1 lists the properties of the various auditory stimuli. The deviants were pseudo-randomized so that in an array of 6 deviants, each deviant was presented once and the same deviant was never presented twice in a row. A different environmental sound was presented on each trial so that none of the environmental sounds were repeated. The environmental sounds were downloaded from the New York Psychiatric Institute and described in detail by

Fabiani et al. (1996). A total of 77 different environmental sounds were used. They consisted of 6 different categories of stimuli including, animal (e.g. dog, cat, frog) sounds, bird sounds, human-produced sounds (e.g. laughter, coughing, sneezing, hiccup), musical instruments (e.g. piano, violin, guitar), sounds within daily environments (e.g. water dripping, drilling, car, video games), and mechanically produced sounds. Their duration was however manipulated to be 200 ms. The first 10 tones in the sequence consisted of only standards in order to establish a memory trace for the standard stimulus. All stimuli had a duration of 200 ms and a rise-and-fall time of 5 ms, with the exception of the duration deviant. The stimulus onset asynchrony (SOA; onset-to-onset) was 600 ms. A total of 932 stimuli were presented in a single sequence, consisting of 470 trials of standards and 77 trials of each deviant, lasting 9.5 minutes.

Three blocks of auditory stimuli were presented while subjects were awake watching a silent subtitled video. A brief 5-minute rest period was given between blocks. The waking testing period thus lasted about 40 minutes. Subjects were then permitted to fall asleep at about 23:30. Auditory stimuli were again presented as subjects were falling asleep. In order to ensure a sufficient amount of stage N1, repeated sleep-onset periods were used where subjects were allowed to fall asleep, passing through wakefulness and then stages N1 and N2 of sleep. Once the subjects entered stage N2 sleep defined by the presence of spindles and K-Complexes, they were awakened and the entire procedure repeated enough times to allow for 3 blocks of auditory stimuli to be presented during stage N1. After the completion of the three sleep onset periods, subjects were permitted to sleep without awakenings. Three blocks of auditory stimuli were then presented when

during stage N2 sleep. Sleep stages were initially classified in real-time by an experienced sleep researcher using standard scoring procedures.

Stimulus Type	Intensity	Frequency	Duration	Probability
Standard	80 dB SPL	1000 Hz	200 ms	.50
Deviants				
Frequency	80 dB SPL	<i>1100 Hz</i>	200 ms	.08
Increment	<i>90 dB SPL</i>	1000 Hz	200 ms	.08
Decrement	<i>60 dB SPL</i>	1000 Hz	200 ms	.08
Duration	80 dB SPL	1000 Hz	<i>100 ms</i>	.08
White Noise	<i>~80 dB SPL</i>	<i>random</i>	200 ms	.08
Environmental Sounds	<i>~80 dB SPL</i>	<i>mixed</i>	200 ms	.08

Table 1. The intensity, frequency, duration, and probability of the standard stimulus and the six deviant stimuli.

2.4 Sleep stage scoring

Offline, definitive sleep staging of wakefulness, stage N1 and stage N2 was performed by two independent sleep scorers using the American Academy of Medicine (AASM) task force criteria (Silber et al., 2007), with the exception that a 20 s epoch was employed rather than the usual 30s to increase scoring precision. In the cases of sleep stage changes or scoring ambiguity, the data within these epochs were rejected. Stage N1 data was further subdivided into early and late stage N1 based on the extent of alpha and theta activity. Early stage N1 contains more 8-12 Hz alpha activity, while late stage N1 contains more 4-7 Hz theta activity (Colrain et al., 2000; Gora et al., 1999). The human raters' classification was verified using spectral analysis. The stage N1 data were reconstructed into 4 s epochs. EEG power densities (0.50 Hz resolution, 10% duration Hann non-rectangular window) were calculated using a Fast Fourier transform (FFT) on the 4 s epochs. Artifact-free 4s epochs were then averaged over the 20s epoch in order to align spectral data with sleep staging. As illustrated in Figure 1, early stage N1 did contain more alpha and late stage N1 more theta activity. A dependent-sample t-test was

conducted for each frequency range (Delta, 0.5-3 Hz; Theta, 4-7 Hz; Alpha, 8-12 Hz) to compare early and late stage N1 EEG activity. The statistical analyses confirmed the validity of the human scoring of the stage N1 sub-stages. There was significantly more alpha during early stage N1 and significantly more theta during late stage N1, $t(11) = 2.90$ and 2.39 , respectively, $p < .05$. There was also a significant increase in delta activity during late stage N1, $t(11) = 3.82$, $p < .01$.

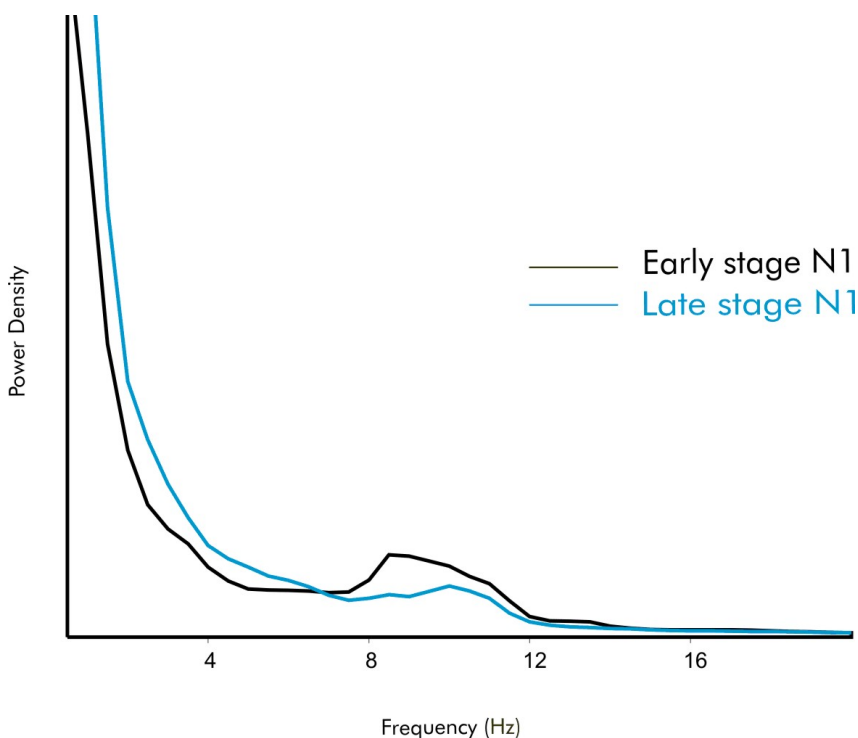


Figure 1. FFT analysis of both early and late stage N1. There is significantly more alpha activity (8-12 Hz) during early stage N1, while there is an increase in theta (4-7 Hz) and delta (0.5-4 Hz) activity during late stage N1.

2.5 ERP analysis

The waking, early and late stage N1, and stage N2 data were then reconstructed using Brain Products' Analyzer2 software to analyze the ERP data. To attenuate the large amplitude waves commonly observed during sleep, the continuous EEG data was

digitally band-pass filtered between 0.5-20 Hz (slope of 24 dB/octave). A vertical EOG channel was computed by subtracting activity recorded at supra-orbital and infra-orbital ridges of the left eye. A horizontal EOG channel was computed by subtracting activity recorded at the outer canthus of each eye. Independent Component Analysis (Chaumon et al., 2015; Makeig et al., 1996) was used to identify eye movements and blink artifacts that were statistically independent of the EEG activity. These vertical and horizontal eye movements were then partialled out from the EEG trace. The continuous data were subsequently reconstructed into discrete single trial 700 ms segments, beginning 100 ms before stimulus onset and then baseline corrected. During wakefulness, early, and late stage N1, segments in which EEG activity exceeded $\pm 100 \mu\text{V}$ relative to the baseline were excluded from further analyses. During stage N2, this threshold was changed to $\pm 200 \mu\text{V}$ to accommodate the large amplitude slow wave EEG that often occurs during this stage of sleep. No more than 5% of total trials were rejected from further analyses per subject. There was no variation in the rejection of trials across deviants. The single trials were then sorted and averaged on the basis of stage (waking, early stage N1, late stage N1, stage N2), stimulus type (standard and 6 deviants), and electrode site.

2.6 Quantification and statistical analyses

The auditory deviant stimuli elicited a series of deflections not apparent in the standard ERP waveform. These deflections are best observed in a difference wave computed by subtracting, point-by-point, the standard from the deviant waveforms at each electrode site in the same condition. This process removes the commonalities in processing between the standard and the deviant, leaving only processing unique to the deviant. From this difference wave, the DRN and P3a were initially identified using the

grand averaged data (the average of all subjects' averages) within wakefulness and stages N1 and N2. They were then quantified for each individual subject using the mean of all the data points that were within ± 25 ms of the peak in amplitude that was identified in the grand average.

Previous studies have indicated that not all deviants will elicit a P3a during wakefulness. It was also possible that the P3a would be absent to all deviants during sleep. The statistical analysis of absent ERP components with the usual ANOVA procedure is problematic. This is because the observation of a significant amplitude difference with, for example, the P3a between the waking state and sleep onset cannot be used as evidence that a specific deviant did in fact elicit this component during sleep onset. It must be first demonstrated that significant ERP components were elicited by the deviant. Thus, confidence intervals were computed for the DRN and P3a within each stage. In the case of DRN, when the upper limit of a confidence interval was significantly less than 0 μ V, (i.e., was negative-going), the interval was considered to contain a significant negativity. Similarly, in the case of the P3a, when the lower limit of the interval was significantly greater than 0 μ V (i.e. in a positive direction), it was considered to be a significant positivity. The procedure was run on the Fz electrode site for the DRN and at Cz for the P3a where each tends to be at maximum amplitude. Because directionality was predicted (negativity in the case of the DRN and positivity in the case of the P3a), one-tailed tests of significance ($p < 0.05$) were applied to the confidence intervals. To restrict the likelihood of chance findings, the negativity had to conform to the usual latency (100–250 ms) and scalp distribution (fronto-central maximum, inversion in polarity at the mastoids) of the DRN, while the positivity had to conform to

the usual latency (180–350 ms) and scalp distribution (centro-frontal maximum) of the P3a.

Electrode sites were grouped into regions of interest (ROIs), to include 9 electrode sites where the ERP components of interest were largest. The ROIs allowed for an analysis of an anterior–posterior and an inter-hemisphere factor. Specifically for the anterior–posterior electrode factor, three electrodes for frontal (F3, Fz, F4), centro-frontal (FC3, FCz, FC4), and central (C3, Cz, C4) sites were chosen for analysis. The DRN and P3a components were thus quantified at each of these sites within the latency range identified at Fz, and Cz, respectively. For the inter-hemisphere factor, three electrodes for left (F3, FC3, C3), midline (Fz, FCz, Cz), and right (F4, FC4, C4) sites were chosen for analysis.

Analysis of variance testing was only conducted when a significant DRN or P3a was observed in any of the stages. A four-way analysis of variance was conducted with repeated-measure on stage (waking, early stage N1, late stage N1, stage N2), deviant type (frequency, duration, decrement, increment, white noise, and environmental sounds), frontality (frontal, centro-frontal, central electrode regions), and laterality (left, midline, right electrode regions). Separate ANOVAs were conducted for the DRN and P3a. Significant main effects and interactions were followed up with Fisher's LSD post-hoc testing. For all statistical analyses, a Geisser-Greenhouse correction was used when appropriate (Geisser & Greenhouse, 1958).

3. Results

3.1 DRN

A negativity, peaking at about 150 ms, was observed in the difference waveforms (Fig. 2). In some cases, this probably reflected a larger N1 component to the deviant than

to the standard. In cases in which the intensity of the deviant increased relative to the standard (i.e., increment, white noise, environmental sounds) this negativity probably reflected a composite N1 and MMN (i.e., the DRN). In the cases of the frequency, duration, and decrement deviants, the negativity probably reflects a true MMN, although for consistency will be labelled as a DRN. It was maximum over frontal areas of the scalp and inverted in polarity at the mastoids. In the waking state, confidence interval testing at Fz revealed that all deviants, with the exception of the decrement, elicited a DRN significantly different from the zero-voltage baseline ($p < .05$ in all cases). During early stage N1, all deviants, with the exception of the white noise deviant, elicited a significant DRN ($p < .05$ in all cases). During late stage N1, the amplitude of the DRNs were reduced; only the increment deviant continued to elicit a significant DRN ($p < .01$). During stage N2, none of the deviants elicited a significant DRN.

As a result, a four-way ANOVA with repeated measures on stage (waking, early stage N1), deviant type (frequency, duration, decrement, increment, white noise, environmental sounds), frontality (frontal, centro-frontal, central), and laterality (left, midline, right) was run to compare the DRNs during wakefulness and early stage N1. There was no significant difference in the amplitude of the DRN between waking and early stage N1 ($F < 1$). There was an effect of deviant type, $F(5, 55) = 3.86$, $MSE = 19.56$, $p < .01$, $\eta^2_p = 0.26$. Overall, the DRN was largest following the increment deviant and smallest following the white noise deviant. As is typical of the DRN, it was largest over frontal regions of the scalp, $F(2, 22) = 5.86$, $MSE = 2.92$, $p < .01$, $\eta^2_p = 0.34$. The DRN was largest over midline electrode regions, although this difference did not attain significance, $F(2, 22) = 2.94$, $MSE = 2.08$, $p > .05$, $\eta^2_p = 0.21$. The stage x deviant type interaction was not

significant, $F(5, 55)=1.13$, $MSE=20.80$, $p>.05$, $\eta^2_p=0.09$. Interactions involving electrode site were not significant ($F<1$).

The increment deviant during late stage N1 also elicited a significant DRN. A t -test was run to compare its amplitude to the waking DRN at the Fz electrode site. There was no significant difference in the DRN amplitude between waking and late stage N1 for the increment deviant ($t<1$).

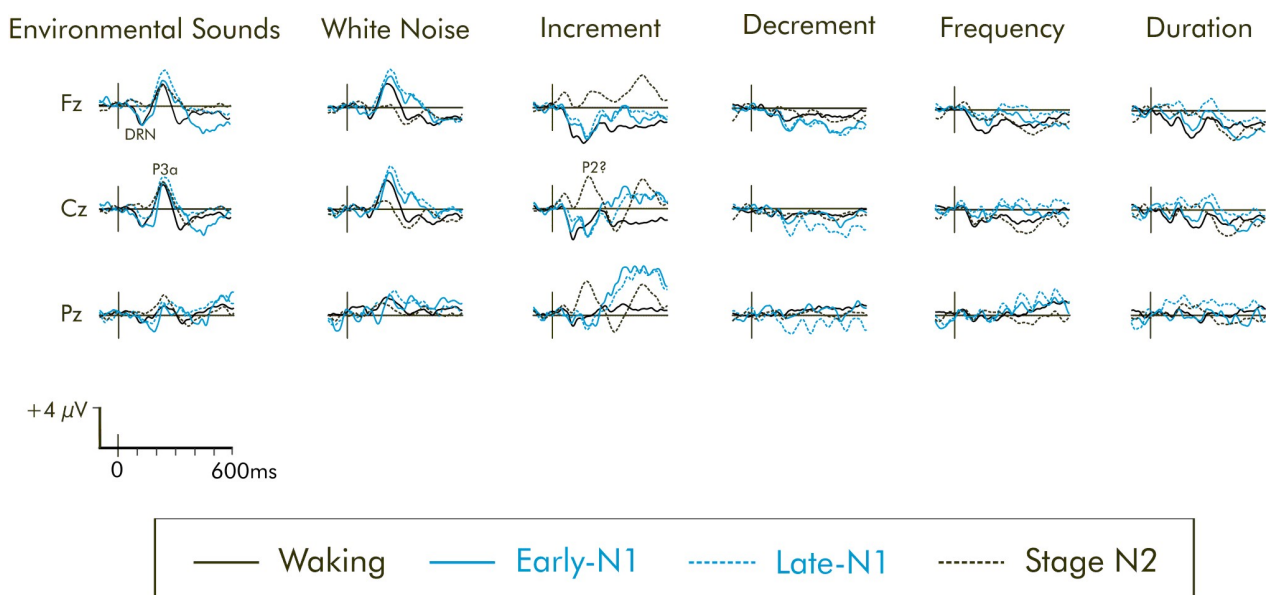


Figure 2. Grand average difference waveforms of the 6 deviants at the Fz, Cz, and Pz electrode sites. The waveforms for the four different stages are superimposed for each deviant stimulus. A significant P3a was elicited by the environmental sounds and white noise deviant during waking, early stage N1, and late stage N1. Only the environmental sounds elicited a significant P3a during stage N2.

3.2 P3a

Not all of the deviants elicited a significant P3a in the waking state (Fig. 2). In the difference waves, a large amplitude centro-frontal maximum P3a, peaking at about 220

and 240 ms, was found to be significant following only the white noise and environmental sound deviants ($p < .001$), respectively. The mean amplitudes of the P3a throughout the waking and sleep onset periods are presented in Table 2. Confidence interval testing revealed that the white noise and environmental sound deviants continued to elicit a significant P3a during early stage N1 ($p < .01$) and late stage N1 ($p < .01$). During stage N2, only the environmental sounds continued to elicit a significant P3a-like positivity ($p < .001$). The white noise deviant did not elicit a P3a during stage N2 sleep.

An initial ANOVA with repeated measures on deviant type (white noise and environmental sounds), frontality (frontal, centro-frontal, central), and laterality (left, midline, right) was run separately on the waking P3a data. The amplitude of the P3a to the environmental sounds and white noise deviants did not significantly differ ($F < 1$). Although the amplitude of the overall P3a was largest over centro-frontal areas of the scalp, this difference did not reach significance, $F(2, 22) = 2.13$, $MSE = 0.72$, $p > .05$, $\eta^2_p = 0.16$. The P3a was largest over midline areas of the scalp, $F(2, 22) = 12.13$, $MSE = 0.92$, $p < .001$, $\eta^2_p = 0.52$. Interactions involving electrode site were not significant ($F < 1$).

One-way ANOVAs were subsequently conducted separately for the environmental sound and white noise deviants during the sleep onset period (waking state, early stage N1, late stage N1, stage N2). For the environmental sounds, the amplitude of the P3a did not significantly vary among the different stages, $F < 1$. On the other hand, for the white noise deviants, differences among the stages were significant, $F(3, 33) = 4.12$, $MSE = 4.87$, $p < .05$, $\eta^2_p = 0.27$. Post hoc testing revealed that this was because of the reduction of the amplitude of the P3a during stage N2 compared to the

three other stages. There was no significant difference in the amplitude of the P3a among waking, early stage N1, and late stage N1.

Spline maps of the P3a were also computed for the white noise and environmental sound deviants during the four stages (Fig. 3). As can be observed, the P3a was largest over centro-frontal areas of the scalp, decreasing in amplitude over posterior and lateral regions. The scalp distribution of the P3a across waking, early stage N1, and late stage N1 were very similar. The P3a-like positivity during stage N2 had a slightly more central distribution with a reduced frontal distribution. To further examine this, an ANOVA was run on the P3a to the environmental sound between the waking state and stage N2. Separate ANOVAs were run for frontal (F3, Fz, F4) and central (C3, Cz, C4) sites. Frontally, there was no significant difference in the amplitude of the P3a between waking and stage N2 ($F < 1$). Similarly, at central sites, there was no difference in the amplitude of the P3a between waking and stage N2, ($F < 1$).

Deviant Type	Stage	Amplitude (SD)	CI (95%)
White Noise	Waking	2.65 (2.15)	[1.27, 4.02]
	Early-N1	3.14 (2.77)	[1.38, 4.90]
	Late-N1	3.45 (2.79)	[1.67, 5.22]
	Stage N2	0.57 (2.05)	[-0.72, 1.88]
Environmental Sounds	Waking	2.06 (1.51)	[1.09, 3.02]
	Early-N1	2.38 (2.84)	[0.58, 4.19]
	Late-N1	2.84 (2.45)	[1.28, 4.40]
	Stage N2	2.23 (1.74)	[1.12, 3.34]

Table 1. Mean amplitudes (SD in parentheses) at the Cz electrode site for the difference waves at the time interval of the P3a. Confidence intervals (95%) are also reported for the Cz electrode site.

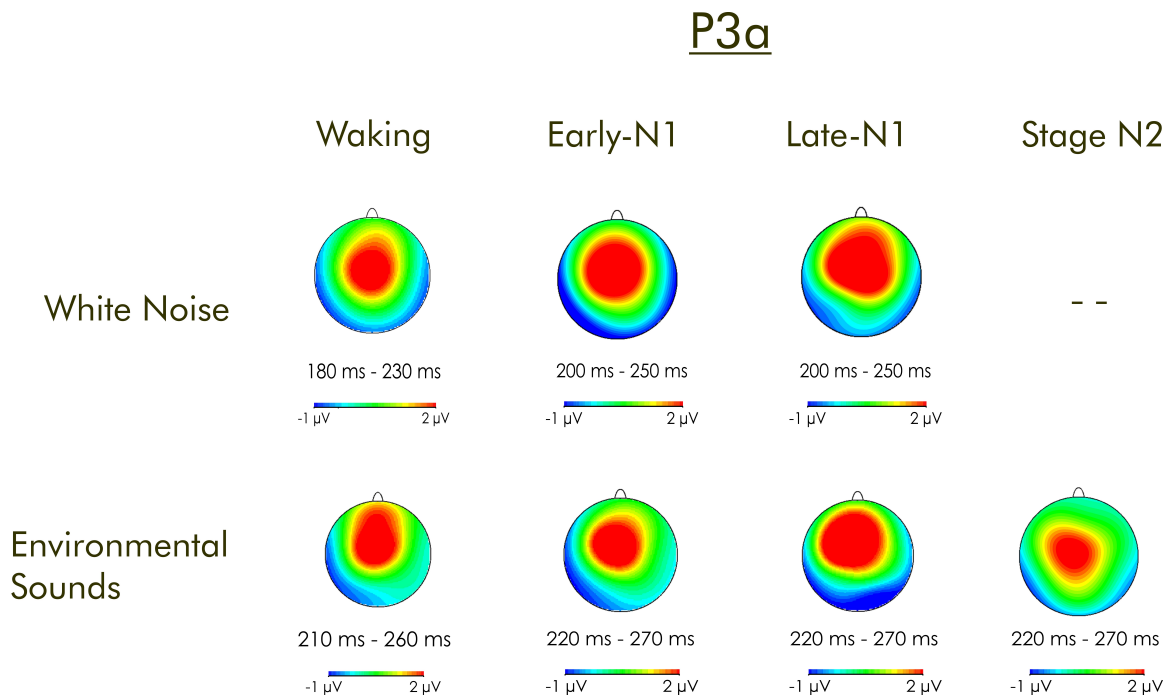


Figure 3. Spline maps of the P3a. Only maps of the P3a that were significantly different from the zero-voltage baseline are presented. The P3a was largest over centro-frontal areas of the scalp and declined in amplitude over lateral and inferior regions. The P3a to the environmental sounds during stage N2 had a more central distribution with limited frontal distribution. Otherwise, the scalp distribution of the P3a was very similar across the stages.

A large positivity, peaking at about 180 ms, was also apparent following the increment deviant during stage N2 sleep. This positivity probably however reflects P2 activity rather than a true P3a. Its peak latency, 180 ms, is unusually early for the P3a, but within the usual latency range of the P2. Importantly, its scalp distribution was also much more centro-parietal maximum (Fig. 4), compared to the usual centro-frontal distribution of the P3a.

Stage N2 Sleep

Increment

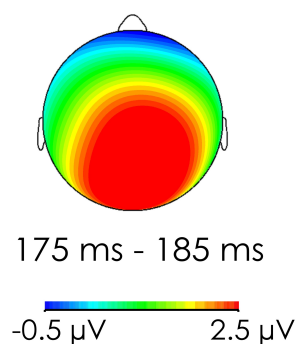


Figure 4. Spline map of the P2 component to the increment deviant during stage N2.

The P2 peaked at about 180 ms and had a centro-parietal distribution. It is therefore very unlikely that this positivity reflects a P3a component as its characteristics are representative of P2 morphology.

4. Discussion

Many ERP studies examining the extent of processing during the sleep onset period have required subjects to actively attend to the auditory channel and detect the occurrence of a rare target stimulus. The use of a behavioural response is undoubtedly the gold standard providing independent evidence that the subject was indeed conscious of the target stimulus. In the waking state, this detection is associated with a large parietal maximum P3b. In studies of sleep onset, this P3b can no longer be observed when subjects are unable to signal detection of the target (Cote et al., 2002; Strauss et al., 2015) or when the EEG shows increasingly large amounts of theta activity (Colrain et al., 2000; Gora et al., 1999).

By contrast, the present study employed a passive paradigm in which subjects were asked to ignore (i.e., not attend to) the auditory sequence while they were awake

and later while they were falling asleep. ERPs were recorded to auditory stimuli presented within an optimal paradigm, including six different deviants, some of which have been demonstrated to elicit a large P3a during wakefulness in previous studies. Because subjects were not actively attending the auditory sequence, the rare deviant stimuli should not have elicited a P3b.

4.1 The DRN during sleep onset

All deviants elicited a significant DRN in the waking state except the decrement deviant. The waking DRN conformed to its usual latency and scalp distribution. The DRN was also elicited in early stage N1. These findings are similar to those of previous studies (Nittono et al., 2001; Strauss et al., 2015). Processes related to the automatic pre-conscious detection of stimulus change appear to be well-preserved during this gradual transitional period.

During late stage N1 and stage N2, the DRN elicited by most deviants was much reduced in amplitude and no longer significantly different from the mean amplitude of the pre-stimulus period. Only the increment deviant continued to elicit a significant DRN during late stage N1. Other studies have also shown similar reductions in the amplitude of the DRN during overall stage N1 (Sabri et al., 2003; Nittono et al., 2001; Winter et al., 1995), presumably reflecting the average of activity across both early and late stage N1. In the present study, only the increment deviant continued to elicit a significant DRN during late stage N1. The intensity of the increment deviant was, of course, higher than that of the standard. The amplitude of the N1 would therefore have been larger for the deviant than the standard. The negativity that was observed in the difference wave might thus be a result of the difference in amplitude of the N1 rather than a reflection of a true

MMN. While N1 is much reduced during late stage N1 (Cote et al., 2002), it still may have been larger for the increment than the standard.

During the first 30 minutes of stage N2, a significant DRN could no longer be recorded. Many studies have also reported the absence or a reduction of the DRN during overall stage N2 sleep (Loewy et al., 2000; Nittono et al., 2001; Ruby et al., 2008; Sabri et al., 2000; 2003; Sabri & Campbell, 2005). It is possible the DRNs that have been reported to occur during might be explained by the fact that in oddball paradigms, the extent of deviance has tended to be large. As such, the deviant might activate auditory cortical populations that are different than those of the standard. Because the deviant is presented rarely, it activates “fresh afferent” neuronal populations (Jacobsen & Schröger, 2001; May & Tiitinen, 2010). As such, the obligatory N1 would be larger to the rarely presented deviant than to the frequently presented standard. The fresh afferent theory views the MMN as reflecting merely the activity of new (or fresh) afferent neuronal populations, as opposed to a result of memory comparison. This confound can be overcome by using acoustic patterns or regularities such that the deviant represents a violation of a pattern rather than a physical change from the standard. The MMN is absent to such violations of a pattern during NREM sleep (Sculthorpe et al., 2009; Strauss et al., 2015).

4.2 The P3a during sleep onset

In the waking state, only the white noise and environmental sound deviants elicited a significant P3a. This replicates the results observed by Tavakoli and Campbell (2016) using an optimal paradigm. Previous studies employing oddball paradigms have also observed a large P3a to environmental sound and white noise deviants compared to

other pure tone deviants (Cahn & Polich, 2009; Combs & Polich, 2006; Frank et al., 2012; Wetzell et al., 2013). During wakefulness, subjects were asked to ignore the auditory channel while watching a silent video. Thus, the P3a that was observed was elicited passively in the absence of active attention.

Tavakoli and Campbell (2016) also noted that the frequency, duration, decrement, and increment deviants did not elicit a P3a in awake and alert subjects. They discussed why only white noise and environmental sound deviants elicited a P3a in the waking state. An increase in the intensity of an auditory stimulus signals the approach of an organism within the environment and is experienced as “looming” and may elicit a fear response in animals (Bach et al., 2007; Freiberg et al., 2001; Maier & Ghazanfar, 2007). Common to the white noise and environmental sound deviants is the fact that their spectral content varied widely from the standard. Because the frequency spectrum of these deviants is very wide, stimulus energy (intensity) will at times be greater than for the standards. It is thus possible that with passive paradigms, only ecologically valid stimuli (those that signal threat) will elicit a P3a. If this is the case, the increment deviant should also have been experienced as looming yet it did not elicit P3a. The increment represented only a change in a single feature of the standard, its intensity. The white noise and environmental sounds were complex stimuli. Other deviants created by varying only a single feature of the standard, failed to elicit a P3a. This might explain why the increment deviant did not elicit a P3a even in the waking state. Torppa et al. (2014) compared the DRN and P3a to changes in piano tone pitch, timbre, duration, and gaps using an optimal paradigm. The standard was a 295 Hz piano tone. The deviant tones differed from the standard in fundamental frequency (pitch), timbre (change from

standard piano tone to cembalo, violin, and cymbal tone), duration, intensity, or by the presence of a silent gap in the middle of the tone. They observed a P3a to sounds that were physically very different from the standard but also sounds that were contextually novel (different musical instrument compared to the standard piano sound). It is thus possible that the environmental sounds elicited a P3a not only because their physical features were very different from the standard but also because their context was qualitatively different.

Both the white noise and environmental sound deviants continued to elicit a large P3a during early stage N1 sleep. This is not surprising as even the P3b, requiring an active detection of the rare target, can be elicited during early stage N1 sleep (Cote et al., 1999; Colrain et al., 2000; Gora et al., 1999). Early stage N1 may be more similar to the waking than the sleeping state. What was surprising was that the P3a continued to be elicited in late stage N1, a period in which alpha activity significantly decreased and theta activity significantly increased. During this period, studies have shown that subjects no longer appear to be able to overtly respond to external stimuli and the P3b dissipates. While both the subject's overt response to an external stimulus and the presence of a P3b do provide convincing evidence of consciousness, their absence is more ambiguous. The absence of a response may not be a reflection of the absence of consciousness (for a review, see Sanders et al., 2012). For example, the P3b may not be elicited in brain-damaged patients who can nevertheless communicate (King et al., 2013). To our knowledge, no other studies have observed comparably large P3a amplitudes during the sleep onset period. This provides strong evidence that the passive processes that may eventually lead to consciousness of the external environment remain active during the

transition into sleep. The observation of a P3a during stage N2 sleep was especially remarkable. While some researchers question whether stage N1 is actual sleep, marked by a lack of consciousness of the external environment, few dispute that this is the case for stage N2. For this reason, for many sleep researchers, stage N2 is “definitive” sleep. During stage N2, only the environmental sounds elicited a P3a, the white noise deviants now failing to do so.

It is possible that the P3a that was elicited in late stage N1 and stage N2 sleep reflected the activity of intracranial generator sources different from those in the waking state and early stage N1. Thus, different brain regions, reflecting different processes, might have been activated during these stages. Spline maps of the P3a were however very similar across wakefulness, stage N1, and stage N2 for both the white noise and environmental sound deviants. There is thus little evidence to support the notion that the intracranial sources of the P3a were different.

During stage N2 sleep, the increment deviant elicited a large positivity at around 180 ms. This is unusually early for a P3a. Its scalp distribution was also different. It was maximum over centro-parietal regions of the scalps compared to the centro-frontal scalp distribution of the P3a. The peak latency and scalp distribution of this positivity is consistent with an earlier P2. The P2 has been shown to increase in amplitude with increasing stimulus intensity (Cote et al., 2001; Crowley et al., 2002; Harsh et al., 1994). The intensity of the increment deviant was 10 dB higher than for the standard. This would explain why the P2 was larger after presentation of the increment than the standard. Consistent with this, when the intensity of the standard was louder than that of the deviant (i.e. the decrement deviant), the P2 was no longer apparent in the difference

wave. Many sleep studies have observed that the amplitude of the P2 may increase during NREM sleep (Cote et al., 2001; Crowley et al., 2002; Harsh et al., 1994; Macdonald et al., 2008). This probably explains why this large positivity was observed in the difference wave during stage N2 and not during wakefulness or stage N1. Macdonald et al. (2008) also observed a large P2 following an increment deviant during stage N2. It also occurred earlier than the waking P3a, and also had a more centro-parietal distribution.

Ruby et al. (2008) did report a P3a to be elicited by their duration deviant during stage N2. This was not the case in the present study. It is possible that the difference in duration between the standard and deviant in the two studies might account for this inconsistency. Ruby et al. employed a relatively short duration 75 ms standard and a 35 ms duration deviant while the present study employed a 200 ms standard and a 100 ms deviant. Their duration deviant also elicited a P3a in the waking state while duration deviant in the present study did not.

Only the environmental sounds elicited a P3a during stage N2 sleep, whereas the white noise that has elicited a P3a in stage N1 did not. The P3a is said to be elicited in the waking state by potentially highly relevant acoustic input. What defines a stimulus as “relevant” is rarely discussed, although it is related to survival and mating behaviour. Most laboratories employ a bottom-up definition, referring to the extent to which the deviant is physically different from the standard. This would explain why the white noise and environmental sound deviants elicited a P3a prior to stage N2 sleep. The environmental sounds were also novel on every trial, each containing a different spectral content. The same white noise stimulus was, however, repeated on each trial. The environmental sounds were thus also contextually novel (Torppa et al., 2014). This might

explain why the environmental sounds continued to elicit a P3a during stage N2. There may however also be top-down aspects. The environmental sounds might be more ecologically valid. In the present study, several different novel sounds were presented representing a mixed category of stimuli, some of which could be recognized (e.g., musical instruments, animal and human sounds) while others could not. Recent studies have separated environmental sounds (e.g., animate and inanimate sources, human, animal and mechanically-produced sounds) and each of these categories may have an influence on the extent of processing (c.f., Stavropoulos and Carver, 2016). Some of the environmental sounds included human utterances. Sorokin et al. (2010) indicated that human speech sounds were especially likely to elicit a P3a. It is also possible that some of the sounds might have been interpreted as a threat, initiating a fear response. Pakarinen et al. (2014) employed a multi-feature optimal paradigm that included speech-sounds having emotional valence (happiness, anger, sadness) and these were more likely to elicit a P3a. The authors indicated that while their subjects were later able to categorize the emotionality of the various sounds, the effect on the P3a should to be interpreted with caution. The morphology and spectral content of the emotional sounds was different. The possible reason for a sound evoking a specific emotional reaction, such as fear, may be a result of its physical properties. For example, abrupt and intense stimuli may be perceived as more threatening than less abrupt and intense stimuli. Determining which of these many factors might account for the elicitation of the P3a and possible capture of attention during the sleep onset period would require the sorting of the environmental sounds into the various categories and sub-categories (human vs non-human, familiar vs non-familiar, recognizable vs unrecognizable, emotional vs non-emotional, and within

the emotional category, the various emotions). Sub-categorization would unfortunately reduce the number of trials available for averaging within the brief sleep onset period. As a result, reduction of the background noise of the EEG would be much compromised. Distinguishing the P3a and the very small amplitude DRN might not be possible.

4.3 Disassociation of the DRN and P3a

In the classic Näätänen model, the output of the change detector system, reflected in the amplitude of the DRN, varies with the extent of deviance. When this output reaches a certain threshold level, the P3a is elicited. Thus, only certain deviants, those representing a large extent of change, will elicit the P3a. In this model, it would be expected that the probability of eliciting a P3a should decrease when the amplitude of the DRN is reduced. In the present study, the DRN was reduced or absent during late stage N1 and stage N2 yet a P3a was still elicited. How is this possible? Our results are not unique. Other studies have also noted that the amplitude of the DRN and P3a are not necessarily correlated (Fischer et al., 2008; Horvath et al., 2008; Sussman et al., 2003; Torppa et al., 2014; Wetzel et al., 2006). A deviant might elicit a P3a without eliciting a DRN. Näätänen also points out that other factors can affect the P3a. The likelihood that a stimulus does elicit a P3a is also dependent, for example, on the locus and strength of the listener's attentional focus. The threshold for its elicitation is therefore flexible. It is possible that for survival purposes the threshold to elicit the P3a is lowered during sleep. Thus, even though the output of the change detection system is much reduced, the P3a may still be elicited.

4.4 Consciousness and the P3a

Almost all researchers agree that the P3b is associated with awareness that a rare target has been presented. The design of these experiments requires the subject to either push a button upon detection of the rarely occurring stimulus or keep a running mental of target occurrences. As such, there is positive, independent behavioural evidence that the subject was indeed conscious of the target. Such independent behavioural evidence is not available when the P3a is elicited by a deviant occurring in a stimulus channel that is not the focus of current attention. This is one of the major reasons the functional significance of the P3a remains a subject of much current debate. A passive procedure was used in the waking state in the present study. The use of passive paradigms has other serious limitations. The subject is asked to not attend (i.e., “ignore”) the auditory channel. It is, of course, methodologically very difficult to prove a null hypothesis --that the subject did not attend to the sequence. The subject could, for example, have sampled the auditory stimuli, in spite of instructions not to do so. This “eavesdropping” and resulting awareness of the auditory stimuli might be responsible for the DRN and P3a. In the waking state, almost all subjects will report awareness of the deviants even though they are not attending the auditory sequence. In the present study, a P3a was apparent during late stage N1 and stage N2. It would be difficult to argue that this is because subjects managed to continue to eavesdrop on their auditory environment.

In the absence of an independent measure, determining the functional significance of the P3a will remain speculative. The classic Schröger and Wolff (1998) study did provide this independent measure, examining how an irrelevant deviant stimulus that elicits a P3a will affect performance on the to-be-attended task. Subjects were asked to actively attend to and discriminate the duration of frequently presented “standard”

stimuli. At rare times, the frequency of this stimulus was changed, but this deviant was irrelevant to the duration detection task. The deviant elicited a large P3a. Importantly, performance on a primary task also deteriorated following its presentation. Presumably, processing of this deviant resulted in an involuntary switching of attentional resources away from the task-at-hand and toward the processing of the potentially more relevant deviant. More recent studies have not always found a consistent association between P3a and behavioural measures of distraction (see discussions by Berti, 2013; Parmentier, 2014; Wetzel et al., 2013). Parmentier (2014) has provided an elaborate explanation of the situations in which the P3a and behavioural performance will be associated. As noted earlier, Horvath et al. (2008) and Wetzel et al. (2013) suggest that the P3a might reflect a precursory process that occurs prior to the actual switch of attention. This might be involved in the determination that an event is significant, rather than the actual switch of attention itself. Hölig and Berti (2010) present evidence that the P3a might reflect an initiation of the switch. The central executive may then make a decision to switch attention away from current task demands, leading to the process of attention capture by the intruding event. In this explanation, the individual is not actually conscious of the intruding event at the time of the P3a. This interpretation could account for the presence of the P3a in sleep. In the present study, the subjects did not awaken when a P3a was elicited. In the vast majority of cases when a P3a is elicited, the evaluation of the significance of the stimulus might indicate that it was not significant enough that sleep should be reversed.

Consciousness might only be possible when the sleeper does awaken from sleep. Again, in the absence of a behavioural measure, it is very difficult to know what the

sleeper is experiencing. If subjects are queried the following morning upon awakening, they will rarely report awareness of the auditory stimuli even for those that might elicit a P3a. Of course, the validity of making conclusions regarding what was experienced during a sleeping state from evidence obtained during a different waking state is dubious. Another problem with the use of a measure such as the P3a is that its intracranial sources are not well known, although there is good evidence of widespread multiple generators including the frontal lobe (Giard et al., 1990). The activation of a widespread connective network may be a prerequisite for consciousness (for alternative explanations, see Tononi & Koch, 2017).

Most ERP researchers agree that the late positivities, the P3a and P3b, are intimately related to being conscious that a rarely occurring stimulus has just been presented. The case for the P3a seems to be much weaker because of the fact that it is often elicited passively, in the absence of attention. Knowing what the subject is experiencing remains a formidable task. An individual's mental state is private and personal. Even if one concedes that the P3a does reflect an involuntary intrusion into consciousness, the nature of this consciousness remains largely unknown.

5. Conclusions

The present study examined the extent of passive processing of acoustic change stimuli during the sleep onset period. During the waking state, the white noise and environmental sound deviants elicited a P3a. Other deviants failed to elicit a P3a. In both early and late stage N1, processing closely resembled that of wakefulness, as a large amplitude P3a was still elicited by both the white noise and environmental sound deviants. During stage N2 sleep, a P3a was observed following only the environmental

sounds. Thus, even during sleep, processes leading to eventual consciousness of the external environmental events may be activated. The present study also served to validate the use of a multi-feature optimal paradigm during the sleep onset period, allowing researchers to study the P3a to multiple different deviants in a relatively short duration that would otherwise not be possible during this transition period.

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Chapter 4

Study 3: The extent of processing of different types of acoustic change during sleep.

Rational: Study 1 indicated that when a multi-feature optimal paradigm is employed, which includes 6 different deviants, some will elicit a P3a while others will not. Equivalent results were observed when separate oddball sequences were run for the different types of deviants. Study 2 examined the effects of the loss of consciousness associated with the sleep onset period on the processing of the deviants within the multi-feature optimal sequence. The sleep onset period is, however, transitional and many researchers do not consider it to be sleep (i.e., a period of unconsciousness) at all. Study 2 did however also include a brief period of stage N2 sleep, a period of time that most consider to be definitive sleep. The environmental sound deviants continued to elicit a P3a-like positivity similar to the waking state during stage N2. These results suggest that the passive processes that may lead to an interrupt of the central executive and an intrusion into consciousness remain active during an unconscious state. In Study 2, however, only thirty minutes of definitive very early stage N2 sleep were recorded. Again, it may well be that this early form of sleep is quite different from the later and deeper stages of sleep. Moreover, sleep is not a uniform state. While most researchers consider NREM sleep to be a period of profound unconsciousness, there is good evidence that during REM sleep, the sleeper is almost certainly aware of internal mentation (for example, dreams) and may also show awareness of their external environment. *Study 3* therefore investigated the extent of auditory information processing during an all-night sleep period. Studying the effects of different deviants is problematic because the duration of some of the sleep stages (N3 and REM) may be relatively brief. Thus, a multi-feature optimal paradigm was again used to allow for several different deviants to be presented in each stages of sleep.

Study 3 is to be submitted to the journal *Brain and Cognition* and is formatted based on the requirements of the journal.

Tavakoli, P., Dale, A., & Campbell, K. The extent of processing of different types of acoustic change during sleep.

1. Introduction

For purposes of survival, individuals must have the ability to become aware of external information occurring outside of the current focus of attention, and even in states such as sleep. Furthermore, they must also have the ability to detect external information during a state such as sleep. The present study examines the extent to which an individual can become aware of acoustic stimuli during sleep when awareness of the external environment is minimal. The brain is equipped with mechanisms capable of rapidly detecting acoustic change and taking appropriate action should the need arise. A major difference between sleep and other unconscious states (e.g., coma, general anaesthesia) is that sleep is natural and rapidly reversible. The sleeper must become aware of highly relevant biological or personal information (e.g. a very intense stimulus, the interruption of breathing, a baby's cry), perhaps resulting in an awakening in order to take appropriate action. Nevertheless, for sleep to be of benefit, it needs to remain as undisturbed as possible, and only interrupted when critically necessary. Therefore, even in sleep, a decision must be made about whether a new incoming stimulus is relevant and if so, may require an arousal to wakefulness, or whether it is irrelevant and can be safely ignored. This does not necessarily imply that the individual can become aware of a significant event occurring in the external environment during the sleep state. It is possible that this can only occur following the subsequent awakening.

Sleep is not a uniform state. It consists of a series of sub-stages which can be divided into non-REM (NREM; stages N2 and N3) and REM. The processing of external stimulus input can be differentially affected by the various stages of sleep (for reviews, see Massimini et al., 2009; Scammell et al., 2017). A major problem with the study of

information processing during sleep is that the researcher does not have access to the mental state of the sleeping subject as they are usually unable to signal awareness of the external stimuli. Event-related potentials (ERPs) provide a particularly elegant means to measure the extent of information processing in the brain in the absence of overt behavioural responses (for reviews, see Campbell et al., 1992; Drykstra et al., 2017; Koch et al., 2016).

1.1 Auditory ERPs and information processing

During wakefulness, all auditory stimuli elicit an obligatory negativity peaking at about 100 ms, N1, and a positivity peaking at about 200 ms, P2. The obligatory N1-P2 are mainly affected by the physical properties of the stimulus and are especially large to loud and infrequently presented auditory stimuli. N1 and P2 undergo dramatic changes during NREM sleep (for a review, see Campbell & Colrain, 2002). N1 gradually decreases in amplitude during sleep onset until it reaches near baseline levels during stage N2 sleep. On the other hand, P2 has been observed to increase in amplitude during sleep (Cote et al., 2001; Crowley et al., 2002; Harsh et al., 1994). In addition to these changes, some ERP components are unique to sleep and cannot be elicited in the waking state. For example, during stage N2, external stimuli may elicit a large negativity at about 350 ms (“N350”), which may be quite similar to the vertex sharp wave, associated with sleep onset (for a review, see Bastien et al., 2002). The N350 may be followed by a positivity at about 450 ms (“P450”). An infrequently occurring stimulus may also elicit a K-Complex during NREM sleep, which consists of an extremely large amplitude negativity (“N550”), often exceeding 100 μ V followed by a later positivity (“P900”).

In the waking state, the detection of change is often studied using a so-called auditory ‘oddball’ paradigm. The oddball paradigm consists of a frequently occurring homogeneous “standard” stimulus. At rare and unpredictable times, a feature of the standard is changed to form a “deviant”. The presentation of the frequently occurring standard stimulus elicits the obligatory N1 and P2 components. The deviant stimulus also elicits the N1-P2, but in addition elicits a mismatch negativity (MMN; Näätänen 1990; 1992). The MMN is a negative component occurring at about 100-200 ms after stimulus onset. It is maximum over fronto-central areas of the scalp inverting in polarity at the mastoids. In the classic Näätänen model (1990; 1992), the encoded features of the frequently occurring standard stimulus are automatically stored in a very brief-lasting sensory memory, where feature and temporal integration take place. When a deviant is presented, its features fail to match those of the sensory representation and change is detected. The output of this change detector system is reflected by the MMN. A more recent model maintains that the MMN is elicited by a mismatch between the current auditory input and the predictions formed on the basis of the trends or rules that are automatically detected in recent auditory stimulation (Näätänen et al., 2011; Paavilainen, 2013; Winkler, 2007; Winkler et al., 2009). The repeating, homogenous standard used in the oddball sequence is a special case of an acoustic rule (a standard follows a standard), the presentation of the deviant thus violates this rule. The detection of the deviant occurs largely automatically, independent of attention and task demands (for a review, see Sussman, 2007). For this reason, in many auditory oddball studies, the subject’s attention is therefore often directed to a visual task such as reading a book or watching a video. The MMN can be elicited by a change in almost any feature of the standard stimulus

including its frequency, location, duration, and intensity. In the case of a change representing an increase in stimulus intensity, the negative-going ERP that is observed is not a “true” MMN. This is because the amplitude of the N1 would be larger for the deviant than the standard. The increase in intensity also signals stimulus change and thus would also elicit an MMN. The negativity that is observed following presentation of this deviant would represent a composite N1+MMN. This composite negativity is often called a deviant-related negativity (DRN). In this article, the negativity that is elicited by the deviants will be described as a DRN.

The output of the change detection system is forwarded to the central executive, controlling the allocation of attentional and cognitive resources. When this output reaches a certain critical level, attention to ongoing cognitive tasks is interrupted and switched to the auditory channel. The contents of sensory memory are then probed for further possible perceptual processing. This content may then become available to conscious awareness. This involuntary capture of attention or “intrusion into consciousness” is associated with a later positivity, termed the P3a (Escera et al., 1998). The P3a occurs at about 200-300 ms following stimulus onset and is largest over centro-frontal areas of the scalp. There is much current dispute about the extent to which the P3a reflects actual conscious awareness of the auditory sequence. Some authors suggest that it reflects a precursory process occurring prior to the switch of cognitive resources to the auditory channel, leading to conscious awareness (Parmentier, 2014; Wetzel et al., 2013). There is however general agreement that the P3a does reflect processes associated with the involuntary capture of attention.

In the waking state, while any perceptible stimulus change will elicit a DRN, only a small number of these deviants will also elicit a P3a. Deviants whose features vary widely from the standard pure tones, such as novel environmental sounds (e.g., musical instruments, animal sounds, etc...) and white noise, have been demonstrated to elicit a large amplitude P3a in waking passive paradigms (Cahn & Polich, 2009; Kushnerenko et al., 2007). A change in a single feature of the standard stimulus can also elicit a large P3a especially if the change represents an increase in the intensity of the standard (Macdonald et al., 2008; Muller-Gass et al., 2007; Rinne et al., 2006). By contrast, deviants that reflect decreases in intensity and small changes in the frequency, duration or location will elicit only a small amplitude or absent P3a (Grimm et al., 2008; Macdonald et al., 2008; Muller-Gass et al., 2006; 2007; Rinne et al., 2006).

1.2 DRN during sleep

Results from studies examining the DRN during sleep have not always been consistent. Many studies have failed to observe a distinct DRN during NREM sleep (Loewy et al., 1996; Nashida et al., 2000; Nielsen-Bohlman et al., 1991; Niiyama et al., 1994; Nordby et al., 1996; Winter et al., 1995; Loewy et al., 2000; Macdonald et al., 2008; Strauss et al., 2015; Sculthorpe et al., 2009). On the other hand some authors have reported the presence of a DRN during NREM sleep (Ruby et al., 2008; Sabri et al., 2000; 2003; 2005). It is possible that the nature of the stimulus change (frequency, intensity, duration) or the extent of the change could account for these differences.

During REM sleep, many studies have now reported that a DRN can be elicited by many different types of deviants (Atienza & Cantero, 2001; Atienza et al., 1997, 2000; Loewy et al., 1996; Nashida et al., 2000; Sabri et al., 2005; Cote et al., 2001; Macdonald

et al., 2008 Ruby et al., 2008; Sculthorpe et al., 2009), although with reduced amplitudes compared to the waking state. Other researchers have been unable to observe a discernible DRN during REM (Lowey et al., 2000; Niiyama et al., 1994; Sallinen et al., 1996; Strauss et al., 2015), particularly if the extent of deviance was small. Again, it is possible that the type of deviant and the extent of deviance may play a crucial role.

1.3 P3a during sleep

Far fewer studies have examined the P3a during sleep. Most of the DRN studies did not report a P3a during sleep, possibly because the extent of deviance was not sufficiently large. Cote and Campbell (1999) observed a frontal positivity at about 250 ms to rarely occurring deviant stimuli that represented a large increase in intensity (90 dB) from the standard (70 dB) during REM. This positivity was accompanied by a large centro-parietal P3b-like component, occurring at about 320 ms, similar to that which was recorded in wakefulness. Macdonald et al. (2008) also observed a P3a-like positivity during REM sleep, at about 270 ms, following a 10 dB increase in intensity of the 80 dB standard. They did not observe a P3a following a 20 dB decrease in intensity deviant during REM. The P3a can also be elicited by deviants that are not obtrusive. Ruby et al. (2008) employed a duration deviant and reported the presence of both a P3a-like positivity and a later positivity (P3b-like) occurring at about 200 ms and 300 ms respectively in both stage N2 and REM.

1.4 Optimal paradigm

Studies examining the effects of sleep on the DRN and P3a are inconsistent. Unfortunately, the studies have employed many widely varying methodologies, including the nature and the extent of the stimulus change. Resolving this controversy requires a

comparison of different deviants in a single sleep study. This may not be possible when the usual oddball paradigm is used. To do so would require a separate oddball paradigm to be used for each type of deviant. In the waking state, most researchers present the oddball paradigm for approximately 20 minutes in order for a sufficiently large number of deviants to be presented to allow the ERP signal to emerge from the background noise of the EEG. In the case of sleep, and especially NREM sleep, the background EEG amplitude is much larger than in the waking state and recording times will need to be longer. If several different oddball sequences are to be presented, testing times will be very long, lasting 2 to 3 hours. For most subjects, the duration of stages N3 and REM will not be sufficiently long to permit these extended testing times. A second or third night of testing could be employed but the reliability of testing over different nights becomes a serious concern. An alternative multi-feature optimal paradigm (Näätänen et al., 2004) provides a solution to this problem, which as its name implies, permits several deviants to be presented in a single sequence significantly reducing testing time.

The multi-feature optimal paradigm consists of an alternating standard-deviant pattern in which five or more deviants can be presented in a single auditory sequence, each separated by a standard stimulus. Each deviant typically represents a change in a different feature of the standard. The DRN that is elicited by the multiple deviants in an optimal paradigm compares very favorably to the DRN that is recorded by the same deviants in multiple oddball sequences in the waking state (Näätänen et al., 2004; Tavakoli & Campbell, 2016). Tavakoli and Campbell (2016) also demonstrated that the P3a can be faithfully recorded in a single optimal compared to multiple oddball paradigms. The different deviants that were selected have in previous waking-state

passive paradigms been demonstrated to either not elicit a P3a or elicit a P3a that varied in amplitude (Berti & Schröger, 2001; Combs & Polich, 2006; Deacon et al., 1998; Escera et al., 2001; Frank et al., 2012; Jankowiak & Berti, 2007; Muller-Gass et al., 2006, 2007; Pakarinen et al., 2007; Rinne et al., 2006). Only white noise and novel environmental sound deviants elicited a significant P3a in the different oddball sequences. This was however also the case when a single optimal sequence was run. Frequency, intensity, and duration deviants did not elicit a P3a although all elicited a DRN.

1.5 Present Study

The present study employs the multi-feature optimal paradigm used by Tavakoli and Campbell (2016), to examine if a P3a can be elicited within sleep. Six different deviant stimuli were presented to determine the likelihood of each in eliciting a P3a. The optimal paradigm was presented passively to subjects during the waking state while the subject's attention was engaged in watching a silent, subtitled movie, and subsequently across the entire night of sleep.

2. Methods

2.1 Subjects

Sixteen self-reported good sleepers (14 women) between the ages of 20 and 28 years (mean=23.12 years, SD=2.68 years) spent a single night in the sleep laboratory. All subjects reported normal sleep time to be between 23:00 to 24:00. None reported any history of hearing, neurological, or sleep disorders. Written informed consent was obtained prior to the start of the study and subjects received an honorarium for their participation. Subjects refrained from caffeine and alcohol in the 24 hours prior to the

start of the study. The study was conducted according to the Canadian Tri-Council guidelines (Medical, Natural, and Social Sciences) on ethical conduct involving human subjects. These guidelines are similar to those used by the Declaration of Helsinki.

2.2 Physiological Recordings

EEG and electrooculography (EOG) activity were recorded using Grass gold-cup electrodes, filled with electrolytic paste, and affixed to the skin by surgical tape and to the scalp by gauze. Brain Products Recorder software and BrainAmp amplifiers were used for the EEG recording. The EEG was recorded from 18 electrodes across frontal, central, parietal, and occipital sites (FP1, FP2, FT9, FT10, F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4, O1, O2) placed according to the 10/10 system of electrode placement. Two additional electrodes were placed on the left and right mastoids (M1 and M2). A vertical EOG was recorded from electrodes placed at the supra-orbital and infra-orbital ridges of the left eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. A defining characteristic of the MMN/DRN is that it inverts in amplitude (is recorded as a positive amplitude) at the mastoids when a nose reference is used. For this reason, the tip of the nose served as a reference for all channels, including the EOG channels. Inter-electrode impedances were kept below 5 k Ω . The high cut-off filter was set at 75 Hz and the time constant was set at 2 s. The physiological data were digitized continuously at a 500 Hz sampling rate and stored on hard disk for later analyses.

2.3 Procedure and stimuli

Auditory stimuli were presented monaurally to the right ear using EAR 3A insert earphones. A multi-feature auditory optimal paradigm was presented. It consisted of six

deviant stimuli presented in the same sequence so that every other tone was an 80 dB SPL 1000 Hz “standard” tone burst ($p=0.5$) and every other was one of 6 deviants (each with a $p=0.08$). Thus, the standards and deviants alternated. Deviants in the optimal sequence included (a) a 90 dB SPL “increment” pure tone, (b) a 60 dB SPL “decrement” pure tone, (c) an 80 dB peak SPL white noise burst, (d) different environmental sounds (with an average intensity of 80 dB SPL), (e) a higher frequency, 1100 Hz, pure tone, and (f) a shorter duration, 100 ms, pure tone. The order of presentation of the deviant was pseudo-randomized so that in an array of 6 deviants, each deviant was presented only once and the same deviant was never presented two times in a row. A different environmental sound was presented on each trial so that none of the environmental sounds were repeated. The features of the environmental sounds have been described in detail by Fabiani, Kazmerski, Cykowicz, and Friedman (1996). They included animal, bird, human vocalizations, musical instruments, environmental, video-game sounds, and mechanically produced sounds. Their duration was however manipulated to be 200 ms. The first 15 tones in the sequence consisted of only standards in order to establish a memory trace for the standard stimulus. All stimuli had a duration of 200 ms, with the exception of the duration deviant, and a rise-and-fall time of 5 ms. The stimulus onset asynchrony (SOA; onset-to-onset) was 600 ms. A total of 932 stimuli were presented in a sequence lasting 9.5 minutes.

The waking data were collected between 22:00 and 23:00 while subjects were seated in a sound-attenuated room and asked to watch a silent, subtitled movie of their choice and ignore the auditory stimuli. Three blocks of auditory stimuli were presented during wakefulness. A brief break was provided between blocks. Auditory stimulation

lasted for approximately 40 minutes. Subjects were then permitted to fall asleep. Once subjects entered stage N2 sleep (verified by the presence of K-complexes and spindles) auditory stimulation was commenced and continued throughout the whole night. A brief 5-10 minute silent period was provided following the presentation of each sequence. Sleep stages were classified in real-time by an experienced sleep researcher using standard scoring procedures. Stimulation was halted if there was evidence of arousal or awakenings and the data were rejected.

2.4 Sleep stage scoring

Sleep staging was later performed on each 9.5-minute sequence by two experienced sleep scorers using the American Academy of Medicine (AASM) task force criteria (Silber et al., 2007). Both scorers were blind to the real-time staging of the EEG. A 20 s epoch was employed rather than the usual 30 s to increase scoring precision. In cases of sleep stage change or scoring ambiguity, the data within these epochs were rejected.

2.5 ERP analyses

The data were then reconstructed using Brain Products' Analyzer2 software. To attenuate the large amplitude waves commonly observed during sleep, the continuous EEG data was digitally band-pass filtered between 0.5-20 Hz. A vertical EOG channel was computed by subtracting activity recorded at supra-orbital and infra-orbital ridges of the left eye. A horizontal EOG channel was computed by subtracting activity recorded at the outer canthus of each eye. In the waking state and during stage REM, independent component analysis (Chaumon et al., 2015; Makeig et al., 1996) was used to identify eye movements and blink artifacts that were statistically independent of the EEG activity.

These eye movements were then partialled out of the EEG trace. The continuous data were subsequently reconstructed into discrete single trial 700 ms segments, beginning 100 ms before stimulus onset. A 0-50 ms post-stimulus baseline correction was applied because the pre-stimulus interval was not stable and varied between the waking state and sleep stages. During wakefulness, segments in which EEG activity exceeded $\pm 100 \mu\text{V}$ relative to the baseline were excluded from further analyses. During stage N2, N3, and REM, this threshold was changed to $\pm 200 \mu\text{V}$ to accommodate the large amplitude slow wave EEG that often occurs during sleep. The single trial segments were then sorted and averaged on the basis of state (waking, stage N2, stage N3, stage REM), stimulus type (standard and 6 deviants), and electrode site.

2.6 Quantification and statistical analyses

The auditory deviant stimuli elicited a series of deflections that were not apparent in the standard ERP waveform. These deflections are best observed in a difference wave computed by subtracting, point-by-point, the standard from the deviant averaged waveforms at each electrode site. This process removes the commonalities in processing between the standard and the deviant, leaving only processing unique to the deviant. From this difference wave, the DRN and P3a were initially identified using the grand averaged data (the average of all subjects' averages) within waking and stages N2, N3, REM. They were then quantified for each individual subject using the mean of all the data points within ± 25 ms of the peak in amplitude that was identified in the grand average.

Previous studies have indicated that not all deviants will elicit a P3a during wakefulness. It was also possible that the P3a would be absent to some or all deviants

during sleep. The usual ANOVA statistical procedure determines whether a difference in amplitude among conditions is statistically significant. It cannot be used to identify the absence of a response. Thus, confidence intervals were computed to determine whether a deflection was significantly less or greater than the baseline setting (in the case of the DRN and P3a, respectively). The procedure was run on the Fz electrode site for the DRN and at Cz for the P3a where each tends to be at maximum amplitude. Because a directionality was predicted (negativity in the case of the DRN and positivity in the case of the P3a), one-tailed tests of significance ($p < 0.05$) were applied to the confidence intervals. To restrict the likelihood of chance findings, the negativity had to conform to the usual latency (100–250 ms) and scalp distribution (fronto-central maximum, inversion in polarity at the mastoids) of the DRN, while the positivity had to conform to the usual latency (180–350 ms) and scalp distribution (centro-frontal maximum) of the P3a.

Electrode sites were grouped into regions of interest (ROIs), to include 9 electrode sites where the ERP components of interest were largest. The ROIs allowed for an analysis of an anterior–posterior and an inter-hemisphere factor. Specifically for the anterior–posterior electrode factor, three electrodes for frontal (F3, Fz, F4), centro-frontal (FC3, FCz, FC4), and central (C3, Cz, C4) sites were chosen for analysis. The DRN and P3a components were thus quantified at each of these sites within the latency range identified at Fz and Cz, respectively. For the inter-hemisphere factor, three electrodes for left (F3, FC3, C3), midline (Fz, FCz, Cz), and right (F4, FC4, C4) sites were chosen for analysis.

ANOVA procedures were then run to compare the amplitude of the DRN and P3a across waking and sleep stages. ANOVA testing was only run when a significant DRN or P3a was observed for a deviant during any of the sleep stages. Specific ANOVA procedures thus varied among the different deviants and will be described in the Results section. Significant main effects and interactions were followed up with Fisher's LSD post-hoc testing. For all statistical analyses, a Geisser-Greenhouse correction was used when appropriate (Geisser & Greenhouse, 1958).

3. Results

3.1 DRN

3.1.1. Waking State

The difference waves for the various deviants across the waking and sleep states are illustrated in Figure 1. In the waking state, a negativity peaking at about 150 ms was observed following all deviants. In cases in which the intensity of the deviant increased relative to the standard (i.e., increment) or at times increased (white noise, environmental sounds), this negativity probably reflected a composite N1 and MMN (i.e., the DRN). In the cases of the frequency, duration, and decrement deviants, the negativity probably reflects a true MMN, although for consistency will be labelled as a DRN. The DRN was maximum over frontal areas of the scalp and inverted in polarity at the mastoids. Confidence interval testing in the waking state revealed that all deviants, except the decrement deviant, elicited a DRN significantly different from the baseline ($p < .01$ in all cases).

An ANOVA with repeated measures on deviant type (frequency, duration, decrement, increment, white noise, environmental sounds), frontality (frontal, centro-

frontal, central), and laterality (left, midline, right) was run on the waking DRN data. There was a significant main effect of deviant type, $F(5, 75)=5.76$, $MSE=12.77$, $p<.0001$, $\eta^2_p=0.28$. The DRN was largest to the increment deviant and smallest to the decrement deviant. The overall amplitude of the DRN was largest over frontal areas of the scalp, $F(2, 30)=12.24$, $MSE=1.35$, $p<.0001$, $\eta^2_p=0.45$ and it was significantly reduced at central sites. The DRN was also largest over midline electrode sites, $F(2, 30)=6.33$, $MSE=0.70$, $p<.01$, $\eta^2_p=0.30$. Fisher's LSD revealed no inter-hemispheric differences in the amplitude of the overall DRN between left and right areas of the scalp. Interactions involving deviant x electrode site were not significant ($F<1$).

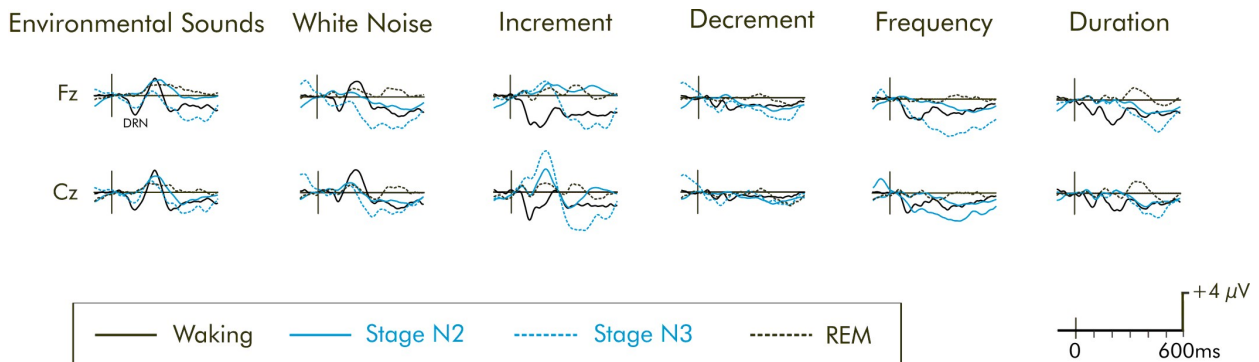


Figure 1. Grand average difference waveforms of the 6 deviants. ERPs shown at the Fz and Cz electrode sites. The waveforms for the four different stages are superimposed for each deviant stimulus.

3.1.2 DRN during sleep

During stage N2 sleep, confidence interval testing indicated that none of the deviants elicited a DRN that was significantly different from the baseline ($p>.05$ in all cases). Surprisingly, during stage N3 sleep, the frequency and the decrement deviant did elicit a significant negativity during the time interval of the DRN ($p<.05$ in both cases).

As can be observed in Figure 1, this could be due to an overall long-lasting negative drift that began prior to stimulus onset. The amplitude of the frequency DRN was nevertheless significantly larger during the waking state compared to stage N3, $t(16)=4.21$, $p<.01$, but the decrement DRNs did not significantly vary ($t<1$). All other deviants failed to elicit a significant DRN during stage N3. During REM sleep, none of the deviants elicited a significant DRN ($p>.05$ in all cases). A small negativity could be observed for the increment, but it was not significantly different from the baseline ($p>.05$).

3.2 P3a

3.2.1 Waking State

Not all of the deviants elicited a significant P3a in the waking state (Figure 1). In the difference waves, a large amplitude centro-frontal maximum P3a was apparent only for the environmental sound and white noise deviants, peaking at about 240 and 215 ms, respectively. Confidence interval testing (Table 1) of the Cz data indicated that its amplitude was significantly different from baseline levels only for these deviants ($p<.001$ in both cases). An initial ANOVA with repeated measures on deviant type (white noise, environmental sounds), frontality (frontal, centro-frontal, central), and laterality (left, midline, right) was run on the waking P3a data. The amplitude of the P3a to the environmental sounds and white noise deviants did not significantly differ ($F<1$). The overall amplitude of these P3a data were largest over centro-frontal areas of the scalp, $F(2, 30)=3.78$, $MSE=0.60$, $p<.05$, $\eta^2_p=0.20$, and was significantly reduced at frontal sites. The P3a was largest over midline areas of the scalp, $F(2, 30)=15.46$, $MSE=0.85$, $p<.0001$, $\eta^2_p=0.51$. Fisher's LSD again revealed no inter-hemispheric difference between left and right scalp regions. Interactions involving electrode site were not significant ($F<1$).

Deviant Type	Stage	Amplitude (SD)	CI (95%)
Environmental Sounds	Waking	1.89 (1.31)	[1.19, 2.59]
	Stage N2	1.71 (1.44)	[0.94, 2.48]
	Stage N3	1.09 (3.09)	[-0.55, 2.74]
	Stage REM	0.94 (1.34)	[0.22, 1.88]
White Noise	Waking	2.06 (2.19)	[0.89, 3.23]
	Stage N2	0.81 (0.96)	[0.29, 1.32]
	Stage N3	0.33 (2.88)	[-1.21, 1.87]
	Stage REM	0.73 (1.48)	[-0.04, 1.52]

Table 1. Mean amplitudes (SD in parentheses) at the Cz electrode site for the difference waves at the time interval of the P3a. Confidence intervals (95%) are also reported for the Cz electrode site.

3.2.2 P3a during sleep

During sleep, again not all of the deviants elicited a significant P3a-like positivity. For some deviants, a positivity at the time of the P3a was observed when it was not apparent in the waking state. Figures 2 to 5 illustrate the deviants at multiple scalp sites for which a P3a-like positivity was observed either during the waking state or during sleep. During stage N2, confidence interval testing at Cz revealed that the environmental sound and white noise deviants elicited significant positivities at about 250 and 190 ms, respectively ($p < .01$ in both cases). The amplitude of the P3a was also compared in stage N2 occurring within the first and second halves of the night to determine possible time of night differences. The P3a did not significantly differ as function of time-of-night for either the environmental sounds or white noise deviants ($p > .05$ in both cases). The stage N2 data were therefore collapsed across early and late halves of the night. These deviants did not elicit a significant P3a-like positivity in stage N3. During stage REM, the environmental sounds again elicited a significant P3a-like positivity at about 220 ms

($p < .01$). The positivity to the white noise, at about 190 ms, just failed to attain significance ($p > .05$). In the case of the increment deviant, a significant positivity, at about 200 ms, was also observed during stages N2 and N3 ($p < .01$). Again, no significant differences were found between early and late stage N2 ($p > .05$). Again, the stage N2 data were therefore collapsed over the entire night. This positivity was also observed during stage REM, but it did not attain significance ($p > .05$).

For the environmental sounds (Figure 2), an ANOVA with repeated measures on stage (waking, stages N2, N3, REM), frontality (frontal, centro-frontal, central), and laterality (left, midline, right) was run. The amplitude of waking P3a and the P3a-like positivities in sleep were not significantly different ($F < 1$). Significant scalp differences were observed, $F(2, 30) = 4.13$, $MSE = 0.79$, $p < .05$, $\eta^2_p = 0.21$. It was largest at centro-frontal electrode sites and was significantly reduced at frontal sites. The positivity was also largest over midline regions, $F(2, 30) = 5.58$, $MSE = 1.19$, $p < .01$, $\eta^2_p = 0.27$. There were no inter-hemispheric differences between left and right scalp regions. Interactions involving stage $\times$ electrode site were not significant ($F < 1$). Spline maps (bottom portion of Figure 2) showed the waking, and stage N2, and REM P3a-like positivities to be largest over centro-frontal regions, decreasing in amplitude over posterior and lateral regions. During stage N3, the distribution was more centro-parietal.

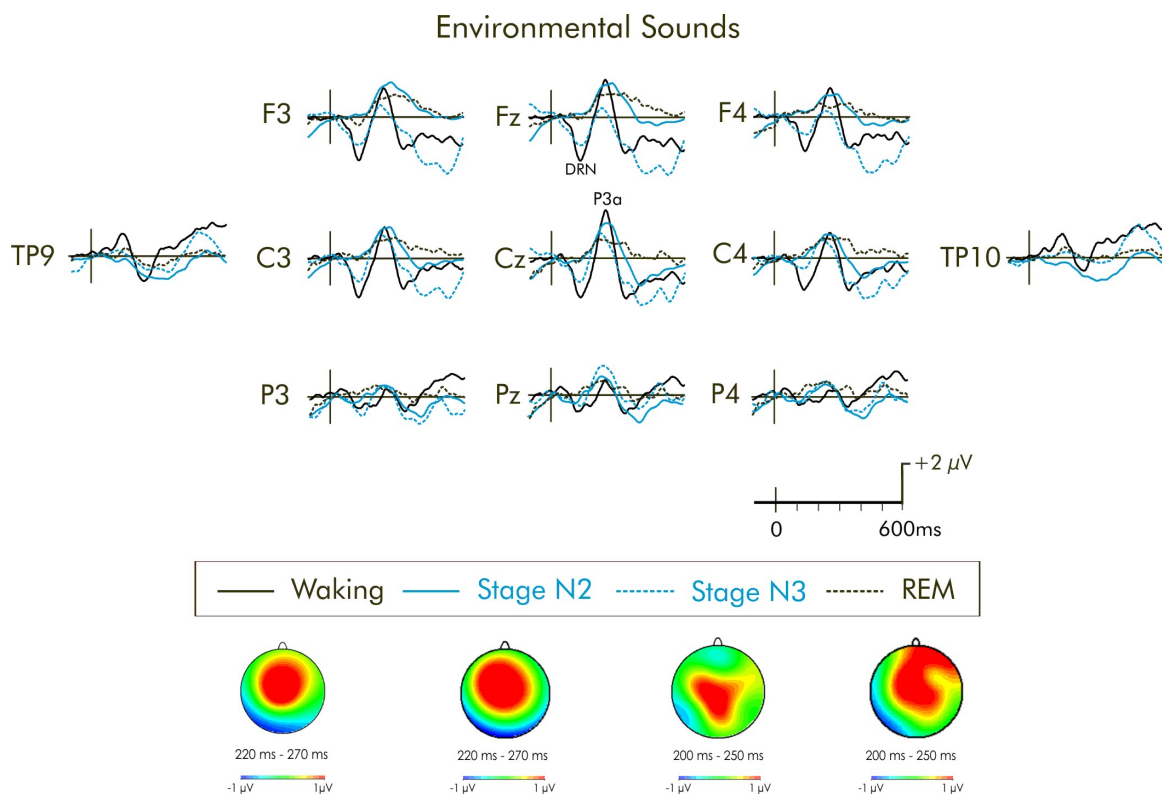


Figure 2. Grand average difference waveform for the environmental sounds at multiple scalp sites. The waveforms for the four different stages are superimposed. A significant P3a was observed in the waking state. A significant P3a-like positivity was also observed during stages N2 and REM. A subsequent positivity at about 320 ms can also be observed unique to REM sleep. Spline maps (bottom portion of Figure) are also presented for waking and stages N2, N3, and REM at the time interval of the P3a-like positivity. During waking, stage N2, and stage REM, the P3a-like positivity was largest over centro-frontal regions, decreasing in amplitude over posterior and lateral regions. During stage N3, the distribution was more centro-parietal.

For the white noise deviant (Figure 3), the positivity observed during stages N2, N3, and REM occurred earlier (190 ms) than the waking-P3a and its scalp distribution

(bottom portion of Figure 3) was centro-parietally maximum, unlike the usual centro-frontal P3a. Given the centro-parietal maximum distribution, the ROI analysis was adjusted with an ANOVA being run with repeated measures on stage (waking, stages N2, N3, REM) and electrode site (Fz, Cz, Pz). The amplitude of the waking P3a and the positivity in sleep were not significantly different, $F(3, 45)=1.83$, $MSE=8.94$, $p>.05$, $\eta^2_p=0.11$. The stage x electrode site interaction was significant, $F(6, 90)=4.36$, $MSE=0.92$, $p<.001$, $\eta^2_p=0.22$. During waking and stage N2, the positivity was largest at Cz, while during stages N3 and REM the positivity was largest at Pz. Spline maps confirm the distribution differences between the stages.

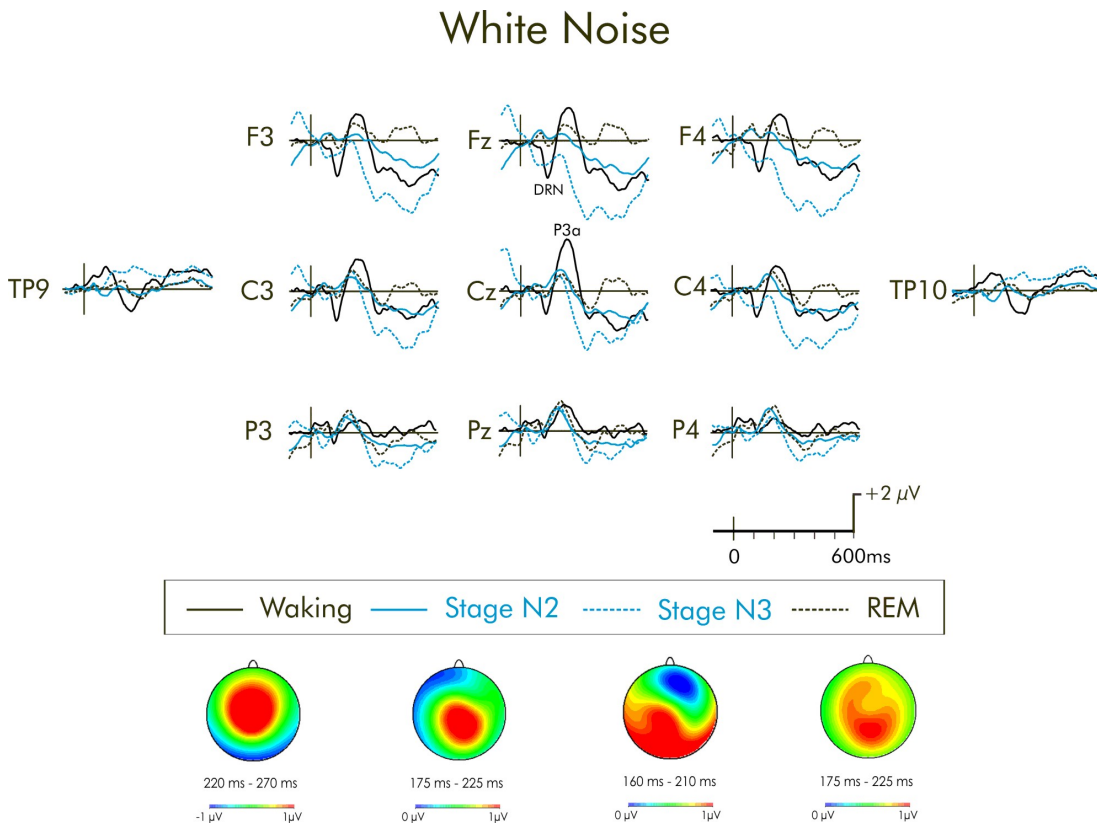


Figure 3. Grand average difference waveform for the white noise deviant at multiple scalp sites. The waveforms for the four different stages are superimposed. A significant P3a was observed in the waking state. A significant positivity was also observed during

stage N2, it did not attain significant during stages N3 and REM. A subsequent positivity at about 400 ms can also be observed unique to REM sleep. Spline maps (bottom portion of Figure) are also presented for waking and stages N2, N3, and REM at the time interval of the P3a-like positivity. During waking, the P3a was largest over centro-frontal areas of the scalp while during stages N2, N3, and REM it was largest over centro-parietal areas.

For the increment deviant (Figure 4), a large positivity was observed during stages N2 and N3. This positivity occurred unusually early (190 ms) for a P3a and its scalp distribution (bottom portion of Figure 4) was centro-parietally maximum, unlike the usual centro-frontal P3a. Similar to the white noise, an ANOVA was run with repeated measures on stage (waking, stages N2, N3, REM) and electrode site (Fz, Cz, Pz). Overall, the positivity was significantly reduced during wakefulness compared to all sleep stages, $F(3, 45)=9.67$, $MSE=10.10$, $p<.001$, $\eta^2_p=.40$. Additionally, Fisher's LSD revealed the positivity in stage N3 was also significantly larger than that of stage REM. The stage x electrode site interaction was also significant, $F(6, 90)=4.16$, $MSE=1.24$, $p<.001$, $\eta^2_p=.22$. During stages N2 and REM, the positivity was largest at Cz, while during stage N3 it was largest at Pz. Overall, the amplitude of the positivity was significantly smaller at Fz, compared to both Cz and Pz, $F(2, 30)=14.45$, $MSE=1.87$, $p<.001$, $\eta^2_p=.49$. Spline maps of the positivity during stage N2 and N3 emphasize this centro-parietal distribution. During REM, this distribution was very broad, spanning from frontal to parietal regions.

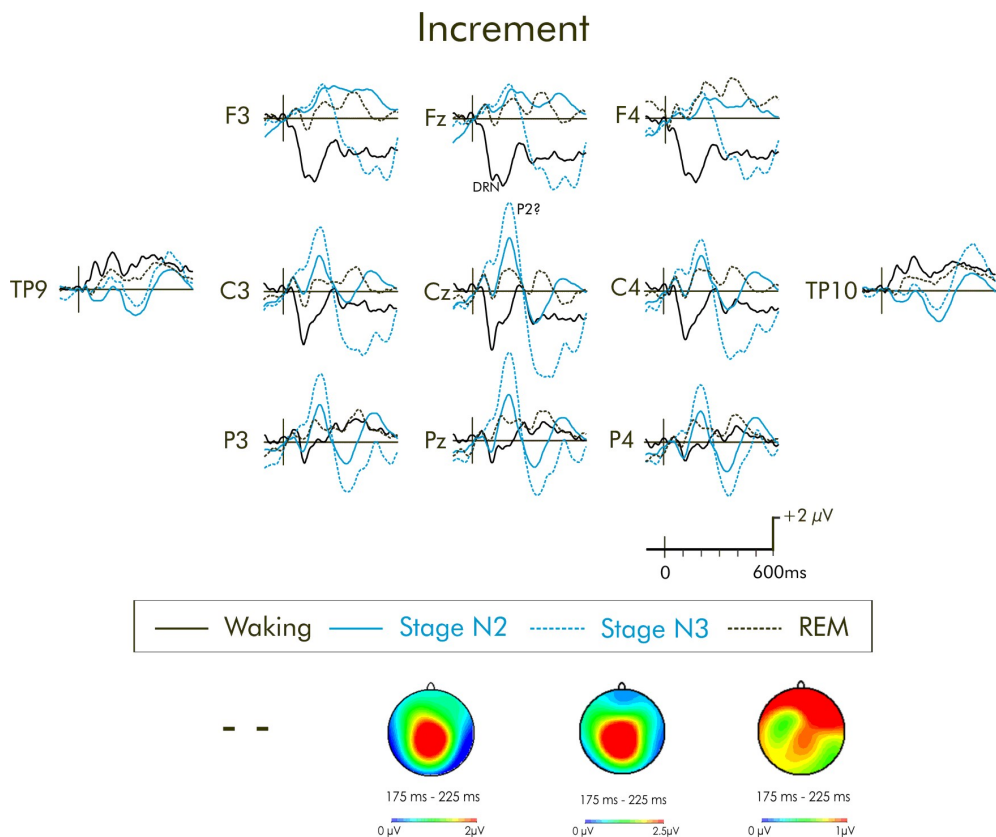


Figure 4. Grand average difference waveform for the increment deviant at multiple scalp sites. The waveforms for the four different stages are superimposed. A P3a was not elicited in the waking state. A significant positivity was observed during stages N2 and N3, it did not attain significance in REM. A subsequent positivity at about 350 ms can also be observed unique to REM sleep. Spline maps (bottom portion of Figure) are also presented for stages N2, N3, and REM at the time interval of the initial positivity. This positivity during stages N2 and N3 has a centro-parietal distribution, while during REM, this distribution was very broad, spanning from frontal to parietal regions.

3.3 Late positivity during REM

A later positivity, at about 300-400 ms, occurring at about the same time as a positivity observed by Ruby et al. (2008), was also observed following some of the

deviants, but only during REM sleep. This positivity was large over fronto-central areas of the scalp (Figures 2-5). When measured at Fz, it was significantly different from the baseline following the duration deviant (Figure 5), ($p < .01$) and the increment deviant (Figure 4), ($p < .05$). It did not reach statistical significance following either the environmental sound or white noise deviants ($p > .05$ in both cases). Previous studies have also reported a positivity at this time, however, with a parietal distribution (Bastuji et al., 1995; Cote et al., 1999; 2001; Ruby et al., 2008). For this reason, it was measured at Fz, Cz and Pz. For the stage REM data, a two-way ANOVA with repeated-measure on deviant (environmental sounds, white noise, increment, and duration) and electrode site (Fz, Cz, Pz) was run. The amplitude of the positivity did not significantly differ among deviant types ($F < 1$). The overall amplitude of the positivity was slightly larger at Fz compared to Cz and Pz, although this difference was not significant ($F < 1$). The deviant type x electrode site interaction was also not significant ($F < 1$).

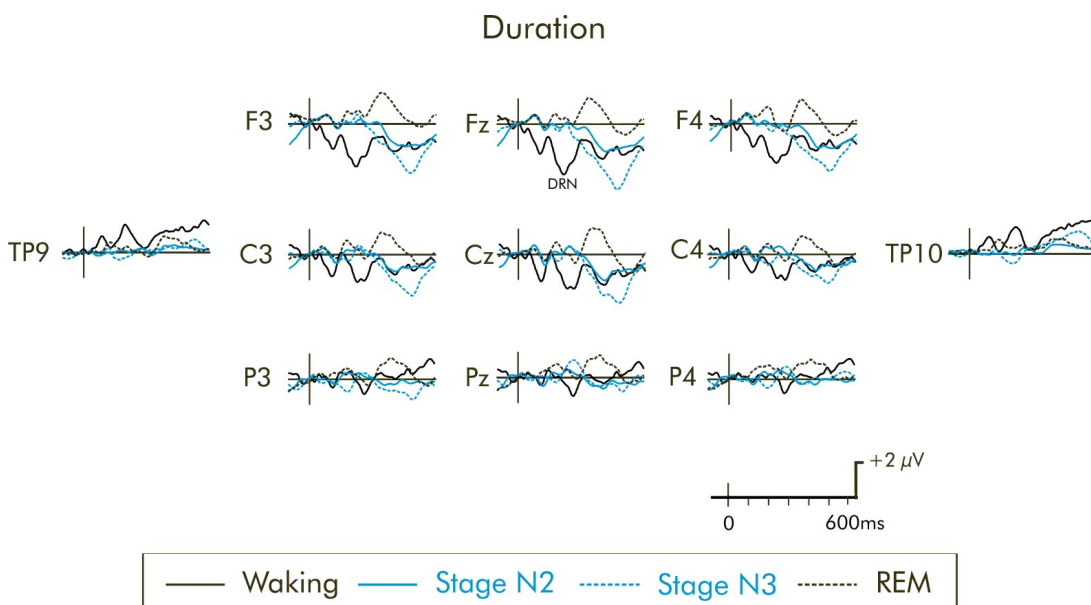


Figure 5. Grand average difference waveform for the duration deviant at multiple scalp sites. The waveforms for the four different stages are superimposed. A significant

P3a was not elicited in the waking state or any of the sleep stages. A later positivity at about 350 ms can be observed unique to REM sleep.

4. Discussion

In the waking state, the P3a has traditionally been associated with processes related to the involuntary capture and orientation of attention towards auditory input. Of course, while subjects are asked to ignore the auditory channel, they might still sample (“eavesdrop on”) these task-irrelevant stimuli. This is highly unlikely to occur during unconscious states such as natural sleep. The purpose of the present study was to determine if deviant stimuli that elicited a P3a in the waking state would continue to do so during sleep. ERPs were recorded to auditory stimuli presented within an optimal paradigm that included six different deviants.

4.1 DRN in wakefulness and sleep

The highly time-efficient multi-feature optimal paradigm proved to be successful in permitting a significant DRN to be elicited by all deviants in the waking state, except for the decrement. A small DRN was, in fact, observed following the presentation of the decrement, but it did not attain significance. The waking DRN conformed to its usual latency and scalp distribution and importantly, essentially replicated the DRN data of Tavakoli & Campbell (2016) in spite of the fact that subjects were tested at very different times (during the day in their study and late at night in the present study). Thus, even if subjects are very sleepy, the DRN appears to be well preserved, provided subjects are awake. During both NREM (stages N2 and N3) and REM sleep, a discernible DRN was not apparent following any of the deviants. The lack of a DRN during NREM is in agreement with most previous studies that have used either frequency or intensity

deviants (Loewy et al 1996; 2000; Nashida et al., 2000; Nielsen-Bohlman et al., 1991; Winter et al., 1995). During REM, some studies have reported the presence of a DRN (Atienza et al., 1997; Loewy et al., 1996; Sabri & Campbell, 2005) while others have not (Loewy et al., 2000; Macdonald et al., 2008; Sallinen et al., 1996). Ruby et al. (2008) did report a significant MMN during both NREM and REM when a rarely occurring 30 ms deviant signaled a change from a 75 ms standard. In the present study, the duration deviant did not elicit a DRN. The duration of the standard and deviant stimuli (200 and 100 ms, respectively) were much longer than that used by Ruby et al. (2008). It is possible that the sleeping brain can only detect brief and abrupt changes in stimulus duration. Additionally, the relative change in duration was larger in the Ruby et al. (2008) study than in the present one. Sabri et al. (2003) and Sabri and Campbell (2005) have also noted that a very large frequency change (1000 Hz standard; 2000 Hz deviant) elicited a DRN in stage N2 and REM but a smaller change (1100 Hz) did not. The frequency deviant in the present study represented the same extent of change as the small frequency deviant used by Sabri et al (2003; 2005) and also did not elicit a significant DRN during stages N2, N3 or REM.

It is also possible that while in wakefulness, the presentation of multiple deviants in a single optimal paradigm can reliably record the DRN; this may not be the case during sleep. The optimal pattern employed six different deviants each occurring quite rarely. Nevertheless, the overall probability of occurrence of deviants was .50, the standards and deviants being presented in an alternating pattern. Each different deviant does, however, share many features with the standard and as such, strengthens the sensory memory for the standard. Sabri and Campbell (2005) suggested that the failure to elicit an MMN

during NREM sleep might be because of a rapidly fading sensory memory for the standard. In the case of the optimal paradigm, it is possible that the sensory memory for the standard is also poorly formed during sleep as its probability of occurrence is reduced to 50%.

4.2 P3a during wakefulness

During wakefulness, a significant P3a was only observed following the environmental sounds (at 240 ms) and white noise deviants (at 215 ms). The amplitude of the P3a elicited by these two deviants was not significantly different. This replicates the results observed by Tavakoli and Campbell (2016). Previous studies employing oddball paradigms have also observed a large P3a to environmental sound and white noise deviants compared to other pure tone deviants (Berti, 2012; Cahn & Polich, 2009; Combs & Polich, 2006; Frank et al., 2012; Wetzel et al., 2013). Tavakoli and Campbell (2016) also noted that the frequency, duration, decrement, and increment deviants did not elicit a P3a in the waking state. When a passive paradigm is used, it does appear that a larger extent of deviance is required to elicit the P3a compared to active paradigms in which subjects are attending to the stimulus sequence containing the deviant (Berti et al., 2013; Grimm et al., 2008; Rinne et al., 2006). The environmental sound and white noise deviants varied widely in terms of their frequency spectrum and stimulus energy (e.g., intensity) from the pure tone standards. All other deviants only represented a change in a single feature from the standard. Increments in previous waking studies have repeatedly been shown to also elicit a P3a. The duration of the stimulus might again explain the discrepancies. In these studies, the duration of the increment deviants was very brief, typically 50 ms (Macdonald et al., 2008; Muller-Gass et al., 2006; 2007) compared to the

much longer 200 ms used in the present study. It has been known for some time that the perceived intensity of a stimulus is directly affected by stimulus duration (Stevens and Hall, 1966; Zwislocki, 1960). The perceived intensity of a stimulus increases as the duration of the stimulus is increased. However, in the case of oddball or optimal paradigms, the perceived intensity of the deviant *and* the standard increases. This may make the increment deviant less obtrusive.

4.3 P3a during sleep

No previous studies have used environmental sound deviants during sleep. The environmental sounds did elicit a large P3a during wakefulness. Within sleep, a positivity at the time of the waking P3a (230 ms) continued to be elicited during both NREM (stages N2 and N3) and REM sleep. Its amplitude at centro-frontal sites did not differ from that observed in the waking state. In addition, the spline maps of the scalp distribution between the waking P3a and the P3a-like positivity in sleep were very similar. There is thus little evidence to support the notion that the intracranial sources of the P3a were different between the waking state and sleep stages. The positivity recorded to the environmental sound deviants thus appears to be a “true” P3a. The environmental sounds, unlike any other deviant, differed on every trial, each containing a unique spectral content. By comparison, the spectral content of the other deviants were the same on each presentation. These environmental sounds are also more ecologically valid as most are sounds that are experienced daily. The environmental sounds represented mixed category of stimuli, some of which could be recognized (musical instruments, animal and human sounds) but others could not (mechanically produced sounds). Recent studies have separated environmental sounds into those that can be recognized and those that cannot

as well as within sub-categories (e.g., animate and inanimate sources, human, animal and mechanically-produced sounds) and have shown that these have major influences on the extent of processing (c.f., Stavropoulos and Carver, 2016). It is possible that certain highly salient and relevant sounds, such as one's own voice compared to others (Pratt et al., 1999; Perrin et al., 1999) or an emotional context (Pinheiro et al., 2016; 2017) might be processed more extensively than others.

During NREM sleep, the increment and white noise deviants also elicited a positivity. This positivity however occurred around 190 ms, unusually early for a P3a. Ruby et al. (2008) also observed a positivity in stages N2 and N3 that peaked earlier than the P3a in the waking state. In their case, the scalp distribution maps of the positivities in waking and sleep were similar. In the present study, the scalp distributions were different. For both deviants, it was maximum over centro-parietal regions of the scalp during stages N2 and N3 compared to the centro-frontal scalp distribution of the P3a. ERP components that have different scalp distributions must have different intra-cranial generator sources (Picton et al., 1995). Given the earlier latency and different scalp topography, it is unlikely that the positivity to the increment and white noise deviants solely reflects true P3a activity. Additionally, the increment deviant did not elicit a P3a in the waking state. Given this, it is unlikely it would now begin to do so within sleep. The peak latency and scalp distribution of this positivity following both increment and white noise is more consistent with earlier P2 activity. P2 amplitude does vary directly in intensity of the auditory stimulus. The intensity of the increment deviant was 10 dB higher than for the standard. Similarly, at times the intensity of the white noise would have been higher than the standard. As such, it would be expected that P2 would be larger for both types of

deviants compared to the standard. The P2 in the difference wave was much larger in NREM (stages N2 and N3) than in wakefulness. Again, this is to be expected. Many sleep studies have observed that the amplitude of the P2 may increase during NREM sleep (Crowley et al., 2002; Macdonald et al., 2008; Nittono et al., 2001; Nielsen-Bohlman et al., 1991; Winter et al., 1995). Campbell and Muller-Gass (2011) examined the processing of different stimulus intensities and reported that the P2 increase in amplitude during NREM sleep compared to wakefulness was especially large for higher intensity stimuli. Consistent with this, when the intensity of the standard was louder than that of the deviant (i.e. the decrement deviant), the P2 was no longer apparent in the difference wave during NREM sleep. The amplitude of the increment positivity was much larger during stage N3 compared to stage N2. In their review, Crowley et al. (2004) have suggested that the amplitude of P2 reflects inhibition of processing. This is why it is larger in NREM sleep than in the waking state. Therefore, it is possible that the increase in the amplitude of the P2 in the difference wave reflects a greater need for the protection of sleep and for it to remain undisturbed during deep ‘slow wave sleep’ (stage N3) than in the lighter stage N2. It is also possible that the increase in the amplitude of P2 simply reflects background noise. While the averaging process will reduce the amplitude of this random noise with a sufficiently large number of stimulus presentations, the deviants were presented rarely and among very high amplitude delta wave activity during stage N3.

During REM, a positivity, occurring at about 200 ms, was also observed following both the increment and white noise deviants. This occurred at about the same time as the waking P3a. Again however, the scalp distribution of the waking P3a and the

REM positivity was different. The REM positivity had a much broader scalp distribution. In the case of REM sleep, other studies have also reported P3a-like deflections, especially if the extent of deviance is large (Macdonald et al., 2008; Ruby et al., 2008; Sabri et al., 2005). Macdonald et al. (2008) observed a P3a only following the presentation of an increment but not a decrement deviant. Similarly, Sabri and Campbell (2005) noted a small P3a during REM following presentation of a large frequency deviant, but not following the small frequency deviant. Unfortunately, they did not record from extensive electrode sites allowing for a mapping of the scalp distribution of these positivities. Ruby et al. (2008) also observed an early positivity during REM sleep; its scalp distribution being consistent with a P3a. In their case, their duration deviant was not more intense than that of the standard and thus, it is unlikely that their positivity reflects P2 activity. This is not the case with the white noise and increment deviants. It is possible that what was observed during REM sleep was a composite P2+P3a. This would explain the slightly earlier latency and more widespread scalp distribution. Nevertheless, in the case of the increment deviant, it would be still be puzzling that it would elicit a P3a during REM sleep but not in the waking state.

4.4 Late positivity during REM

A later positivity, at about 300-400 ms, was also observed that was unique to REM sleep. It was not apparent in either wakefulness or in NREM sleep. What was especially surprising was that it was elicited by many different deviants. The amplitude of this later positivity did not significantly differ between the environmental sound, white noise, increment, and duration deviants. It had a fronto-central distribution. Some studies have reported the presence of a late positivity (around 300-500 ms) during REM (Bastuji

et al., 1995; Cote et al., 1999; 2001; Perrin et al., 1999; Ruby et al., 2008), although with a distinctly centro-parietal scalp distribution. It is possible that these parietal positivities reflect a P3b (also labeled P300) process. A P3b, largest over centro-parietal areas of the scalp, normally occurs in the waking state when subjects signal their overt awareness of the rarely occurring deviant stimulus. A P3b is not elicited in the waking state when the subject's attention is not directed to the detection of the various deviants.

In a study conducted in the waking state, Escera et al. (1998) observed that their P3a to environmental sounds had two distinct subcomponents. The early portion of the P3a, peaking at around 230 ms, had a centrally dominant scalp distribution with a polarity reversal at posterior and lateral regions. The late portion of the P3a, on the other hand, peaked at around 330 ms and displayed a frontally maximum scalp distribution. The latency and scalp topography of the late P3a observed by Escera et al. is in line with the late positivity in REM observed in the present study. However, it is surprising that a similar morphology of early and late subcomponents was not observed in the waking state and only during REM sleep. The functional significance of late positivity in the present study occurring only in REM sleep is difficult to interpret. Because of its long latency, it is unlikely to reflect a true P3a, however, its fronto-central maximum scalp distribution is unlike that of a P3b.

4.5 Disassociation of the DRN and P3a

A DRN was not observed during either NREM or REM sleep, yet a P3a-like positivity was still elicited following some deviants. Based on the classic Näätänen model, it would be expected that the probability of eliciting a P3a would decrease as the amplitude of the MMN/DRN is reduced. Other studies have however demonstrated that

the amplitude of the MMN/DRN and P3a are not necessarily correlated (Fischer et al., 2008; Horvath et al., 2008; Sussman et al., 2003). Therefore, a deviant might elicit a P3a without eliciting an MMN. Näätänen also points out that other factors can affect the P3a; the threshold for its elicitation is therefore flexible. It is possible that during sleep the threshold to elicit the P3a is significantly lowered in order to possibly awaken and alert the individual to the external environment. Thus, even though the amplitude of the MMN/DRN is reduced, the P3a will still be elicited.

5. Concluding remarks

The purpose of this study was to determine whether a P3a could be elicited during sleep and if so, by what type of stimulus deviance? The present study was not designed to determine the functional significance of the P3a. The classic view was that the P3a signalled a switch of attention to the processing of the incoming but unattended deviant events (Escera et al., 1998; Gaeta et al., 2001), resulting in distraction and in deterioration of performance (Berti et al., 2004; Oja et al., 2016; Schröger and Wolff, 1998). Thus, the P3a was thought to provide a measure of “attention capture”. From this perspective, the P3a occurring during sleep might thus provide a means to allow the sleeper to become aware of external environmental events. The intriguing question is whether this P3a serves the same role in the waking and sleep states? If the P3a reflects a process by which the sleeper can become aware of an external auditory input, why did subjects not awaken? There was, in fact, little evidence that subjects became more aroused or were awakened following the occurrence of the P3a. Importantly, while most researchers do agree that the P3a is involved in a passive process that may result in forced awareness of an external event, the view that it reflects the actual awareness no longer seems to be

tenable. More recent studies have not always found an association between the P3a and behavioural evidence of deterioration in performance (see discussions by Parmentier, 2014; Wetzel et al., 2013). The current thought is that the P3a reflects the evaluation of events as significant, rather than the actual switch of attention itself (Horvath et al., 2008; Wetzel et al., 2013). This may also explain why subjects did not awaken following the P3a. Most often this evaluation determines that the stimulus is not critical or significant enough that sleep should be reversed.

The present study examined whether various deviant stimuli might elicit a P3a during sleep. Results from previous studies of the P3a during sleep have been inconsistent. This may be because of the use of very different methodologies and the use of different types of deviant stimuli. The present study employed a multi-feature optimal paradigm, permitting the comparison of the effects of many different types of deviants. A P3a, maximum over centro-frontal regions of the scalp was elicited in the waking state by environmental sound deviants when the subject's attention was engaged in watching a silent, subtitled movie. The environmental sounds also elicited a similar central-fronto maximum positivity occurring at about the same time during NREM and REM sleep. Other deviants failed to elicit a definitive P3a during sleep. Another earlier positivity having a different scalp distribution than the P3a was however elicited following the white noise and increment deviants during stages N2, N3, and REM, although it did not attain significance in REM following either deviant. This positivity may be an earlier P2 often reported to increase in amplitude during sleep. The environmental sounds, white noise, increment, and duration deviants also elicited a later fronto-central maximum positivity unique to REM which has not been reported in previous studies.

The current study also has implications for other unconscious states such as general anesthesia and coma. Researchers are currently employing ERP techniques to probe the extent of information processing in patients who do not exhibit overt behavioural responses (for reviews, see Gawryluk et al., 2010; Harrison & Connolly, 2013; Morlet & Fischer, 2014). The multi-feature optimal paradigm may be a useful tool in these clinical and applied studies.

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Chapter 5: Summary and Conclusions

The present thesis employed event-related potentials to examine the extent to which stimulus change is processed passively, independent of attention. Importantly, the various studies examined processes associated with the interruption of the central executive and the subsequent intrusion of deviant stimuli into conscious awareness. This process is reflected by a positive-going centro-frontal maximum ERP, the P3a, occurring from 200-250 ms after onset of the deviant. Most studies have used oddball paradigms to study the P3a. The time required to collect the ERP data to examine the processing of a single deviant is long. The time required to study the effects of several different deviants would thus be exceedingly long and impractical for many clinical and applied settings. A highly time efficient auditory multi-feature optimal paradigm was therefore used in all studies to determine the likelihood of eliciting the P3a to multiple deviant types.

What has been learned in these studies:

Study 1

1. A multi-feature optimal paradigm was used in which 6 different deviants were presented and alternated among standards. It was not known whether this optimal paradigm could be used for the study of attention capture. Certain deviants did, however, elicit a P3a, often associated with processes leading to attention capture.
2. As expected, all deviant stimuli elicited a DRN. This indicates that the multi-feature optimal paradigm can be used to efficiently study the change detection process.
3. Deviant stimuli whose features vary widely from pure tone standards were more likely to elicit a P3a. The P3a was observed only following deviants that varied

from the standard on more than one feature. Deviants in which only one feature was varied did not elicit a P3a, even though they did elicit a DRN.

4. Some of the deviants that did not elicit a P3a in the present optimal paradigm have been demonstrated in previous studies to elicit a P3a when presented within an oddball paradigm. When the data from the optimal and oddball paradigms were compared, results were similar.
5. Only the deviants that represented the greatest extent of change from the standard elicited a P3a. This might be because subjects could perceive these deviants better than the ones that represent a lesser extent of change. This was not the case, however. There was little relationship between the perceptibility of the deviant and the probability of eliciting a P3a.

Study 2

1. In order for sleep to be of benefit, the processing of all but the most relevant of stimuli must be inhibited. As demonstrated in Study 1, certain deviant stimuli are considered to be so relevant that they will cause an interruption of the central executive controlling attention and conscious awareness. The results of Study 2 indicate that even the sleep onset process may be affected by these deviant stimuli.
2. Previous studies have demonstrated that ERPs are much altered during the sleep period. Many authors consider the early portion of stage N1 to be more similar to the waking than the sleeping state. The same white noise and environmental sound deviants that elicited a waking P3a continued to do so during early stage N1. This might be because the processing of the external environment is still not inhibited during this early form of sleep.

3. Late stage N1 is considered to be much more characteristic of true sleep.

Nevertheless, the white noise and environmental sound deviants continued to elicit P3a. Thus in spite of the attempt to fall asleep, certain highly relevant stimuli might still interrupt the central executive overcoming its attempt to inhibit the processing of information from the external environment.

4. Most researchers agree that stage N2 marks true sleep and the individual is now no longer conscious of the external environment. Nevertheless, the environmental sound deviants continued to elicit a P3a during stage N2. The environmental sounds were unlike any other deviant. A unique environmental sound was presented on each trial hence each sound was novel. Novelty might thus be a critical factor associated with the interruption of the central executive during an unconscious state such as natural sleep.

Study 3

1. The early stage N2 period that was studied in Study 2 is probably not typical of the overall sleep period. It probably represents a lighter form of sleep than that which occurs later in the night. The multi-feature optimal paradigm was therefore presented during all-night sleep. This is the first time that multiple different deviants have been presented throughout the entire night.
2. Processing of auditory stimuli is much altered by sleep. For example, most previous oddball studies have noted that the DRN is much attenuated in NREM sleep. Some studies have indicated that a DRN can still be recorded but these studies have used different deviants. The use of the multi-feature optimal paradigm permitted a

comparison of the different deviants in a single study. The DRN was much attenuated in both NREM and REM sleep for all deviants.

3. A striking finding was that the environmental sound deviant continued to elicit a P3a throughout the sleep period, in stages N2 and REM sleep. Remarkably, it was also observed during stage N3, considered to be very deep sleep, although it did not attain significance. While the appearance of the P3a does reflect the interruption of the central executive and possible awareness of the external stimulus, subjects did not awaken.
4. The intensity increment and white noise deviants elicited a positivity, peaking at about 180 to 200 ms. The intensity deviant did not elicit a P3a in the waking state. Increases in intensity have special significance in nature. It signifies an approaching or “looming” sound and elicits a fear response. The intensity of the white noise deviant was of course random and as such at times would be more intense than that of the standard. This might also have signified an approaching sound. The latency of this positivity was however too early for the longer latency P3a and its scalp distribution more posterior than the centro-frontal P3a. This morphology is more consistent with an earlier P2, affected by stimulus features such as intensity. A number of studies have indicated that the P2 may increase in amplitude during sleep.
5. A number of deviants also elicited a later positivity. Some studies have reported a more posterior positivity during sleep but in the present study, the late positivity was widespread and largest over frontal regions. The functional significance of this late positivity is unknown.

5.1 Implications

5.1.1 The Environmental Sounds

During the waking state, across all three studies, and during sleep onset in Study 2, the white noise and environmental sounds were the only deviants to elicit a P3a. This could be due the fact that these deviants varied widely in spectral content from the standard, compared to the pure tone deviants. During stage N2 sleep, in both Study 2 and 3, the environmental sounds were the only deviant to continue to elicit a P3a. It is possible that during sleep the threshold for eliciting the P3a is increased in order to protect the sleeper from further processing and possible subsequent awakening. As a result, only the most relevant stimuli may elicit a P3a, as reflected in the present thesis by the ecologically valid environmental sounds compared to the other deviants.

Why are these stimuli so relevant that they will even initiate processes related to attention capture during an apparently unconscious state, natural sleep? Several features distinguish these stimuli from all other deviants. As already mentioned, the spectral content of the environmental sounds was widely different from the standards. The spectral content of the white noise deviants also differed widely from the standards. Each environmental sound was, however unique, never repeated twice within the auditory sequence. It remains to be determined whether they would have been as effective if the same environmental sound had been repeated on each trial. These sounds represented a mixed category of stimuli, some recognizable (human voices, animal and musical instrument sounds...) and some not recognizable (mechanically produced sounds). As a result, some of these environmental sounds were semantically meaningful, unlike the other deviants. Studies have also shown differential processing of environmental sounds, especially based on whether they were recognizable, human-made sounds or

unrecognizable, mechanically produced sounds (c.f., Stavropoulos and Carver, 2016). Heightened attention to non-human made mechanical sounds is, nevertheless, important, as they often require immediate attention in daily life (e.g. a car horn, alarm systems). This may also explain why the environmental sounds were more likely to elicit a P3a. Some of the environmental sounds included human utterances. Sorokin et al. (2010) indicated that human speech sounds were especially likely to elicit a P3a. Additionally, many of the environmental sounds were familiar to the subjects and could be named. Familiarity of the sound might however act as another variable, increasing the likelihood of interrupting the central executive. It is also possible that some of the sounds might have been interpreted as a threat, initiating a fear response. Pakarinen et al. (2014) employed a multi-feature optimal paradigm that included speech-sounds having emotional valence (happiness, anger, sadness) and these were especially likely to elicit a P3a. The authors did point to a possible confound, however. They indicated that while there is general agreement about the emotionality of the various sounds, the effect on the P3a should to be interpreted with caution. The morphology and spectral content of the emotional sounds was different. For example, sounds detected as being angry rose rapidly in intensity (i.e. had fast rise-times). The possible reason for a sound producing a specific emotion, such as fear, may be a result of its physical properties. For example, abrupt and intense stimuli may be perceived as more threatening than softer and less intense stimuli. Determining which of these many factors might account for the interruption of the central executive would require sorting of the environmental sounds into the various categories and sub-categories (unique vs repeated, human vs non-human, familiar vs non-familiar, emotional vs non-emotional, and within the emotional category, the various emotions).

Sub-categorization would unfortunately reduce the number of trials available for averaging and with it, an increase in the background noise of the EEG.

5.1.2 Altered States of Consciousness

The present thesis has many implications for studies of unconscious states. The presence of MMN in response to rarely presented deviant stimuli can be used as a measure of the pre-conscious detection of change. While the MMN is thought to occur pre-consciously, prior to awareness that the deviant has been presented, it has been shown to be markedly affected or absent in unconscious states. This thesis indicated that the MMN/DRN was absent during sleep. Thus, it would appear that being in a conscious state is necessary for the MMN to be elicited, even though this does not imply that the individual is conscious of the deviant stimuli.

Altered states of consciousness are very commonly seen in clinical sciences. Patients in comatose or unresponsive states, as well as patients undergoing surgery with general anaesthetics are some examples. During general anaesthesia, the MMN and P3a are used to detect unintentional intraoperative awareness during surgery. Research has shown that the MMN is abolished in humans during propofol-induced unconsciousness (Blain-Moraes et al., 2016; Heinke et al., 2004). Heinke et al. (2004) also showed that the P3a remained present during wakefulness and light propofol sedation, but disappeared during deep propofol sedation. Plourde, Joffe, Villemure, and Trahan (1993) also did not observe a P3a during sufentanil-induced anaesthesia. These studies of general anaesthesia can also provide important insight for interpreting brain activity in patients with disorders of consciousness.

Many patients remain in a state of coma or unresponsive wakefulness for numerous months or years. The cost to the health care system is thus enormous. Treatment and rehabilitation of these patients is highly dependent on the “depth” of coma or unresponsiveness. Because the MMN is a good measure of the depth of unconsciousness, it has often been used as a prognostic marker for recovery in these patients (Bekinschtein et al., 2009; Daltrozzo, Wioland, Mutschler, & Kotchoubey, 2007; King et al., 2013; Fischer et al., 2008; 2010; Naccache et al., 2005; Tzovara et al., 2012). The P3a, unlike the MMN, is associated with a process leading to conscious awareness of the external environment. It has, thus, also been used in studies of recovery from coma (for reviews, see Harrison & Connolly, 2013; Morlet & Fischer, 2014).

A study by Fischer et al. (2008) examined the prognostic value of the P3a in a coma by using an auditory oddball paradigm with the patient’s own name as deviants. Three months after coma onset the patients were assessed and classified as either non-awake (minimally conscious state, unresponsive wakefulness, or dead) or awake (good recovery, minor or severe disability). Their results showed a high correlation between the presence of the P3a that was recorded during coma and awakening from coma at the three-month assessment period. The P3a was observed in 21 out of the 50 patients that were tested. Of these 21 patients showing a P3a, 17 of them awakened while 4 did not. The P3a was absent in 29 out of the 50 patients; 22 of these 29 patients did not awaken after three months, while 7 did awaken. Compared to MMN, the P3a was more sensitive at predicting recovery from coma. Sensitivity is measured by the proportion of patients who display a P3a among patients who have a good outcome at three months (i.e. awake with good recovery or moderate to severe disability). This thesis may explain why this is

so. The P3a can be elicited during unconscious states when the MMN/DRN is absent. Fischer et al. (2008) also observed this, as 11 of the 21 patients that displayed a P3a did not display an MMN. Thus, the MMN may “miss” cases in which recovery is imminent that the P3a accurately detects. This may also be related to the higher amplitude of the P3a compared to the MMN. The signal/noise ratio is much higher for the P3a. More recent studies have also attempted to examine the detection of change in sound sequences in the absence of consciousness (King et al., 2013; Tzovara et al., 2015). There have been inconsistencies in the result of these studies. Some researchers have used frequency deviants (Bekinschtein et al., 2009), while others have used duration deviants (Tzovara et al., 2015). Furthermore, some researchers rely on auditory oddball paradigms (Fischer et al., 2008; 2010; Holeckova et al. 2008) while others have used local-global paradigms, which are composed of two embedded levels of auditory regularity, one local (at the single trial level) and one global (across trials) (Bekinschtein et al., 2009; King et al., 2013; Naccache et al., 2005; Tzovara et al., 2015). The slightest change in the design of the study can dramatically alter the detection of underlying awareness. It is possible that the use of different deviant types within multi-feature optimal sequences will prove to be an even better predictor of recovery. The optimal paradigm can be designed to maximize the probability of eliciting a P3a.

5.2 The P3a as a Measure of Conscious Awareness?

As mentioned earlier, there is much debate surrounding the functional significance of the P3a. While this thesis was not designed to determine the functional significance of the P3a and how it is related to the highly controversial term, consciousness, a few comments are warranted.

Researchers have used numerous terms such as: attention capture, intrusions into consciousness, evaluation of significance, probing of sensory memory, switching of attention, among others, to describe the processes associated with the P3a. The initial notion that the P3a reflected involuntary capture of attention and resulting consciousness of the external auditory stimuli is now subject to much debate. Nevertheless, it is generally accepted that the P3a is associated with the overall passive and involuntary capture of attention by external acoustic change. The exact stage at which it operates is, however, questioned. Methodologically speaking, it is extremely difficult to determine the extent of information processing in the absence of overt responses. The problem with the passive paradigm is that researchers do not actually know what the subject “is doing” or more formally, do not have access to their mental state. It is possible to examine the effects of the deviant on performance on an ongoing task, and then infer the extent to which the deviant was processed. This was precisely the logic of the Schröger and Wolff (1998) study. It could be implied that performance must have deteriorated because attention was directed to the processing the deviant. Subjects had thus switched attention. More recent studies, however, have not always found an association between the P3a and behavioural evidence of deterioration in performance. Therefore, the notion of the P3a reflecting the actual switch of attention is no longer tenable.

The current understanding is that the presence of the P3a reflects higher-level detection processing, such as the evaluation of events as significant. The central executive may then make a decision to switch attention away from current task demands, leading to the process of unintended consciousness of the intruding event. In this explanation, the individual is not actually conscious of the intruding event at the time of

the P3a. This interpretation could account for the presence of the P3a in unconscious states. In sleep, for example, the P3a can be observed following potentially salient auditory deviants. But, it is only if the sleeper becomes conscious of the deviant that sleep is reversed and awakening occurs. Similarly, in disorders of consciousness, the P3a may assess depth of information processing but not consciousness itself. This depth of processing may be required before the comatose patient can emerge from coma, but may not be an indication of consciousness itself.

5.3 Concluding Remarks

Taken together, the studies of this thesis provide convincing evidence that a P3a can be reliably elicited using a multi-feature optimal paradigm during wakefulness, sleep onset, and sleep. The P3a is not elicited following presentation of all deviants. Its elicitation is dependent on the potential significance of the stimuli and the extent of change from the standard. The environmental sounds elicited the most consistent P3a across waking, the transition into sleep, and definitive sleep. Their higher ecological validity and novelty compared to the other deviants could make the elicitation of the P3a more likely. Overall, the present thesis demonstrates that the mechanisms associated with the involuntary capture of attention are active during wakefulness, but also during sleep when awareness of the external environment is diminished. This is especially critical because sleeping organisms can be vulnerable to external danger, and hence requires the ability to orient attention to incoming information and have it lead to awakening and conscious awareness.

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Appendix 1

Tavakoli, P., Muller-Gass, A., & Campbell, K. (2015c). Partial sleep deprivation does not alter processes involved in semantic word priming: Event-related potential evidence. *Brain and Cognition*, 94, 17-23.

Partial Sleep Deprivation Does Not Alter Processes Involved in Semantic Word Priming:
Event-Related Potential Evidence.

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Abstract

Sleep deprivation has generally been observed to have a detrimental effect on tasks that require sustained attention for successful performance. It might however be possible to counter these effects by altering cognitive strategies. A recent semantic word priming study indicated that subjects used an effortful predictive-expectancy search of semantic memory following normal sleep, but changed to an automatic, effortless strategy following total sleep deprivation. Partial sleep deprivation occurs much more frequently than total sleep deprivation. The present study therefore employed a similar priming task following either 4h of sleep or following normal sleep. The purpose of the study was to determine whether partial sleep deprivation would also lead to a shift in cognitive strategy to compensate for an inability to sustain attention and effortful processing necessary for using the predicative expectancy strategy. Sixteen subjects were presented with word pairs, a prime and a target that were either strongly semantically associated (*cat...dog*), weakly associated (*cow...barn*) or not associated (*apple...road*). The subject's task was to determine if the target word was semantically associated to the prime. A strong priming effect was observed in both conditions. RTs were slower, accuracy lower, and N400 larger to unassociated targets, independent of the amount of sleep. The overall N400 did not differ as a function of sleep. The scalp distribution of the N400 was also similar following both normal sleep and sleep loss. There was thus little evidence of a difference in the processing of the target stimulus as a function of the amount sleep. Similarly, ERPs in the period between the onset of the prime and the subsequent target also did not differ between the normal sleep and sleep loss conditions. In contrast to total sleep deprivation, subjects therefore appeared to use a common predictive expectancy strategy in both conditions. This strategy does however require an

effortful sustaining of attention, and may not have been entirely successful when sleep was restricted. A slight but significant decrease in accuracy was noted.

1. Introduction

Sleep deprivation has been consistently shown to degrade performance on many cognitive tasks especially for those that require sustained attention for successful completion. (reviewed by Lim & Dinges, 2010). Not all studies however find this decline in performance perhaps because subjects may be able to compensate for the effects of sleep deprivation by altering cognitive strategies. (Drummond et al., 2005; Lim & Dinges, 2008).

Recently, López Zunini et al. (2014) provided empirical evidence of dynamic changes in cognitive strategy after subjects had been totally sleep deprived. They employed a word priming task in which an initial word (the “prime”) appeared and subsequently followed by a “target” word that was either strongly (e.g., *cat...dog*), weakly (*cow...barn*), or not semantically associated (*apple...road*) with the prime. The subject’s task was to determine if the target was in fact semantically associated with the prime. Following normal sleep, the usual priming advantage was found. Reaction times (RTs) were faster and accuracy was higher following presentation of strongly primed targets. The strong priming advantage was still maintained following total sleep deprivation (TSD), although there was a small non-significant overall deterioration in accuracy.

Priming tasks are especially useful for the study of sleep deprivation because the similarity in performance that López Zunini et al. observed can be obtained through the use of two very different cognitive strategies. The results suggest that subjects might have used one strategy following normal sleep but then switch to a different strategy to maintain performance following total sleep deprivation. Most cognitive researchers agree that the presentation of the prime activates a semantic memory network with strongly

associated semantic concepts represented in neighbouring nodes and weakly associated concepts represented in more distant nodes. Targets that are not associated with the prime are not represented in the semantic network and are thus not available to memory prior to their onset (Collins & Loftus, 1975; Neely, 1991). The search is completed more rapidly for strongly associated targets than for either weakly associated or unassociated targets. The extent to which effortful processing is required to search the semantic network is disputed. One theory proposes that the subject can use the prime to intentionally predict a set of semantically associated target candidates (Becker, 1980; Neely, 1976; Posner & Snyder, 1975). There is however a cost to the use of this strategy as it requires active and effortful processing in order to generate possible target candidates and maintain them in working memory. This strategy would be appropriate following normal sleep, when sufficient cognitive resources are readily available. The use of an effortful expectancy-predictive strategy was promoted in the López Zunini et al. study by having subjects intentionally determine if the target was associated with the prime. Moreover, the time between the onset of the prime and the target was 700 ms in duration, long enough to permit the use of this strategy. A second theory proposes that the search of semantic memory can be initiated automatically and effortlessly, without the need for active and sustained attention (Collins and Loftus, 1975). This strategy could thus have been used to maintain performance following sleep deprivation when considerably fewer cognitive resources were presumably available.

López Zunini et al. also recorded event-related potentials (ERPs) following the presentation of the primes and targets to monitor in real-time whether performance following sleep deprivation was maintained through the use of a similar or different

cognitive strategy compared to that employed following normal sleep. In the normal sleep condition, a negative-going waveform peaking at about 400 ms (thus the “N400”) elicited by the target was much larger when it was not semantically associated with the prime, a finding replicating many others (reviewed by Kutas & Federmeier, 2011). This was also however the case in the TSD condition. Importantly, the overall N400 across all stimulus types was significantly reduced following TSD. Holcomb (1998) had previously noted that the use of an automatic, effortless search of semantic memory will result in a reduction of the N400 compared to when an effortful, intentional search is employed. Thus, the difference in the overall N400 amplitude following TSD might be explained by a change from an effortful to a relatively effortless cognitive strategy. The use of different cognitive strategies should have especially been apparent between the presentation of the prime and the subsequent target words, the time when the semantic network is searched. A long-lasting negativity beginning at about 300 ms following the prime and continuing until the onset of the target word was indeed significantly larger in the normal sleep condition. This might reflect additional effortful processing or may be a reflection of a so-called contingent negative variation (CNV) which has long been known to be attenuated following sleep deprivation (Naitoh, 1971).

While total sleep deprivation conditions are often employed in the study of the cognitive effects of sleep loss, in real-life situations, total sleep deprivation occurs much less frequently than partial sleep deprivation. The American Centers for Disease Control (CDC) analyzed data obtained from interviews on more than 15,000 workers and indicated that more than 30% of its sample slept on average for less than 6 hours a day (CDC, 2012). Sleep restriction is thus a hallmark of modern society due to a broad range

of societal and medical factors such as recreational opportunities, work schedules and sleeping disorders. In many cases, sleep is delayed, such that the onset of sleep begins later than normal.

While partial sleep deprivation occurs much more often than total sleep deprivation, relatively few studies have examined its effects on cognitive processing. The results of studies investigating partial sleep deprivation are less consistent although tasks that require sustained attention are more likely to show a deterioration in performance (see Dinges et al., 2005; Shekleton et al., 2010 for reviews). When partial sleep deprivation does affect performance, the effects are generally reduced compared to TSD (Van Dongen et al., 2003; Otmani et al., 2005; Casement et al., 2006). The effects may vary with the extent of sleep deprivation (Belenky et al., 2003) and can affect ERPs related to both automatic and controlled aspects of attention (Zerouali et al., 2010).

The present study examines the effect of 4 hours of sleep on the word priming task used by López Zunini et al. The interest is whether a common strategy will be used in the normal and partial sleep condition or as was the case with TSD, a different cognitive strategy will be adopted to maintain consistent performance following partial sleep deprivation.

2. Methods

2.1. Subjects

Sixteen young adults (10 females) between the ages of 20 and 30 years (Mean=23.1, SD=2.9 years) volunteered to participate in this study. All were right-handed, with good self-reported health, normal or corrected-to-normal eyesight and were

not taking any medications known to affect cognitive function. None had any history of neurological or psychiatric disorder. Absence of sleep disorders was verified using the Pittsburgh Sleep Index (Buysse et al., 1989). Subjects were required to maintain a regular sleep schedule (no night or shift work). Subjects were asked to abstain from alcohol and caffeine in the 24 h period prior to the start of data collection. This study was conducted following the guidelines of the Canadian Tri-Council (Health, Natural, and Social Sciences) on ethical conduct involving humans. All subjects gave written informed consent prior to the beginning of the experiment and were paid an honorarium for their participation.

2.2. Procedure

All subjects participated in two experimental sessions, one following a normal night of sleep, and one following partial sleep deprivation. The order of the sessions was counterbalanced across subjects and at least one week separated the two sleep conditions.

Subjects were asked to retire for sleep at their normal bedtime and to awaken at their normal wake time for four consecutive nights prior to both normal sleep and sleep deprivation sessions. They completed sleep logs each morning upon awakening. The sleep logs were subsequently verified to assure compliance. The sleep patterns did not differ prior to the normal sleep and sleep deprivation sessions. On the sleep-deprived night, subjects were instructed to sleep at 03:00 and were awakened at 07:00. Subjects were required to wear a wrist actigraph on the night prior to testing. Subsequent analyses of the actigraph data did indicate that subjects followed this sleep schedule. Data collection began the following morning between 08:00 and 10:00. While awake at night, subjects played computer games or watched videos/television. Upon coming to the lab in

the morning, subjects completed the Stanford Sleepiness Scale, a 7-point rating scale (1 = awake and alert, 7 = falling asleep).

2.2.1. *Experimental task*

Subjects engaged in a word association priming task in both testing sessions. Details of this task can be found in Lopez Zunini et al. (2014). In brief, two versions of the task were available, each with a different sequence of words in order to avoid stimulus repetition priming effects. Each trial started with a fixation point (“+”) presented in the center of the monitor for 2000 ms. The prime word was then presented for 200 ms followed by a 500 ms inter-stimulus interval (ISI). A target word was then presented for a maximum of 1200 ms or until the subject responded. Three different target types were employed: strongly associated (e.g. *dog-cat*), weakly associated (e.g. *cow-barn*), and unassociated (e.g. *apple-road*) with the prime. Subjects were asked to press one mouse button if the target was semantically associated with the prime and a different button if the target was not associated with the prime. They were instructed to respond while the stimulus was still displayed (i.e., within 1200 ms). The strength of association of the prime-target pair was determined by a normative data set, the Edinburgh Associative Thesaurus (Kiss et al., 1973). There was no semantic association for the unassociated prime and target words.

A total of 420 prime-target pairs were constructed and were randomly divided into two lists (i.e., 210 prime-target pairs) that included 70 pairs of each of the prime-target association types. Subjects were presented with both lists, one during each experimental session. Subjects did not therefore repeatedly see the same prime-target. Half the subjects were presented with one list initially and the other half, with the other

list. Stimulus presentation and response monitoring were controlled by E-prime software (Psychology Software Tools Inc., Sharpsburg, Pennsylvania) using a PC with a Windows XP operating system.

2.2.2. ERP recording

EEG activity was recorded from 32 sites using active silver-silver chloride electrodes attached to an electrode cap (Brain Products, GmbH, Munich, Germany). An EOG electrode was placed on the infra-orbital ridge of the left eye to record vertical eye movements. The nose was used as a reference for all channels.

Inter-electrode impedance varied from 20 to 50 k Ω . A high filter was set at 250 Hz. The time constant was 2 s. The physiological data were sampled every 2 ms (i.e., a 500 Hz sampling rate). Offline, the data were reconstructed using Brain Products' Analyzer2 software. Vertical EOG activity was computed by subtracting activity recorded at the FP1 channel from that recorded at the infra-orbital ridge of the eye. Horizontal EOG activity was computed by subtracting activity recorded at the FT9 channel from that at FT10. The continuous data were digitally filtered using a high filter set at 20 Hz and a low filter set at 0.08 Hz (i.e., a time constant of 2 s). The EEG was visually inspected for channels containing high levels of noise. These channels were replaced by interpolating the data of the surrounding electrode sites (Perrin et al., 1989). None of the subjects had more than 4 EEG channels that required interpolation. Independent Components Analysis (Makeig et al., 1996) was used to identify eye movement and blinks that were statistically independent of the EEG activity. This factor was then partialled out of the EEG traces.

2.3. Data analyses

2.3.1. Behavioural performance data

Performance was measured in terms of accuracy (hit rate) and reaction time (RT). RTs longer than 1200 ms were removed from the analysis. Two-way ANOVAs with repeated measures on target association (strongly associated, weakly associated, unassociated) and sleep condition (normal sleep, partial sleep deprivation) were conducted for the accuracy and RT data.

2.3.2. ERP data

The continuous EEG activity was segmented into epochs for the prime and target words. Each epoch began 100 ms before the onset of the word. The prime and target epoch continued for 800 and 1200 ms respectively following stimulus onset. The single trial epochs were sorted and averaged according to electrode position and prime-target association strength. The 100 ms pre-stimulus period served as a baseline.¹ Epochs were baseline corrected prior to averaging. Only correct trials were averaged. Any epochs containing EEG activity exceeding $\pm 100 \mu\text{V}$ on any channel were rejected from averaging. This was relatively rare because the major source of artifact, eye movements and blinks, had already been corrected in the EEG channels.

ERP components were measured relative to the average of all data points within the pre-stimulus baseline. The prime word waveform consisted of a central maximum positive deflection at about 200 ms followed by a long-lasting negativity beginning at about 300 ms. The P200 was quantified initially at Cz by averaging all data points within ± 30 ms of the peak identified in the grand average and then measured using the same

¹ López Zunini et al. employed a 125 ms post-stimulus baseline because the pre-stimulus interval was not stable and varied between the two sleep conditions. This was not the case in the present study.

procedure at all other electrode sites. The long-lasting negativity was quantified as the average of all data points between 350 and 450 ms.

A P200 was again visible following presentation of the target and was quantified in the same way as the P200 elicited by the prime. A large central maximum negativity N400 was elicited by weakly associated and unassociated targets. It was also quantified initially at Cz as the average of all data points ± 30 ms of the peak identified in the grand average.² A late positivity was also apparent after the N400. This late positivity was quantified as the average of all data points between 600 and 800 ms.

Electrode sites were grouped into regions of interest (ROIs), to include 9 electrode sites where the ERP components of interest were largest. The ROIs allowed for an analysis of an anterior-posterior and an inter-hemisphere factor. Specifically for the anterior-posterior electrode factor, three electrodes for frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) sites were chosen for analysis. The P200 and N400 components were thus quantified at each of these sites within the latency range identified at Cz. For the inter-hemisphere factor, three electrodes for left (F3, C3, P3), midline (Fz, Cz, Pz), and right (F4, C4, P4) sites were chosen for analysis. A four-way ANOVA with repeated measures on target association (strong, weak, unassociated), sleep (normal sleep, partial sleep deprivation), anterior-posterior (frontal, central, parietal), and hemisphere (left, midline, right) were run on each of the intervals for the prime and target data. For all statistical analyses, a Geisser-Greenhouse correction procedure was used when appropriate (Geisser & Greenhouse, 1958).

3. Results

² López Zunini et al. measured N400 over a 300-500 ms interval because it was often small and a distinct peak difficult to discern following TSD. A distinct N400 was apparent in grand averages in the present study following partial sleep deprivation.

3.1. *Stanford Sleepiness Scale*

Subjective ratings of sleepiness significantly increased following the sleep-deprived compared to the normal sleep condition. The mean subjective rating was 2.00 (SD=0.63) following normal sleep and 3.18 (SD=1.10) following sleep deprivation, $t(15) = 4.28$, $p < 0.001$.

3.2. *Behavioural Data*

The mean accuracy and RT data are presented in Table 1. The usual priming effect was found following both normal sleep and partial sleep deprivation. Accuracy was thus significantly affected by the target type, $F(2, 30) = 22.28$, $p < 0.001$. Accuracy was higher following presentation of the strongly associated and lower following presentation of the weakly associated and unassociated targets. For all target types, accuracy did decrease following partial sleep deprivation, $F(1, 15) = 6.52$, $p < 0.02$. There was no significant interaction between target type and sleep condition ($F < 1$).

----- Insert Table 1 here -----

Likewise, the RT data revealed a similar priming effect, regardless of the amount of sleep. Thus, RTs were faster for strongly associated than for weakly associated targets and slowest for unassociated targets, $F(2, 30) = 27.29$, $p < 0.001$. Surprisingly, RTs were about 17 ms faster following sleep deprivation but the difference was not significant $F(1, 15) = 2.58$, $p < 0.12$. The interaction between target type and sleep condition was also not significant ($F < 1$).

3.3. *Physiological Data*

3.3.1 *Target words*

The left portion of Figure 1 illustrates ERPs to target words following normal sleep and sleep deprivation. As can be observed, target ERPs consisted of an initial positivity peaking at about 200 ms (P200), followed by a large negativity at about 400 ms (N400). A long-lasting later positivity at about 600-800 ms was also apparent. The mean amplitudes of these ERP components at midline electrode sites are presented in Table 2.

----- Insert Figure 1 and Table 2 here -----

The positivity in the 170-230 ms interval was largest in amplitude at fronto-central sites, declining at more posterior sites. The amplitude of the P200 did not significantly vary as a function of either target type, $F < 1$ or sleep condition, $F(1, 15) = 1.87$, $p < 0.19$. The interaction between target type and sleep condition was also not significant, $F < 1$.

A main effect of target type was found, $F(2, 30) = 32.96$, $p < 0.001$ on the amplitude of the N400. It was largest following presentation of the unassociated targets and smallest following presentation of the strongly associated targets. Although the overall N400 following normal sleep tended to be slightly larger than following sleep deprivation, this difference was not significant, $F(1, 15) = 1.35$, $p < 0.26$. The sleep condition x target type interaction was not significant, $F < 1$.³

The right portion of Figure 1 presents spline scalp distribution maps of the N400 following normal sleep and sleep deprivation. The ROI analyses did reveal significant variance in its amplitude across the scalp; N400 was largest over central regions

³ The N400 data were also reanalyzed using a 0-125 ms post-stimulus baseline to be consistent with the scoring method used by López Zunini et al. (2014). The results were very similar; a main effect of target type was found but the main effect of sleep deprivation and the target type X sleep interaction were not significant. The N400 data were also reanalyzed averaging all data points within a wider 300-500 ms time interval. Again, there was a main effect of target type, but no significant main effect of sleep condition. The target type X sleep interaction was also not significant. Finally, it is possible that the inclusion of the multiple electrode data factor in the ANOVA might have smeared specific N400 effects. The ANOVAs were therefore re-run only on the Cz data, where N400 was largest. The results were essentially identical.

declining in amplitude over anterior and posterior regions, $F(2, 30)=2.54$, $p<0.09$. As is apparent in the maps of the N400, its scalp distribution did not differ between normal sleep and partial sleep loss. The ROI analyses did not reveal significant interactions between sleep condition and electrode position, $F<1$.

For the positive waveform between 600 and 800 ms, the main effect of target type just failed to reach significance, $F(2, 30)=3.01$, $p<0.06$; it was smallest following presentation of the unassociated compared to the weakly or strongly associated targets. Again, the amount of sleep did not however have a significant effect and the target type $\times$ sleep interaction was not significant, $F < 1$ in both cases.

3.3.2. *Prime Words*

Figure 2 illustrates the ERPs to the prime words following normal sleep and partial sleep deprivation. P200 was not affected by sleep condition, $F<1$. Similarly, the long-lasting negativity following the P200 was also not affected by the amount of sleep, $F<1$. As expected, the strength of the association of the subsequent target did not significantly affect the amplitude of either the P200 or the later negativity, $F<1$.

----- Insert Figure 2 here -----

4. DISCUSSION

The purpose of this study was to investigate whether partial sleep deprivation (4h of night sleep) would have similar effects on a priming task when compared to those found following a night of total sleep deprivation. A large priming effect was found following both normal and partial sleep. Accuracy was lower, RTs were faster and N400 larger to target words that were not semantically associated with the prime, regardless of the amount of sleep. This finding is thus consistent with those reported by López Zunini

et al. (2014). What was different in the present study was that the overall N400 was not significantly reduced in the sleep restriction condition. Similarly the scalp distribution of the N400 did not vary between the two sleep conditions. Moreover, processing between the time of the onset of the prime and the subsequent target also did not differ between the two sleep conditions. Neither the amplitude of the P200 nor the negativity between 350 and 450 ms were affected by sleep condition. Therefore, in contrast to total sleep deprivation, neither the target nor the prime ERPs revealed a difference in cognitive processing following partial sleep deprivation.

The priming paradigm was specifically designed to allow for the use of a predictive-expectancy strategy. The subject's task was to explicitly determine if the target was semantically associated with the prime. This encouraged the subject to predict possible target candidates following the presentation of the prime. To further ensure the use of this strategy, the time between the onset of the prime and the subsequent target was long (700 ms), sufficient to intentionally predict possible target candidates. The ERP evidence suggests that subjects used the predictive expectancy strategy following both normal sleep and sleep restriction. The predictive expectancy strategy does however require active and sustained attention in order to search possible target exemplars and maintain them in working memory. It would therefore appear that sufficient cognitive resources were available following partial sleep deprivation to use such an effortful, attention-demanding strategy. On the other hand, the López Zunini et al. (2014) findings indicate that insufficient resources are available to allow for the use of this effortful strategy following TSD. Thus, in the latter case, subjects may switch to an alternate strategy, one that searches the semantic network automatically and effortlessly.

While subjects might have attempted to use the predictive-expectancy strategy following sleep restriction, the performance data indicate that it may not have been entirely successful. A slight but statistically significant deterioration (about 2.5%) in accuracy of performance was observed following sleep restriction. López Zunini et al. found a somewhat larger decrease in accuracy (5%) but in their case, the difference failed to attain significance, perhaps due to a smaller sample size or because of a larger inter-subject variability. An alternate explanation for the present performance results is that the small loss of accuracy might have been a result of a speed-accuracy trade-off (Kim et al., 2001; Dorrian et al., 2005; Gosselin et al., 2005). RTs were slightly, but not significantly, *faster* following sleep loss. Cognitive psychologists have long noted that the accuracy and RT do interact. Accuracy of performance can be sacrificed for speed of responding. Even small changes in RT can result in large changes in accuracy (Meyers et al., 1988). The faster RTs following partial sleep deprivation might be a result of a willingness to risk error in the accuracy of detection.

In summary, a strong priming effect was observed following normal sleep and sleep restriction. The ERP measures of cognitive processing did not however differ between the two sleep conditions. In both conditions, a common effortful, predictive-expectancy strategy may thus have been adopted. This suggests that sufficient resources are available following 4 h of night sleep to maintain such effortful processing. However, this may not have been entirely successful as accuracy of responding did decrease following sleep restriction.

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Figure Legends

Figure 1

Grand average ERPs to target words that were either strongly, weakly, or not associated with the prime. In this and Figure 2, negativity at the scalp relative to the reference is indicated by a downward deflection. The early P200 was not affected by the amount of sleep. The amplitude of N400 showed a strong priming effect but was not affected by the amount of sleep. The right portion of the Figure provides the spline maps of the N400 to unassociated targets. The N400 was maximum over central areas of the scalp and declined over anterior and later regions. Importantly, the scalp distribution of the N400 did not vary as a function of the amount of sleep.

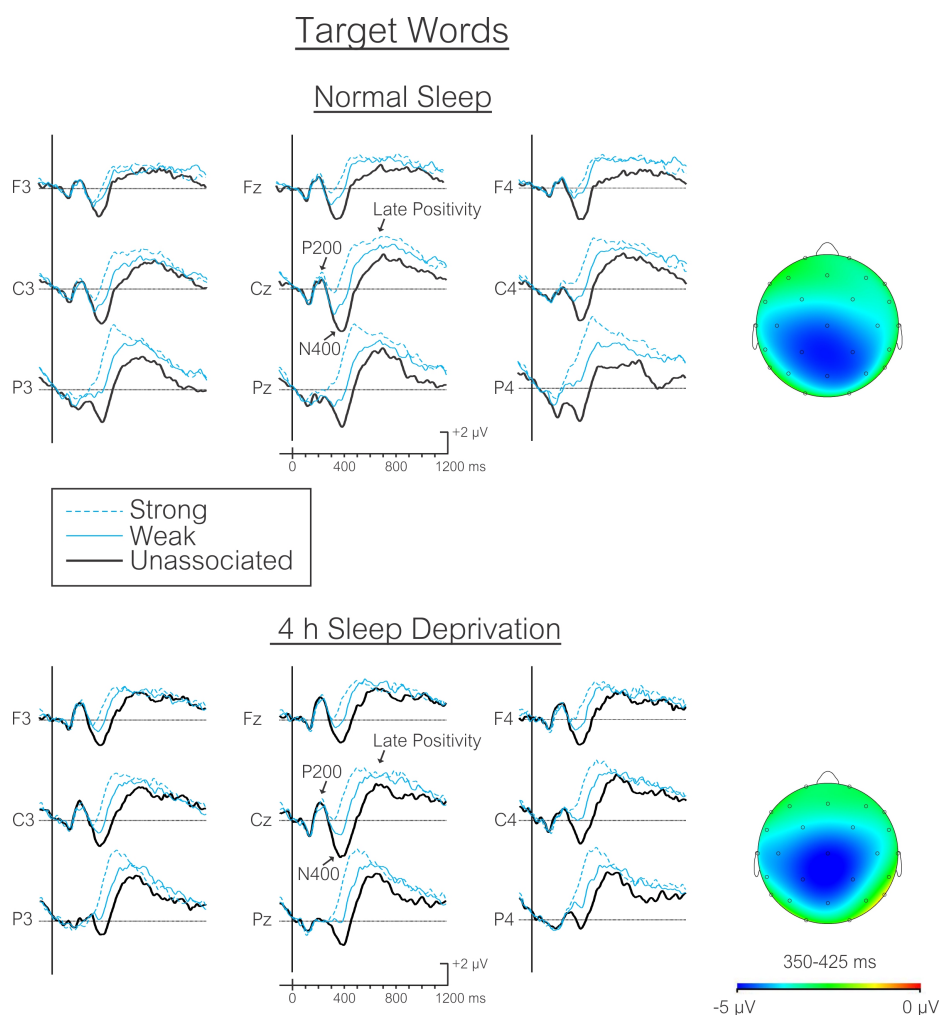


Figure 2

Grand average ERPs to the initial prime word. Neither the P200 nor the negativity beginning at about 300 ms was affected by the amount of sleep.

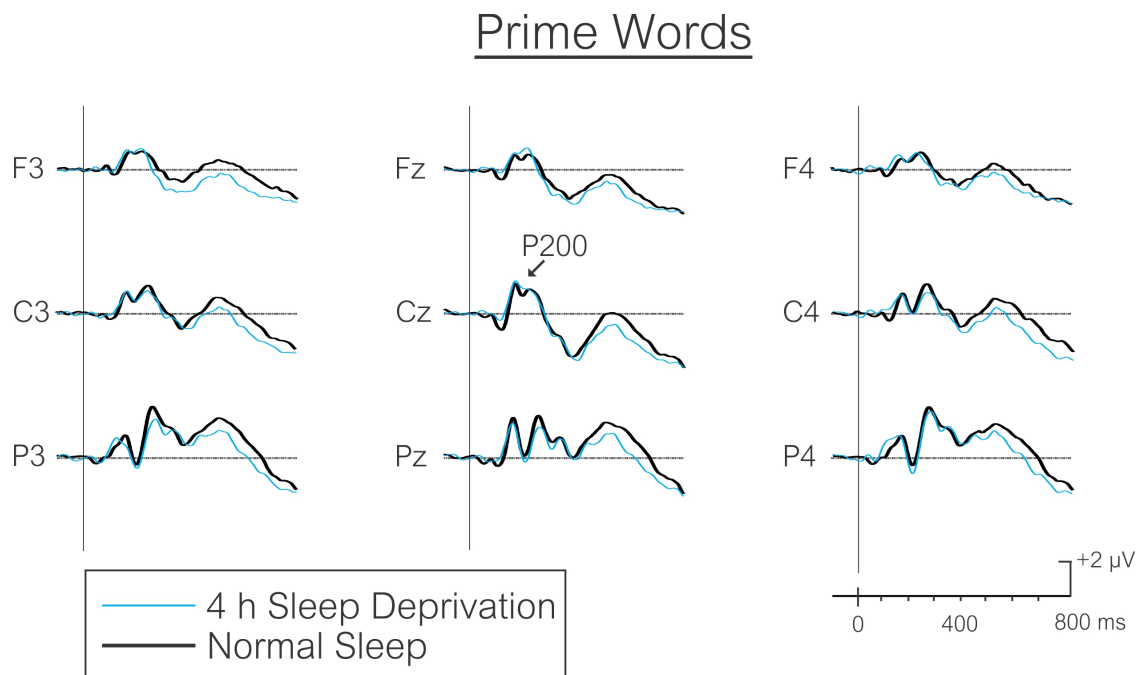


Table 1

Mean (SD in parentheses) accuracy and Reaction Time (in ms) k

Prime-Target Association	Accuracy		Reaction Time	
	NS ^a	PSD ^b	NS	PSD
Strong	0.92 (.06)	0.89 (.08)	596 (72)	582 (72)
Weak	0.77 (.08)	0.76 (.09)	668 (74)	638 (58)
Unassociated	0.88 (.08)	0.84 (.11)	679 (70)	669 (58)

^aNormal Sleep^bPartial Sleep Deprivation

Table 2

Mean (SD in parentheses) ERP amplitudes at midline electrodes following presentation of the target word.

Prime-Target Association	Electrodes	Condition	ERP Component Amplitude (in μ V)		
			P200	N400	Late Positivity
Strong	Fz	NS ^a	1.20 (3.23)	-0.93 (3.44)	3.51 (3.07)
		PSD ^b	2.79 (2.44)	-0.63 (1.67)	2.99 (3.16)
	Cz	NS	0.51 (3.44)	-1.68 (3.97)	5.25 (3.61)
		PSD	2.61 (2.94)	-1.10 (2.35)	4.49 (3.75)
	Pz	NS	-2.00 (4.02)	-1.04 (5.23)	5.15 (3.41)
		PSD	0.57 (3.62)	-0.86 (4.01)	4.74 (3.69)
Weak	Fz	NS	0.68 (3.60)	-2.33 (3.73)	3.13 (3.64)
		PSD	2.57 (2.68)	0.95 (3.09)	3.95 (3.62)
	Cz	NS	1.53 (3.04)	-4.36 (3.82)	3.84 (3.65)
		PSD	2.13 (3.64)	-2.58 (3.43)	4.61 (3.63)
	Pz	NS	-0.24(3.54)	-3.41(4.66)	4.42 (3.51)
		PSD	0.41 (3.94)	-1.70 (3.31)	5.20 (3.32)
Unassociated	Fz	NS	1.25 (3.53)	-3.60 (3.20)	2.00 (3.13)
		PSD	2.77 (2.29)	-2.89 (2.19)	3.02 (2.49)
	Cz	NS	0.34 (3.31)	-5.82 (3.34)	2.62 (3.66)
		PSD	1.41 (3.19)	-5.15 (2.81)	3.11 (2.42)
	Pz	NS	-2.07 (3.59)	-5.35 (4.02)	3.56 (3.60)
		PSD	-1.18 (3.84)	-4.31 (3.80)	3.78 (3.16)

^aNormal Sleep

^bPartial Sleep Deprivation

Appendix 2

Tavakoli, P. & Campbell, K. (2015a). The Recording and Quantification of Event-Related Potentials: I. Stimulus Presentation and Data Acquisition. *The Quantitative Methods in Psychology*, 12, 89-97.

The Recording and Quantification of Event-Related Potentials:
I. Stimulus Presentation and Data Acquisition

Paniz Tavakoli, Kenneth Campbell

Abstract

Event-related potentials (ERPs) are the changes in the ongoing electrical activity of the brain (the EEG) that are elicited by either an external physical stimulus or an internal psychological “event”. This article provides a tutorial review of the methods used for the collection of ERP data. Because ERPs are influenced by both stimulus parameters and the mental state of the subject (what the subject is “doing”), precise control over how the stimulus is presented and how the subject’s response is monitored must be described. ERPs are generally recorded from electrodes placed on the scalp. How the electrodes are placed (the montage) and the choice of the reference to which the electrical activity of the scalp are compared will have a large influence on the results. Electrodes will also pick up extraneous artifact or “noise”. Methods to reduce this noise are described. ERPs provide high temporal resolution of the extent of information processing allowing researchers to access to both sensory and cognitive processes involved in complex decision-making.

Keywords: Event-related potentials, data acquisition, stimulus parameters, EEG, noise, artifact

Introduction

Event-related potentials (ERPs) are becoming an increasingly important tool in the study of cognitive neuroscience. The novice can however be easily overwhelmed with the need to learn a vast array of techniques. This article provides a tutorial review of stimulus presentation and acquisition techniques for an ERP study. An ERP is a change in the ongoing electrical activity of the brain associated with either an external physical stimulus or an internal psychological “event”. The amplitude of the ERP that occurs to the stimulus or psychological event is typically very small and is embedded in the much larger amplitude of the ongoing electroencephalogram (EEG). Thus, what is recorded is a mixture of a true “signal” (the response) occurring in the ongoing random “noise” (not related to the stimulus) of the EEG. In addition, many other electrical sources from the head and body (eye movements, electrocardiogram, and muscle movements) and electromagnetic sources coming from cabling within the lab will also get picked up by the electrodes. This is also considered to be noise artifact. The signal is thus very difficult to isolate because it is embedded in the much larger background noise. Signal averaging techniques, originally developed in the 1950s (Dawson, 1954) can however be used to extract the ERP signal from the background noise.

ERPs consist of a series of positive and negative-going deflections or “components”, reflecting different hypothetical stages of cognitive processing. These components can be classified as being either “exogenous” when the ERP waveform is mainly affected by the physical properties of the stimulus, or “endogenous” when they are mainly affected by the more psychological properties such as decision-making, memory search, and meaningfulness (Sutton, Braren, Zubin, & John, 1965). For this

reason, many researchers use the terms, sensory and cognitive evoked potentials, to refer to the exogenous and endogenous ERPs, respectively. There has also been a recent tendency to consider ERPs to be only endogenous, although this was not the original definition (Vaughan, 1969). In general, ERPs that mainly reflect sensory processing occur early in processing while those that reflect mainly psychological events occur later. Some researchers thus classify ERPs according to their time (or latency) of occurrence as early (or “fast”), middle and late (or “slow”) components.

Stimulus Presentation

Purely exogenous ERPs are affected only by the physical characteristics of the stimulus while purely endogenous ERPs are not affected by the physical features. They are however affected by factors such as the psychological relevance of the stimulus to the subject. For example, the subject’s own name will elicit a large ERP, particularly for later components, not because of the physical features of the stimulus but because of the relevance of the stimulus to the subject. Another person’s name, unknown to the subject, will elicit a very different ERP (Perrin et al., 2005).

Manipulation of the physical features of a stimulus should affect the exogenous but not the endogenous components of the ERP. In actual practice, distinguishing between the two types of components can be difficult. As an example, a subject is presented with an oddball paradigm in which they hear a frequently occurring “standard” 80 dB SPL 1000 Hz auditory tone. A tone is presented every 2 s (note that the physical characteristics of the stimulus must be described precisely because they will affect exogenous ERPs). At odd and unpredictable times, the intensity of the standard tone is increased to 90 dB. The subject is asked to press a button upon detection of this rarely

occurring increment “target”. The standard tone will elicit a negative-component occurring at about 100 ms after stimulus presentation. This is called “N1”. The target will also elicit an N1, but it will be larger in amplitude. Why would N1 be larger to the target? The most obvious explanation is that the target is physically different from the standard. It is more intense. N1 might vary directly in amplitude with the intensity of the auditory stimulus. In this case, N1 might be considered to be an exogenous ERP because it was altered by the manipulation of a physical feature. But in order for the subject to distinguish the target from the standard, they presumably will need to initially extract the features of the standard, store these features in working (or short-term) memory, and subsequently upon presentation of the target, compare its features to those that exist in memory for the standard. Memory comparison is a psychological process and thus perhaps the larger N1 reflects comparison of the features of the presently-occurring target to those that exist in memory for the standard. The detection of the target will also elicit a positive component occurring at about 300 ms, often labelled as “P3” (or “P300”). A P3 will not be apparent following presentation of the standard. P3 is often considered to be a classic endogenous component, related to the extent of the updating of working memory. How could the researcher resolve the problem of whether N1 and P3 are exogenous or endogenous? A simple way is to switch the standard and the target. What was formerly the standard stimulus (the 80 dB tone) is now the target and what was formerly the target stimulus (the 90 dB tone) is now the standard. If N1 varies only because of the physical features of the stimulus (its intensity in this example), it should be larger for the now more intense standard than the less intense target. On the other hand, if its amplitude reflects an endogenous process, such as a memory comparison process, then it should

now be larger for the lower intensity target than the higher intensity standard. In actual fact, the N1 will still be larger to the higher intensity stimulus even though it is no longer a target. The N1 is thus largely exogenous in nature. Similarly, if P3 is an exogenous process (it occurred previously because the rare stimulus was more intense), then it should now also be larger to the more intense stimulus, in this case, the frequently occurring standard. In actual fact, the P3 will be larger to the infrequently presented target, regardless of its physical intensity. In other words, the occurrence of the P3 appears to almost exclusively reflect endogenous processing.

Even though the researcher might be mainly concerned about cognitive and psychological processing, care must be taken to ensure that the ERP component has not been affected by an incidental manipulation of physical features. At the same time, what the subject “is doing” (i.e. the subjects “task”) is obviously critical if the ERP is affected by cognitive processing. Thus, the researcher must precisely describe (1) the physical characteristics of the stimuli and how often they are presented and (2) what is expected of the subject during the experimental task. The subject is often asked to signal their decision by button pressing, thus allowing the experimenter access to their cognitive (or “mental”) state. In the example above, if the subject fails to detect the target, a P3 is not elicited although the exogenous N1 is. But, had the subject been asked to ignore the stimuli and simply relax, how would the experimenter have known what the subject was doing? Perhaps the subject did, in fact, ignore (i.e., not attend to) the stimuli and hence a P3 would not be elicited by the target. It is however also possible that the subject did attend to the stimuli and, in this case, a P3 would be elicited by the target. The mental

state of a subject is essentially private but the researcher must design their experiment in a manner that allows access to it.

Recording of Performance Measures

In the majority of ERP recording systems, two computers are used. One, the stimulus presentation computer, controls the presentation of the stimuli and the monitoring of subject responses. The second computer collects the EEG data. Both commercial software, such as E-Prime, Presentation, Psyscope, and open source software, such as PsychToolbox (within MatLab), or PsychoPy can be used for stimulus/response control and management (what stimulus is presented, when it is presented, and what the subject is asked to do). In general, the stimulus presentation and EEG data collection computers function independently and thus need to be synchronized. The EEG computer must know exactly when the stimulus is being presented and when a response has been made. A “trigger” being sent from a port on the stimulus presentation computer to a port on the EEG computer is often used for this purpose. In order to ensure at least millisecond precision for the analysis of the ERPs, the trigger must be sent out at precisely the time of stimulus presentation. The onus is on the researcher to ensure that an actual stimulus was presented exactly at the time the trigger is sent. In reality, there are often delays between the time the trigger is sent and the time a stimulus is actually presented. To verify the precision of visual stimulus presentation, light sensors can be used to detect the onset of the stimulus on the monitor. These sensors typically operate by detecting a change in the contrast and can be interfaced to the EEG electrode input box. It is also possible to employ an auditory sensor (a microphone) attached to the headphones used for auditory stimulus presentation. The auditory signal, in this case, can also be

connected to the electrode input box. It is possible to connect the “line out” from the auditory generator to the electrode input box. In the case of both the visual and auditory stimuli, the output of the actual stimulus can be displayed on an EEG channel and then compared to the time of onset of the trigger (time 0). These should occur at the same time.

Most stimuli are now computer-generated. The sound chip in most computers does not have the quality required for precise scientific studies. A sound card should be added to the computer, if possible. The intensity of the sound needs to be precisely calibrated with a sound pressure level (SPL) meter. Different headphones have different impedances. Thus, a sound that measures 70 dB SPL using one headphone may not measure 70 dB SPL with another headphone. Importantly, headphones also have different frequency response characteristics. Thus, a 1000 Hz tone may measure 70 dB and also 70 dB at 2000 Hz but may measure 65 dB at 2000 Hz with a different pair of headphones. It is thus critical to examine the frequency response curve of the headphones.

Manufacturers and websites may provide this information. As an example, the HeadRoom Inc web site, www.headphone.com, provides frequency response curves for various commercial headphones. These are used in Figure 1, to compare the frequency response curve of an Etymotic ER-4P insert earphone (often used in ERP research), and Sony MDR-V6, and Sennheiser HD280 headphones. A 90 SPL 1000 Hz signal is presented through each and the intensity of the signal is adjusted to be equal for all headphones at this frequency (i.e., the 90 dB 1000 Hz tone measures 90 dB for the three headphones). Most ERP studies present auditory stimuli ranging in frequency from about 500 to 2000 Hz, but can be as low as 250 Hz and as high as 4000 Hz. In Fig.1, the

frequency response curves between 200 and 4000 Hz are highlighted. Between 200 and 2000 Hz, the frequency response of the three headphones is relatively flat although the intensity of 1500-2000 Hz pure tones will be attenuated by 2 to 3 dB with the Sennheiser headphones. At 3000 to 4000 Hz, the ER-4P and Sennheiser's intensity may fall as much as 3 to 6 dB. This is not incidental. If the N1 ERP component is recorded to 1000 and 4000 Hz tones using the ER-4P and Sennheiser headphones, N1 will be reduced in amplitude for the 4000 Hz tone. Is this because of a difference in processing of the higher frequency (i.e., N1 is lower in amplitude for higher frequencies even if the headphone faithfully presents a 4000 Hz frequency) or is it because of the fact that the intensity is lower for the 4000 Hz stimulus when presented through these headphones? As may be observed, the three headphones (and almost all others) perform poorly above 5000 Hz. Other factors such as subject comfort and the ability to isolate/attenuate ambient noise also need to be considered. In the examples above, the Sony headphones provide an excellent frequency response between 200 and 4000 Hz and are comfortable, but at a cost. Their ability to isolate ambient noise is poorer than, for example, the Sennheiser headphones. The tightly fitting in-ear ER-4P earphones offer excellent noise isolation but also at a cost; many subjects find them to be uncomfortable.

----- Insert Figure 1 here -----

Visual stimuli are usually presented on a monitor. The researcher should, however, be aware that most monitors are poorly calibrated in terms of their colour spectrum, intensity and contrast. Thus, if it is essential that a pure "red" stimulus be presented, on a pure "white" background, then the researcher would need to measure the wavelength of the stimuli. Calibrators exist for precisely this purpose. Intensity of the

light wave may also be critical. Nevertheless, in many cognitive studies, approximation is sufficient. Thus, if a researcher is studying selective attention and asking subjects to detect red triangles among red rectangles, green triangles, and green rectangles, there is obviously much less need to be extremely precise. The red stimulus, even if it not a pure red, will still be much redder than the green stimulus. What is perhaps more important in visual research is the fact that there may be a very long delay between the time a trigger is sent to the EEG computer and when the stimulus is actually presented on the monitor. This can be as long as 40 ms especially for some LCD monitors, depending on the software that is used. This is much less of a concern for older CRT monitors. The precision of timing can be determined by using a simple sensor that detects change in contrast on the monitor. The output of this device can then be sent as an input to an EEG channel allowing a comparison of when a trigger was sent to when the stimulus was actually presented.

Subjects normally signal a response by button pressing. Often, a keyboard or mouse click is used. Neither keyboard nor mouse buttons provide precise 1 ms timing. Researchers who need 1 ms precision often employ external response devices. As an example, if reaction times (RTs) in an experiment to one type of stimulus are expected to be 10 ms faster than to another type of stimulus, it is unlikely that a keyboard or mouse will provide this type of precision. On the other hand, if the experimental effect is expected to be very large (e.g., more than a 100 ms difference), then special hardware will not be required. Some researchers have also noted that keyboards and mice can reveal even small changes in RT provided the data are averaged over a sufficiently large number of trials. Thus, the difference in the mean RTs will be precise even if single trial

RTs are not (Segalowitz & Graves, 1990; Shimizu, 2002), but again, the cost will be that many trials will be needed.

EEG Acquisition

Small amplitude ERPs are embedded in the ongoing larger amplitude EEG. The EEG reflects the summed activity of thousands of postsynaptic potentials (the voltage that arises when a neurotransmitter binds to a postsynaptic site). EEG is almost always recorded from scalp electrodes in human subjects but the delay between the actual source signal within the brain and that recorded on the scalp is minimal. The intra-cranial neuronal population creates a dipole, resulting in positive and negative electrical charges separated by a small distance. Brain matter, the skull and skin do however cause large resistance to the flow of the dipole and the activity recorded on the scalp and will thus reduce the amplitude of the signal recorded at the scalp. As will be discussed throughout this article, it is critical to minimize the amount of resistance on the scalp in order to record good quality data.

Electrode Montage. In order to interpret ERPs, the EEG must be recorded simultaneously from multiple electrode sites. ERPs consist of a series of negative- and positive-going components. One way to distinguish the various components is on the basis of their scalp distribution (where the response is large or small). Some components may, for example, be largest over frontal areas of the scalp. Other components might be largest over perhaps the right parietal areas. The two components are thus distinguished on the basis of different scalp distributions. Obviously, the scalp distribution of a component cannot be determined without recording the EEG from many different electrode sites. If the intra-cranial (within the brain) sources of the scalp-recorded ERP are already known, only a few electrodes will need to be placed. When only a few

electrodes are employed, these can be attached to the scalp using a paste/cement. A gel is used to conduct the signal from the scalp to the electrode. While we do understand the sources of many of the exogenous components, generally little is known about the more endogenous components. For this reason, the endogenous components are often recorded using 32 to 256 electrode placements. For the placement of a multichannel montage, electrode caps with the electrodes embedded within the cap are usually preferred.

The placement of these electrodes on the scalp is called the “montage”. A standardized placement and naming system, the 10-20 system, was developed in the early days of EEG recordings (Jasper, 1958). The head is divided into proportional distances from prominent skull landmarks (e.g. the nasion and inion) and the middle of the two ears (pre-auricular points) to provide adequate coverage of all regions of the brain. The label 10-20 refers to proportional distances where electrodes are located relative to these landmark points (Figure 2). Thus, electrode Oz is located 10% of the distance from the inion to the nasion. Electrode Pz is located 30% of the distance from the inion to the nasion (i.e., it is 20% anterior to Oz). Electrode letters correspond to the major regions of the brain (FP = Frontal Polar, F=Frontal, C= Central, P = Parietal, T=Temporal, O=Occipital) followed by a number indicating the distance from the midline (designated by “z”) and whether the electrode is over the left (odd numbers) or right (even numbers) hemisphere. Thus, electrode placement F7 is located over the left frontal region. It is more lateral (or farther) from the midline (electrode Fz) than electrode F3. The original 10-20 system did not allow for electrodes that were closely spaced and was thus subsequently modified (American Electroencephalographic Society, 1991) permitting intermediate positions. This is often called the 10-10 system. Thus, electrode POz is

located 10% of theinion-nasion distance anterior from Oz (or more simply, it is halfway between Oz and Pz). Non-standard placements can also be used and these placements can be measured using modern 3-dimensional scanners. The use of scanning techniques to measure electrode placement has the advantage that the electrodes can be more or less placed arbitrarily on the scalp. In addition, the digitization of the electrode location permits the determination of the shape of the skull.

----- Insert Figure 2 here -----

The Reference. All electrical signals are recorded from two points. In a referential montage, each of the EEG channels record the difference in the electrical activity between the scalp electrode and a common “reference” electrode. Ideally, the reference electrode should be inactive. A recording from a truly neutral reference electrode would be a straight line measuring 0 μ V. It would not record any electrical activity from the brain. In reality, no reference site is truly inactive. The electrical activity of the brain spreads to all areas of the scalp including the reference site. Many articles have now described the effects of different reference sites. Common references include the mastoid, the ear lobes, or the tip of the nose, all of which pick up minimal brain electrical activity. Some researchers employ an average reference (the average of electrical activity from all electrode sites). The average reference does approximate a true zero voltage. However, in order to operate properly, electrodes must be placed not only on the upper and inferior, lateral surface of the scalp but also the face and neck regions. For this reason, it is not often used. Mastoid and earlobe references pick up some activity from the both the auditory visual regions. Another problem with the choice of a reference using only a single placement, on for example, the left or right mastoid or ear lobe, is that

if the cognitive activity is lateralized to one hemisphere of the brain, asymmetry of processing might either be canceled or enhanced by the reference. Had a truly neutral reference been employed, the lateralization might not have been observed. Many researchers thus opt to use a linked mastoid/ear lobe reference, averaging the activity from both sites. Unfortunately, this solution will also be problematic if the impedance (described below) of the two reference sites varies over the course of the recording session, the virtual location of the reference would then be unknown. Some researchers use a midline scalp location for the reference. For example, a midline frontal (Fz) reference is often used for visual ERPs. This overcomes the problem of lateralized reference on one side of the scalp, when the ERP is thought to be lateralized. Scalp sites are however often very active. Some researchers thus prefer the tip of the nose as a reference. Even the tip of the nose is not truly inactive, although it does have the advantage that it is not lateralized. A major advantage of modern digital data acquisition systems is that the EEG can later be re-referenced to a different site, or even the linked mastoid/ear lobe reference, assuming of course that the EEG has also been recorded from the site(s) that will later become the reference (see Luck, 2014 for a review on referencing). Figure 3 illustrates an averaged ERP waveform elicited by a moderate intensity auditory stimulus. The effects of different references, the nose (left portion) the right mastoid (middle portion; M2), and the average of all electrode sites (right portion), are apparent. The EEG was recorded from 64 different electrode sites including inferior sites, thus allowing the use of an averaged reference. A large downward deflection apparent at Fz and Cz can be observed to occur at about 100 ms after stimulus onset. When a nose reference is used, N1 is recorded as a negative wave at Fz (measuring about

– 5.1 μV) and Cz but as a positive wave at the mastoids, M1 and M2 (measuring about +3.0 μV at M2). It is thought that the intracranial (within the brain) dipole sources of N1 are located within the auditory cortex of the temporal lobe. The dipole is oriented such that one pole “points” to the frontal region (thus explaining the negativity over frontal region) but the other pole points to the mastoid region and hence N1 is recorded with an opposite (or positive) polarity. The mastoids are therefore not inactive for auditory stimuli. Many researchers do employ a mastoid reference (centre portion). When the data were referenced to the right mastoid, the amplitude of N1 at Fz and Cz now becomes larger, measuring -8.1 μV (reflecting the difference in activity between Fz and M2 = -5.1 – +3.0 μV). The data were also referenced to an average reference. Now, N1 measures -2.7 μV whereas it measures +5.4 μV at the mastoids. The choice of the reference may widely affect the data.

----- Insert Figure 3 here -----

Impedance. A good electrical signal between the scalp and the electrodes is essential in the recording of high quality data. The quality of this connection can be quantified by measuring the impedance between the scalp and electrodes. Impedance is the tendency of a particular material to impede the flow of an alternating electrical current (the EEG in this case). The scalp is covered by a layer of dead skin cells and oils and has an impedance of about 50 or more kOhms. Minimizing the electrode impedance will result in a cleaner signal (see Teplan, 2002 for a detailed account). This impedance should be below 5 kOhms for so-called passive electrode systems. It can be much higher (20-50 kOhms) for active systems. To reduce impedance below 5 kOhms requires the scalp to be rubbed vigorously and often abraded using a blunt needle to break the initial

layer of skin. Such vigorous rubbing and abrading is not required with active electrode systems.

Active vs. Passive Electrode Systems. EEG is recorded from metal electrodes attached to the scalp. Many different types of electrodes exist, each with different characteristics. Most metals used in the electrodes act as capacitors and store a charge after the electrode is removed. Thus, when it is placed on the next subject, an electrical charge may be recorded not because of the electrical activity from the brain of that subject but because of the stored charge on the electrode. For this reason, silver-silver chloride electrodes are often used in modern systems because of their non-polarizing properties, thus not storing a charge (Kutas, 1997; Rösler, Heil, & Hennighausen, 1995). These electrodes are however very expensive relative to other types of electrodes.

Brain activity rarely exceeds 100 μV . An amplifier is required to make this signal visible. Most EEG systems use “passive” electrode amplifier systems. The EEG, once picked up by the electrodes, is relayed to the EEG amplifier usually via a cable measuring about 1-2 metres in length. Unfortunately, the cable connecting the electrodes to the amplifier also acts as an antenna and can pick up other electro-magnetic signals in the testing room. The amplifier, therefore, also amplifies artifactual noise and this will summate with the true brain signal. The EEG signal is thus a combination of a true EEG signal and noise. Electrical activity is picked up from the point of least resistance. This is why electrode impedance must be significantly reduced (with passive systems). “Active” electrode systems embed a small pre-amplifier within each electrode casing. Therefore, the distance required for the signal to travel from the electrode to the amplifier is very short; hence, the possibility of picking up additional noise is minimized. They also

overcome the need for vigorous abrasion of the scalp and thus are often the electrodes of choice with infants, young children and patient populations. Active electrode systems are nevertheless quite expensive and are also quite large because of the attached amplifier. They may not be appropriate in all situations, for example, during sleep studies when the smaller and flatter passive electrodes are less intrusive.

Conclusion

Modern technological innovations now permit the recording of the EEG from as many as 256 different channels. Low cost but highly sophisticated hardware and general purpose software now enable many now researchers to record real-time mental processing using well-established cognitive paradigms. In this article, we have highlighted some of the techniques required for the presentation of stimuli and the acquisition of good quality data. In spite of the power of new techniques, due diligence must still be afforded to the careful and precise presentation of the stimulus and a monitoring of the behavior/performance of the subject. Poor research design will not result in good cognitive neuroscience. While the EEG recording capabilities have expanded enormously over the past decade, the researcher must always be aware that the electrical activity that is recorded is a summation of a true brain signal and background noise. Part II of this article will describe methods that can be used to reduce this background noise activity and quantify the signal, but it is always best to reduce the noise as much as possible in original, real-time recording. “Prevention is better than cure” (Picton, 1995, p.20).

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Figure Captions

Figure 1. The frequency response curves of three different headphones are compared.

The Etymotic earphone inserts are commonly used in ERP research. The choice of headphones is not incidental. A 1000 Hz tone was passed through each headphone and its intensity (90 dB) equated for each of the headphones. Thus, the response is identical for all three headphones at 1000 Hz. From about 500 to 1000 Hz, the intensity that is presented by each of the three headphones is about the same. From 1000-2000 Hz, the intensity of the tone is attenuated somewhat when presented through the Sennheiser headphones. At about 3000 Hz, the intensity is attenuated by more than 5 dB for both the Sennheiser and ER-4P earphones but faithfully reproduced by the Sony headphones. As may be observed, the three headphones perform poorly above 4000 Hz. This image is courtesy of www.headphone.com.

Figure 2. Standardized system for the placement of electrodes on the scalp. The head is divided into proportional distances from prominent skull landmarks, the nasion (Nz), theinion (Iz) and the middle of the two ears (pre-auricular points). Electrodes used traditionally in the 10-20 system are darkened. Electrodes between these positions and more lateral and inferior that are used in the 10-10 system are shaded in grey.

Figure 3. The effects of choice of reference site. The activity of all scalp sites is usually compared to that at a neutral, inactive reference site. In reality, no reference site is truly neutral. All reference sites will record some EEG activity. In this example, an auditory ERP was elicited by a moderate intensity, 1000 Hz tone presented every 2 s. In the left

column, the tip of the nose was chosen as a reference. A large downward (negative) deflection is apparent at the Fz and Cz sites. The mastoid is often used as a reference site in many ERP studies. Note however that it is certainly not inactive when auditory stimuli are presented. A large positive deflection is apparent at the mastoids when the tip of the nose is used as a reference. This inversion of polarity of N1 at the mastoids can be explained by the vertical orientation of a dipole source located in the nearby temporal lobe. In the middle portion of the Figure, the data were re-referenced to the right mastoid (M2). Now, the N1 is much larger at both Fz and Pz when the positivity at the right mastoid is subtracted from the negativity recorded at these scalp sites. In the right column, the data were again re-referenced but an averaged reference (the average of activity at all electrode sites) was used. A clear inversion of polarity is again visible at the mastoids.

Figure 1.

Headphone Frequency Response Curve

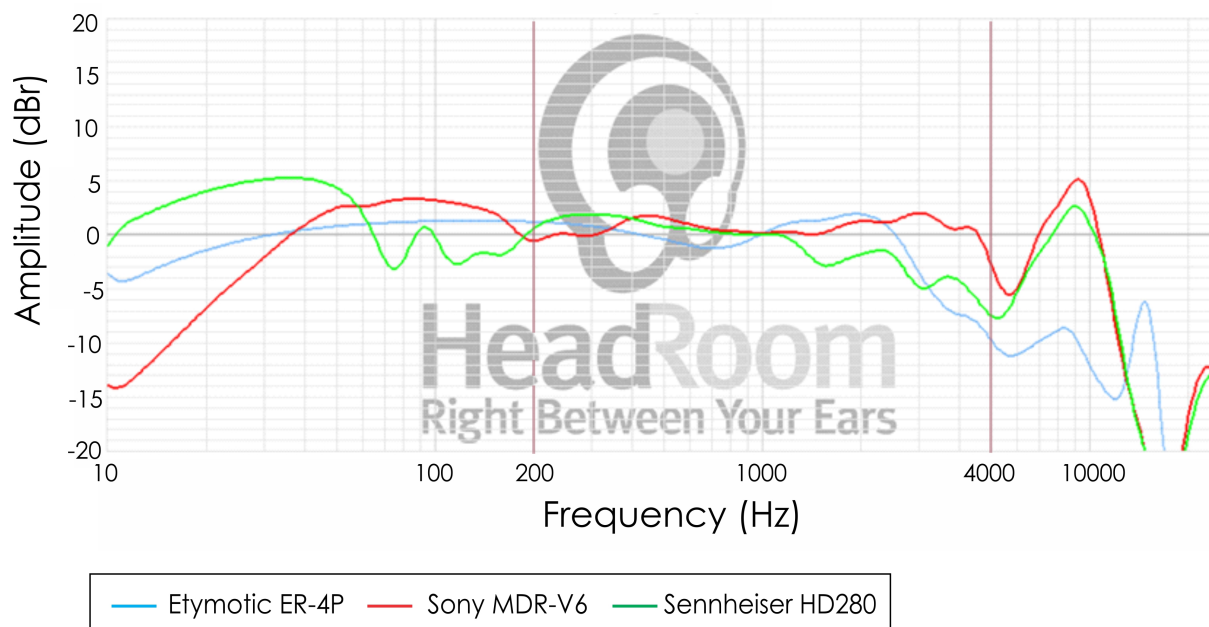


Figure 2.

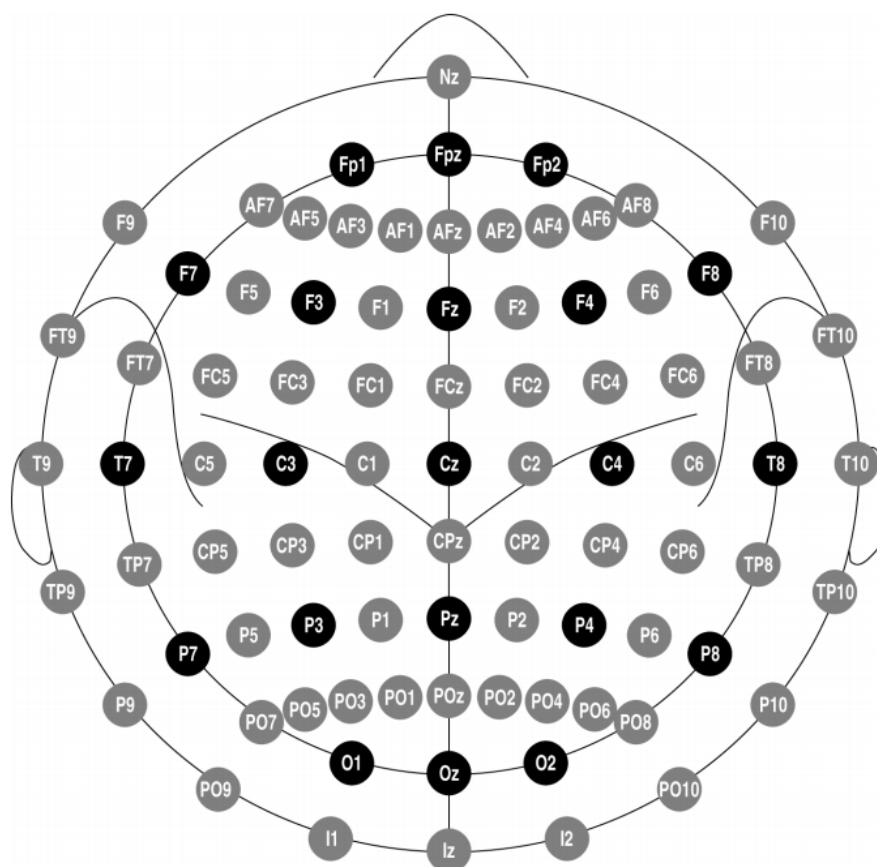
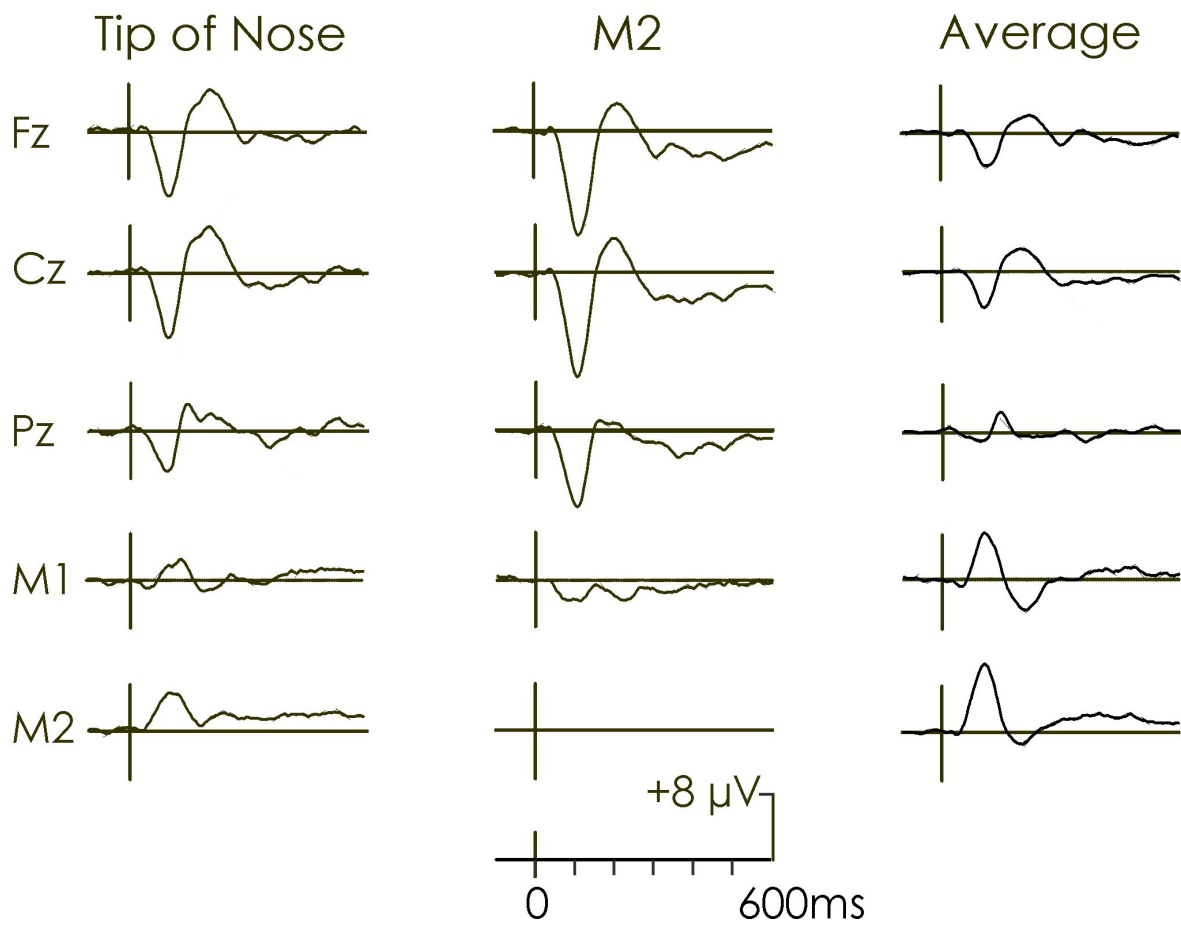


Figure 3.

Reference Site



Appendix 3

Tavakoli, P., & Campbell, K. (2015b). The recording and quantification of event-related potentials: II. signal processing and analysis. *The Quantitative Methods for Psychology*, 12, 98-112.

The Recording and Quantification of Event-Related Potentials:
II. Signal Processing and Analysis

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Abstract

Event-related potentials are an informative method for measuring the extent of information processing in the brain. The voltage deflections in an ERP waveform reflect the processing of sensory information as well as higher-level processing that involves selective attention, memory, semantic comprehension, and other types of cognitive activity. ERPs provide a non-invasive method of studying, with exceptional temporal resolution, cognitive processes in the human brain. ERPs are extracted from scalp-recorded electroencephalography by a series of signal processing steps. The present tutorial will highlight several of the analysis techniques required to obtain event-related potentials. Some methodological issues that may be encountered will also be discussed.

Keywords: Event-related potentials, signal processing, quantification, cognitive processes.

Introduction

Event-related potentials (ERPs) are the minute changes in the electrical activity of the brain that are elicited by a physical stimulus or a psychological event. The first article in this series (Tavakoli & Campbell, in press) discussed the need for careful control over the physical characteristics of the stimulus but also the need to monitor psychological events – what the subject is doing. One of the major reasons for this is that there is little the researcher can do to correct errors in the design of the study, once the data have been collected. It is not possible to correct for poor stimulus-response control in an off-line manner. This is not the case for the collection of the EEG data. While care must also be taken to assure high quality acquisition of the EEG, as this second article will discuss, it is possible to clean and correct “noisy” EEG data. Still, as emphasized in the first article, prevention is better than cure. A series of steps should be employed to assure a high quality EEG signal. Nevertheless, even with exceedingly high quality data, the ERP “signal” will always be much smaller than the background “noise” of the EEG.

Several methods exist for extracting the ERP signal from the background electroencephalogram (EEG) noise. The most powerful means to do so is through the use of signal averaging (Dawson, 1954). Averaging works best when the amount of noise is more or less constant from one stimulus repetition to the next. Prior to averaging, a series of steps can be employed to “clean up” the raw EEG data in an attempt to reduce the amplitude of the noise. There are two major sources of artifact within the EEG. The first is caused by electromagnetic fields around the subject such as power lines and electric transformers or motors. During the original recording of the EEG, these can be reduced substantially by placing the subject as far away from these sources of artifact as possible,

grounding the subject and ensuring inter-electrode impedance is low. The second major source of artifact is a result of the picking up of extraneous electrophysiological signals from the subject, for example, the electrocardiogram, skin potentials (“GSR”), muscle movement and most importantly, eye movement artifact. A good deal of this artifact can be reduced by proper electrode application and instructions to the subject to reduce movement and to fixate the eyes on a fixed point. Nevertheless, in spite of the best attempts, subjects will still move and blink. The present article will discuss the necessary steps required for the extraction of the ERP from the noisy background of the EEG and the eventual analyses and quantification of the ERPs. Methodological issues encountered throughout this process will also be discussed.

Very powerful commercial software exists for the analysis of EEG/ERP data (e.g. Brain Products, NeuroScan). Each of these commercial programs offers different general-purpose options for data quantification. Some researchers do, however, choose to write their own ERP analysis program often using open source software (e.g., EEGLAB, ERPLAB). These have the obvious advantage of being low cost, providing many of the same quantification procedures available in the commercial systems, albeit perhaps not as “user friendly”. They also allow the researcher to write their own software for analyses that are not available in the general-purpose commercial systems. The choice of which software to use largely depends on what type of analyses are being carried out. Signal processing, artifact correction and scoring methods that are used in most ERP labs will be discussed here.

Reduction and Correction of Noise

Filters

Many of the sources of artifact can be largely attenuated through the judicious use of filters, providing the artifact contains frequencies that are lower or higher than those of the actual ERPs of interest. Two stages of filtering can be applied; initial real-time analog filters used for the recording of the EEG and subsequently, off-line filters. Both types of filters provide for a low filter (attenuating low frequencies but allowing higher frequencies to pass) and a high filter (attenuating high frequencies but allowing low frequencies to pass). Because a low filter allows higher frequencies to pass while the high filter allows for lower frequencies to pass, they are also called high- and low-pass filters respectively.

With older EEG systems, analogue filters were typically applied to the data by effectively adjusting the resistor and capacitor circuitry in the amplifier. Such analog filters are applied in real-time during data acquisition (within the EEG amplifiers), before the signals are converted to digital format. Analog filters are however imperfect and can shift the latency of signals causing distortions in the data. With the advent of modern, rapid computers, digital filtering is now the preferred method of choice, eliminating the need for precise analog filtering. For this reason, a very broad range of frequencies is typically allowed to pass unfiltered through the analog system. The EEG signals can then be filtered more precisely off-line using digital filtering techniques.

Digital filters can be designed to avoid latency shifts in the signal. Because the digital filter is applied after data collection, its effects can be later removed and different filter parameters can subsequently be employed. They can operate in either the time or frequency domain. For example, a very simple time domain filter can be created using a smoothing or “moving average” algorithm. Each data point is replaced by the average of

“n” data points. For example, in a 3-point moving average, the second data point might be replaced by the average of the first, second and third data points; the third data point would be replaced by the average of the second, third and fourth data points. Again, with the advent of powerful and low cost computers, much more sophisticated time-based algorithms are now available. Digital filters can also operate in the more computational-demanding frequency domain. Often, the frequency spectrum of the EEG signal is computed using a Fourier transform. This algorithm would allow for different weightings for each of the frequencies within a signal. The EEG signal is then filtered by applying an inverse Fourier transform.

Many other different digital filters can be designed, using different mathematical computations. Common to all digital filters is what is called the transfer function and it is the mathematical modelling of the filter that describes how a given input will be attenuated. There are now several different digital filters that are available and each may affect the EEG in some way, although these changes are often subtle. The computational bases for many of these digital filters are beyond the scope of the present article. Several other articles are however available that provide a detailed account of different filtering procedures and their effects on the EEG data (Cook & Miller, 1992; Luck, 2014; Picton, Lins, & Scherg, 1995, Picton, 2011).

Artifact containing frequencies above or below those of interest can be attenuated through the use of high and low filters, respectively. A separate “notch” filter is often used to attenuate line frequencies (50 or 60 Hz). The cut-off frequency is the frequency at which the filtered *power* (can be considered as the area under the curve) is reduced by half (-3 dB). This corresponds to a 71% reduction in amplitude of the EEG. Most ERP

components in cognitive neuroscience studies consist of frequencies between 0.01 and 30 Hz. Often a high filter between 20 to 40 Hz is thus applied to cognitive ERP data. The use of a high filter is illustrated in the left portion of Figure 1. The ERP in this figure is contaminated by muscle artifact (frequencies above 100 Hz) and 60 Hz line frequency. Using a high frequency cut-off below 40 Hz will largely attenuate these sources of artifact. In addition, the raw EEG may appear to slowly “drift” over a period of seconds, appearing as a slow waxing and waning of waveforms. This is often a result of skin potential artifact caused by perspiration. Changes in electrode impedance can also lead to slow drifts in the EEG signal. A low filter of about 0.3 Hz is often employed in clinical EEG settings to remove this slow drift. In the cognitive laboratory, it is not unusual to observe drifts in the ERP signal associated with long-lasting and slow mental processes (i.e., actual brain activity). A 0.3 Hz low filter might thus inadvertently remove a true brain signal of interest. In such cases, a 0.01 Hz low filter might be applied. It is usually easier to understand the low filter cut-off as a “time constant”, the time required for a slow frequency to be reduced by 50% of its power. A 0.3 Hz low filter corresponds to a time constant of about 0.5 s. Slow ERP potentials are often observed when the subject develops an expectancy for an upcoming stimulus. For example, if the subject is presented with two stimuli, S1 and S2, the time between them being 3 s, a slow negative potential will develop between the onset of S1 and the onset S2 if the subject is asked to prepare to respond to S2. This slow negative potential will therefore last about 3 s. If the 0.3 Hz low filter is used, it would much attenuate the true ERP negative slow potential. To avoid this, a time constant of perhaps 6 s (about 0.02 Hz) or more might be employed. Thus, a slowing drifting EEG would be attenuated by 50% of its power (again, 71% of its

amplitude) after 6 s. This would thus allow a 3 s negative slow wave to pass unattenuated. The use of a low frequency filter is illustrated in the right portion of Figure 1.

----- Insert Figure 1 here -----

Although filters can be a great asset in increasing the signal-to-noise ratio, they can also severely distort ERP components. This is particularly the case when the frequency range of the noise and the true ERP signal overlap. As is apparent in Figure 1, the data becomes much smoother with severe high filtering (for example, when a 5 Hz high filter was applied). This may cause researchers to believe that the heavier the filter, the cleaner the data. Filtering will always distort the true EEG signal, whether this is noticeable with visual inspection or not. In Figure 1, the progressively lower cut-off frequencies for the high filter have caused the amplitude of the positivity at about 300 ms (the “P3” component) to become attenuated. Similarly, the higher cut-off values for the time constant have caused the entire waveform to be shifted in a negative direction. Filters can also change the onset or duration of ERP components, turn monophasic waveforms into multiphasic ones, and interfere with source localization techniques (Cook & Miller, 1992; Luck, 2005). Luck (2005) describes this distortion in filtering as “precision in the time domain is inversely related to precision in the frequency domain” (p. 182). The more heavily the data are filtered, the more distorted the signal will become. Filtering can result in considerable distortions in the latency and amplitude of a signal and, therefore, should be used with great caution (see Luck, 2014; VanRullen 2011, Widmann & Schroger, 2012 for detailed accounts). In most situations, some amount of filtering will be necessary to appropriately interpret the EEG/ERP data. In

these instances, it is essential to know and understand the effects of filtering on the data and to carefully adjust filter-cutoff frequencies for an optimal balance between suppression of noise and distortion of the ERP waveform.

Ocular correction

Certain types of artifact will share the frequency characteristics of a true EEG signal. If filtering is used to attenuate these artifacts, it will also attenuate the true ERP signal. Other methods can be used to remove these sources of artifact. Signal averaging techniques (discussed later) will attenuate noise that is not time-locked to the stimulus. The heart beat is a low frequency source of artifact that may share the same frequency spectra as the ERP. Filtering, hence, cannot be used to remove this source of artifact. The heart beat is however not time-locked to the stimulus or response. Because it occurs at random times with respect to the stimulus, signal averaging techniques will attenuate it, providing that sufficiently large number of stimuli are presented.

The most prevalent types of artifact occurring in the EEG are blinks and eye movements. The electrical potentials created by these sources may be much larger than the EEG signal and can propagate across much of the scalp. The artifact is especially large near the eyes and over frontal regions of the scalp. To avoid these sources of artifact, subjects should be provided with a fixation point and instructed to focus on it during the experimental task and to avoid blinking as much as possible. Inevitably, however, the EEG will be contaminated by at least some eye movement and blink artifact. The frequency spectrum of eye movement artifact does overlap partially with the actual EEG and therefore filtering cannot be applied. Signal averaging techniques are also problematic because the eye movements may be time-locked to either the stimulus or

the response. A subject might, for example, occasionally blink immediately following a highly relevant stimulus and less often following stimuli that are not relevant. Thus, the blink occurs at predictable times after stimulus onset and is not a truly random event (i.e., it is time-locked to the stimulus). In these cases, the researcher may misinterpret the much larger apparent ERP over the frontal regions of the cortex following the presentation of the very relevant compared to the less stimulus as reflecting activation of the frontal lobe rather than true eye movement (EOG; electrooculogram) artifact.

Various methods exist for the rejection and/or correction of ocular artifacts within the EEG. A common, older method is to reject any trial in which eye movement artifact exceeds an amplitude voltage that would be considered to be abnormal for the EEG. Eye blinks will typically exceed 100 μV but an EEG signal this large would most likely be considered abnormal (the waking EEG rarely exceeds 100 μV). Thus all data in any trial in which the EOG exceeds $\pm 100 \mu\text{V}$ could be rejected from further analyses. Some blink artifacts may be missed if they do not exceed this predetermined threshold and for this reason, other researchers lower this threshold to a more conservative +75 μV or even $\pm 50 \mu\text{V}$. Relying on this more conservative threshold will, however, result in increased numbers of trials being rejected because of artifact contamination. The artifact rejection method is quite effective if the amount of artifact is limited. In cases of young children, the elderly and different patient populations, a very large number of blinks and movements may occur. If the rejection method is used, much of the data might therefore be rejected.

EOG correction, rather than rejection, methods have now been developed to avoid a large loss of data. Several ocular correction techniques have been developed for this

particular purpose, some operating in the time domain (e.g., Gratton, Coles & Donchin, 1983) while others also in the frequency domain (e.g., Woestenburg, Verbaten, & Slangen, 1983). Common to all correction methods is the use of mathematical/statistical algorithms to subtract or partial out the EOG activity within the EEG. The EOG artifact is considerably larger over anterior than over posterior sites. EOG correction methods thus calculate the propagation factor of the EOG signal across all areas of the scalp, and subtract this proportion of activity from the EEG at each corresponding electrode site. Another method employs source localisation modelling to identify the sources of the artifact (EOG activity) independent of true brain source activity (Lins, Picton, Berg, & Scherg, 1993a; 1993b). A more recent technique employs independent component analysis (ICA; Jung, Makeig, Humphries, Lee, McKeown, Iragui, & Sejnowski, 2000; Jung, Makeig, Westerfield, Townend, Courchesne, & Sejnowski, 2000). ICA aims to decompose data into statistically independent components utilizing higher-order statistical measures (beyond those used by principles component analysis; PCA). These methods represent a subclass of the blind source separation (BSS) algorithms (Belouchrani, Abed-Meraim, Cardoso, & Moulines, 1997; Joyce, Gorodnitsky, Kutas, 2004). Figure 2 illustrates a 10 s segment of ongoing EEG data that has been corrected for ocular artifacts using ICA procedures. The blinks in the data have been identified by the algorithm, and any blink activity deemed statistically independent of the brain activity has been partialled out of the EEG trace. ICA methods provide a more realistic outcome of ocular correction because they take into account the statistical independence of the varying components. Running this algorithm can, however, become quite time-consuming and does require a substantial amount of both EEG data and electrode sites.

The algorithm will not be able to properly determine the localization and independence of components if too few data or electrode placements are provided.

----- Insert Figure 2 here -----

Segmentation & Baseline correction

Segmentation. Once initial filtering and correction methods have been applied⁴, the EEG is then segmented into discrete “epochs” typically beginning before a stimulus is presented and extending for a period of time after it. An epoch is created for every single “trial” (i.e., every stimulus presentation). If 1000 stimuli had been presented, then 1000 different epochs would now be created. These will also need to be sorted for every stimulus and response category. Suppose the researcher uses an oddball paradigm in which 500 stimuli were presented, 400 of these being frequently occurring “standards” and then at odd times (the remaining 100 trials), a “target” being presented that the subject is asked to detect by pressing a button. The single trial epochs are thus sorted into 400 standards and 100 targets. The targets may further be sub-divided on the basis of performance into targets that were correctly detected (“hits”) and those that were not (“misses”). Obviously, the cognitive processes involved in a hit and a miss may be very different. How does the researcher determine the duration of the single trial epoch (also called the “sweep time”)? The epoch should include EEG activity prior to the onset of the stimulus in addition to the activity following its presentation. The pre-stimulus period serves as a “baseline” from which the amplitude of the ERPs of interest will be measured.

⁴ It is also possible to filter following segmentation of the single trials and the resulting averaged ERPs should be identical. The filtering of the single trials will be more rapid because fewer data points are involved in the computation. However, with the use of powerful, modern computers, this time difference is incidental. Most researchers therefore prefer to filter the raw, continuous EEG and doing so does have advantages. Attenuating high frequencies by initially filtering the continuous EEG better enables the researcher to visually identify intervals in which the EEG is obviously “bad”. Moreover, ICA eye correction methods best operate on data in which very noisy intervals in the EEG have already been excluded.

This is because prior to the stimulus, there should be no EEG activity that is related to the stimulus. In actual fact, there may be some pre-stimulus activity related to processes such as expectation or prediction of occurrence of the upcoming stimulus. There may also be activity related to the processing of the previous stimulus. The length of the post-stimulus epoch will depend on the cognitive processes of interest. Certain ERP components will have very short latencies, while others may occur much later. It is therefore important to select an appropriate epoch length to ensure that the ERP component of interest is not excluded from the segment. A general rule-of-thumb used by ERP researchers is that the epoch should extend two to three times the period of the major peak of interest. For example, the P3 ERP component is a positive-going ERP component peaking at about 300 ms after the onset of a target. This peak may occur earlier or much later in different subjects. Therefore, in the case of the P3, the recording epoch should extend to at least 800 to 1000 ms following stimulus onset. Another means to determine the post-stimulus epoch length relies on the actual behavioural response made by the subject following the stimulus, assuming that it is recorded. The reaction time (RT), the delay between stimulus onset and the response, will vary from trial-to-trial. In this case, the post-stimulus epoch should also be very liberal and extend well beyond the mean RT. Thus, in the example above, if the mean RT were 450 ms, the post-stimulus epoch might be set to be 1000 ms. Also, it is essential that the recording epoch be long enough to allow the ERP activity to return to baseline. Again, because the data are analyzed off-line, the duration of the epoch can always be altered in a subsequent analysis.

The segmentation procedure is illustrated in Figure 3. The Figure displays 10 s of EEG activity during which time a stimulus (S1) is presented 3 times. The EEG is thus

segmented into epochs for each stimulus presentation. In this Figure, the shaded epoch begins 100 ms prior to the onset of S1 and continues for 900 ms following it. The total epoch thus lasts for 1 s. An ERP is elicited by each stimulus presentation but the amplitude of this response is very small relative to the ongoing EEG. Signal averaging techniques (described below) will be required to allow the researcher to visualize the minute response that is embedded in the much larger amplitude EEG.

----- Insert Figure 3 here -----

Baseline correction. The average of all activity prior to the onset of the stimulus is used to compute a zero voltage pre-stimulus baseline. The pre-stimulus baseline is not necessarily identical to the voltage of the ground electrode (i.e., zero Volts). If the EEG slowly drifts away from the true zero level, the pre-stimulus baseline will also drift in this direction (i.e., not be recorded as a true 0 voltage). This drifting in a negative and positive direction, therefore, needs to be corrected. It could, of course, be corrected by changing the low frequency, time constant. However, the drift may represent a true, slow potential ERP component. In such cases, baseline correction can be used. The algorithm is quite simple and therefore very rapid to compute. The average of all pre-stimulus activity is computed. In Figure 4, the baseline is drawn through the true zero voltage (the ground voltage). The pre-stimulus activity on this trial is however “above” this baseline; it has drifted in a positive direction. The average of this pre-stimulus activity is about +5 μV . The +5 μV average baseline is then subtracted from every data point in the pre- and post-stimulus interval. This procedure is then subsequently repeated for every epoch.

----- Insert Figure 4 here -----

Artifact rejection

As previously indicated, several types of artifacts can contaminate the EEG. Among these, the most prevalent types of artifact include blinks, eye movements, muscle activity, and heartbeats. These artifacts are typically very large compared to an ERP signal and do not reflect true brain activity. Some of these artifacts, as has also been noted, can be corrected through filtering and correction procedures. Other artifact may still remain.

The artifact rejection process involves the identification and rejection of epochs contaminated by artifact. Again, what constitutes an artifact must be defined. This is usually done by stating that the waking EEG should rarely exceed an arbitrary level, for example. Thus, if any of single trial epochs contain EEG activity that exceeds $\pm 100 \mu\text{V}$, it would be rejected and removed from further analysis. Assuming that the EEG has been filtered to attenuate high and low frequency noise and then corrected for common EOG artifact and pre-stimulus baseline drift, the loss of data due to rejection techniques should be minimal. The selection of the actual criterion of artifact detection, while arbitrary, must be sufficiently sensitive in order to eliminate all trials in which artifact occurs. However, it must also be liberal enough to avoid false alarms and an excessive loss of data. Thus, some compromise is inevitable.

Signal Averaging

Signal averaging is a procedure in which a constant signal (the ERP component of interest) occurring in repeated trials emerges from the random, ongoing background EEG, or noise within these trials. In most cases, the amplitude of the ERP is very small while the amplitude of the ongoing EEG can be very large. Even when filtering and artifact rejection methods have been applied to attenuate noise, ERPs will almost always

be difficult to distinguish from the background EEG. Signal averaging techniques are used to reduce the amplitude of the background noise, resulting in an increase in the signal-to-noise (S/N) ratio, allowing the constant signal to emerge.

Certain assumptions must be met for signal averaging techniques to function correctly. The EEG data collected in a single trial is assumed to consist of both the signal (the ERP) and random noise (the ongoing EEG + other artifact). Importantly, the ERP is assumed to be identical (invariant) from one trial to the next. Thus, its amplitude and its peak latency do not vary. Across the trials, the average of an invariant constant is constant (the average of +5, +5, +5, +5 across 4 different trials, is of course +5). The noise is, however, assumed to be completely unrelated to the time-locking event (e.g. the stimulus or the response). Its amplitude across the different trials is thus random. It may be positive- or negative-going. Its amplitude might be high or low. The average of a random event over a sufficiently large number of trials should tend towards zero (on the 4 trials above, the noise might measure +15, -4, -26, +32, the average being +4.25). With a sufficiently large number of trials, the average of the random events should approach zero allowing the average of the constant signal to emerge.

The amplitude of the random noise decreases as a function of the square root of the number of trials. Thus, after 4 stimulus presentations, the amplitude of the background EEG is reduced by 2 (i.e., it is now $\frac{1}{2}$ of its single trial amplitude). Therefore, if the researcher wishes to halve the amplitude of the noise (thus doubling the S/N ratio), the number of trials must increase 4 times. If after 16 trials, the S/N is not sufficient to allow the signal to emerge and the researchers wants to double it (make the signal twice as large as the noise), 64 trial presentations will now be needed, not 32. And,

if that is still not sufficient, 256 trials will be needed to again double the S/N ratio and not 128. Figure 5 illustrates the averaging procedure. The upper left portion of the figure illustrates 4 unaveraged superimposed single (or “raw”) trials. These single trials contain both background noise and the signal of interest. Immediately below the single trials, the average of the 4 trials is presented. A positive component at about 200 ms is beginning to emerge. Again, to double the S/N ratio of the average, 4 times the number of trials (i.e., 16 trials) must be presented. The upper middle portion superimposes 4 averages of 4 trials each. The average of these 16 trials is presented below the superimposed averages. Now, both the negative and positive components are beginning to emerge from the background noise. To double this S/N ratio, 64 trials must be presented. The upper right hand portion superimposes again 4 averages, but each trace is now the average of 16 trials. On the bottom right portion of the Figure, the average of the 64 trials has been computed. The ERP components of interest can be viewed much more clearly here; a negative-going peak at about 100 ms and a positive peak at about 200 ms. Compare this average to the upper left portion of the Figure in which 4 single trials are superimposed in which the ERPs of interest are embedded in the much higher amplitude background noise.

----- Insert Figure 5 here -----

While signal-averaging techniques provide an exceedingly powerful means for low amplitude ERPs to emerge in very high amplitude background EEG, there is a cost. As can be observed, the number of stimulus repetitions may have to be exceedingly large. This can be rather discouraging for the researcher and of course, can be very time-consuming. To reduce the number of stimulus presentations that will be required and still

ensure a high S/N ratio, either the amplitude of the signal must be high or the amplitude of the noise must be low. Although the researcher does not have any control over the amplitude of the signal, they do have some control over the amplitude of the background EEG. It is often much easier to obtain high quality data by decreasing possible sources of noise during the collection of the raw data, rather than increasing the number of trials. To reiterate, priority must be given to obtaining the best possible clean, artifact (noise) free raw data. Filtering, correction of artifact and signal averaging techniques will reduce the amplitude of the background noise of the raw data. It is much better however to minimize sources of noise during the actual recording of the EEG.

Quantifying ERPs

The final step in an ERP experiment is the measurement and quantification of the different ERP components, and applying these measurements to statistical analyses. Most ERP experiments compute the amplitude and latency of the various components. This section will discuss the quantification of these components using different measurement techniques, and the statistical analysis options available. An important warning: the terms peaks and components are often interchangeably used when discussing ERP waveforms. Peaks and components are *not* the same. The point at which the voltage reaches a maximum value (the “peak”) does not necessarily reflect an ERP component. Certain factors such as noise and importantly, other and overlapping components, can influence the maximum voltage in a waveform.

Baseline-to-Peak Measurement. Two common methods are used to measure the amplitude of an ERP component. Most labs now use a baseline-to-peak measure. Thus, the average of all activity in the pre-stimulus period is used as a zero voltage baseline

from which the various components are measured. Some labs also use a peak-to-peak measure (the trough of one peak is measured relative to the trough of the next peak) but if there is an experimental effect, it is difficult to know if this outcome is a result of an effect on the first or second peak.

Peak Amplitude Measurement. The first quantification method, peak amplitude measure, finds the maximum amplitude of a peak in a predetermined window of time for each individual subject. Thus, an auditory “N1” ERP component usually occurs at about 100 ms following stimulus presentation. It might thus be defined and quantified as the maximum negative peak occurring between 60 and 140 ms. This method can be problematic in that the maximum amplitude in a certain time interval may not reflect the actual peak of an ERP *component* (Luck, 2014; Picton et al., 2000). For example, there may be several peaks within a particular time window and some of these peaks will be remaining unaveraged noise. Peak amplitude measures will arbitrarily measure the largest of these peaks, regardless of whether this truly reflects the actual ERP component of interest or the ERP component + noise. The mean of all subjects’ maximum peak amplitude will inevitably be larger than the maximum peak that is apparent in the grand average (again, the average of all subjects’ averages). See the section below describing the alternate, mean amplitude measurement technique, for additional discussion of this issue.

Mean Amplitude Measurement. A second method, mean amplitude measure, calculates the mean voltage of the waveform in a predetermined window of time. This method is often applied when there is no single distinct peak for an ERP component of interest within the time interval (Duncan et al., 2009; Luck, 2014; Picton et al., 2000). It

is also based on the fact that cognitive processes do not occur at a definitive point in time with perhaps millisecond precision. This is implicitly what the peak amplitude measurement however assumes. Rather a cognitive process occurs over several milliseconds and thus the averaging of all data within the pre-defined time period would be more appropriate. Another advantage of this method is that it is less sensitive to high-frequency noise or multi-peak intervals because the average of a range of data points is used rather than a single time point. The mean amplitude measure thus effectively acts as a type of high filter, by averaging together rapidly alternating negative- and positive-going peaks. A major problem with the maximum peak detection method is that background noise will often contribute to the peak in question. Averaging over several peaks and valleys overcomes this problem. The mean amplitude measurement technique is also a linear measure. As such, the mean amplitude of a component averaged across all subjects is equal to the mean of this component in the grand average (Luck, 2014). This is illustrated in Table 1. In this Table, an interval containing 5 hypothetical data points are presented for 3 subjects. On the bottom of the Table, the grand average of these 3 subjects within the 5 data point interval is computed (i.e., the average of data point 1, the average of data point 2...the average of data point 5 for the 3 subjects). In the right-column the mean peak detection method averages the amplitude of the 5 data points for the 3 subjects. The mean of the mean amplitude measures for the 3 subjects is identical to the mean of the 5 data points in the grand average. On the other hand, the maximum peak among the 5 data points is 11, 9 and 15 μV for subjects 1, 2 and 3 respectively. Thus, the mean of the maximum peaks (11.7) of the 3 subjects overestimates the peak in the grand average. The use of the mean amplitude measurement technique thus makes it possible

to directly compare the grand-averaged ERP waveforms to the mean of this component in the statistical analyses. This is not the case when peak amplitude measurement techniques are used.

There are also different methods to determine the time interval within which the mean amplitude of the component of interest is measured. One method is based on existing literature, such as the 60-140 ms time interval window used for the N1 example above. Thus, for each subject, N1 would be measured as the mean amplitude of all data points within the 60-140 ms interval in each individual subject. Another method uses the grand average (again, the average of all subjects' average). Because the grand average should contain very little noise, the peak of the component of interest should be easily identifiable. Again, in the example of N1, perhaps N1 reaches a maximum amplitude (or "peaks") at 100 ms in the grand average. N1 might then be measured as the mean of all data points within ± 25 ms of this peak (i.e., from 85 to 135 ms) in individual subjects.

Latency Measurement. ERP latencies are usually measured at the time of when a peak reaches its maximum amplitude (Duncan et al., 2009; Luck, 2014; Picton et al., 2000). Hence, peak latency techniques are commonly paired with peak amplitude measures. All of the disadvantages associated with peak amplitude measures also apply with peak latency measures. Most notably, if there are multiple peaks within a time window, or if the peak of a component is rather flat, the maximal voltage in that time window may not reflect a true measure of the ERP component's latency

Another method, fractional area latency, is analogous to mean amplitude measures. This technique computes the area under the ERP waveform over a predetermined time interval and then finds the time point that divides this area into a

predetermined fraction (Hansen & Hillyard, 1980). Commonly, the fraction will be a half; therefore, the time point that divides the area under the curve in half is deemed the latency of the ERP component (Luck, 2014). This technique is not appropriate for measuring the absolute latency of a component, or if overlapping ERP components are present within the same time window. Measuring the latency of ERP components can thus be extremely difficult as all methods have multiple drawbacks. Therefore, whichever technique better suits the experimental design of an ERP study should be used. The method used must be clearly specified and extreme caution must be applied in interpreting these results.

Topographical maps. Multi-channel ERPs allow for the display of cognitive activity as it varies over time (the temporal dimension) and as it varies across the scalp (spatial dimension). Variations in ERPs across the scalp are usually displayed as multiple waveforms as a function of time at the different electrode locations. The previous Figures in this article use this convention. However, the spatial aspects of the various ERPs, where the component is maximum and where it is minimum in amplitude, are not easily visualized in this method. The spatial dimension of ERP components is better displayed using voltage distribution maps. Various kinds of maps can be computed and displayed. Of course, there are no actual data between electrode sites. Voltage maps are however made to be continuous by interpolating values between electrode sites where actual data exist. Thus, let us assume that a component measures 8 μV at Fz and 4 μV at Cz. One could interpolate the value for FCz (half way between Fz and Cz) to be 6 μV . Similarly, the value for a site half way between FCz and Cz could also be interpolated to be 5 μV ($(6+4 \mu\text{V})/2$). Interpolations of data do need to take into account other “nearest

neighbours”, for example, electrodes located laterally, and weigh their values accordingly. The upper portion of Figure 6 provides a 64-channel recording of an auditory ERP. The reference site was the tip of the nose. A brief duration, moderate intensity binaural auditory stimulus was presented every 2 s. As can be seen, a large negativity (the N1) is apparent at about 100 ms. An enlargement of the Fz, Cz and M2 electrodes is illustrated on the right portion of the Figure. N1 is maximum in amplitude over frontal and central sites of the scalp. At inferior and lateral sites such as M1 and M2 (or TP9, TP10, the left and right mastoids), N1 inverts in polarity and is recorded as positive-going. In the lower, right portion of the Figure, a topographic map of the scalp distribution of N1 is presented. A non-linear and a linear view are provided. The non-linear view presents both a top and side perspective. These linear aspects reflect the views of the head as seen by the human eye. Thus, in the top view, electrodes at the top of the head (e.g., Cz-C1-C3, Cz-C2-C4) are spaced farther apart than electrodes at lateral-inferior regions (e.g., C5-T7-C6-T8). Consequently, in order to obtain a better view of the lateral and inferior electrodes, a lateral, side projection is also required, in this case, the right side of the head. In this case, electrodes near the ears are placed farther apart than electrodes near the top and anterior-posterior portions of the head, again in keeping with how the eye would view the side-to-top of the head. It is also possible to calculate topographic maps with the use of a linear, equidistant perspective. Thus, the distance between the electrodes is equal. In this view, the projection may be extended down 20° below the Fp1-T7-Oz-T8-Fp2 circumference to show data from the most inferior electrodes. A top, linear-equidistance map extended down 20° is illustrated in the bottom right portion of the Figure.

----- Insert Figure 6 here -----

As mentioned, the simplest maps are computed using a “nearest neighbour” algorithm (Duffy, Burchfiel, & Lombroso, 1979). Most often, a four nearest neighbours algorithm is used. A serious issue with the nearest neighbours approach is that discontinuities may appear in the maps. Spline interpolations provide for smoothly changing maps. Because the head is spherically shaped, spherical spline maps (Perrin, Pernier, Bertrand, & Echallier, 1989) currently tend to be most often used. The maps in Figure 6 were computed using spline-interpolated maps.

A major issue with the use of maps is that they are often misinterpreted as reflecting underlying sources or “generators”. In the Figure above, N1 was maximum over frontal regions of the scalp. Maps of the scalp voltage distribution are not however maps of the sources! Although N1 might be maximum in amplitude over frontal regions, it is not necessarily the frontal regions that were most activated by the auditory stimulus. Indeed, in the case of N1, it has long been known that its fronto-central scalp distribution is probably best explained by the orientation of source dipoles in and around the auditory (not the frontal) cortex (Scherg, Vajsar, Picton, 1989). Scalp distribution maps do not directly provide a map of the areas of the brain activated in a particular condition. Nevertheless, even if the scalp distribution maps cannot be used as maps of the underlying sources, they can be used in a different way. Components whose scalp topographies vary must have different intra-cranial generators. Thus, it also logically follows that if the scalp distribution of an ERP component is different in two conditions, then the underlying cerebral generators must be different in these conditions. It does not logically follow however that if the scalp distribution is the same in two different

conditions, then the underlying sources must be the same. It is possible to have identical scalp maps as a result of different source dipole activity (Picton et al., 1995).

Statistical Analyses of Scalp Distribution Data. Statistical analyses of the scalp distributions of the different ERP components across conditions or between groups need to be interpreted with caution (Picton, 1988). These analyses are fraught with difficulties. Most of the data in the scalp distribution maps are not “real” data. Rather they are interpolated. In the example above, the researcher did not have any real data for the FCz placement. Rather it was interpolated using a nearest neighbour computation. Statistical analyses should only be applied to the actual data.

One of the major reasons for collecting data from multiple electrode sites is to determine if an experimental manipulation affects the scalp distribution of an ERP component. This would usually be compared by a 2-way analysis of variance (ANOVA) to examine the interaction between the experimental condition and the scalp distribution. Unfortunately, the ANOVA procedure is poorly suited for this purpose. An assumption for the use of the ANOVA is that the experimental manipulation will result in an additive effect (a constant is added to each variable). The experimental manipulation causes a multiplicative effect on ERP scalp voltages. This issue has been discussed by McCarthy and Wood (1985) and Picton et al. (1995). Again, let us assume that the amplitude of the N1 component measures $-8 \mu\text{V}$ at the frontal electrodes site (where N1 is largest) when the subject actively attends to the auditory stimuli. At central sites, it might measure half this amplitude, $-4 \mu\text{V}$, and at parietal sites, $-2 \mu\text{V}$. Note that this is a multiplicative effect (the voltage drops by $\frac{1}{2}$ from Fz to Cz to Pz), not a linear one (the voltage does not drop by $4 \mu\text{V}$ at each equidistant electrode site as one moves in an anterior to posterior

direction). Now, let us suppose that in a second “ignore” condition, the amplitude at Fz drops to $-4 \mu\text{V}$. In short, the amplitude decreases by $4 \mu\text{V}$. The additive model of the ANOVA procedure would also examine if the amplitude also decreases by $4 \mu\text{V}$ at both Cz and Pz. Thus, N1 would now measure 0 and $+2 \mu\text{V}$ at Cz and Pz respectively. If so, this would be reflected in a significant main effect of the experimental condition and a non-significant condition x electrode site interaction (i.e., the effect is the same across all electrode sites). In reality, the amplitude would tend to be halved (a multiplicative effect) at Cz and Pz, thus measuring -2 and $-1 \mu\text{V}$ respectively. Thus, the ANOVA might point to a significant condition x electrode site interaction because the effect was larger at Fz (a $4 \mu\text{V}$ difference) than at Pz (a $1 \mu\text{V}$ difference). This would lead to a false interpretation of the experimental effect. The experimental effect had the same, constant multiplicative effect at all electrode sites. The ignoring of the stimuli caused the amplitude of N1 to be reduced by 50% at all sites. The presence or absence of a significant interaction cannot therefore be easily interpreted. McCarthy and Wood (1985) have provided a scaling method to normalize the scalp distribution data. Unfortunately, the McCarthy and Wood normalization procedure has also been demonstrated to potentially produce erroneous results and cannot correct for the multiplicative effects on interactions involving an electrode factor (Urbach and Kutas 2002).

Conclusion

The two articles in this series have described the real-time recording of the EEG from multiple electrode sites and how these are affected by various cognitive paradigms. The present article discussed the basic approaches for the analysis of ERP data. The advent of extremely powerful, but inexpensive, microcomputers and low cost

multichannel amplifier systems has made the collection of both the performance and physiological data almost exponentially easier than in the past. ERP research has a long history dating back to the pioneers in the 1950s and 1960s. One of the major benefits of modern computer systems is that many complex off-line analyses can now be carried out on the data. An advantage of the off-line approach is that the raw data are not altered. Thus, any analyses that are carried out can later be reversed and modified. The EEG data are typically examined for artifacts. Many sources of artifact can be removed using digital filtering techniques. A common artifact is that caused by eye blinks and movements. This source of contamination is especially problematic over anterior regions of the scalp. Sophisticated algorithms, such as independent component analysis, can be used to correct for eye movement artifact, although the EEG does need to be recorded from a large number of scalp electrodes. The filtered and corrected continuous EEG data then need to be “cut” into segments, or epochs, of varying lengths and sorted according to the different stimuli that have been presented and types of responses made by the subject. Waxing and waning of the EEG within the epoch can be corrected. Epochs in which the amplitude of the EEG is unusually large are often rejected. The amplitude of the actual change in the electrical activity that is elicited by the physical stimulus or cognitive task demands (i.e., the ERP signal) is usually much smaller than the ongoing EEG in which it is embedded. Signal averaging techniques have long been employed to reduce the amplitude of the background noise, allowing the ERP signal to emerge. If the amplitude of the ERP is very small and the amplitude of the ongoing EEG is very large, many stimulus repetitions will probably be required and the time required to collect the data may thus be quite long.

With the arrival of modern imaging techniques such as PET and the fMRI, it was thought that ERP research would fade away unable to compete with the spatial resolution capabilities of these (much more expensive) systems. As discussed in this article, it is possible to map the scalp distribution of the different ERP components. Nevertheless, the scalp distribution maps should not be interpreted to be maps of the underlying intracranial sources. Source localization techniques that rely on the scalp distribution maps can be used to mathematically compute the possible intracranial dipole sources. Source localization methods do require considerable human expertise and are not fully automated and for this reason, were not discussed in this article. There are several disadvantages to the use of hemodynamic measures imaging systems. Most importantly, their temporal resolution is much slower (in the order of seconds) than that afforded by ERP methods (millisecond resolution). For this reason, if anything, there are now many more ERP researchers than in the past. ERPs have thus become an integral part of the cognitive neuroscientist's toolbox and modern imaging systems can now record ERPs concurrently during the fMRI imaging procedure.

Ease of data collection and analysis is no substitute for carefully designed studies and the collection of high quality raw data. It is best to remove sources of noise and artifact during the actual data collection. In spite of the best efforts of the researcher, subjects will blink and move. Modern systems also allow for the low cost collection of data from many different scalp sites. Even though data are now routinely recorded from 64, 128 and 256 electrode sites, how these multichannel data are to be analyzed is still however much debated.

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Table 1

A comparison of peak amplitude and mean amplitude measurement techniques. An interval of 5 data points have been “cut out” from the averaged ERP waveform. The data for 3 subjects appear in each row. The maximum peak is identified in italics. The grand average, calculated by averaging data points 1, 2 ...5 of the 3 subjects appears in the last row. The mean amplitude of the 5 data appears in the right column for the 3 subjects. The mean of this column (i.e., the mean of the mean amplitudes is identical to the mean of the 5 data points within the grand average). On the other hand, the mean of the peak amplitudes does not equal the mean of the data points within the grand average.

Subject	Data Point					Mean
	1	2	3	4	5	
1	7.0	9.0	<i>11.0</i>	10.0	8.0	9.0
2	6.0	<i>9.0</i>	7.0	7.0	3.0	6.4
3	11.0	14.0	12.0	<i>15.0</i>	10.0	12.4
Grand Average	8.0	10.7	10.0	10.7	7.0	9.3

Figure Captions

Figure 1. Effects of filtering. An averaged ERP was computed beginning 100 ms prior to the onset of a stimulus and continuing for 600 ms following it. Different high and low filter cutoffs were applied to the raw EEG prior to averaging. In the left portion of the Figure, the effects of high filtering are illustrated. The ERP contains a large amount of high frequency noise after a 100 Hz filter is applied. Much of this is 60 Hz activity comes from the mains power. This is much attenuated with a 40 Hz high filter cutoff. A 20 Hz high filter further attenuates most of the remaining noise. A 5 Hz filter however distorts the actual ERP frequencies. In the right portion of the Figure, an ERP that contains a large amount of “drift” is illustrated. This can be attenuated by reducing the time constant from 1 to 0.3 s. The use of a 0.3 s time constant may also however distort the true ERP. This is especially apparent when a 0.1 s time constant is employed. Thus, the use of increasingly extreme high cut-off frequencies does result in a “smoother” but more distorted ERP waveform. Similarly very short time constants will remove much of the slow drift in the ERP but may be attenuating the true ERP waveform. Caution must be taken to choose the most appropriate filter setting without severely distorting the ERP response of interest.

Figure 2. Independent component analysis (ICA) ocular artifact correction. A 10 second segment of continuous EEG data are displayed. The EOG activity is displayed on the first line (vEOG; vertical electrooculogram). As is apparent, two very large upward deflections (greater than +300 μ V) are apparent. These are eye blinks. The uncorrected EEG is displayed in blue. The blink artifact is propagated to a much greater extent over

anterior than posterior regions of the scalp. An ICA algorithm was applied to the data. It identified eye blinks and then partialled out this artifact. The corrected EEG is shown in black.

Figure 3. Segmenting the “raw” EEG. A 10 s display of the “raw”, continuous EEG recorded from electrode sites, Fz, Cz and Pz is illustrated. A stimulus (S1) was presented 3 times during this 10 s period and the raw EEG is thus cut into 3 different single trial segments or epochs (shaded). Each epoch begins 100 ms before the onset of S1 and continues for 900 ms after the stimulus (i.e., a 1000 ms total duration epoch). An ERP is elicited following presentation of S1 but its amplitude is minute (about 5 μV) and very difficult to observe because it is embedded in the much higher amplitude ongoing raw EEG (about 25-50 μV). The “signal” is thus buried in the “noise”. Signal averaging procedures will be required to enhance the signal-to-noise ratio, allowing the ERP to emerge.

Figure 4. Baseline correction procedure. A 700 ms, single trial epoch from the Cz electrode is displayed. The average of all activity in the 100 ms interval prior to the stimulus is used as a baseline. The Figure illustrates the single epoch before (in blue) and after (in black) baseline correction. The baseline is drawn through a true electronic zero volt voltage. Prior to baseline correction, the pre-stimulus activity on this trial is almost +40 μV “above” zero. The average activity in this pre-stimulus period is then subtracted from every data point in the post-stimulus interval.

Figure 5. Theory of signal averaging. Again, a 700 ms epoch is illustrated beginning 100 ms prior to stimulus onset. The upper left portion superimposes 4 unaveraged (i.e., single trial) epochs. The small amplitude ERPs are buried in the background noise of the EEG. Averaging procedures are subsequently used to reduce the amplitude of this noise. Immediately below, the average of the 4 trials is presented. This should reduce the amplitude of the background noise by 2 (i.e., the amplitude of the noise should be halved). A small amplitude negativity at about 100 ms and a larger positive component at about 200 ms are beginning to emerge from the noise. The upper middle portion superimposes 4 averages of 4 trials each. The average of these 16 trials is presented immediately below this. This should again reduce the amplitude of the noise by 2 compared to when the average was based on 4 trials. Now, the negative and positive components are quite apparent. The upper right hand portion superimposes again 4 averages, but each trace is now the average of 16 trials. On the bottom right portion of the Figure, the average of the 64 trials has been computed. The ERP waveform is now clearly apparent against what is now only small amplitude noise.

Figure 6. Scalp distribution mapping. Left portion: a 64-multichannel channel recording. The reference site was the tip of the nose. The ERP was elicited by a 200 ms moderate intensity auditory stimuli presented every 2 s. The waveforms are “grand” averages based on 8 subjects (the average of the 8 subjects’ averages). To the right, a zoom of the Fz, Cz and M2 electrodes are presented. The downward deflection at about 100 ms is the auditory N1. It was largest in amplitude over fronto-central areas of the scalp. At sites inferior to the Sylvian fissure (e.g., M1 and M2), N1 inverts in polarity and is recorded as a positive-going component. The scalp distribution of N1 is best displayed in a map.

These are illustrated in the bottom of the Figure. A spline-interpolated algorithm was used to compute a continuous topographic map of N1. Non-linear and linear views are illustrated. The non-linear view provides a visualization of the electrodes as would be observed by the human eye from, in this example, the top and the side of the head. Thus, in the top view, electrodes over the lateral and inferior scalp are closely spaced. In the side view, electrodes near the top of the head are closely spaced. In the linear view, electrodes are evenly spaced and the top view projection continues farther down the scalp to include very inferior FT9 and FT10 and the two mastoid (TP9 and TP10) electrode sites. In both nonlinear and linear views, the map indicates that the amplitude of N1 is maximum over fronto-central areas of the scalp while a polarity inversion (N1 is recorded as a positive potential) is apparent at inferior regions.

Figure 1.

Effects of Filtering

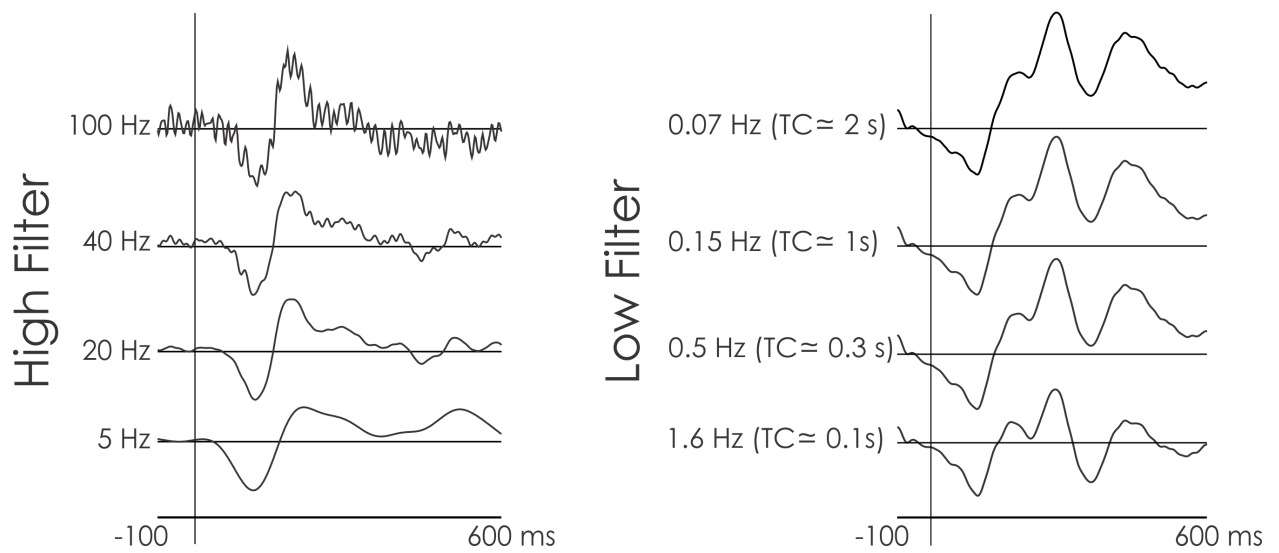


Figure 2.

ICA Ocular Artifact Correction

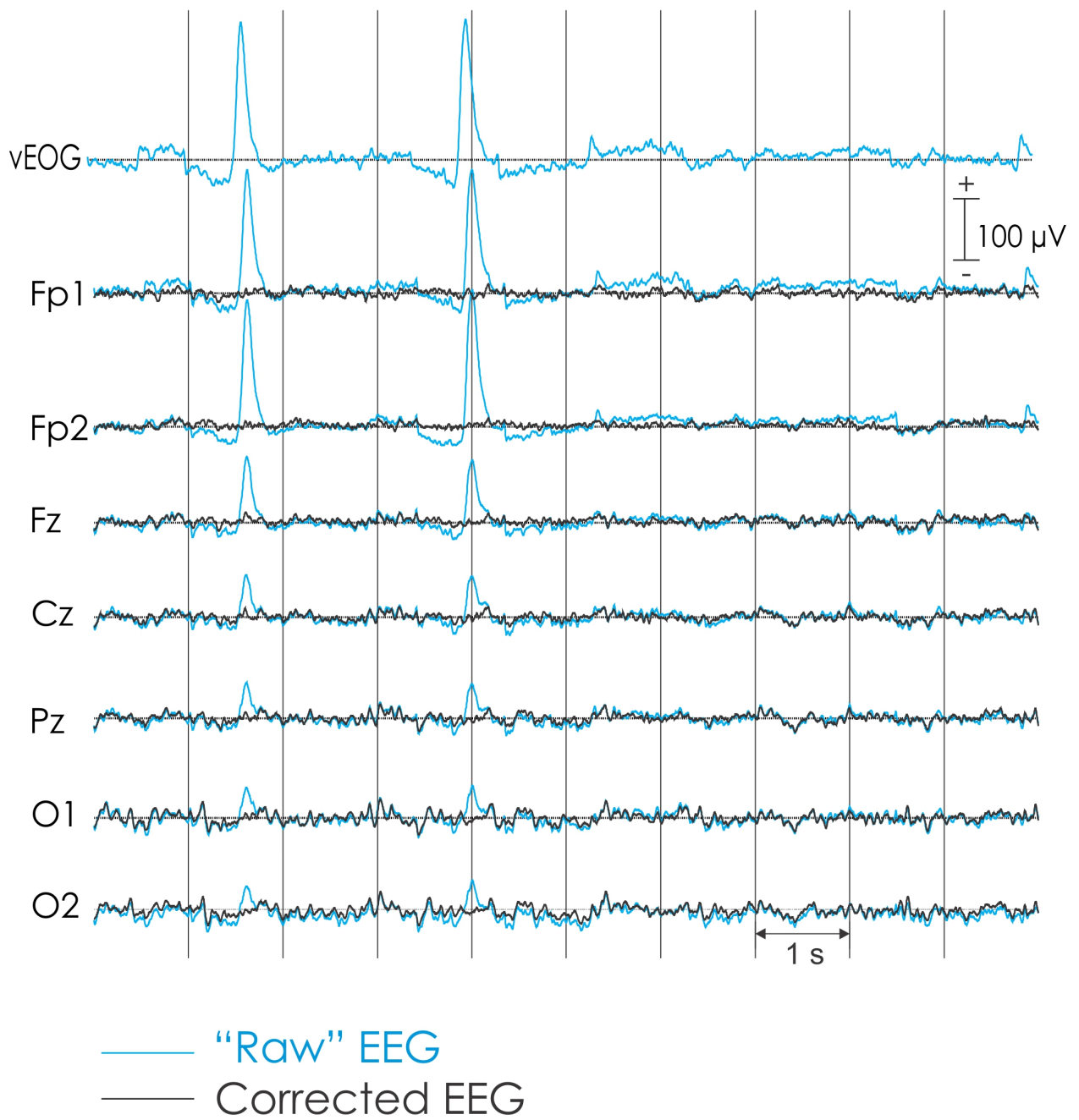


Figure 3.

Segmenting the “Raw” EEG

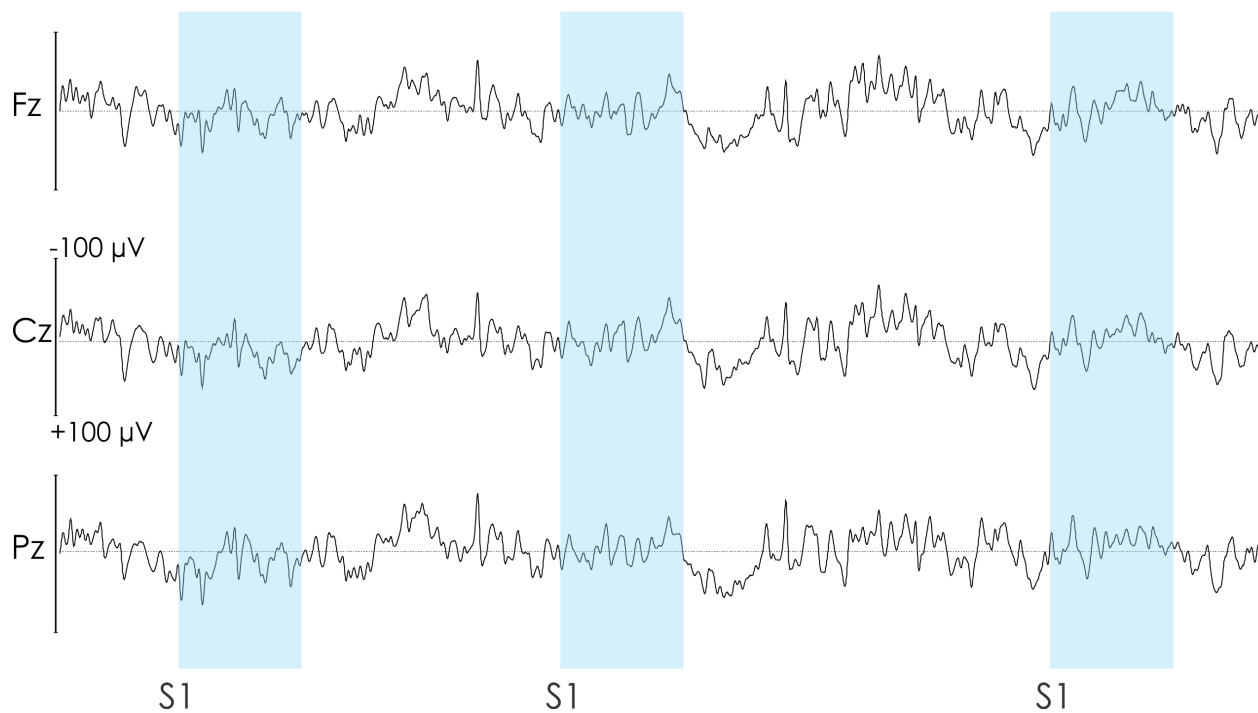


Figure 4.

Baseline Correction Procedure

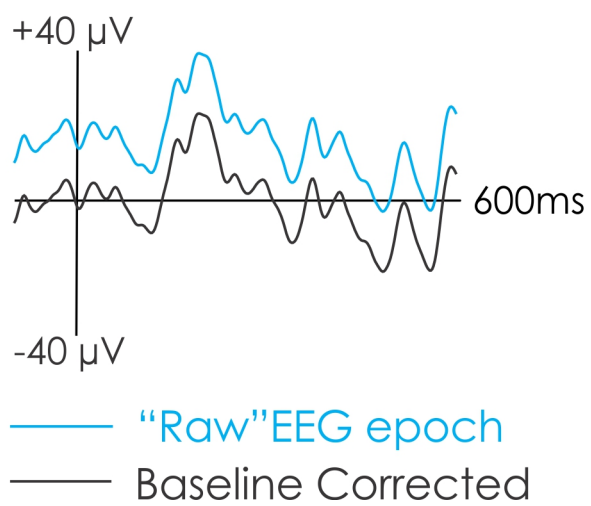


Figure 5.

Theory of Signal Averaging

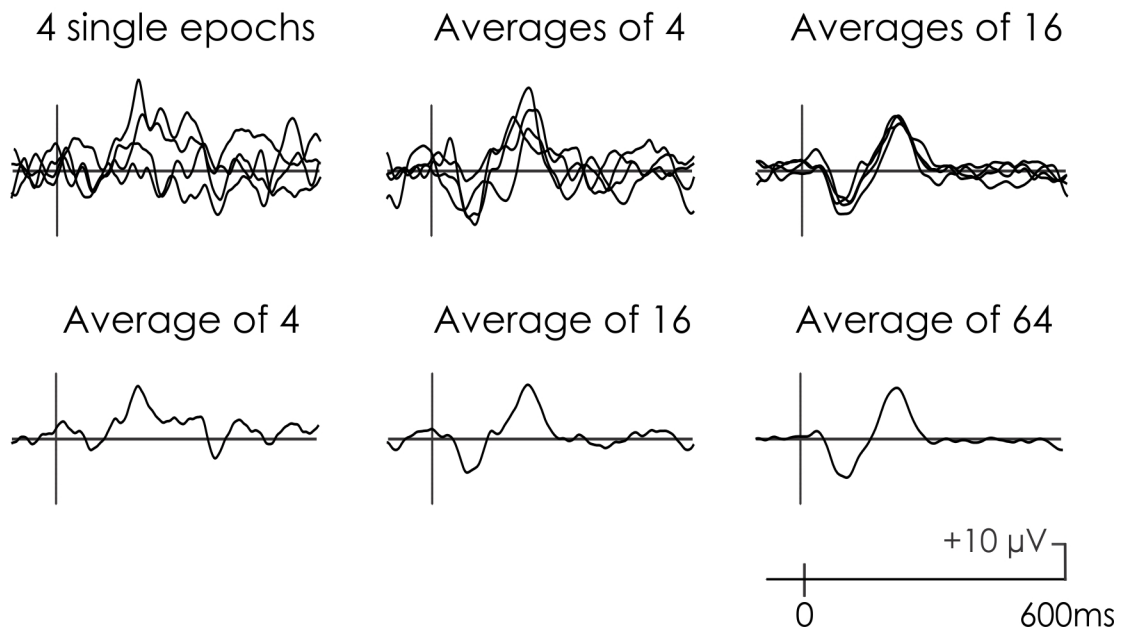


Figure 6.

Scalp Distribution Mapping

