Exploring the Nature of Neural Correlates of Language, Attention and Memory:

Reliability and Validity Studies of Event Related Potentials

Daniele Ortu

Submitted as a requirement for the degree of PhD

University of Stirling 2012

Declaration

The work included in this thesis was completed under the supervision of Professor David I. Donaldson and Dr. Kevin Allan and conducted at the University of Stirling and the University of Aberdeen, United Kingdom.

I declare that this thesis is a presentation of my original work that has not been submitted for any other degree or award. All additional sources of contribution have been acknowledged accordingly.

Daniele Ortu

Abstract

Comparing data from different subfields of research may help in understanding emerging patterns and refining interpretations. This is especially true in neuroscience because brain functions can be studied at multiple levels of analysis, spatially and temporally, and with a variety of complementary measurement techniques. Within the ERP domain, several subfields of research have evolved over time, typically reflecting the specific time-window of interest and brain function investigated. The current investigation focused on three widely studied ERP effects reflecting a variety of key brain functions: the N400 effect, the P3b effect and the Left Parietal effect. The N400 effect has attracted researchers interested in language processing, the P3b effect researchers interested in attentional processes and the Left Parietal effect researchers focused on episodic recollection.

Even though the ERP technology constitutes a common thread across these sub-fields, there is often a lack of communication across groups of researchers. The literatures on the N400 effect, P3b effect and Left Parietal effect have been written by relatively non-overlapping groups of researchers, and as such the kind of analysis carried out in the current thesis is not a common one, as it compares effects investigated within different subfields. Specifically, the approach taken in the current thesis involves assessment of the comparative reliability of the three effects of interest, and at the same time allowing refining their validity. Results showed that all three effects were found to be reliable at the group level and the N400 effect and the P3b effect were also found to be reliable at the single participant level. A correlational analysis involving all three effects yielded a significant correlation between the P3b and the Left Parietal effect but not between the P3b and the N400, or between the Left Parietal effect and

the N400. Following up on the significant correlation, suggesting a convergence between the P3b effect and the Left Parietal effect, a probability manipulation of the Left Parietal effect was carried out to investigate if the old/new effect is sensitive to probability changes similarly to the P3b. The size of the Left Parietal effect was found to be sensitive to the relative probability of old and new items, in a manner consistent with the P3b effect's sensitivity to probability manipulations. The results pointing to a relationship between the P3b effect and the Left Parietal effect suggest that attentional processes sensitive to probability may temporally overlap and confound memory processes as indexed by the Left Parietal effect.

The N400 effect, in the initial correlational study, was found to be independent from attentional processes as reflected by the P3b, and from episodic recollection as indexed by the Left Parietal effect. The validity of the N400 effect as a measure of semantic processing was then assessed by manipulating associative relationships while keeping constant semantic relationships, with results showing that the effect can be clearly modulated by associative changes when semantic relatedness is kept constant. The same association norms were then used in an old/new recognition experiment to assess if the Bilateral-Frontal old/new effect behaves in reaction to association relationships similarly or differently from the N400, in the attempt of assessing if the N400 is only a measure of associative relationships or also a measure of the process of familiarity. The observed pattern suggests independence between the N400 and the Bilateral Frontal effect. Overall, the N400 effect was found to be independent from memory processes occurring in the same time window, but, contrary to the dominant interpretation of the effect, the effect was modulated by changes in association strength while keeping semantic relatedness constant, suggesting that the N400 effect may be sensitive to a contiguity-based associative learning process not constrained to the linguistic domain.

Acknowledgments

I would like to thank my family: Tomaso, Gianna and Fabrizio for their precious support. A special 'thank you' goes to my friends in the Psychological Imaging Laboratory: Ida-Maria Skavhaug, Iain Harlow, Johanna Simpson, Rory Simpson, Catherine MacLeod, Jennifer Lines, Jamie Murray and Joanne Park, for sharing this journey and numerous bowling sessions.

Thanks also to Catriona Bruce for invaluable technical advice and support.

I would also like to thank Professor David Donaldson and Dr. Kevin Allan for their supervision, support and insights provided throughout my project.

Publications

The following journal article and conference presentations have been adapted from experimental work reported in this thesis:

Ortu, D., Allan, K., & Donaldson D.I. (submitted). *The N400: a neurophysiological index of association relationships?*

Ortu, D., Allan, K., & Donaldson D.I. (2010). Reinterpreting the N400 effect as a measure of associative response strength. *Poster presented at The Forum of European Neuroscience Meeting, Amsterdam, Holland.*

Ortu, D., Allan, K., & Donaldson D.I. (2010). Reliability Indices for Neurophysiological Event Related Potentials Effect. *Poster presented at the Sinapse Annual Scientific Meeting, Edinburgh, United Kingdom.*

Ortu, D., Allan, K., & Donaldson D.I. (2011). Associative strength, unitization and the bilateral frontal old/new effect. *Poster presented at The Annual Cognitive Neuroscience Society Meeting, San Francisco, California.*

Contents

Introduction

Scientific advancement may occur by investigating one specific domain in a progressively more detailed manner, or by comparing results obtained across different subfields of research. In the case of brain research, an experimental effect may be considered to index a specific brain function, but such an interpretation might be refined when data across subfields are compared. Comparisons across subfields may illuminate what an experimental effect measures, establishing the effect's wider validity (Kerlinger, 1986). In the current work we explicitly compared experimental effects within different sub-domains of the electrophysiology literature to investigate their functional independence or interdependence, with the ultimate goal of refining their validity.

Validity assessments are however only possible after an effect has been shown to be reliable. In the case of biological sciences including neuroscience, where variability is an intrinsic component of the investigated subject matter (Donahoe, 2003) and where the measured variables are often not as stable as in other scientific domains (e.g. brain activity is not as stable as the length of a table), reliability assessments are especially

important. The variability intrinsic to neural phenomena needs to be understood and controlled for, and in turn the measurement tools used to describe variables need to be reliable and capable of adequately addressing the subject matter.

Reliability is typically defined as the degree to which a measurement procedure yields the same results across repeated tests (Kerlinger, 1986). In short, it is the stability or consistency of a measurement across time. An example of a reliability assessment across time would be repeating a test within the same laboratory, while keeping the same exact procedure and equipment constant, to test if results are consistent across repetitions. An example of a reliability measurement across space would be testing the same procedure in different laboratories (with the same or different equipment).

A measurement procedure is said to yield stable or consistent results when the same or similar values are obtained with repeated testing. If results are not reliable across laboratories and research groups, scientific progress may slow down as conflicting patterns of results may be found across laboratories. Such a scenario could create contrasting theories and interpretations without solid foundations. By regularly checking for reliability across laboratories, unnoticed technical issues may be discovered. Such a practice may thereby facilitate further research and favour selection over time of strong and reliable results.

When we speak of reliability we are not only referring to reliability across laboratories. An experimental effect may be reliable at the group level but may be less reliable than another experimental effect at the single participant level. For instance, Effect A may be measurable in all participants and Effect B may be measurable only in a portion of the participants, while still being replicable at the group level. When the effect is not measured in some individuals, the experimenter may ask the question: "Why was the effect not present in this specific participant?" One option is to consider the data exclusively at the group level and treat the proportion of participants not showing the effect as "statistical noise", a natural form of variation present within normally distributed groups.

An alternative option consists in taking a pragmatic approach and asking what could be done procedurally to tighten the relationship between the independent and the dependent variable so that the effect of interest will be clearly measurable in each participant. It has been argued in fact that if psychology is the science involved in studying the behaviour of individuals (and not groups or populations) then an experimental effect should theoretically be measurable in all participants (Sidman, 1960). It is possible, however, that procedural adjustments would not increase the degree of experimental control. In that case, the measured variability across participants may be due to the phylogenetic history of the individual. Those sources of variability may in some cases be controlled for to a degree but not completely eliminated, even with tight procedures.

Even if reliability is a necessary prerequisite for a validity assessment, a reliable measurement does not imply validity, as the experimenter may be reporting a measurement that is consistent and stable but inaccurate (see Figure 1). While the validity of non-abstracted measurements such as weight might be determined narrowly by the quality of measurement tools, abstract variables present many more potential sources for inaccuracy.

Validity is traditionally divided into different types: construct validity, predictive validity and external validity. Construct validity reflects the adequacy of the operational measurement in representing the theoretical construct to be assessed. Construct validity requires generalizing from the raw measured variable to a conceptual label considered to be representative of what has been measured. For example, when it is said that a neuroscientific measurement is considered to reflect language processing, what are the bases upon which such labeling occurs? What are other possible ways to conceptually label such measurements? Can some experimental data be 'explained' by multiple conceptual labels and, if that is the case, do the different conceptual labels overlap? If they overlap, which criteria should be used to decide what conceptual label is more appropriate? Predictive validity refers to how well the score obtained with a specific measurement tool predicts other variables (e.g. how the score on a test supposed to measure a psychotic personality trait is able to predict future psychotic behaviour). External validity, similarly to construct validity, involves a form of generalization: how do the results obtained in the laboratory within a

carefully controlled environment generalize to other, less controlled, situations? How relevant are the results obtained in the laboratory to the 'outside world'?

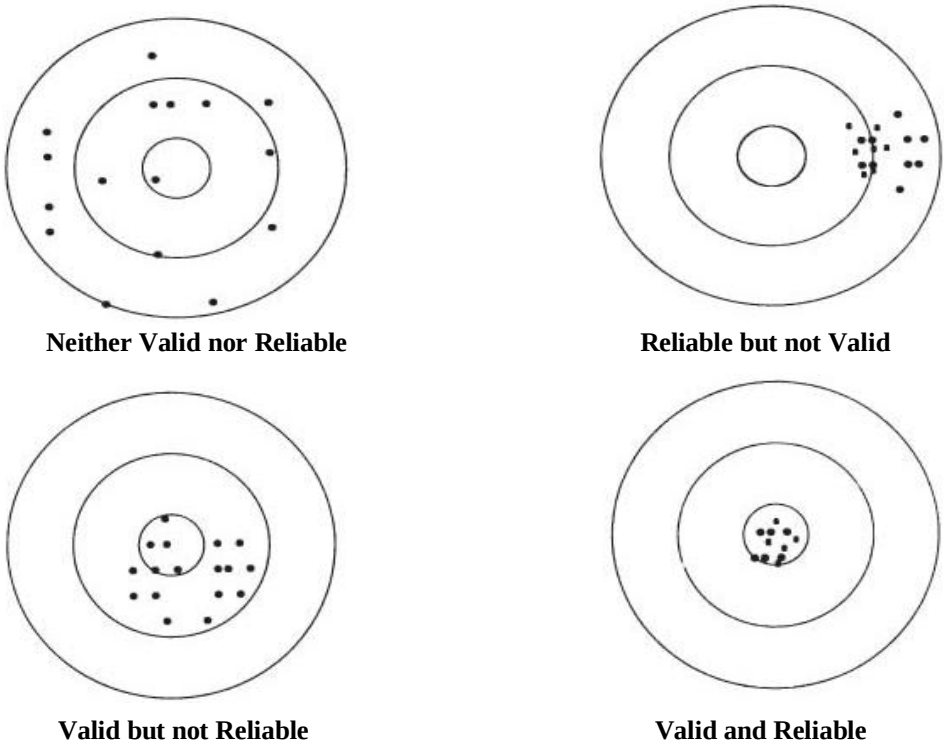


Figure 1 Graphic analogies of possible reliability/validity combinations. The top left quadrant shows research outcome of a measurement tool that does not measure the variable of interest and also yields unstable results over repeated measurements. The top right quadrant shows the outcome of a measurement tool that yields consistent results across repeated measurements but does not measure the variable of interest. The bottom left quadrant shows a fairly valid but relatively unreliable measurement. The bottom right quadrant shows outcome of a measurement tool that measures the variable of interest and at the same time yields consistent results across repeated measurements (Adapted from http://web.idrc.ca/en/ev-56604-201-1-DO_TOPIC.html).

Validity can also be convergent or discriminant. Convergent validity refers to the degree to which different measures that are theoretically connected by the same overarching conceptual label are indeed tightly interrelated. For example, a behavioural and a neural measure of episodic memory should converge with each other. The related concept of discriminant validity refers instead to measures that are theoretically not supposed to be covered by the same conceptual label and in practice are found not to be interrelated.

In the current work we investigated how adequately specific conceptual labels cover several neuroscientific variables of interest. By investigating empirically the convergent and discriminant validity of the neuroscientific variables we attempted to refine current perspectives on their construct validity. Specifically we investigated the validity and reliability of three widely studied neuroscientific effects in the field of electrophysiology (see Chapter 1 for a description of the Event Related Potential technique used in the current thesis). The effects of interest are the N400 effect, the P3b effect and the Left-Parietal old/new effect. They occur in different, partially overlapping, time windows following stimulation and, importantly, are considered to reflect distinct linguistic, attentional and memory processes (see Chapters 2, 3 & 4 for detailed descriptions of each effect). The N400 effect is, in fact, typically described as a language-specific effect (e.g. Kutas, 2011; for alternative interpretations see Chapters 2 and 8; see also Rhodes & Donaldson, 2008). The P3b is considered to reflect stimulus categorization, attentional, processes (e.g. Polich, 2007). The Left Parietal

effect is found in memory tasks and is considered to reflect the process of recollection (e.g. Rugg & Curran, 2007). Taken together the effects allow providing a comprehensive picture of reliability and validity of neuroscientific effects across some of the most important brain functions and across a variety of time-windows.

A possible outcome of the current reliability analysis could be that there are differences in inter-individual reliability across experimental effects: some effects may be more reliable than others. Differences in reliability measures across effects would suggest a higher level of inter-individual variability for an effect compared to others. A higher degree of inter-individual variability in an effect compared to the others could be interpreted in terms of the phylogeny or ontogeny of behavioural and neural variables. Specifically, there may be differences across individuals in the set of genes involved in expressing a specific brain function or, given the same genetic endowment, different strategies used across individuals in the experimental tasks (e.g. in memory tasks some individuals may rely more on imagery than others) or there may be an interaction between genes and experience-related strategies (e.g. genetic differences may lead to increased inter-individual variability when a behavioural strategy but not another is adopted).

Despite the fact that the effects studied in the current thesis have been widely investigated, there is still no consensus about what they are a measure of. There are

uncertainties about the accuracy of the generalization from the raw measured variable to the correspondent conceptual label. As we will describe in Chapters 2 & 8, the widespread agreement that the N400 is a neural correlate of language/semantic processing is put into question by a variety of experiments suggesting that a more general associative process may be involved. The P3b has also not been clearly characterized in terms of its validity. There is some agreement that the P3b reflects a form of stimulus categorization/evaluation (see Chapter 3), but so far the effect has eluded a definitive interpretation. Moreover the Left-Parietal old/new effect, considered by memory researchers to be a correlate of conscious recollection (see Chapter 4) has also been described (Andreassi, 2006; Polich, 2007) not as an independent effect, but as a subset of the P3b. It is therefore clear that for each of these effects the validity has yet to be completely explored, and the current thesis represents a step towards that direction.

To achieve those goals a correlational study with a large number of participants (N=64) was initially setup to investigate the reliability of the effects (Chapter 5) and their discriminant/convergent validity, i.e. their independence or inter-dependence (Chapter 6). For instance, a significant correlation between the P3b and the Left Parietal effect would suggest that the two temporally overlapping effects may be influencing or confounding each other. Conversely, an absence of a relationship between the investigated effects would instead suggest (with all the cautions necessary in interpreting null results) that in spite of the temporal overlap they represent

independent measures of neural activity. Targeted studies were then carried out to further investigate validity of the effects of interest. Specifically, since the correlational study revealed correlations between the P3b and the Left-Parietal effect but not between the P3b and the N400 or between the Left-Parietal effect and the N400, the follow-up studies were then designed to:

1. Further investigate if the P3b and the Left parietal effect may be influencing or confounding each other by assessing if the Left-Parietal effect is sensitive to probability similarly to the P3b (Chapter 7).

2. Investigate the N400's validity by assessing its sensitivity to changes in degrees of association, while keeping semantic relatedness constant (Chapter 8). If the effect is modulated by changes in degree of association even when semantic relatedness is kept constant, then the typical conceptual labels applied over the N400 describing the effect as a measure of semantic processing may need to be revised.

3. Once assessed the N400 effect's sensitivity to association relationships, we explored (Chapter 9) the possible overlap between the N400 and the Bilateral Frontal old/new Effect (a neural correlate of episodic familiarity, see Chapters 2 & 4). Some researchers have in fact argued that the two effects are indistinguishable and therefore reflect the same underlying process.

4. As a corollary, the experiment described in Chapter 9 also allowed refining the conceptual label applied over the Bilateral Frontal effect as a measure of episodic familiarity.

Summarizing, Chapters 2, 3 and 4 describe the ERP effects explored in the current thesis: the N400 effect, the P3b effect and the Left-Parietal effect. Chapters 5, 6, 7, 8 and 9 present the empirical results of the experiments carried out in the current work. Specifically, Chapter 5 focuses on inter-laboratory and inter-individual reliability of the three effects of interest; Chapters 6 and 7 focus on the validity of the P3b and the Left Parietal effect; Chapters 8 and 9 focus instead on what the N400 effect is (Chapter 8), and is not (Chapter 9) a measure of, therefore refining current perspectives on its validity. Chapter 10 summarizes all empirical results and describes possible theoretical implications.

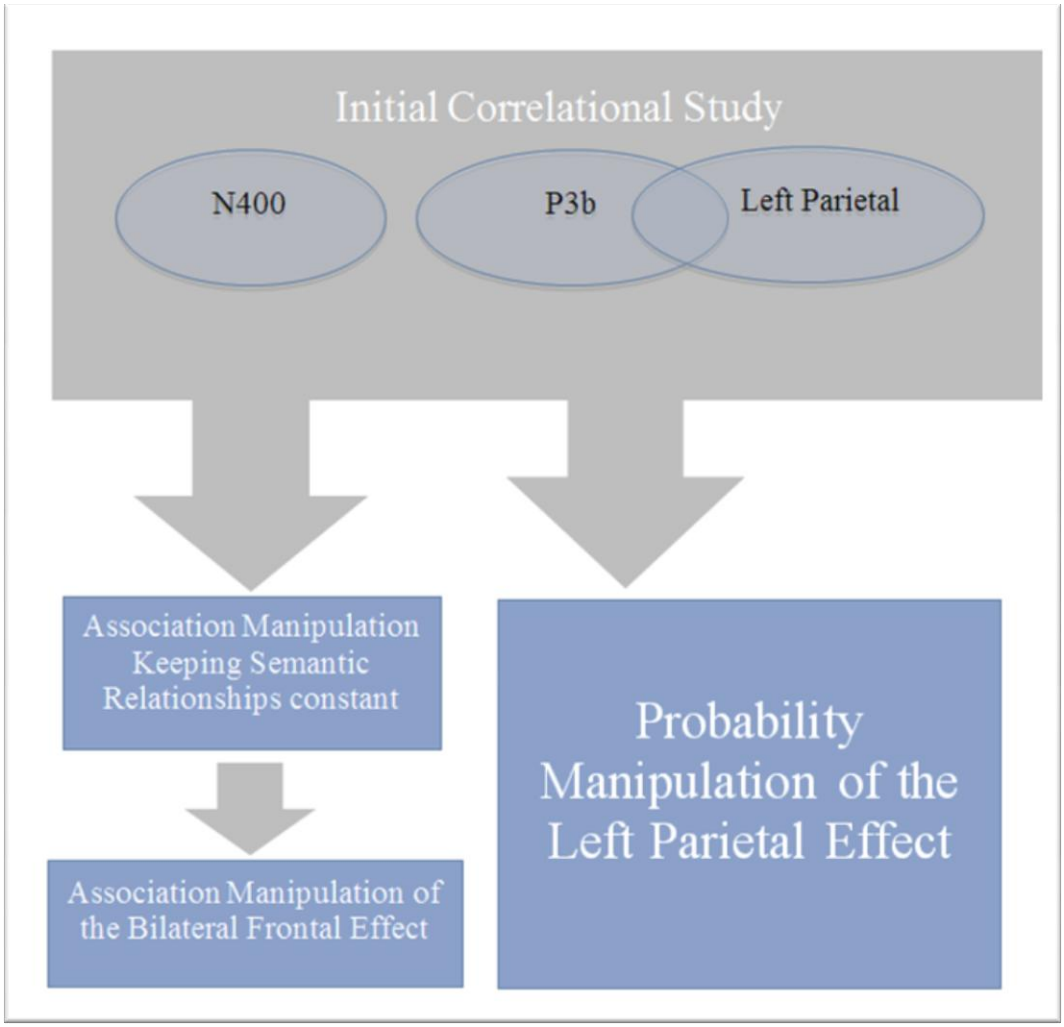


Figure 2 The diagram shows the experiments carried out within the current thesis. The initial correlational study yielded a significant correlation between the P3b and the Left Parietal effect but not between the P3b and the N400 or the Left Parietal effect and the N400. Following up on the initial study, a probability manipulation of the Left Parietal effect was carried out to investigate if the old/new effect is sensitive to probability changes similarly to the P3b. The N400 effect, found to be unrelated to the P3b and the Left-Parietal effect in the initial correlational study, was investigated by manipulating association relationships while keeping constant semantic relationships, to investigate if the effect can be elicited solely by associations – and therefore refining its validity by showing the effect is not a measure of semantic processing. Finally, the same association norms were used in an old/new recognition experiment to assess if the Bilateral-Frontal old/new effect behaves in reaction to associative relationships similarly or differently from the N400, to assess if the N400 is only a measure of association relationships or also a measure of familiarity memory.

Chapter 1

Event Related Potentials

As the current thesis focuses on the validity and reliability of some of the most widely studied late Event Related Potential effects, we will briefly introduce Electroencephalography and the relationship between Electroencephalography and Event Related Potentials (ERPs). We will also give an overview on ERP data analysis before directly addressing the reliability and validity of the ERP effects of interest.

1.1 Neural Origins of ERPs

Electroencephalography (EEG) has proven to be a fundamental tool in investigating brain activity and its relation to behaviour and cognition (Swartz & Goldensohn, 1998). The first measurements were carried out by Hans Berger (Berger, 1969) and throughout the last century the nature of the EEG signal has been extensively investigated. We now understand that EEG is a measure of brain activity typically originating from electrical dipoles produced by large populations of pyramidal neurons. However, EEG measures do not allow the experimenter to make inferences about how the brain responds to specific stimuli. To achieve that goal, scientists started

measuring Event Related Potentials (ERPs). ERPs are obtained by time-locking EEG activity to the presentation of stimuli and investigating the average neural response to many presentations. The electrophysiological response obtained is a waveform depicting changes in voltage overtime that are reliably associated with the specific event of interest.

The ERP technique has allowed a vast amount of research to be carried out in many domains, and the high temporal resolution – in the order of the millisecond – makes ERPs important in investigating moment-to-moment changes in brain activity, since brain activity itself takes place at the millisecond speed. The purpose of this chapter is to describe how neurons generate the electrical activity that is measurable at the scalp, to describe EEG measurements and the ERP technique, and to show how ERP data are analyzed and interpreted. Finally, the concepts of reliability and validity, core elements of the current thesis, will be discussed in relation to ERP measurements.

1.1.1 Neurons and synapses

The neurosciences, considered as a subset of biological sciences, have investigated the fundamental constituents of the nervous system (Glickstein, 2006). Specifically, an important assumption underlying modern neuroscience is that neurons, the cells comprising the nervous system, are the basic building blocks - both from a structural and a functional perspective (Cajal, 1909). The structure of a neuron typically

comprises a body (also described as “soma”), “dendrites” and an “axon”. The soma is the part of the neuron that contains the nucleus and where protein synthesis occurs. The dendrites are branched projections of the neuron responsible for conducting into the soma stimulation originating from other neurons. By contrast the axon is a single projection, originating from the soma, responsible for conducting stimulation to other neurons (see Figure 1.1).

Neurons are linked to each other via an intercellular space called "synapse" that typically connects the axon of the presynaptic neuron with the dendrites of the postsynaptic neuron (e.g. Palay, 1956). The pre-synaptic neuron may send an excitatory or an inhibitory signal to the post synaptic neuron, and typically different neurotransmitters (molecules generated within the soma and released at the synaptic button at the end of the axon) have excitatory or inhibitory functions (e.g. glutamate is a typical excitatory neurotransmitter while GABA is an inhibitory neurotransmitter (e.g. Mattson & Kater, 1989). The neural dendrites are extensively branched and receive excitatory or inhibitory signals from many presynaptic neurons. When excitatory or inhibitory neurotransmitters enter the synaptic cleft, they reach receptors on the dendritic membrane of the postsynaptic neuron (e.g. AMPA receptors) and determine variations in the post-synaptic potential. When variations in the post-synaptic potentials exceed a specific threshold neuronal depolarization occurs, leading to an action potential (e.g. Giuliodori & Zuccolilli, 2004).

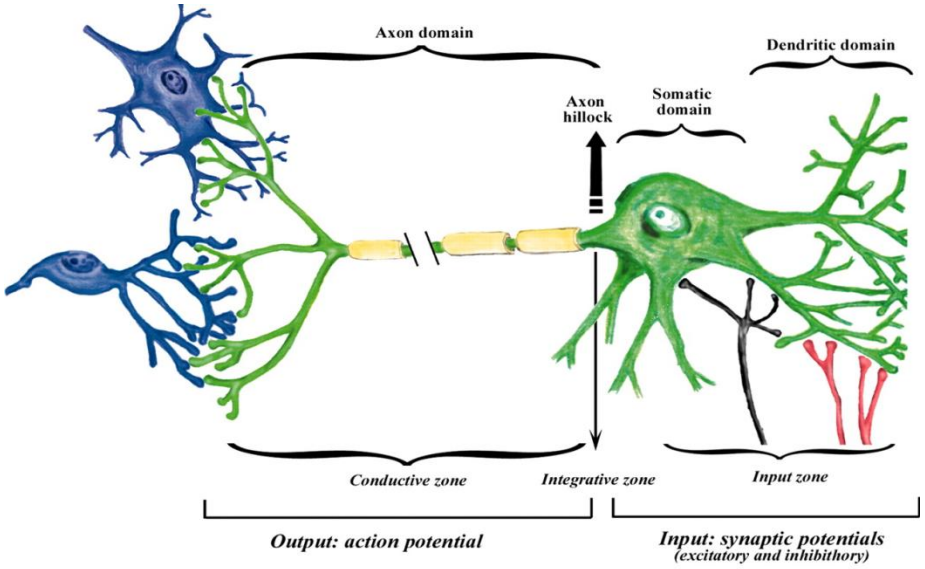


Figure 1.1 The structure of a neuron with dendrites, a soma and an axon. The figure also shows multiple synaptic connections between the presynaptic neuron and the postsynaptic neurons. (Adapted from Giuliodori & Zuccolilli, 2004).

1.1.2 Generating an EEG signal

Neurons typically have a negative electrical potential (-60mV) between the inside and the outside of their cellular body, determined by the relative selectivity of the sodium-potassium "pump" (e.g. Morth et al, 2007). When depolarization takes place, sodium channels open and there is a temporary change of 100mV in electrical potential across the membrane. Concurrently, an action potential is generated. Action potentials are considered to be all-or-none expressions of brain activity, as they do not vary in intensity or magnitude. Similarly to digital means of communication, action potentials carry information via frequency or rate (e.g. Alle & Geiger, 2006). Although action potentials are a central part of neural activity, the neural activation measured by EEG

though is not the action potential, but the post-synaptic potential. Importantly the post-synaptic potentials vary continuously in their magnitude and are therefore an analogue transmission of signal (e.g. Teplan, 2002).

When active each neuron generates an electrical dipole: a difference in electric potential between the soma and the apical dendrites. The dipole generated by a single neuron, however, is too small to be detected using scalp electrodes. Simultaneous activity of a large number of neurons (thousands to millions) is required to generate a dipole measurable at the scalp level (Wood & Allison, 1981; Luck, 2005, pp. 29-31). In addition to simultaneous activation, measurement of postsynaptic potentials requires that the neurons in question be aligned with each other: many neurons with the same orientation will functionally become one dipole whose voltage affects scalp electrodes. If neurons in the same area are not oriented in the same direction, dipoles may cancel each other (Allison, Wood, & McCarthy, 1986). Also, as the distance of the neurons from the scalp electrodes increases, it becomes less likely that their activity will be measured. Thus, an EEG recording generally measures well-aligned cortical pyramidal neurons (Kutas & Dale, 1997), and changes in post-synaptic potentials from deep structures are less likely to be captured by scalp electrodes (Luck, 2005, pp. 29-31).

An important factor to be taken into account when discussing the neural origins of EEG is the electrical conductance of the structures surrounding the brain itself. The

structures between the brain and the surface electrodes are the meninges, the skull and the scalp. While the meninges and the scalp are good conductors of electric signals, the skull is not - it significantly attenuates the magnitude of the electrical signal (Koles, 1998).

1.2 Recording Brain Activity

1.2.1 Active Electrodes

EEG measures voltage differences across different sites using electrodes placed over the scalp. As the interest is on voltage differences, at least two electrodes are necessary to measure EEG: the active electrode and the reference electrode. Moreover, since the EEG will also record a certain amount of noise (e.g. due to external electromagnetic sources) a third electrode is fundamental in any basic EEG recording: the ground electrode. Oscillations in activity originating from the ground electrode will be removed by subtraction, leaving only the voltage between the two scalp electrodes of interest. The most widely adopted arrangement and naming classification for scalp electrodes is the International 10/20 system (Jasper, 1958). The international 10-20 system can be described in terms of electrodes placed on different scalp locations, from fronto-polar, frontal, centro-frontal, central, centro-parietal, parietal, parietal occipital to occipital sites (see Figure 1.2). The electrodes located closer to the midline are usually described as superior electrodes, while the electrodes located farther from the midline are termed inferior. Electrodes on the left side of the head have odd

numbers, while electrodes on the right side of the head have even numbers; electrodes on the midline are labeled with a "z" (e.g. Fz, Cz, and Cpz). In the 10/20 system electrodes are placed 10 and 20 percent of the distance from specific points of reference in the human head (nasion, inion and preauricular points). As the number of electrodes placed on the scalp increases, it is possible to discriminate with a higher spatial resolution the distribution of experimental effects over the scalp (Gevins, 1990). In many research laboratories there has been an increase over time in the number of electrodes adopting an extension of the 10/20 system, including up to 256 electrodes (Tucker, 1993).

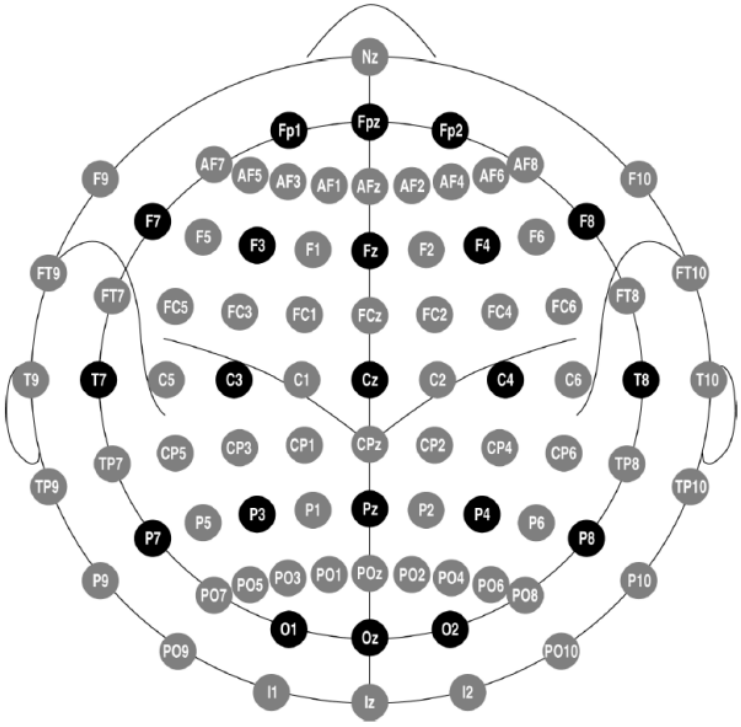


Figure 1.2 Electrodes placed over the scalp according to the International 10/20 system. Black circles indicate the position of the original 10/20 system; gray circles indicate the additional positions introduced with the 10/10 system. (Adapted from Oostenveld & Praamstra, 2001).

1.2.2 Reference Electrodes

If the experimenter is interested in measuring EEG activity from many electrodes at the same time, it is important to use a common reference electrode. The level of electrical activity measured from the reference site will contribute equally to all the other electrodes and therefore voltage differences between the active electrodes will not be influenced (Dien, 1998). Throughout the history of EEG research many reference sites have been used, and their choice depends on the specific experimental questions involved (Osselton, 1965), but typically researchers have chosen reference sites as neutral as possible: sites that do not generate a brain signal such as the ear lobes, the tip of the nose and the mastoid bones. Using the linked mastoids as a reference is a common solution within cognitive neuroscience, because it has the advantage of avoiding measuring an inflated activation in one of the two hemispheres (Miller, Lutzenberger & Elbert, 1991). Other options exist, however, such as using an average of all electrodes as a reference (Bertrand, Perrin & Pernier, 1985). Importantly, because reference sites contribute equally to all electrodes, the choice of reference will not influence the scalp distribution of ERPs.

1.2.3 Analogue to Digital Conversion

As noted above, because of its neural origins, brain activity detected by surface electrodes can be considered equivalent to an analogue signal. Modern amplifiers and computers convert the continuous analogue voltage into a discrete digital signal, allowing further processing and analysis to be carried out. The analogue signal is

sampled at a specific rate (e.g. 250Hz: one data point every 4 millisecond) that needs to be high enough to avoid aliasing (see Figure 1.3). According to the Nyquist Theorem undersampling may lead to aliasing (i.e. the digitized function does not reflect the sampled analogue function) when the sampling rate is less than twice the highest frequency in the analogue signal (Srinivasan, Tucker & Murias, 1998). By implication, the sampling rate will have to vary accordingly to the highest sampling rate present in the ERPs of interest.

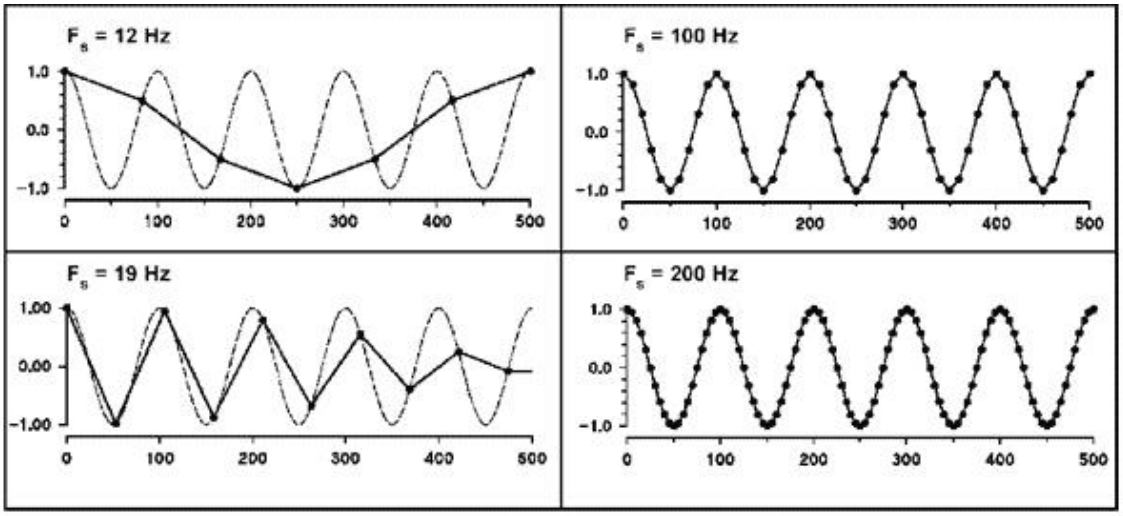


Figure 1.3 Analogue to digital conversion occurring at increasing sampling rates. The top and bottom left quadrants show aliasing due to a low sampling rate compared to the frequency of the analogue signal. The top and bottom right quadrants show adequate digital sampling.

1.2.4 Filtering

When recording brain activity the EEG data is typically filtered to decrease various sources of noise, including environmental noise and noise due to the participant

moving or sweating during the experiment (Nitschke, Miller & Cook, 1998). Typically high and low-pass filters are controlled during recording via the data acquisition software, directly by the amplifiers, or are applied as one of the post-experimental processing steps. Typical high and low-pass filters values used in neuroscientific research are 0.1Hz high pass and 40Hz low pass. These values vary necessarily as a function of the frequency of the specific ERPs to be measured. For example measurement of the early auditory brainstem ERPs requires special attention in the choice of both high and low-pass filters (e.g. see Doyle & Hyde, 1981). Similarly when investigating "slow" ERPs such as the Contingent Negative Variation the choice of high pass filter would need to be set in such a way (e.g. 0.01Hz) to avoid eliminating the frequencies of interest (e.g. see Chiu, Ambady, & Deldin, 2004).

1.3 From EEG to ERPs

1.3.1 Ocular Artifact Reduction

In the raw EEG data the neural signal is inevitably contaminated by different kinds of artifacts. The main artifacts that need to be eliminated from the EEG are muscular noise, blinks (the eye can be considered a dipole whose movements are detected by electrodes in close proximity) and electrical noise picked up by the surrounding environment (e.g. 50Hz noise). A common solution to eliminate blink artifacts is to measure blink activity during the experiment by placing electrodes below and above one of the eyes (VEOG), and to also measure activity due to horizontal eye movements

(HEOG). A correction procedure can then be applied to eliminate blink artifacts. The procedures involved typically employ a regression technique to compute regression coefficients for each electrode: a percentage of EOG activity can then be subtracted from every electrode. Typically the subtraction is more substantial at fronto-polar and frontal electrodes compared to central and parietal electrodes, reflecting the distribution over the scalp of an average blink (Lins et al., 1993). Key reasons for the prevalence of these correction procedures (Brunia et al., 1989) are 1) that they allow larger number of trials to be retained for subsequent analysis than would otherwise be the case (i.e. trials that would be otherwise rejected) and 2) they allow participants not to attend to their own blinking behaviour. A possible downside to the described subtraction techniques is however that the EOG activity removed via correction procedures may incorporate some EEG signal, and some real effects may therefore disappear with the procedure (especially when investigating frontally distributed effects).

An alternative approach to ocular artefact reduction consists in rejecting all the trials contaminated by EOG artifacts. One problem with this method is that it requires the experimenter to set a threshold for rejection of the contaminated trials. The threshold will not allow the rejection of very weak blinks (of magnitude comparable to the ERP signal) because a similar threshold would also reject ERP activation. Because of this limitation, rejecting trials contaminated by eye blinks may lead to a more subtle contamination by non-detected weak blinks (Croft & Barry, 2000). Moreover, this

approach may unintentionally lead to an arbitrary selection of a subset of trials that are not representative of the whole population – because there is a close relationship between blinking behaviour and cognition (Anthony, 1985). Another possibility consists in instructing participants not to blink, or to only blink only at set times (e.g. in between trials). This option would however super-impose another task over the often already quite complex behavioural tasks typical of experimental procedures.

Although blink artifacts are a potentially major issue it is important to recognize that they are not inherent to ERPs per se. For example if the experimenter is interested in studying ERP components occurring in the first 50ms post stimulus (e.g. brainstem evoked potentials) it is unnecessary to monitor ocular artifacts as the latency of time-locked artifacts would be longer than the epoch under consideration (Picton et al., 2000).

1.3.2 Averaging

ERP signals are relatively small compared to the typical EEG signal. EEG data is in fact very rich in variability and a large part of the EEG signal is unrelated to stimulus presentation and therefore not of interest for the experimenter. Also, extraneous sources of noise related to movements or environmental noise are a part of the EEG. All of these elements of the EEG are effectively noise that limit the experimenter from detecting the signal of interest. These limitations can be overcome by averaging

together the portions of the EEG of interest measured over multiple trials. By extracting epochs and averaging them the experimenter can increase the signal to noise ratio and make sure that the subsequent statistical analysis is not contaminated by noise and is instead focused on the subset of brain activity correlated with the experimental manipulation. Importantly, the signal to noise ratio will increase as a function of the square root of trials included in the average (Perry, 1966), so including more trials will improve the ratio, but to obtain successive increases in signal to noise ratio progressively higher number of trials will have to be added to the average.

While averaging is considered to be fundamental for increasing the signal to noise ratio, one important limitation of averaging is introduced by latency jitter (see Figure 1.4). When the latency of an ERP signal varies, averaging may lead to a substantial misrepresentation and distortion of the averaged waveform compared to the raw data (see Brazier, 1964). Another potential problem related to averaging is due to the fact that background noise can potentially be not completely random in relation to the signal. For example, participants may move slightly when stimuli from one condition (but not another) are presented, leading to the muscular artefacts to be averaged in and becoming a potential confound any subsequent statistical analysis.

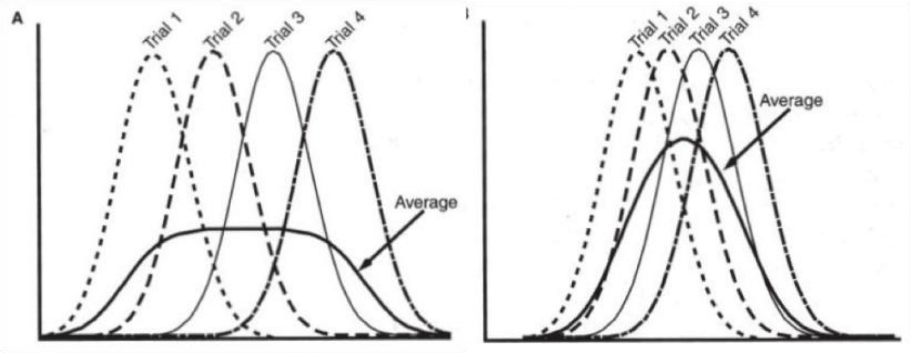


Figure 1.4 The diagrams show how latency jittering yield a distorted average waveform. Peak amplitude and latency of the average waveform do not reflect the corresponding measures of the original trials. (Adapted from Luck, 2005).

1.4 Interpreting ERPs

When ERPs have been processed the experimenter typically describes and interprets the data in relation to the initial experimental hypothesis. As ERPs are used in a wide variety of fields, descriptions and interpretations will depend on the background specific to the experimenter. Nonetheless, there are some general ways to describe ERP data that are common across fields, related to specific characteristics of the ERP components. In particular, two criteria used to describe ERPs are the latency and polarity of ERP components.

1.4.1 Components and Effects

Originally ERPs were identified based on their latency and polarity. For example, the P300 effect was named as such because its peak had positive amplitude occurring around 300ms post stimulus. Similarly, the N400 label derived from the fact that the component had a negative peak maximal 400ms after stimulus presentation. While in some cases this initial way to describe ERPs proved to be accurate and has survived to current research, in other cases the initial descriptions were found not to be entirely accurate and were adjusted. For example peak latency in the P300 was found to be variable and therefore the P300 name did not reflect accurately the described phenomenon (Luck, 2005, p. 11). The N400 component, on the other hand, was found to be remarkably consistent in terms of peak latency, independently from which procedures or modalities were used in the experiment. The "N400" label is still widely popular, while the "P300" label has been replaced by the P3a and the P3b ones, as the initial P300 component was found to be actually the summation of two subcomponents, the P3a and the P3b, distinguishable both in terms of their timing and their scalp topography (Comerchero & Polich, 1999; see Chapter 3).

Importantly, researchers found a useful way to investigate brain functions by subtracting ERPs to stimuli elicited by experimental conditions from one another. For example, in memory research the Left Parietal effect (see Chapter 4) is obtained by subtracting ERPs to correctly classified new items from ERPs to correctly recognized old items. The subtraction procedure allows for common processes occurring across

conditions to be excluded from the analysis, and to focus instead on differential processing occurring across experimental conditions. For example, subtracting ERPs to new items from ERPs to old items may help isolating the active memory function while excluding sensory-perceptual processes common across conditions. In general, 'component' is a term referred to individual waveforms while 'effect' is referred to a difference across waveforms.

1.4.2 Descriptions based on Topographical Considerations

Another way to describe ERP results relies on the specific scalp distribution of the effect. The Left-Parietal Old/New effect is an important example for the present thesis. Although the time course of the effect is important, typically occurring between 500-700ms post stimulus, the distribution of the old/new difference over the scalp – or topography – is what essentially defines the effect (e.g. Wilding, 2000). Similarly, the early Bilateral-Frontal effect – occurring prior to the Left-Parietal Effect – and the late Right-Frontal effect – occurring after – are also defined based on their topography (Allan, Wilding & Rugg, 1998; Friedman & Johnson, 2000; Rugg, 1995; Rugg & Curran, 2007).

1.4.3 Descriptions based on Procedural and Behavioural Variables

Other ERP effects, such as the Mismatch Negativity (MMN) or the Error Related Negativity (ERN) are defined in relation to procedural and behavioural variables. In

the case of the MMN the effect is defined as an early negativity (occurring 150-250ms post stimulus) following presentation of a mismatching, or deviant, stimulus compared to other standard stimuli (Näätänen et al., 2007). In the case of an auditory experiment for example, the deviant may be different from the standard stimuli in terms of its frequency (Hz). The deviant stimulus typically yields an early negativity compared to the standard stimuli, so the name of the effect reflects the relation between the procedure and typical ERP results. The ERN represents an early negativity typically detected in the ERPs at the moment when participants responded incorrectly in reaction-time tasks (Falkenstein et al., 1990; Gehring, 1992). Although the ERN is typically maximal at fronto-central areas of the scalp, the denomination of the effect is not based on its topographic distribution, but purely on the relation between behavioural and electrophysiological variables.

1.4.4 Making Inferences from ERPs

1.4.4.1 Differences in Topography and differences in Magnitude

Within the context of ERP experiments there are two ways in which positive results are typically interpreted. If the difference in the experimental effect across conditions entails the topographic distribution (and if this difference survives further analysis with rescaled data, McCarthy & Wood, 1985), then the experimenter can assume different neural generators being responsible for the two topographies (or at the very least that there are differences in the relative contributions of a common set of generators, e.g. Wilding, 2006). If, on the other hand, the topography of the effect is consistent across

experimental conditions, but the magnitude of the effect differs, then the experimenter can conclude that the same neural generators are differentially involved across conditions. It is important to note, however, that absence of differences, both in topography and magnitude, are hard to interpret because they may be due to a lack of statistical power, an inadequate statistical analysis or to the fact that EEG/ERP measures only detect a subset of brain activity.

1.4.4.2 Time-course of the Effects

Another factor that plays an important part in interpreting ERP data is the timing of the effects. In fact, both topographic and magnitude differences considered above may also involve the timing factor. If, for example, one of two topographies occurs later than another or, in the case of the magnitude difference, if, for example, the effect with lower magnitude occurs earlier than the effect with higher magnitude. In that specific case, given equal topography but different timing and magnitude across conditions, the experimenter could make inferences about the reason why the same set of neural generators are involved differentially at different points in time.

The time course of different ERP effects may also overlap in time. Consequently, to avoid possible confounds, ERP researchers try to develop experimental procedures that allow for a clean temporal separation of different experimental components and effects. One example relevant to the current thesis is represented by the P3b

component, a very large amplitude component whose presence may mask other, smaller components such as the N400. In priming experiments, for example, researchers have developed a specific procedure (e.g. see Hill, 2005) that postpones responding to a specific target until a subsequent probe has appeared. This allows the N400 component to be measured after the target because the P3b occurs after the probe; if the N400 and P3b were allowed to overlap in time the P3b would completely overshadow the N400 (see also Chapter 8).

1.4.4.3 Source Location

There is one kind of inference that the ERP researcher cannot safely make about ERP data relating to localization of the source generating the effect. In fact, given that a specific scalp distribution can originate from a potentially infinite number of combinations of sources, it is not possible to deduce what neural generators are involved (Helmholtz, 1853). Typically when ERP researchers apply source localizations algorithms to their data they also have to introduce a number of parameters about the supposed location of the generators themselves (Luck, 2005). To some degree this (necessary) input from the experimenter renders the subsequent analysis to some degree subjective and influenced by the experimenter's assumptions/perspective. Moreover, because of the fact that the same topography could theoretically be determined by an infinite number of sets of generators, an important cautionary comment is warranted. If two topographies are consistent with one another, both visually and statistically, it does not necessarily imply that the effect

has been generated by the same neural populations across conditions – because different sets of generators can potentially lead to the same topography.

1.4.4.4 Statistical Analyses

Once averaged ERPs are formed the waveforms are compared using statistical tests, allowing the magnitude and topography of any ERP differences to be characterized. Typically the experimenter will first decide which specific dimension of the ERPs to analyse (e.g. differences in mean amplitude, in peak amplitude, in peak to peak amplitude or in peak latency). Within the cognitive domain the most common approach is analysis of mean amplitudes within a specific time-window (because peaks are not always reliably measurable at the individual level). There are however some cases though in which peak measures are most prevalent, as in the case of the P3b, whose peak latency has been extensively investigated in relation to a large number of independent variables (Polich, 2007). The choice of mean amplitude measures is especially important when investigating slow components (e.g. the Contingent Negative Variation, the Lateralized Readiness Potential, the Left Parietal old/new effect) in which there are usually no detectable peaks.

Event Related Potential data are typically analysed by means of repeated measures ANOVAs. In particular, it is common to investigate the distribution of the effect over the scalp by including a factor of location (where each location represents a horizontal

chain of electrodes from frontal to parietal sites) that allows, for example, assessing whether an effect is frontally distributed or parietally distributed, or perhaps evenly distributed over the scalp. Similarly, distributional patterns are assessed using the factor of hemisphere, which allows an effect to be described as symmetrical or asymmetrical over the scalp. In general, choice of factors to include in the ANOVA depends on the specific distribution of the ERP effect, and should allow the experimenter to describing the effects in the most accurate way. For example, the factor "hemisphere" is fundamental in assessing effects whose distribution is typically asymmetrical (e.g. the Left-Parietal old/new effect).

As mentioned earlier, topographic analyses represent an attempt to discern qualitative differences across conditions in the distribution of the effect over the scalp. This assessment is complicated by the fact that differences in dipole strength are multiplicative, while ANOVAs are based on an additive model, potentially leading to differences in magnitude to be mistaken for differences in topography. For example, a condition by location interaction may in fact be the outcome of the same neural generators being differentially activated across conditions. To avoid this possibility, the condition by location interaction can be followed by a similar analysis carried out using rescaled data that are normalized to minimize the multiplicative effect (McCarthy & Wood, 1985).

1.5 Reliability and Validity of ERPs

1.5.1 Reliability of ERPs

Within ERP research there are have been many studies reporting the reliability of ERP components and effects (e.g. Pekkonen, Rinne & Naatanen, 1995; Roth et al., 1975; Kuperman et al., 1995; Alexander et al., 1994; Gasser, Bacher & Steinberg, 1985; Tello et al., 2010; Segalowitz & Barnes, 1993; Segalowitz et al., 2010). For instance, ERP research has shown that the auditory N1 (a negative deflection occurring approximately 100ms post-stimulus) has high replicability (Roth et al., 1975). Another study was carried out by two separate laboratories in Germany investigating reliability of the early ERP components involved in visual information processing (Busch et al., 2006), with results showing consistency across laboratories with respect to both latency and topography of the ERP effects.

Kuperman and colleagues (1995) assessed reliability of ERP data across six different research centers to be able to pool data together in the creation of large data sets. The N400 effect was chosen by the authors to carry out the reliability assessment and, except for the participants and the experimenters, everything else in the experiment was kept constant. More specifically all the laboratories involved used the same type of cap, amplifier, acquisition hardware and software. Analysis of the ERP data across laboratories did not reveal significant differences across conditions (see Chapter 2 for further details). A similar multi-centre comparison (Alexander et al., 1994) using the

P3b as the ERP effect to be compared across locations yielded similar results across experimental locations (see Chapter 3 for further details).

In general there are three main goals to achieve when assessing the reliability of ERP results across laboratories (Kuperman et al., 1995).

- The results from each test should not differ significantly from each other
- The overall shapes of the waveforms from each of the tests should be similar
- The designed paradigm should produce components and effects that are analogous to those seen in other investigations in the ERP literature.

If the reliability investigation involves examining the same effect across different laboratories – as in the current thesis – the experimenter should assess if the effect being investigated is topographically consistent with descriptions of the effect in the literature (e.g. in the case of the N400 effect elicited with written stimuli there should be a centro-parietal maximum validated by a significant Condition x Location interaction) within a time window similar to the ones used traditionally (e.g. 300-500ms post stimulus in the case of the N400 effect, see Chapters 2 & 8). Importantly, this topographic characterization within a time-window compatible with previous established research should be consistent across laboratories. After topographic reliability has been assessed, the experimenter should also evaluate if the magnitude of the effect is consistent across laboratories.

1.5.2 Inter-individual reliability: the example of the Mismatch Negativity

Inter-individual reliability of ERPs – the consistency of ERP effects across individuals – was investigated by Pekkonen and colleagues (1995) within the context of a Mismatch Negativity (MMN) experiment. The MMN is considered to reflect automatic stimulus discrimination (Näätänen, 1992). While the effect showed high overall stability, a large variation of the MMN amplitude was found across individuals. Inter-subjective variability is considered to be due to the underlying physiological fact that each individual has a specific folding pattern of the cortex (and the mapping of specific functions to specific areas also varies across participants). The specific cortical folding pattern in each individual will necessarily influence the alignment and direction of the electrical dipoles measured by ERPs, and consequently the shape of the waveforms and the size of the experimental effect may vary considerably across individuals (Luck, 2005. pp. 17-20).

1.5.3 Validity of ERPs

When assessing the validity of ERP measures, the goal of the experimenter is to evaluate if the ERP measure is actually quantifying what it is supposed to quantify. In practice, however, there are a number of strategies that can be adopted when assessing the validity of ERP effects. One strategy consists of finding correlations with other variables that have already been subjected to a validation process. For example, correlations with behavioural variables often serve this purpose. In that case validity is

assessed by comparing different levels of analysis. Another possibility is validating an ERP effect by comparing it with other established ERP effects whose validity has already been assessed. Similarities in the time-course, waveform shape and topographical distributions may point towards similarities in the processes involved, especially if in both cases there is also a correlation with behavioural variables.

Validation in neuroscientific research proceeds by successive approximation: often what an effect *is* deduced by excluding what an effect *is not*, given the previous literature. New experiments are often designed to limit the interpretative scope with regards to an effect: by excluding some interpretations the interpretations that are still standing will be stronger. For example, to answer the questions: "does the Left-Parietal effect measure recollection?", or "is the amplitude of the P3b a measure of stimulus categorization?", it is therefore necessary to gradually exclude alternative hypothesis and refine *how* the effects measure what they measure.

1.5.3.1 Example: Validating the Mismatch Negativity

An interesting example of validation of an ERP effect is represented by the Mismatch Negativity (MMN). The mismatch negativity, considered to be an automatic form of discrimination occurring in the auditory cortices, has been deeply investigated to understand exactly what kind of discrimination it is correlated with. Does it measure a relatively simple form of memory present in the auditory cortices and, if so, is this

form of memory dependent on the physical characteristics of the stimuli or on their relative probability? As MMN experiments typically involve the presentation of standard stimuli (high probability) intermixed with deviant stimuli (low probability), experimenters have tried to understand if the differential activation of auditory cortices occurred as a function of the different probabilities, or of the physical dissimilarities between standard and deviant stimuli, or was independent from those factors.

A key experiment investigating the MMN allowed excluding two of the possible interpretations. Tervaniemi and colleagues (1994) showed how the MMN did not depend on probability or physical features of the stimuli. The experiment used regularly descending pitch sequences intermixed with an ascending tone. The MMN negativity was present in the contrast between ERPs to descending pitch stimuli with ERPs to the deviant ascending tone, independent of the probability or physical features of the stimuli. Those results suggest that the MMN is sensitive to deviations to preceding stimulation, even when the preceding stimulation constitutes an "abstract rule", such as a descending sequence of tones. The validation process used to examine the MMN led to the conclusion that the effect is the product of a discrimination process where the deviant stimulus is incongruent with the memory representation of the preceding stimulation (Naatanen et al., 2007), regardless of the probability or the physical characteristics of the deviant. More generally this example illustrates the importance of a gradual exclusion of alternative hypothesis when investigating what an experimental effect is actually measuring. Similarly in the current work we

investigated what the N400 effect is and is not a measure of, by showing the effect's sensitivity to association relationships when semantic relationships are kept constant (Chapter 8) and excluding the possibility that the N400 effect and the Bilateral Frontal old/new effect reflect the same underlying phenomenon (Chapter 9).

1.5.3.2 From validation to Application

When the validity of an ERP effect has been assessed, the effect can then be used in applied and clinical settings, for example, as a diagnostic tool. Assessing the validity of ERP measurement is therefore a necessary prerequisite before the measure of interest reaches clinical and other applied domains. Importantly, however, the validity of an ERP measure is necessary but not sufficient in assessing its utility in applied settings (similarly to reliability being a necessary but not sufficient prerequisite for validity). The degree of importance of an ERP measure within the applied domain will be a function of many factors, including for example how the ERP measure discriminates between clinical and non-clinical populations, how reliable the ERP measure is at an individual level.

Importantly, reliability of ERPs at the individual level is a fundamental criterion in assessing if an ERP measure can be used as a diagnostic tool. If an ERP effect is not reliably seen at the individual level, but is seen only at the group level, it cannot be included by clinicians among their diagnostic tools. Results presented in Chapter 5 and

further discussed in Chapter 10 suggest that amongst the three effects investigated in the current thesis, the N400 effect and the P3b effect are reliably seen at the individual level and can have potential applied and clinical applications, while the Left Parietal old/new effect is measured reliably only at the group level.

1.6 Summary

ERPs are the product of postsynaptic potentials reliably associated with experimental stimuli of interest, originating mainly from cortical pyramidal neurons. ERPs are extracted from the raw EEG, measured by placing electrodes over the surface of the scalp while participants perform experimental tasks. Once the raw EEG is digitized, filtered and artifacts are removed the stimulus-locked sections of the EEG are averaged to obtain waveforms reliably concomitant with experimental stimulation. Using this approach the experimenter is able to compare different experimental conditions and examine specific ERP effects. Critically, differences may reveal useful information about the underlying processes engaged during task performance.

Validation of what an ERP effect is a measure (or an index) of may be achieved by finding correlations across experimental effects (e.g. see Chapter 6) or with already validated behavioural variables, morphological similarities with other validated ERP effects and, more generally, by designing experiments to gradually exclude alternative

hypothesis about what the effect may be a measure of (e.g. see Chapters 8 & 9). However, whilst validity assessments are dependent on the reliability of measurement tools, reliability itself does not imply validity. Critically, it is only once both reliability and validity of ERPs have been assessed that the effects can become useful tools in applied and clinical settings. In the ERP literature studies of reliability have typically focused on the reliability of ERP effects across laboratories and within laboratory, and when inter-individual reliability was investigated (e.g. Pekkonen et al., 1995) it was not investigated across effects. To our knowledge, inter-individual reliability of ERPs has yet to be investigated within the same pool of participants on a range of established effects representing different cognitive functions (see Chapter 5).

Chapter 2

The N400 Effect

The N400 is one of the three late ERP effects investigated in the current thesis. Enormous amounts of research on the effect have been carried out since its discovery in 1980 but, as for to the P3b and the Left Parietal Effect (described in Chapters 3 & 4, respectively), some questions remain about what the effect is actually measuring. The purpose of the current chapter is to describe factors influencing the N400 effect and to review existing perspectives on its validity and reliability, providing a context for the experimental accounts described in Chapters 5, 8 & 9.

2.1 What is the N400 effect?

The N400 effect is a modulation of the N400 component obtained originally by contrasting ERPs to congruous sentence endings with ERPs to incongruous endings (Kutas & Hillyard, 1980, see Figure 2.1). Specifically, the incongruous ending was found to elicit a relative negativity compared to the congruous ending, and this difference was named the N400 effect. Topographically the effect has a broad distribution, maximal over centro-parietal electrodes with written words (see Figure

2.2) and more frontally distributed with pictures. The effect onsets around 200-250ms post stimulus in experiments with written stimuli. Experiments with auditory stimuli have shown an earlier onset (e.g. Anderson & Holcomb, 1995; Holcomb & Neville, 1991), but in general the N400 effect's timing, maximal within the 300-500ms interval, is remarkably stable across a variety of procedures (e.g., Kutas & Hillyard, 1980; Van Berkum, Hagoort, & Brown, 1999).

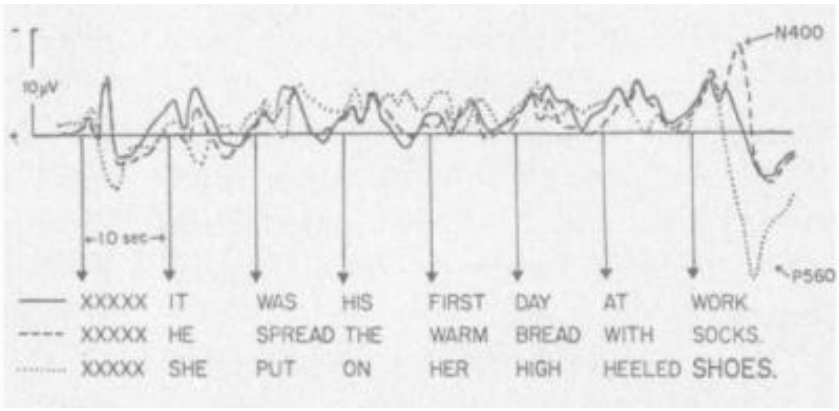


Figure 2.1 The graph, representing a grand average of ERPs across participants, shows the timing of word presentation for three sample sentences composed of seven words. An N400 effect was obtained by contrasting ERPs to congruous sentence endings (solid line) with ERPs to incongruous endings (dashed line). The dotted line represents instead ERPs to words within a sentence ending with a physically deviant word. Negative is plotted up. (Adapted from Kutas & Hillyard, 1980).

Linguistic experiments with the N400 have been performed not only with spoken and written words, but with a variety of stimuli including sign language, drawings, pictures and sounds (Kutas, Neville, & Holcomb, 1987; Holcomb & Neville, 1990; Federmeier & Kutas, 2001; McPherson & Holcomb, 1999; Van Petten & Rheinfelder, 1995; Kutas

& Federmeier, 2011; Chao, Nielsen-Bohlman, & Knight, 1995; Ganis & Kutas, 2003; Ganis et al., 1996; Nigam, Hoffman, & Simons, 1992).

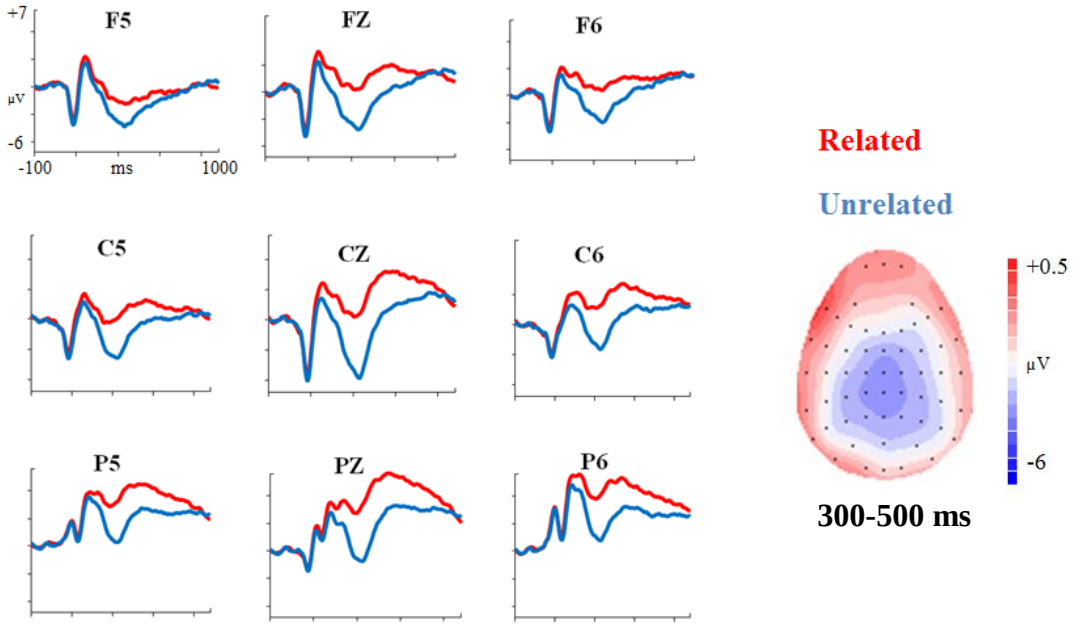


Figure 2.2 Example N400 effect obtained in a semantic priming experiment with written word-pairs by contrasting ERPs elicited by related targets to ERPs elicited by unrelated targets. The waveforms and the topographic map show the centro-parietal distribution of the effect in the 300-500ms time-window.

2.2 Factors influencing the N400

2.2.1 Amplitude

The amplitude of the N400 has been found to be influenced by a number of factors. A strong predictor of N400 amplitude in experiments using sentences as stimulus

material is "cloze probability", that is the percentage of experimental participants mentioning a word as the most likely to end a sentence. The higher the cloze probability, the more positive is the N400 component, and the larger is the N400 effect compared to a low cloze probability baseline (e.g. Kutas & Hillyard, 1984). In other words, a large N400 effect can be elicited by contrasting unexpected sentence endings to expected sentence endings.

As a component, the N400 can be considered a relative negativity that is more pronounced with unexpected stimulation (given the preceding context), and reduced given predictable stimulation. However, not any kind of "unexpected" stimulation has been found to elicit the N400 effect. N400 amplitude, in fact, does not appear to be influenced by grammatical errors (Kutas & Hillyard, 1983) or syntactic violations (Ainsworth-Darnell, Shulman & Boland, 1998). The kind of unexpected violation considered to be responsible for the effect is generally described as meaning-related in nature (Kutas & Federmeier, 2011).

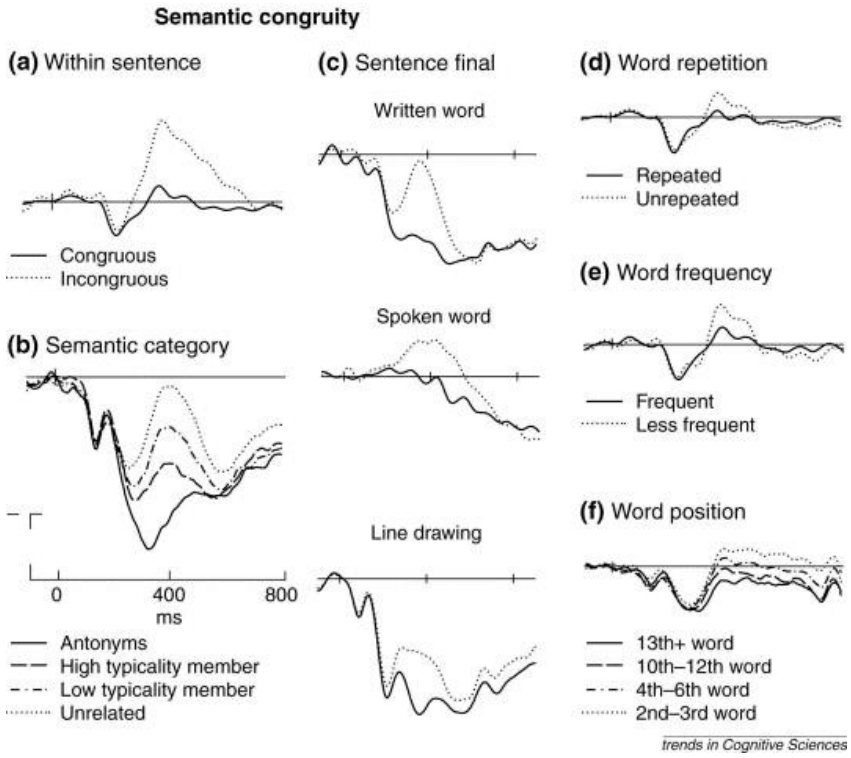


Figure 2.3 Example of variations in N400 amplitude across different experimental paradigms and stimulus materials. (Adapted from Kutas and Federmeier, 2000).

Within entirely congruent sentences, for example, the amplitude of the N400 component elicited by each of the words within a congruent sentence decreases as word position increases (Van Petten & Kutas, 1990, 1991; see Figure 2.3 for examples of N400 amplitude modulations across paradigms and stimulus materials). The amplitude of the N400 component has also been found to be larger for low-frequency compared to high-frequency words (e.g. Van Petten & Kutas, 1990), and is enhanced by tasks requiring imagery (West & Holcomb, 2000). Furthermore, words used metaphorically elicit a larger N400 component compared to words used literally

(Coulson & Van Petten, 2002; 2007). The amplitude of the N400 component is also found to be reduced by stimulus repetition (Van Petten et al., 1991; Olichney et al., 2000). Importantly, in experiments with word-pairs presented in the auditory modality, the N400 effect is sensitive to the delay between the priming and the target stimulus. Specifically, the N400 effect is larger with a Stimulus Onset Asynchrony (SOA) of 800ms compared to 0 and 200ms (Anderson & Holcomb, 1995).

The amplitude of the N400 component is also influenced by the abstract logical structure of a sentence. For example, negative sentences (e.g. X is not Y) will elicit a larger N400 peak compared to positive sentences (e.g. X is Y), regardless of whether they constitute accurate descriptions (Fischler et al., 1983). This pattern of results points to the interpretation that the N400 effect is indicative of brain responses occurring in a preliminary stage of language comprehension, where a negative sentence such as "X is not Y" is interpreted as a mismatch, even if it may actually constitute an accurate statement (e.g. "the dog is not a building"). According to Fischler and colleagues comprehension of negative statements such as "X is not Y" occurs at later processing stages compared to the 300-500ms N400 time window. While negative sentences seem to be automatically evaluated as mismatches during the N400 time-window, Figure 2.4 shows how in positive statements such as "X is Y" the N400 effect appears to index differences between true and false statements (Fischler et al., 1985), both when a behavioural response is required and when the task involves purely language comprehension.

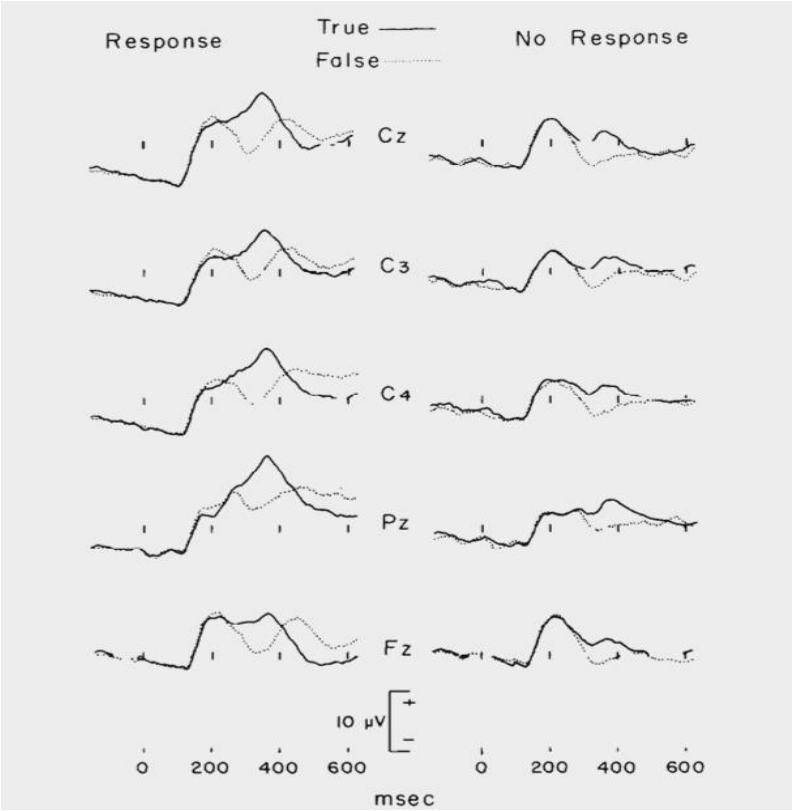


Figure 2.4 Example of N400 effects elicited by true and false statements. The column on the left shows the effect across five midline electrodes when an overt response requirement was present; the column on the right shows the effect across the same midline electrodes when no overt response requirement was present. (Adapted from Fischler et al., 1985).

2.2.2 Duration and Latency

The duration of the N400 effect is, similarly to its amplitude, influenced by procedural variables. For instance in semantic priming experiments with word pairs, the time course of the N400 effect is a function of the SOA between the prime and the target. Specifically, in an experiment with written word pairs (Anderson & Holcomb, 1995),

an SOA of 0 yielded a more temporally extended N400 effect, lasting into 500-800ms post stimulus, compared to asynchronies of 200 or 800ms; moreover an SOA of 0 yielded a later onset of the effect compared to the 200 and 800 SOA conditions.

Compared to N400 amplitude and duration, the N400 latency is typically stable across experimental procedures. However, it has been found to decrease from childhood to adulthood (Kutas & Iragui, 1998; Holcomb, Coffey, & Neville, 1992), and then to increase again in the elderly at the average rate of 2ms per year (Kutas & Iragui, 1998). Moreover, there are two interesting exceptions to the stability of the N400 latency within participants. The first is that N400 latency, in a bilingual population, is shorter for L1 compared to L2 (Ardal et al., 1990), denoting perhaps a different speed of processing in the native language compared to languages that were acquired later on in life. The second exception is revealed by experiments (Kutas, 1987) in which sentences with anomalous endings are shown with a fast rate of presentation of each word (e.g. 100ms per word), causing the effect to be delayed by 80-100ms compared to a slower presentation rate.

Effects on N400 latency have also been shown during sleep. The N400 effect is measurable during sleep, proving to some degree the relative automaticity and independence from "controlled" processes in the generation of the N400. However, during sleep the effect occurs in a later time window compared to during a wakeful

state, depending on the specific sleep stage considered. Brualla et al. (1998) recorded ERPs during a semantic priming paradigm involving presentation of word-pairs while the participants were awake and while they were asleep, during sleep stages REM and II. Importantly, N400 peak latency varied significantly between the awake condition and the sleep conditions. As can be seen from Figure 2.5, while, as expected, peak latency for the awake condition was 430ms post stimulus, for the REM condition peak latency was found to occur at 570ms post stimulus and occurred even later – 680ms post stimulus – during sleep stage II.

Not finding distributional differences across conditions, Brualla et al. suggested that the same neural generators may be active across conditions, with the experimental manipulation influencing exclusively the latency of peaks and effects. More specifically, the authors proposed that the reduction in arousal levels between the awake and sleep conditions could be responsible for the latency increase, causing the lexical processes supposedly involved in generating the N400 effect to slow down. The typical consistency of the N400 effects and peaks seen across modalities and paradigms could, then, be attributed to the relatively constant degree of arousal across modalities, procedures and experimental subjects in awake participants. After having described some of the variables influencing N400 amplitude and latency, the following section will address evidence and perspectives on the effect's validity.

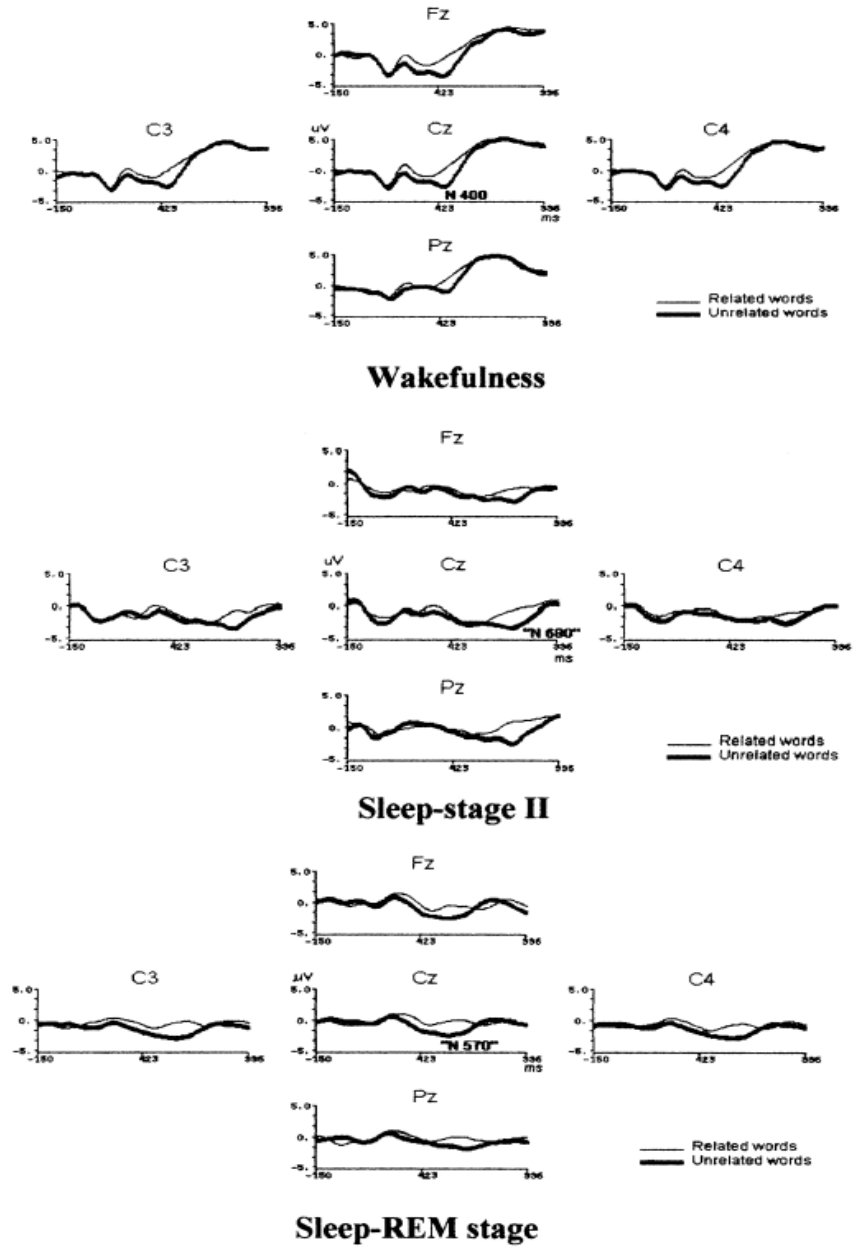


Figure 2.5 Example of variations in N400 latency across different sleep stages. The graphs show the typical N400 latency during wakefulness and a delayed onset during REM stage and especially during Sleep-stage II. (Adapted from Brualla et al., 1998).

2.3 N400 Validity

What is the N400 a measure of? Is it a measure of semantic processing, as most of the contemporary literature suggests, or is it perhaps a measure of a more general contiguity-based associative process as suggested by some recent evidence (Rhodes & Donaldson, 2008)? Does the ERP effect parallel the behavioural phenomenon of priming? Is the N400 independent from other effects occurring in the same time-window such as the Bilateral-Frontal old/new effect (also described in Chapter 5, in relation to the Left-Parietal old/new effect)? What does the clinical literature suggest in terms of the effect's validity? The following sections will attempt to answer these questions, some of them outstanding despite more than three decades of research.

2.3.1 N400 and priming

Priming experiments have shown that participants are typically slower when reacting to a word preceded by an unrelated context compared to a word preceded by a related context (Neely, 1991), where the context may be represented for instance by another word, a sentence or a picture. Typically behavioural priming and the N400 effect have been found to mirror each other, however there are important exceptions. For instance a dissociation between behavioural semantic priming and the N400 effect has been found in stimulus degradation experiments. Holcomb (1993) has, in fact, shown that in a priming procedure an experimental condition with a degraded target-stimulus yielded an increase in the size of behavioural priming effect (compared to a condition

presenting intact targets), while the N400 effect did not vary in size as a function of stimulus degradation. This pattern of results lead the author to propose that the kind of processing indexed by the size of the N400 effect is different from the priming indexed by RT data.

Another dissociation between behavioural priming and the N400 effect has been found in experiments using masked and non-masked priming (Brown & Hagoort, 1993). While a significant behavioural priming effect was measured both in the masked and the non-masked priming conditions, the N400 effect was measured only in the non-masked priming condition.

In general, while the evidence for behavioural masked priming is strong, the evidence for an N400 masked priming effect is scarce (Deacon & Shelley-Trembley, 2000), leading to the interpretation that the N400 effect requires conscious attention to be measured, while the behavioural priming effect is still measured in conditions not requiring conscious attention from the participants. Therefore if the neural generators (i.e. the neural substrates producing the signal) involved in the N400 and in behavioural priming overlap, they only overlap partially.

2.3.2 Is the N400 effect language specific?

Current reviews on the N400 effect point to the conclusion that the effect is an index of semantic processing (e.g. Kutas & Federmeier, 2011). In investigating the validity of the effect it is, of course, important to verify the accuracy of such a statement by looking at the available evidence. In fact, if the effect does not index semantic processing, many published sets of results would have to be reinterpreted.

Because of the fact that the N400 effect was discovered within the context of an experiment involving linguistic stimuli (Kutas & Hillyard, 1980, see Figure 3.1), its initial interpretation, which has had an heavy influence of subsequent research and interpretations, consisted of describing the N400 as a neural correlate of semantic processing (Kutas & Hillyard, 1984; Kutas et al., 1984; Heinze at al., 1998; Kutas & Federmeier, 2011; Federmeier & Laszlo, 2009; Luck et al., 1996; Bentin et al., 1995). The semantic interpretation of the N400 implies that linguistic stimuli, or more generally stimuli that carry a degree of semantic information, require special treatment (e.g. dedicated processing modules) at the neural level. Why would linguistic stimuli be somehow different from other forms of stimulation? One possibility is that perhaps human beings have a specific genetic predisposition for acquiring and producing language. Another possibility is that, even in absence of a specific predisposition for language, other more general human properties (e.g. the ability to learn through observation via a mirror neurons system, as discussed by Stamenov, 2002) may indirectly mediate language acquisition, comprehension and production.

The idea that human beings have a genetic linguistic predisposition was suggested by Chomsky (e.g. 1975). Chomsky proposed that natural selection has equipped humans with a Language Acquisition Device (LAD) that, via social triggers, allows the child to learn a very large number of verbal stimuli and to recombine them in novel ways without explicit training. Chomsky (e.g. 1965) also proposed the idea of inherited Universal grammar (UG) to explain syntactic regularities across languages and cultures. Both ideas have been questioned (e.g. Behme & Deacon, 2008), leading to the possibility that a second hypothesis, i.e. that human linguistic capabilities are related to a general learning process, may constitute a valid alternative in describing how human beings acquire and produce language.

If the first hypothesis is correct, then describing the N400 effect as a manifestation of a process uniquely tied to semantic processing would be justified. By contrast, if the second hypothesis is accurate the N400 can be described as an effect undoubtedly seen with linguistic stimulation, but not constrained to such forms of stimulation and, more importantly, not necessarily reflecting semantic-specific processes. In fact, while the N400 is typically interpreted as a neural correlate of semantic processing, there are reasons to think that the effect may reflect a more general process, non-specific to language.

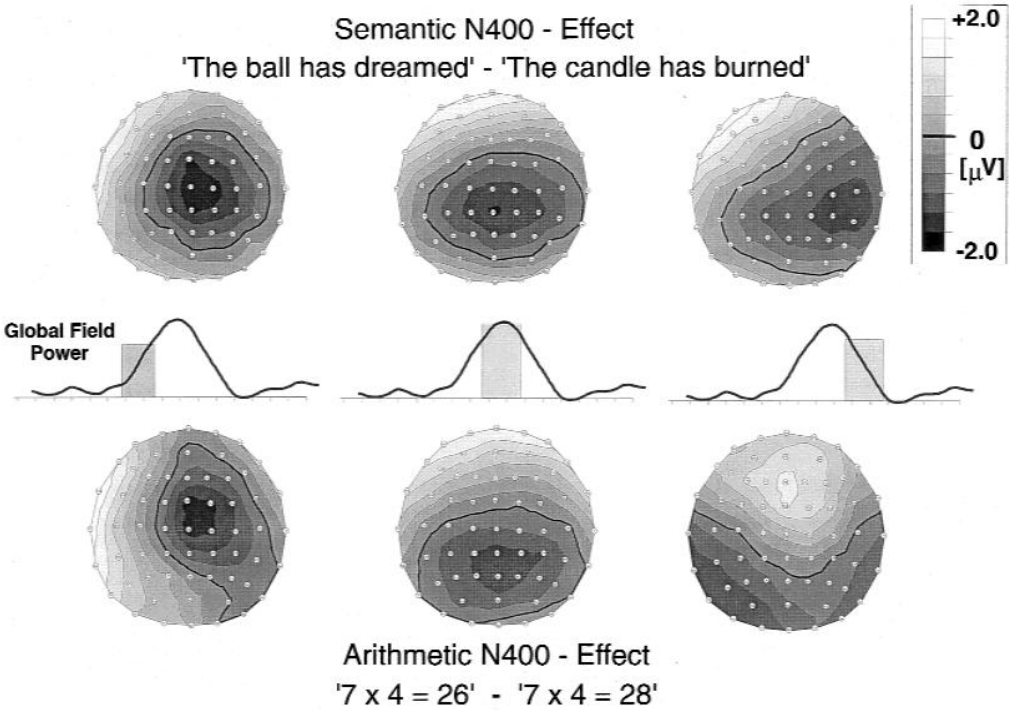


Figure 2.6 Topographic maps showing N400 effects elicited by the semantic and the arithmetic conditions during an early, a maximal and a late N400 time window. (Adapted from Niedeggen, Rosler and Jost, 1999b).

Experiments with mathematical operations (see Figure 2.6) and with intra-experimentally created associations using nonsense stimuli and trigrams have in fact shown that any contrast between associated and non-associated pairs of stimuli may lead to an N400 effect (e.g. Niedeggen, Rosler & Jost, 1999). Associations between nonsense stimuli created via matching to sample procedures lead to N400 effects, suggesting that the effect is content independent (Haimson et al., 2009; see also Barnes Holmes et al., 2005). Of course, it may still be possible to affirm that any association

implies semantic processing, but such a broad definition would raise doubts about the specificity of semantic processing and the usefulness of considering language as an independent cognitive domain, as had been suggested by Chomsky. Overall the results of the experiments described in this section point to a possible alternative interpretation of the N400 effect, described in more detail in the next section.

2.3.3 The associative hypothesis

Recent evidence from ERP studies (Rhodes & Donaldson, 2008) points directly to the fact that the N400 effect is elicited by association relationships and not semantic relationships. Indeed, if the effect is not a measure of semantic processing but instead reflects a more general associative process, then the applied and clinical studies using the N400 as a tool to measure directly language comprehension may have to be reinterpreted as studies measuring a general contiguity-based learning process relevant in many domains *including* the linguistic one. This conceptual difference may appear to be somewhat subtle, but in investigating validity it is important to be as precise as possible in describing what exactly the experimenter is measuring.

2.3.3.1 Temporal contiguity and association relationships

The associative hypothesis is supported by ERP experiments (e.g. Deacon et al., 1998) in which disruption of contiguity between prime and target eliminates the N400 effect (see also Chapter 8). Temporal proximity between stimuli has in fact been found to be

a fundamental variable in the formation of associations at several different levels of analysis, starting from the molecular level (temporal contiguity is a key variable in developing Long Term Potentiation), to a relatively elementary form of learning such as respondent conditioning (e.g. sensory preconditioning). The importance of temporal contiguity between stimuli in the formation of associations seen at different levels of analysis does not, however, necessarily point to a single contiguity-sensitive process. It suggests instead that the sensitivity to contiguity-based associations has been selected phylogenetically at different levels of analysis as an adaptive mechanism to shape neural substrates according to the regularities present in the surrounding environments. When B reliably follows A it is important to learn this association relationship, especially if the relationship has a functional consequence for the organism (e.g. stimulus A is reliably followed by a reinforcer or a punisher).

2.3.4 Clinical Evidence and Validity

After having suggested that the N400 effect could reflect a general process that goes beyond semantic processing and linguistic capabilities, it is useful to review the clinical factors affecting the N400 effect to assess if the clinical evidence is consistent with the predominant semantic-processing interpretation. One way to investigate semantic involvement in generating the N400 has been to compare clinical populations with linguistic deficits to controls. For example, the amplitude of the N400 effect has been shown to be decreased, and latency delayed, in patients who suffered a stroke in the left-temporal lobe, leading to the possibility of using the N400 effect as a tool to

quantify deficits in language comprehension (Connolly & D'Arcy, 2000; Marchand et al., 2002).

The N400 effect has also been used to investigate language comprehension deficits in patients with Broca's and Wernicke's aphasia. Patients with Wernicke's aphasia have been found to be particularly impaired in language comprehension. The impairment was assessed by Zurif et al. (1974) by showing participant triplets of words, and then asking which two out of the three words could be considered to be related. While Wernicke patients were unable to perform the task correctly, Broca patients' performance was instead close to normal. Similarly, the N400 effect has been found to be diminished in Wernicke's patients compared to Broca's patients.

The hypothesis that the N400 effect reflects linguistic processing appears also to be supported in studies investigating the heritability of linguistic deficits. The relationship between the N400 and linguistic deficiencies was investigated in fathers of children with Specific Linguistic Impairment (SLI), starting from the notion that children with SLI often have a family history of language disorders. Ors et al. (2002) found that fathers of SLI children displayed a smaller N400 effect compared to controls, suggesting either a genetic or behavioural link in the linguistic deficit across generations. Overall the clinical evidence appears to support the notion that areas of the brain involved in language comprehension are also involved in generating the

N400 effect. The described pattern of results can however be interpreted in two ways: either that language comprehension – carried out in Wernicke's area – is fundamental in the elicitation of the N400 effect, or that the areas damaged in Wernicke's patients may be involved in learning association relationships, which are in turn fundamental in linguistic capabilities. A more precise look into the neural generators involved in eliciting the N400 may help understanding if it reflects a general associative process or if it is exclusively a measure of semantic relationships.

2.3.5 Neural generators of the N400 and Validity

Reviewing the neural generators involved in eliciting the N400 effect may help answer questions related to its validity. For instance, are the areas typically involved in language comprehension and production involved in generating the N400 effect? The neural generators involved in producing the N400 effect have been studied in experiments using intracranial electrodes (typically in drug-resistant epileptic patients who may benefit from a surgical intervention) to reveal the areas where the effect originates (i.e. the parts of the brain where the largest difference in electrophysiological response is measured). An N400 similar to the one measured by surface electrodes is typically measured in the anterior portion of the Medial Temporal Lobe (aMTL). This aMTL N400 is measured by contrasting, for instance, the electrophysiological response to semantically unrelated/related words in word pairs (Nobre, Allison & McCarthy, 1994; Nobre & McCarthy, 1995). Similarly to the surface N400 the aMTL N400 is reduced by stimulus repetition (e.g., Smith, Stapleton,

& Halgren, 1986; Grunwald, Lehnertz, Heinze. Helmstaedter, & Elger, 1998). The sources of the aMTL N400 are most likely located within the rhinal cortex, specifically the perirhinal cortex (McCarthy, Nobre, Bentin, & Spencer, 1995).

It has to be considered that the medial temporal lobe is in most cases the area where electrodes are implanted in epileptic patients, as it typically contains epileptic foci, and therefore the number of studies focused on this area investigating the neural sources of the N400 may be slightly overrepresented. However, the described intracranial results are corroborated by neuropsychological evidence showing that the anterior part of the medial temporal lobe is the one involved in a measured loss of semantic knowledge known as semantic dementia (Bozat et al., 2000). FMRI data do not converge strictly with the intracranial evidence supporting the idea the aMTL constitutes one of the main neural generators of the N400, showing instead activation of a wide variety of areas, but this may be due to an overall lower signal to noise ratio in fMRI studies compared to ERP studies[1] (Van Petten & Luka, 2005). In general however, the areas involved in generating the N400 as detected by several neuroimaging techniques, appear to converge with the areas involved in semantic processing (Kutas & Federmeier, 2011).

[1] Another reason for this discrepancy is the fact that the scalp-measured N400 may, at least in part, be a function of phase resetting of ongoing oscillatory activity without an actual increase in stimulus-induced EEG power (Fell et al., 2004). Since phase resetting does not lead to an overall change in neuronal activation, it is not measurable by fMRI.

Overall, studies investigating the neural generators of the N400 suggest that the parts of the brain involved in elicitation of the N400 are responsible for semantic processing. By contrast, however, evidence described in section 2.3.1 appears to go against the semantic interpretation of the N400 in favour of an associative interpretation. Taken together, therefore, there appears to be a strong need for an experimental investigation of the N400 effect in relation to the two kinds of relationships described, and such an experimental assessment is described in Chapter 8.

2.3.6 Are the N400 and the Bilateral Frontal Effect the same effect?

A useful way to refine the validity of an ERP effect is to find out if and how it overlaps with other experimental effects. A recent debate in the ERP literature involves the possibility that the N400 and the Bilateral Frontal Effect, typically considered to be a neural correlate of familiarity memory (see Chapters 5 & 10), might reflect the same underlying neural phenomena. The Bilateral Frontal Effect, a frontally distributed difference between correctly classified old and new items in a recognition memory paradigm, occurs in fact in the same time window as the N400 effect (300-500ms post stimulus) and the distributions of the two effects can in some cases be considered to be overlapping. While the N400 effect typically has a centro-parietal distribution with words, it has in fact been shown to have a more frontal distribution with other stimulus materials, pointing to the possibility of an overlap with the topography of the Bilateral Frontal Effect.

Recently Voss and Federmeier (2010) have proposed that the Bilateral Frontal and the N400 effects both reflect semantic processing; specifically that the Bilateral Frontal Effect reflects semantic processing occurring during recognition memory procedures. These authors suggest that the two effects are similar in morphology and timing and compatible in their topographic distribution. While the N400 appears to have a centro-parietal distribution compared to the Bilateral Frontal Effect, Voss and Federmeier argue that, for example, concrete words and pictures elicit a frontal N400 comparable with the Bilateral Frontal Effect. Moreover they propose that the presence of the Left Parietal Effect (described in Chapter 5) in recognition memory paradigms, compared to its absence in language comprehension experiments, may distort the observed distribution of the N400 yielding an exceedingly frontal topography.

Voss and Federmeier also describe how in repetition experiments with a very short delay between repetitions, where familiarity memory should be maximal, the Bilateral Frontal Effect is present for meaningful stimuli but not for non-meaningful stimuli (Danker et al., 2008), further strengthening their perspective that ties together the N400 effect and the Bilateral Frontal effect. Moreover they point out that a large number of published studies do not demonstrate that the Bilateral Frontal effect is related to familiarity memory, but instead that the Bilateral Frontal Effect is *not* related to recollection (another process involved in episodic remembering and reflected by the Left Parietal old/new effect – see Chapter 5). They propose that this logical flaw has contributed to a misinterpretation of the effect. For example, Voss & Paller describe

how in the pivotal experiment by Curran (2000) a manipulation that affected the Left Parietal old/new effect (plurality reversal) did not affect the Bilateral-Frontal old/new effect, showing that the Bilateral-Frontal Effect is dissociable from the Left-Parietal old/new correlate of recollection, but not necessarily that it is a correlate of familiarity memory. Importantly, if the N400 and the Bilateral-Frontal Effect are the same phenomenon, this would suggest a possible alternative interpretation of the Bilateral-Frontal Effect, namely that it reflects a form of priming, and not a form of familiarity memory, as indeed some researchers have proposed (e.g. Paller, Voss & Boehm, 2007).

In the work currently presented we had the chance to examine the relationship between the two effects by manipulating association relationships between words within word pairs. Specifically, we had both low association and high association word-pairs in two different experiments: one a semantic priming paradigm and the other a recognition memory paradigm (see Chapters 8 & 9). Even though it is a between-subjects comparison, the results are meaningful as they show how the two ERP effects appear to behave differently (see Chapter 10 for a discussion), suggesting that the N400 does *not* reflect the same process as the Bilateral-Frontal Effect.

2.4 N400 Reliability

While the N400's validity is still subject to debate, the effect appears to be reliable – as discussed in the current section. When discussing the reliability of ERPs, it is important to take into account two forms of reliability: inter-laboratory reliability or how the effect is consistent when measured across different laboratory settings, and inter-individual reliability, or how the effect is measurable consistently across participants (see also the Introduction and Chapter 1). While N400 inter-laboratory reliability has been thoroughly assessed in the literature, its inter-individual reliability still needs to be adequately described, especially in relation to other ERP effects.

2.4.1 Inter-laboratory Reliability

Kuperman et al. (1995) carried out a thorough investigation on the inter-laboratory reliability of the N400 effect. A large number of participants took part in the study (N=90; N=15 for each of the six research laboratories involved). The study consisted of a semantic priming study involving three experimental conditions: primed words, unprimed words and non-words, with ERPs measured after target word presentation. Results (see Figure 2.7), showing electrode Cz for each of the 6 research facilities involved, reveal a broad consistency of the effect across laboratories. This study constitutes strong evidence in favor of the idea that the effect is reliable across a range of laboratories and across different samples of participants.

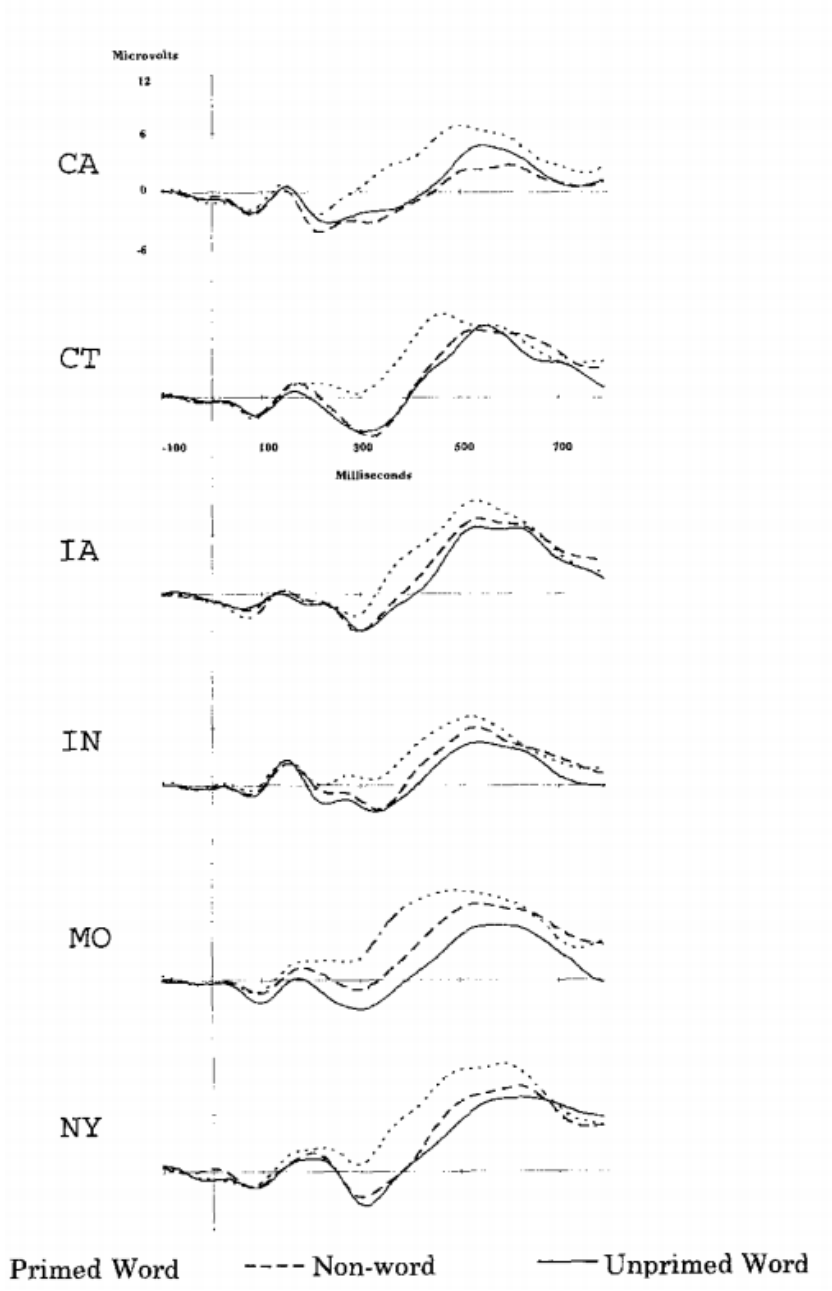


Figure 2.7 The waveforms show the N400 effect measured across the six laboratory locations involved in a reliability study. The graph shows a broad consistency of the effect across laboratories. The apparent inconsistency between the laboratory located at MO compared to the other sets of results did not prove to be statistically significant (Adapted from Kuperman et al., 1995).

2.4.2 Inter-individual Reliability

Clinical studies have shown the presence of the N400 effect in most of the participants having an intact central nervous system; the proportion of participants showing the N400 effect has been shown to decrease substantially only when severe damage had occurred. The N400 has, in fact, been shown to vary across participants with different levels of consciousness due to clinical conditions. Specifically, Shoenle and Witzke (2004) used the N400 successfully to discriminate between clinical patients in a vegetative state, in a near vegetative state and affected by severe brain damage. During the experiment patients listened to sentences with congruous or incongruous endings. An N400 effect was found in 12% of the vegetative state patients, 77% of the near vegetative state patients and 90% of the severe brain damage patients, suggesting the N400 can be used as an effective tool in assessing levels of consciousness in the absence of any behavioural forms of communication. It appears therefore that the N400 is less likely to be elicited when in a vegetative state compared to the sleeping experiments described by Brualla et al. (1998), suggesting that the N400 is a strong, reliable, component present at several degrees of consciousness as long as the brain has not reached a vegetative state due to a clinical condition.

Even though most N400 ERP studies only report group averages, some studies also show (typically a subset of) results at the single participant level. For example, Fischler et al. (1985) report individual data from five participants (shown in Figure

2.8) and all participants show an N400 effect. However, the proportion of participants showing the effect is typically not reported in N400 studies.

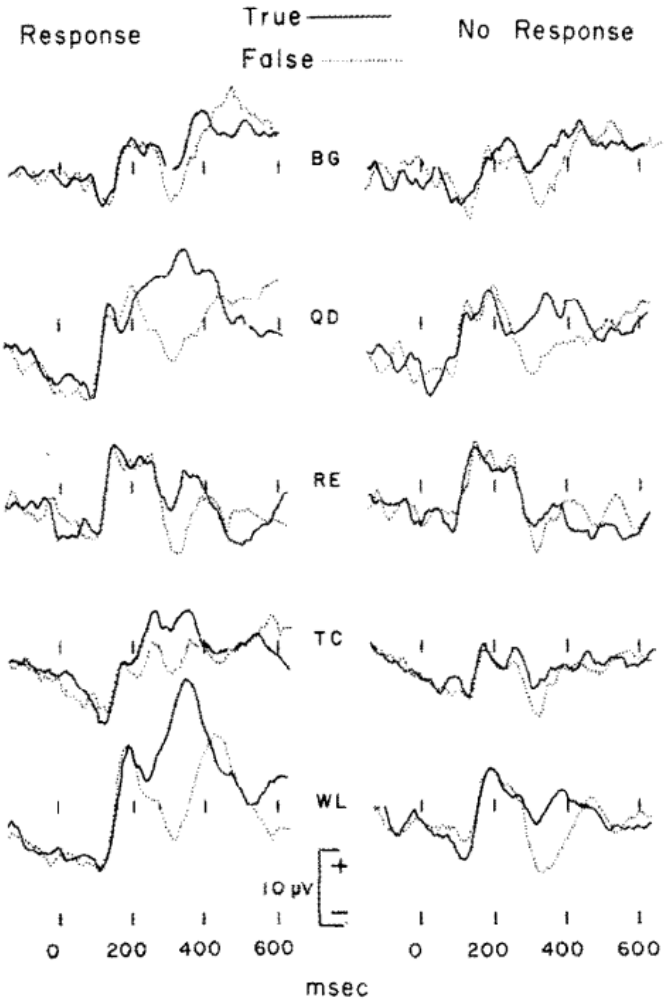


Figure 2.8 The waveforms show the N400 effect measured in five participants. Waveforms show the N400 component to be more negative for false statements compared to true statements across participants and experimental conditions (Adapted from Fishler et al., 1985).

In the current thesis we investigated N400's inter-individual reliability in a large pool of participants (N=64); importantly the effect's inter-individual reliability was compared with the reliability of the other two late ERP components investigated in the current work, the P3b and the Left Parietal Effect. Specifically, we focused (see Chapter 5) on comparing the proportion of participants showing the effect of interest across experimental effects, a kind of analysis that, as far as we are aware, has not been carried out in the previous literature.

2.5 Summary

The N400 effect is one of the most widely studied late ERP effects. Discovered in 1980 in experiments investigating language processing, its amplitude is highly sensitive to a number of factors but primarily to how expected/unexpected current stimulation is compared to the preceding context. N400 latency, even if considered relatively stable compared to its amplitude, is sensitive to factors including the rate of presentation of the experimental stimuli. However, the N400's validity is still debated. While there is a large number of researchers describing the effect as reflecting semantic processing, there is also some experimental evidence suggesting that the effect may actually reflect associative learning. This possibility is further explored in an experiment described in Chapter 8. Moreover, the N400 effect has been proposed to reflect a similar process as the process indexed by the Bilateral Frontal Effect within the same 300-500ms time window. In Chapters 9 and 10 we will further discuss the

relationship between the two effects. Chapter 5, on the other hand, will expand current perspectives on the N400 inter-individual reliability, not examined in the literature as thoroughly as its inter-laboratory reliability, especially in relation to the other effects described in the current thesis.

Chapter 3

The P3b Effect

Another late ERP effect investigated in the current thesis is the P3b effect. Similarly to the N400 effect, large amounts of research on the effect has been carried out on the P3b since its discovery, but it is not yet completely clear what the effect actually measures. The purpose of the current chapter is to describe factors influencing the P3b effect and review existent perspectives on its validity. Previous research on the P3b's inter-laboratory and inter-individual reliability will also be described.

3.1 What is the P3b effect?

Although it was originally named P300 because its peak latency occurs close to 300ms post stimulus in young adults performing a simple discrimination task, subsequent findings show that the P300 is better characterized as a group of sub-components (e.g. Jentzsch & Sommer, 2001). In the rest of the Chapter we will describe the P300 subcomponents and in particular the P3b, shown in Figure 3.1, which is distributed parietally and obtained with stimuli presented with a relatively long Inter-Stimulus Interval (ISI), and is distinguished from other centro-frontal components that are

sensitive to sequence effects and typically obtained with shorter ISIs (see also section 3.2.2).

The P300 was first discovered in 1965 when several studies reported a large positive component elicited by task relevant stimuli (Sutton et al., 1965). Importantly it also became immediately clear that the amplitude of the positive component was inversely related to the probability of the task relevant stimuli. Moreover, researchers found that participants had to attend to the stimuli for the effect to be elicited (i.e. the effect could disappear if the participant listened only passively to the train of standard and target stimuli while engaged in other activity). A number of factors have since been shown to influence the P3b, some of them procedural (e.g. probability, task relevance) and some are intrinsic to individual characteristics (e.g. clinical factors, age, intelligence), as described in the next section. Other members of the "P3 Family" such as the P3a and the no-go P3 will be discussed next, however, with the goal of reviewing the P3b's validity, i.e. understanding what the effect is a measure of in relation to other closely related components/effects. With the same goal, current interpretations of the effect will then be discussed, before the final part of this chapter assesses the effect's reliability both across laboratories and across individual participants, to provide a complete P3b background for the experimental investigation proposed in the current thesis.

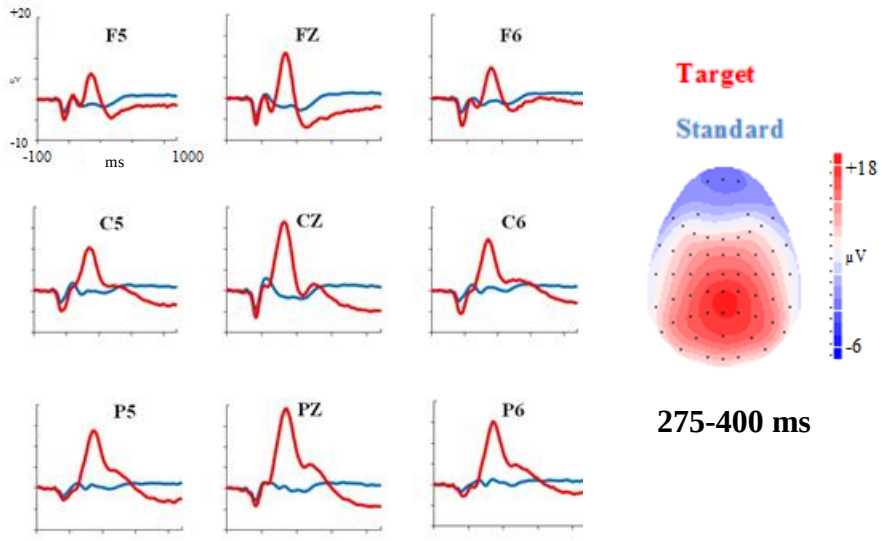


Figure 3.1 Example of P3b effect obtained in an oddball experiment with auditory stimuli, contrasting ERPs elicited by targets to ERPs elicited by standard stimuli. The waveforms and the topographic map (target minus standard) on the right show the classic parietal maximum of the effect in the 275-400ms time window (Adapted from Chapter 5).

3.2 Factors influencing the P3b effect

3.2.1 P3b Amplitude

The amplitude of the P3b effect increases as the relative probability of discriminated target stimuli decreases compared to the probability of standard stimuli[2] (see Figure

[2] Leading directly to the experimental hypothesis underlying the probability manipulation of the Left-Parietal old/new effect described in Chapter 7.

3.2). Moreover, P3b amplitude increases as the target-to-target interval increases (Gonsalvez and Polich, 2002; see Figure 3.3). Rapid stimulus presentation (while keeping target probability constant) leads in fact to an overall decrease of P3b amplitude, compared to slower rates of presentation, leading to the interpretation that attentional resource allocation may be a fundamental variable in regulating P3b amplitude (Polich, 2007).

Other work has revealed that the P3b is sensitive to "consequences" (e.g., Roger & Galand, 1981; Miltner, Larbig & Brown, 1986; Sommer, 1987; Sommer & Schweinberger, 1992). For example, Sommer and Schweinberger delivered reinforcement contingent on peaks with large amplitudes, but not to the peaks with small amplitudes, to see if amplitudes were sensitive to their consequences. In a yoked control condition, consequences were delivered randomly. Only in the condition in which reinforcement was contingent on large amplitudes did the amplitudes increase, thereby suggesting a reinforcement effect. Similarly, Miltner, Larbig and Brown (1986) reported that behavioural reaction times were significantly shorter in a condition where large amplitude P3b waves were reinforced compared to those in a condition in which small amplitude P3b waves were reinforced. Moreover, as the amplitude of the ERP response increased, reaction times decreased (see also Holm, Rantaaho, Sallinen, Karjalainen & Müller, 2006; Begleiter, Porjesz, Chou & Aunon, 1983; Donchin & Lindsley, 1966; Gonsalvez & Polich, 2002; Bahramali, Gordon, Li, Rennie, Wright & Meares, 1998).

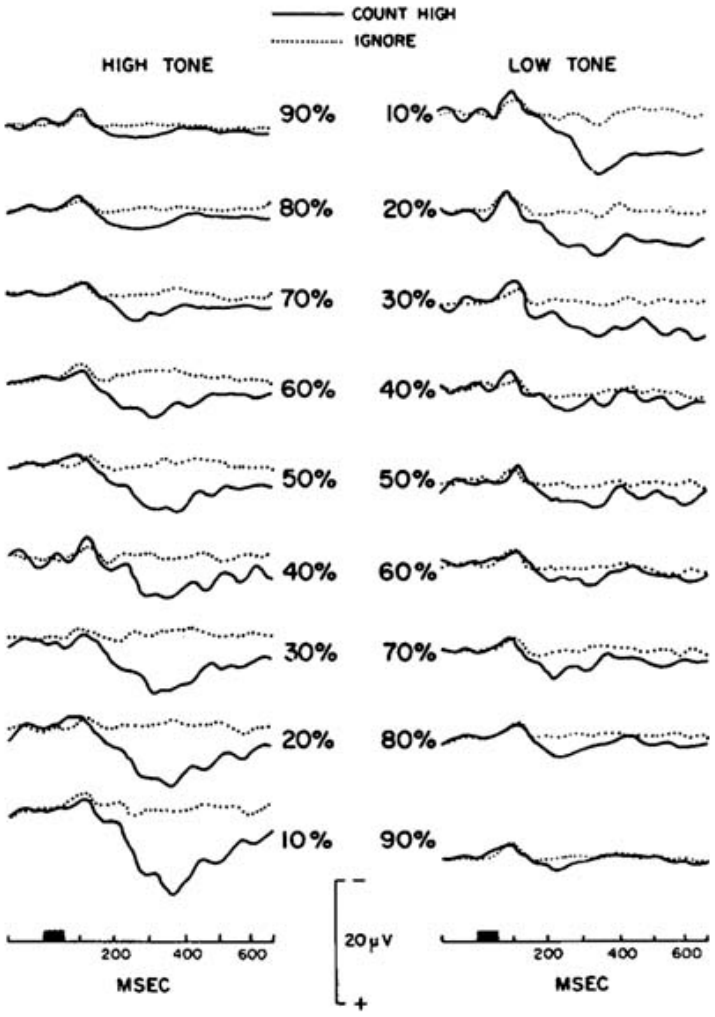


Figure 3.2 P3b Amplitude as a function of target probability. The size of the P3b clearly increases as target probability decreases (Adapted from Duncan-Johnson and Donchin, 1977).

Johnson (1986; 1988) has proposed that there are three general factors involved in determining P3b amplitude. Two of these factors, subjective probability (see also section 3.2.4) and stimulus meaning are both modulated by a third factor representing the overall amount of stimulus information transmitted. According to the model presented by Johnson (1986; 1988) the amplitude of the P3b is therefore a function of the amount of information transmitted to the participant, multiplied by the effects of subjective probability and stimulus meaning which sum together. For Johnson stimulus meaning indicates the salience that a stimulus has given its emotional content, the fact that it contains relevant feedback information and the fact that it is a target stimulus in the task.

Although Johnson accounts for the modulation of the P3b in healthy adults, clinical factors have also been found to influence P3b amplitude. For example, reliable differences have been found in P3b amplitude between Alzheimer patients and controls (Polich & Pitzer, 1999). Moreover, the effect has been used to study clinical psychiatric disorders such as alcoholism, schizophrenia and depression (e.g. Pritchard, 1986; Courchesne, 1990; McCarley et al., 1993; Begleiter & Porjesz, 1995; Bruder et al., 1995; Boutros et al., 1997). For example, the size of the P3b effect has been found to be reduced in individuals at risk of alcoholism compared to controls (Porjesz & Begleiter, 1990). The P3b is clearly reduced in alcoholic individuals but the reduction is not due to the short term effects of alcohol on the brain, as even after prolonged sobriety its reduced amplitude persists (Duncan et al., 2009).

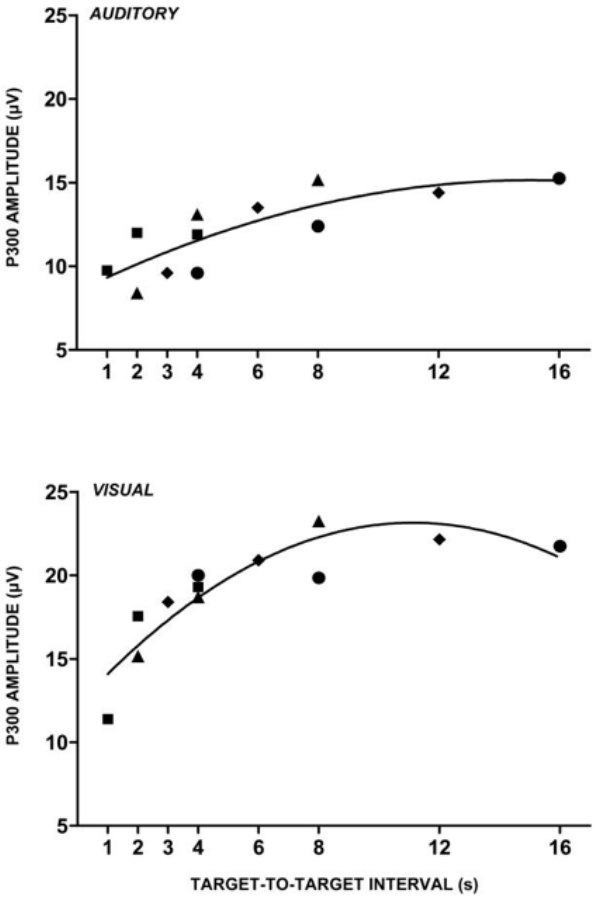


Figure 3.3 P3b Amplitude as a function of target-to-target interval. Both with auditory and visual stimulation the figures show an increase in amplitude of the P3b as target-to-target interval increases (Adapted from Gonsalvez and Polich, 2002).

Schizophrenic patients also show a reduced P3b amplitude; interestingly this reduction is seen for auditory but not for visual stimuli (Duncan et al., 1987) and is also seen in first degree unaffected family members (Price et al., 2006). Individual differences in intelligence have also been found to affect P3b amplitude, producing a correlation with fluid intelligence in an auditory discrimination experiment (De Pascalis, Varriale & Matteoli, 2007). Specifically, high ability participants displayed larger P3b amplitudes compared to lower ability participants. Higher ability participants have moreover been found to perform better at discriminating auditory pattern violations compared to lower ability participants. This superiority in performance is itself correlated with larger P3b amplitude (Sculthorpe, Stelmack & Campbell, 2009).

In sum therefore, P3b amplitude has been shown to be influenced by a number of procedural, clinical and individual factors. Among the procedural factors, subjective and objective probability of target stimuli, together with target-to-target interval, appear to be critical variables in influencing the effect's amplitude. P3b amplitude has also been found to decrease in a number of clinical conditions, including alcoholism and schizophrenia, but to increase in individuals showing a higher degree of fluid intelligence. The next section will examine factors influencing P3b latency.

3.2.2 P3b Latency

P3b latency is typically considered to reflect the timing of stimulus evaluation/categorization. Early studies suggested that P3b latency was a measure of stimulus categorization speed, uninfluenced by response selection processes (Kutas, McCarthy & Donchin, 1977; Duncan-Johnson, 1981), such that peak latency and behavioural reaction time could be manipulated independently (McCarthy & Donchin, 1981). According to this view, overt reaction times represent the summation of stimulus evaluation and response selection processes, with P3b peak latency a measure of the former but not the latter. One of the arguments typically brought in favor of this hypothesis is the fact that P3b peak latency can occur after the behavioural response, leading to the idea that the P3b could not be involved in response preparation and execution[3]. Smulders et al. (1995) studied P3b latency as a function of stimulus degradation and response complexity. Response complexity was defined by requiring in certain trials a single button press (simple condition) while requiring in other trials a specific sequence of button presses (complex condition). P3b peak latency was found to be sensitive to stimulus degradation regardless of response complexity (see Figure 3.4), further strengthening the idea that P3b Latency reflects stimulus evaluation/categorization processes independently from response selection processes.

[3] This finding (Kutas, McCarthy, & Donchin 1977) was observed especially after "error" trials, and might have been confounded by the fact that, unknown at the time, error trials are typically followed by a late error positivity (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000).

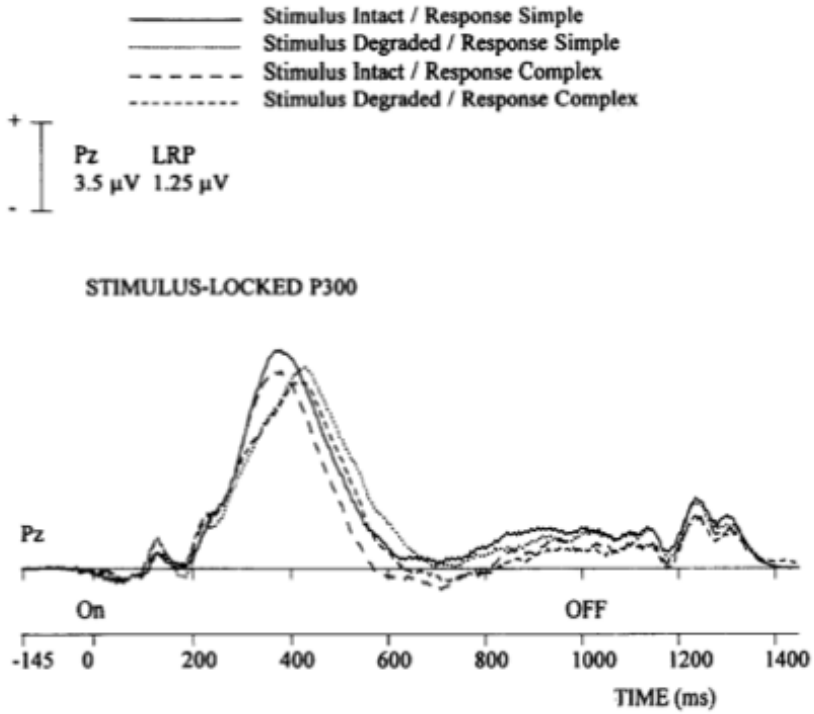


Figure 3.4 P3b Latency as a function of stimulus degradation and response complexity. The figure shows how P3b latency increases when stimuli are degraded, regardless of response requirements (Adapted from Smulders et al., 1995).

Contrary to the stimulus categorization interpretation, Verleger (1997) has described how, when responding is fast, peak latency appears to be influenced by both stimulus categorization and response selection. In fact, Verleger et al. (2005) have also suggested that the P3b may not represent an index of stimulus categorization at all, but instead it may reflect mediation between stimulus categorization and response selection. This hypothesis receives support from data showing that P3b amplitude does

not vary between response locked and stimulus locked ERPs, and that peak latency varies as a function of response speed in both stimulus and response locked ERPs. Verleger and colleagues also suggested that the P3b cannot be a measure of decision making process, because in response locked averages the P3b peak occurs approximately at the same time as the behavioural response, and therefore the moment at which the decision occurred must have been at least 100ms prior to the behavioural response (and to the P3b peak).

To complicate matters further some researchers (e.g., Hohnsbein, Falkenstein, Hoormann, & Blanke, 1991; Falkenstein, Hohnsbein, & Hoormann, 1994) have distinguished between a stimulus related P3 and a response related P3 (named P-SR and P-CR), involved in stimulus updating and response updating, respectively. Similarly to P3b amplitude, P3b latency has been found to correlate with fluid intelligence in an auditory discrimination task (Pascalis, Varriale & Matteoli, 2007). Specifically, high ability participants display shorter P3b latencies compared to lower ability participants.

Overall, P3b latency appears to be influenced by the time required to evaluate/categorize a stimulus in an experiment. When responding is fast, however, P3b latency has been found to be influenced by both stimulus categorization and response selection processes. Similarly to P3b amplitude, individuals with higher

levels of fluid intelligence show shorter P3b latencies. The next section will examine the P3b across different experimental tasks.

3.2.3 Experimental Tasks

The P3b component can be elicited in a single stimulus task, where the target stimulus is presented at varying intervals with no standard stimuli presented (see Figure 3.5). It can also be elicited in an oddball paradigm where standard and target stimuli are presented intermixed with each other (and the target is typically presented less frequently than the standard stimulus). Additionally, the P3b can also be elicited in a three stimulus paradigm, where, together with the standard and the target stimuli, infrequent distractor stimuli are also presented. In this context distractors have been found to elicit a component whose timing and distribution is different from the component elicited by target stimuli. These distractors effects occur earlier and are more anteriorly distributed compared to the P3b component elicited by targets. This distractor effect has been labeled the P3a effect (see Figure 3.5; discussed further in Section 3.3.1). Importantly, however, in all three paradigms ERPs to target stimuli (recorded in young adults) elicit a component that is maximal at parietal sites, with a peak latency of 300ms post stimulus for auditory stimuli, and 400ms for visual stimuli (Polich, 2004; Johnson, 1993).

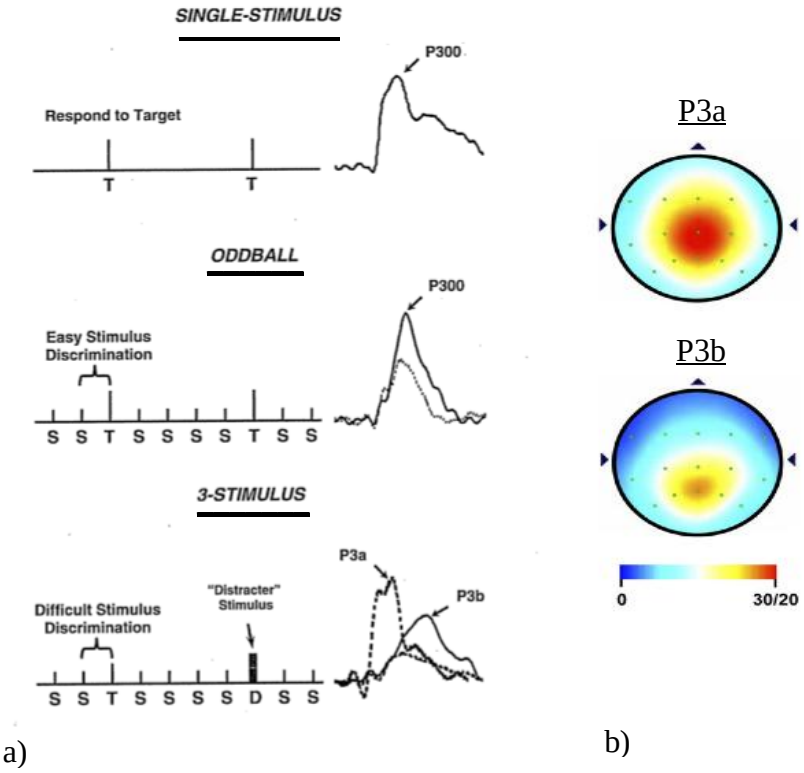


Figure 3.5 Panel a) shows an example of P3b effects obtained in three different paradigms: the single stimulus paradigm, the oddball paradigm and the 3 stimulus paradigm (Adapted from Polich, 2007). Panel b) shows differential topographic distribution of the P3a (shown at the top) and the P3b effects. The distribution of the P3a shows a central maximum while the distribution of the P3b shows a parietal maximum. (Adapted from Conroy & Polich, 2007).

3.2.4 Task Relevance

Task relevance can be described as the amount of attention an individual is paying to a form of stimulation. For example, in an oddball paradigm a P3b effect is measured when the participant is listening to the stimuli and pressing the button to the target stimulus, but might not be present if the participant is engaged in another activity such

as reading a book. Importantly, the task relevance effects and the probability effects interact with each other in such a way that, if the participant is not attending to the train of stimuli, the relative probability of standard and target items is not going to be relevant. Moreover, even when the participant is attending to the stimuli and the relative probability of target and standard stimuli is equal, ERPs to targets are still more positive than ERPs to standard stimuli, indicating that the P3b is sensitive to the task-relevance, or targetness value, of the presented stimuli (Katayama & Polich, 1996, see also Chapter 6). Mecklinger and Ullsperger (1993) carried out a study in which the stimuli were five words, all equally probable, finding that any stimulus that was defined as the target had higher P300 amplitude. Based on these findings Rosenfeld et al. (2005) conclude that stimulus categorization (and therefore target vs. non-target categorization) may play and important role in determining subjective probability and therefore in influencing P3b amplitude.

A clear example of the importance of task relevance is seen when several trains of stimuli are presented concurrently to the participant; the P3b is larger to stimuli the participant is instructed to attend to. For example, if two separate trains of stimuli are presented in the left and the right ear, both of them involving frequent and infrequent stimuli, the P3b effect will be measured exclusively in relation to the ear the participant has been instructed to pay attention to, so that the stimuli presented to the ear that has been ignored will be essentially irrelevant in terms of the elicited ERPs (Hillyard et al., 1973). In experiments involving sensory/perceptual ERP effects such

as the Mismatch Negativity (see also Chapter 1), it is often difficult to "eliminate" the subsequent large P3b due to the fact that the participant is attending to the stimuli. As the MMN is considered to reflect a form of memory originating mainly from perceptual sensory cortices, it is not necessary for the participant to be attending to the train of (standard and deviant) stimuli presented. In fact researchers interested in the MMN typically present a train of auditory stimuli while the participant is engaged in another activity (such as watching images from a TV). The purpose of the other activity is to "capture" the participant's attention, thereby leaving the concurrent MMN effects uninfluenced by the P3b presence. It should be acknowledged, however, that in spite of the experimenter's effort, in some cases attention can "involuntarily" shift to the unattended task, especially when it involves presentation of highly meaningful stimuli (Graham & Hackley, 1991).

The complexity of evoking “attention” as an explanatory factor is highlighted by findings from sleep studies. Findings show that even during sleep, participants may still be “attending” to stimuli as detected by the P3-like effects (similar to the N400 measured during sleeping described in Chapter 2). Passive attentional processes might be engaged during sleep, specifically in Stage II, as shown by a variety of experiments describing a large positive component in a time window between 400 and 800ms (e.g. Salisbury, 1992) in reaction to infrequent stimuli presented in an oddball paradigm. Moreover, during paradoxical sleep participants have been shown to respond differentially to their own name compared to other names, while keeping stimulus

probability constant (Perrin, 1999). In summary, therefore, it is clear that task relevance plays a fundamental role in the elicitation of the P3b effect. If the participant is not attending to a train of stimuli, the effect may disappear. However researchers have also found that there may often be some residual attention occurring when the participant is engaged in concurrent activity and even during some sleep stages. Within a train of stimuli, target stimuli typically show a larger P3b, and it has been proposed that this effect may be due to the subjective probability of target stimuli being lower compared to the subjective probability of non-targets. The next section will examine the P3b's validity in relation to other P300 subcomponents and will also examine neural sources involved in generating the effect, in an attempt to elucidate what the P3b is a measure of. Finally, with the same goal in mind, theoretical interpretations of the effect will also be described.

3.3 P3b Validity

Given the large amount of P3b research carried out in the past 40 years it might be expected that there would be clear consensus on what the P3b is and is not a measure of. However, in spite of the considerable number of studies, researchers have still to reach agreement on what the P3b is measuring. The following section describes some effects that are part of the P3 "family", whose descriptions may help elucidating what the P3b is by describing how it is different compared to the P3a, the novelty P3 and the no-go P3. Subcomponents of the P300 that are differentially sensitive to sequence

effects, and similarities with the old/new Left Parietal effect (described extensively in Chapter 4), will also be discussed. Moreover neural sources and explanatory theories will be discussed in addressing questions related to the P3b's validity.

3.3.1 The P3a, novelty P300 and no-go P300.

The P3a, the "novelty P300" and the no-go P300 are considered to be part of a family of ERP components distinguished from the P3b. While the P3b is elicited by task relevant stimuli, task irrelevant infrequent stimuli have also been shown to elicit a positive waveform (Polich, 2007; Squires at al., 1975). This positivity, whose peak occurs earlier compared to the P3b, has been named P3a (shown in Figure 3.5). The "novelty" P300 is elicited by perceptually novel stimuli (e.g. dog barking) in a train of non-novel stimuli, and the no-go P300 is elicited by non-novel stimuli used as distractors in a three-stimulus paradigm (Polich, 2007). The results of Principal Component Analysis (PCA) suggest that the novelty P300 can be distinguished from the P3b, but not from the P3a (Simons et al., 2001). Polich and Comerchero (2003), using visual stimuli, and Combs and Polich (2006), using auditory stimuli, demonstrated in turn that the novelty P300 and the no-go P300 reflect the same ERP component. As noted above Figure 3.5 shows the difference in topography between the P3a, displaying a central maximum, and the parietal maximum P3b (Conroy & Polich, 2007). The P3a, and novelty processing in general, are considered to reflect contextual effects while the P3b - since it involves repetition of stimuli - is considered to engage top-down processes (Ranganath & Rainer, 2003). Compared to the P3b the

P3a has a relatively shorter latency and habituates more rapidly (Courchesne et al., 1975; Knight, 1984), is considered to reflect frontal lobe activation (Friedman and Simpson, 1994; Knight, 1997) but like the P3b is measurable across modalities (Yamaguchi and Knight, 1991; Fabiani et al., 1998). The next section will show how Independent Component Analysis (ICA) has also helped fractionating the P300 into subcomponents differentially sensitive to sequence effects.

3.3.2 Sequence Sensitive P300 Subcomponents.

ICA has shown the P300 component to comprise a number of different subcomponents, some of which are sensitive to sequence effects – that is a specific sensitivity to repetitions and alternations of stimuli. Behavioural reaction times and P300 amplitude have both been shown to be affected by lower order and higher order sequence effects. For example analyses conducted by Jentzsch and Sommer (2001) showed that the P300 component can be divided into at least three subcomponents, of which two, more centrally distributed, are sensitive to sequence effects, while the third, parietally distributed, did not show sequence sensitivity (see Figure 3.6). Jentzsch and Sommer suggest that the parietally distributed subcomponent is likely to represent what in the literature typically refers to as the P3b: "The sequence-insensitive ICA component shows a parietal distribution in line with the often reported Pz-maximum of the classical P300 component as observed, for example, in response to rare target stimuli (..) it is tempting to speculate that the parietal component may reflect the lion's share of what is usually termed the P3b component, whereas the more anterior

sequence-sensitive components are separate phenomena." (Jentzsch and Sommer, 2001, p. 615). In the next section we examine the possibility of a relationship between the P3b and the Left Parietal old/new effect.

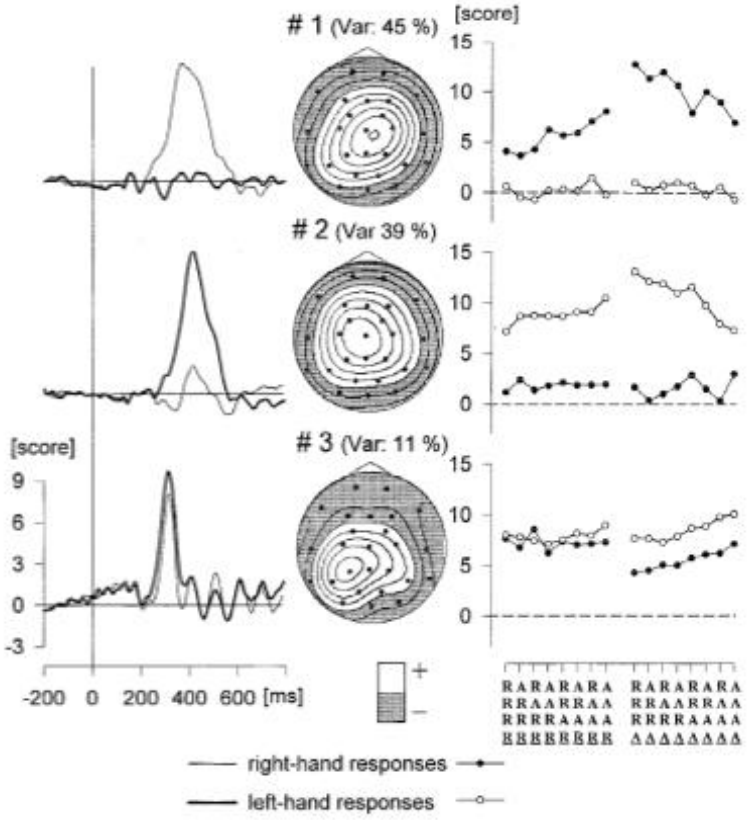


Figure 3.6 P300 subcomponents extracted via Independent Component Analysis show the two subcomponents at the top to be more centrally distributed, to be sequence sensitive and hand specific. The subcomponent at the bottom was instead found to be distributed left-parietally, not to be sensitive to sequences and not to be hand specific (Adapted from Jentzsch and Sommer, 2001).

3.3.3 The P3b and the Left Parietal effect

One important way to investigate the validity of ERP effects is via a direct comparison of effects that are supposed, based on previous experimentation, to be measuring different variables, but nonetheless show some morphological similarity of the waveforms, temporal overlap, or topographical resemblance. On this basis the P3b and the Left-Parietal old/new effect have often been considered related: both are large parietal positivities, occurring within overlapping time-windows. In the current thesis we investigate directly the possibility that the P3b and the Left Parietal effect may not be independent from each other (see also Chapter 4 for a detailed description of the Left Parietal effect and Chapters 6, 7 and 10 for experiments and further discussions about the relationship between the two effects). Here we anticipate some background information on the Left Parietal effect to start drawing a comparison between the old/new effect and the P3b effect.

ERP scientists involved in memory research consider the Left Parietal old/new effect as indicative of episodic recollection, predominantly on the basis of correlations with behavioural measures such as source memory performance. For example, the size of the Left-Parietal effect is in typically enhanced (e.g. Wilding & Rugg, 1996) for trials in which participants correctly recognized an item as old and also remembered specific contextual details about the trial (e.g. the part of the screen in which the word was seen during study) compared to trials in which participants correctly recognized an item as old but did not remember contextual details. Similarly, if ERP data are split according to Remember-Know judgments expressed at test, the size of the Left-Parietal Effect is

larger for the trials in which participants Remember the specific study trial, compared to trials in which participants simply Know the item is old (e.g. Smith, 1993), suggesting that the Left-Parietal effect is correlated with the participant recollecting the specific episode, as compared to having a feeling of familiarity unaccompanied by contextual details. However, despite the specific link with episodic memory, some textbooks report that the Left Parietal Old/New effect is as a subset of the P3b (Andreassi, 2006), even though evidence to the contrary has been also described (Herron et al., 2003). Based on Section 3.2.4 (and later in Chapters 6 & 7), if the Left Parietal old/new effect is a subset of the P3b then the relative positivity of old compared to new items in a recognition memory experiment may simply reflect the task relevance/target value of old items compared to new items in recognition memory tasks. As proposed by Rosenfeld et al. (2005) this targetness effect may be due to the lower subjective probability of target (old) items compared to non-target (new) items, leading to a P3b-like probability effect between old and new items even when the objective probability of old and new items is kept equal, as in the typical old/new recognition experiment.

It has also been proposed that if the P3b is involved in a comparison between external stimulation and an internal representation (see Section 3.3.4), where a "match" or "mismatch" decision is made, with matching stimuli having higher amplitude than non-matching stimuli. From this perspective it makes sense to describe the Left Parietal old/new difference as a subset of the P3b, in line with the description given by

Polich (2007): "Stimulus representations (words, objects) maintained in memory from previous exposures such as in a working memory or recognition task can produce P300 components to the reoccurrence of that stimulus that are larger than those from stimulus items not previously encountered". Chapters 6 & 7 will directly explore the relationship between the P3b and the Left Parietal effect, to investigate if the apparent temporal and topographic overlap between the two effects may be due to what Andreassi and Polich have proposed. As a background for the empirical studies the next section will review evidence regarding neural generators of the P3b, to verify the accuracy of proposed interpretations of what the P3b is a measure of (e.g. stimulus categorization), and to provide further evidence regarding the apparent independence between the P3a and the P3b.

3.3.4 Neural Sources

Initial studies on the neural sources involved in generating the P3b component were focused on the hippocampal formation, starting from the notion that the P3b reflects attentional and memory processes. Many studies using intracranial recordings have also investigated the role of the hippocampal formation in generating the P3b, as intracranial electrodes are often implanted in the medial temporal lobes of epileptic patients for diagnostic and monitoring purposes. These studies suggested an involvement of the hippocampal formation in generating the P3b (e.g. Halgren et al., 1980; McCarthy et al., 1989; Halgren et al., 1995). Specifically an intracranially recorded version of the P3b, named the Medial Temporal Lobe-P300 (MTL-P300)

because it is recorded from Medial Temporal Lobe areas, is elicited by rare stimuli in an oddball paradigm and originates directly from the hippocampus proper (e.g., Halgren et al., 1980; Grunwald et al., 1999). Follow-up scalp recordings on human and non-human animals that had undergone excision of the hippocampus found, however, that the hippocampal formation may only indirectly contribute to generating the P3b, as the P3b was found to be unchanged between hippocampal and non-hippocampal participants (Polich and Squire, 1993). In fact a wide variety of areas have been shown to contribute to the scalp-recorded P3b, but the temporal-parietal lobe junction appears to be especially important (Johnson, 1993; Verleger et al., 1994).

Evidence from other forms of imaging such as MEG and PET (Halgren, Marinkovic, & Chauvel, 1998) also suggests that a variety of areas are involved in generating the P3b, specifically the amygdala, hippocampal formation, cingulate cortex, temporal lobe, thalamus, inferior parietal lobe, orbital frontal cortex and dorsolateral prefrontal cortex. Event Related fMRI experiments have found that processing of low probability visual stimuli is associated with a BOLD signal present in the posterior cingulate, inferior parietal lobe and middle frontal gyrus (McCarthy, Luby, Gore, & Goldman-Rakic, 1997). Overall MEG, PET and fMRI evidence suggests activation of a wide variety of areas during tasks that typically elicit a P3b effect as measured from the scalp. Together with the issue mentioned in Chapter 2 about phase resetting being at least partially involved in scalp-measured ERP cognitive components such as the N400 and P3b, and not measurable in itself by fMRI, it has to be noted that the low temporal

resolution of those imaging techniques makes it difficult to discriminate between temporally contiguous ERP components such as the N2 and the P300, and therefore the areas detected as active during those experiments may be involved in generating both components. In general it is not clear why such a wide variety of brain areas should be involved in stimulus categorization, leading some researchers (Verleger et al., 2005) to formulate alternative hypothesis about the functional role of the P3b, namely a mediating function between stimulus evaluation and response selection. Controversy also exists regarding the specific role of the temporo-parietal junction (noted above) in generating the P3b, which does not fit well with is working memory accounts of the P3b (described in Figure 3.7). Furthermore neuropsychological evidence suggests that the frontal lobe has a fundamental role in the elicitation of the P3a component, as patients with frontal lobe lesions show a clearly reduced P3a effect to distractor stimuli, but a typical parietal maximum P3b effect for target stimuli (Knight, 1984; Knight, 1990; Knight et al., 1995).

At the molecular level it has been proposed (Polich, 2007) that different neurotransmitter systems are involved in the elicitation of the P3a and the P3b. Specifically, the P3a is thought to be regulated by the dopaminergic system and the P3b by the noradrenergic system. The hypothesis that the P3b is regulated by the noradrenergic system originates mainly from experiments measuring ERPs in non-human animals (Nieuwenhuis et al., 1995). Specifically Nieuwenhuis et al. describe how neurons in the Locus Coeruleus (LC), primarily responsible for noradrenergic

activity, are selectively activated by target stimuli that are both task relevant and infrequent (two variables know to influence the P3b) and are only weakly activated or not activated at all by non-target stimuli including, for example, rewarding stimulation. Importantly, during reversal learning training, neurons in the LC started responding to the new targets before any observable change was detected in the overt behavioural responses. Similarly to the P3b, phasic LC responses to target stimuli are found to be larger when the target is presented on 10% of the trials, compared to 50% of the trials, and the second presentation of a target stimulus typically elicits a smaller LC response suggesting sensitivity to local probability (Aston-Jones et al., 1994).

Evidence in favor of the idea that the P3a is regulated by the dopaminergic system is indirect and comes from ERP studies showing a P3a reduction in patients with Restless Leg Syndrome (RLS) compared to controls, with a similar P3b across groups. Since RLS is thought to originate from dopaminergic deficits, it is possible that the P3a is linked to the dopaminergic system. However, the same study describing this finding (Trenkwalder & Winkelmann, 2003) also shows both the P3a and the P3b to be greatly reduced for patients affected by Parkinson's compared to controls. Since Parkinson's is well known to originate from a deficit in dopaminergic production, it seems to be implausible that the dopaminergic system is only involved in the P3a and not the P3b.
Overall, experiments investigating the neural sources involved in generating the P3b do not point to a single generator, but instead to distributed sources, with an important role for the temporo-parietal junction. The sources involved in generating the P3b

appear however to differ from the ones involved in generating the P3a, strengthening the idea put forward in Section 3.3.1 that the P3a and the P3b are dissociable phenomena. A distinction between the neurotransmitter systems involved in generating the P3a and the P3b has been proposed in the literature, but which suggests that the noradrenergic system plays an important role in generating the P3b and the dopaminergic system in generating the P3a. Findings from Parkinson's patients complicate the picture however, pointing to a role for dopamine in both the P3a and the P3b. In the next section we will describe some theoretical models used in the literature to explain the P3b effect.

3.3.5 Theoretical interpretations

There have been several theoretical interpretations of the P3b, but there is still no clear consensus. For instance, P3b amplitude has been considered to be a function of the amount of attentional resources allocated to the oddball task in dual tasks paradigms: when the participant is engaged in two tasks simultaneously (e.g. a cognitively demanding task and an oddball task) the amplitude of the P3b relative to the oddball paradigm will be dependent on how difficult the concurrent task is, suggesting that the P3b is a function of allocation of attentional resources (Kramer et al., 1985; Wickens et al., 1983). Another theoretical interpretation of the P3b describes the effect as indicative of the revision of a memory representation induced by incoming stimulation. According to this "context updating" view (Donchin, 1981; Polich, 2007) the process of interest is attention driven. After sensory processing a comparison is

drawn between the current stimulus representation present in working memory and incoming stimulation, and a mismatch would elicit a P3b effect. This mismatch is considered to occur independently from sensory perceptual mismatches occurring in earlier stages of processing (Polich, 2007; see Figure 3.7).

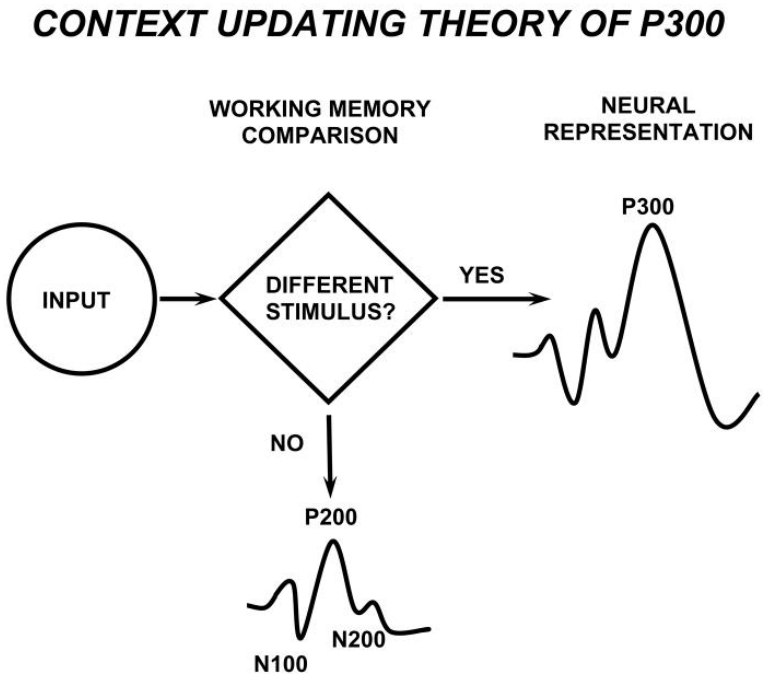


Figure 3.7 The context updating theory of the P300, one of the most influential models of the effect in the literature (Adapted from Polich, 2007).

A similar perspective (Kok, 2001) describes the P3b as an index of "event categorization", in which a comparison is made between the external incoming stimulation and an internal representation. A "match" or "mismatch" decision is then

made, and, given equal presentation probability, matching stimuli have higher amplitude than non-matching stimuli. Squires et al. (1973) found that the closer the match of a stimulus was to a template, the larger was the P300 (see also Chapter 6). These perspectives underscore the role of memory in elicitation of the P3b.

The P3b effect may also be described as sensitive to the difference in neural activation between stimuli that evoke a behavioural response (S^D) and stimuli that do not evoke a behavioural response (S^Δ). This interpretation fits with simple discrimination procedures, but it may seem at odds with the P3 effect measured after no-go trials in go/no-go procedures. Go/no-go procedures represent, technically, a form of conditional discrimination where a specific stimulus A evokes a behavioural response if followed by a stimulus B, but not a third stimulus C. Since stimulus A is typically presented before either B or C, it is legitimate to infer that the behavioural response is strengthened by A regardless of the fact that the following stimulation will be either a go or a no-go stimulus. After presentation of Stimulus A the response is strengthened; when B is presented the response is overtly evoked and if C is presented the overt response is inhibited. Amplitude of the go and no-go responses is similar at parietal sites, leading to the possible interpretation that perhaps inhibiting a response constitutes a form of responding in itself (or that maybe the P3b represents in both cases a form of inhibition of a response – either the response that was strengthened by presentation of the A stimulus or, in the case of the go response, inhibition of other competing responses). Importantly, however, the amplitude of go and no-go P3 differs

at frontal sites (Roberts et al., 1994), with the amplitude relative to the no-go trials larger than the one at go trials, as seen in Figure 3.8.

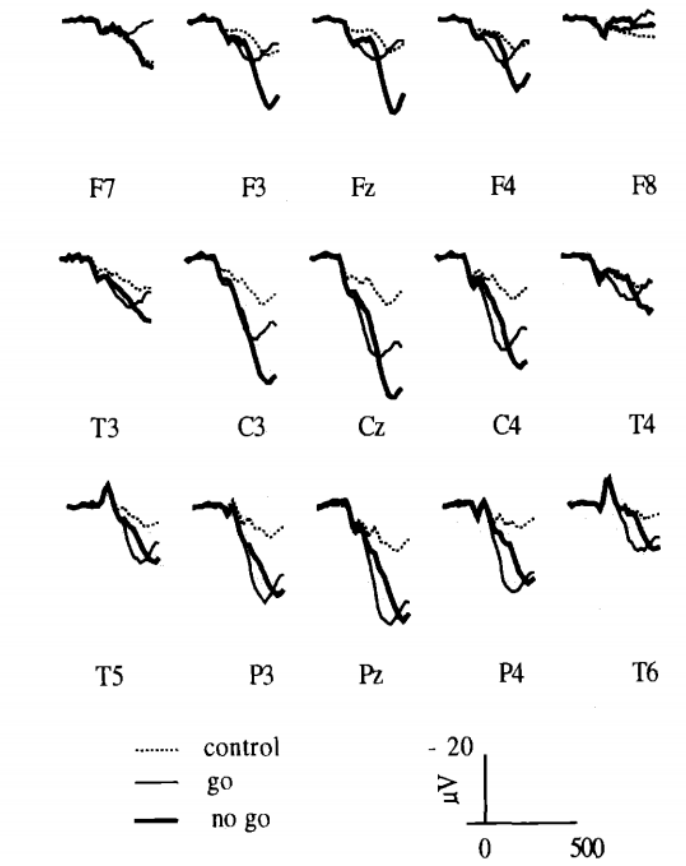


Figure 3.8 The Grand average waveforms show both the frontal distribution of the "no go" effect compared to the "go" condition and the equivalent parietal magnitude of the two effects (Adapted from Roberts et al., 1994).

The difference between the go and no-go waveforms may therefore represent a difference in magnitude of the inhibitory process involved, in general, in generating

the effect. From this perspective as the strength of the competing response(s) to be inhibited increases, the topography of the effect is more frontally distributed. This interpretation fits well with the fundamental characteristic of the P3a effect as distracting, perceptually novel, stimuli not have a discriminative function (i.e. do not lead to a behavioural response) they need to be inhibited because of the lack of clear "meaning" within the constraint of the three-stimulus paradigm. Therefore after novel, surprising, stimulation has elicited a clear sensory/perceptual response, it is inhibited from eliciting also a motor response (which behaviourally would represent a "mistake"). Accordingly, a clear parietal distribution may represent elicitation of a strong response (compared to the competing responses) that did not require a high degree of inhibitory "support" in the process of the motor response being selected and executed. Consistently with this view, it has been proposed (Polich, 2007) that the P3b effect may index inhibition of extraneous brain activity during transmission of information from frontal areas (P3a) to temporo-parietal areas (P3b).

There are problems with the inhibition account however. For example, an anteriorization of the P3b effect is seen in silent counting tasks (Salisbury et al., 2001), where theoretically no inhibition is involved. Salisbury et al. (2001) compared the P300 component elicited by a go task to a P3 component elicited by a silent counting task. The P300 component to the go task was frontally diminished compared to the silent counting task. This reduction was due to a broad negativity that was present for the go task, but not the silent counting task, and to an asymmetrical negativity

contralateral to the hand involved in the behavioural response in proximity to the motor cortex. The authors argued that the behavioural response generated a motor related negativity, whose time-course overlapped with the "pure" P300, thereby cancelling part of the frontal distribution of the effect. Thus from this perspective the differential distribution of the P300 across the go task and the silent counting task reflects the response execution demands that are present in one but not the other procedure (see also Kok, 1988).

In summary, overall, no proposed interpretation of the P3b has gained unanimous consensus in the literature: each appears to have explanatory advantages and weaknesses. The event categorization and context updating interpretation arguably provides the most accurate description of the observed phenomena. While there is still no clear consensus regarding what the P3b is a measure of (i.e., on its validity), the effect has nonetheless been shown to be highly reliable both at the group and at the individual level, as discussed in the next section.

3.4 P3b Reliability

3.4.1 Inter-laboratory Reliability

While it is not yet completely understood what the P3b reflects, leaving the debate on its validity open, the effect is large in its size and clearly seen across individual participants and groups: it is reliable both at the inter-laboratory and inter-individual level. Inter-laboratory validity was investigated by Alexander et al. (1994) within the context of a large scale multi-laboratory experiment, as a prerequisite to carrying out research on the relationship between genetics and alcoholism. The researchers involved in this study were interested in finding out if variables that are known to affect the P3b but which are difficult to match in large scale studies involving many laboratories, might possibly lead to unreliability of P3b results.

Each of the six laboratories involved in the study was identical to the others in terms of the equipment used and the number of participants (N=15). The paradigm used was a typical oddball with auditory stimuli: participants were instructed to press a button after the target tone but not after the standard tone, and the ratio of targets/standards was 12.5/87.5. Results across laboratories are shown in Figure 3.9, showing a pattern of general consistency across laboratories. Statistical analyses showed that the mean amplitude of standard and target stimuli did not differ significantly across laboratory locations, nor did the electrode factor interact with the laboratory location.

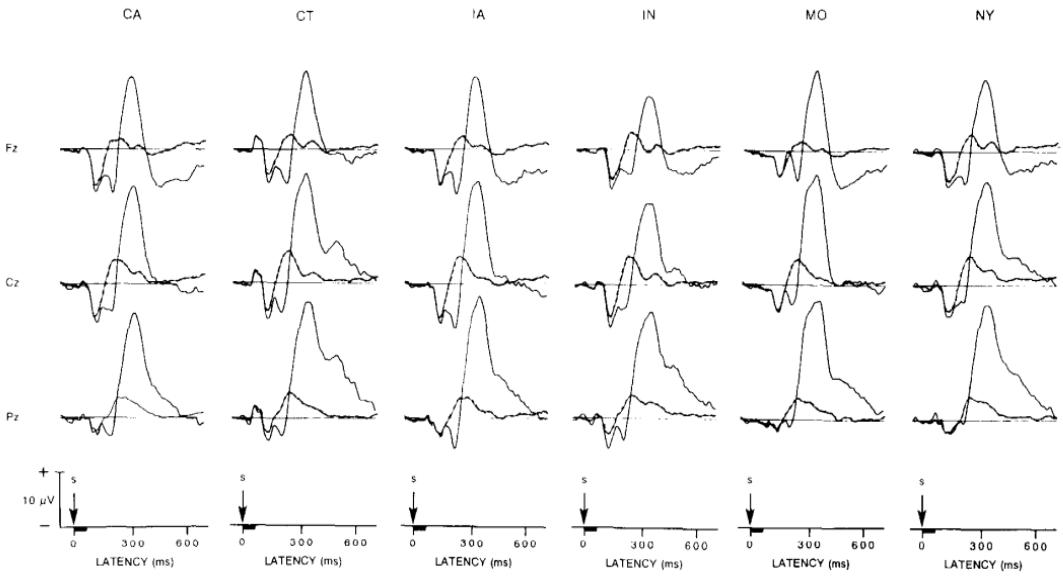


Figure 3.9 Waveforms relative to the P3b Effect obtained in an oddball experiment with auditory stimuli by contrasting ERPs elicited by targets and standard stimuli. The waveforms show compatible effects across the six laboratory locations involved in the reliability study, with a parietal maximum observed consistently across laboratories in the 275-400ms time window (Adapted from Alexander et al., 1994).

3.4.2 Inter-individual Reliability

Similarly to the inter-laboratory reliability, the P3b appears to have a strong inter-individual reliability (see also Chapter 5). Most P300 studies only report group averages, however some studies also show a subset of results at the single participant level. For example, Lembreghts et al. (1995) report individual data from five participants (shown in Figure 3.10) and all participants show a P3b effect. In the current thesis we investigated P300 inter-individual reliability in a large pool of participants (N=64); the effect's inter-individual reliability was compared with the

reliability of the other two late ERP components investigated in the current work, the N400 and the Left Parietal Effect. Specifically, we focused (see Chapter 5) on comparing the proportion of participants showing the effect of interest across experimental effects. Those results suggest a strong inter-individual reliability and other work, discussed in the next section, suggests that the effect is also measurable in non-human species.

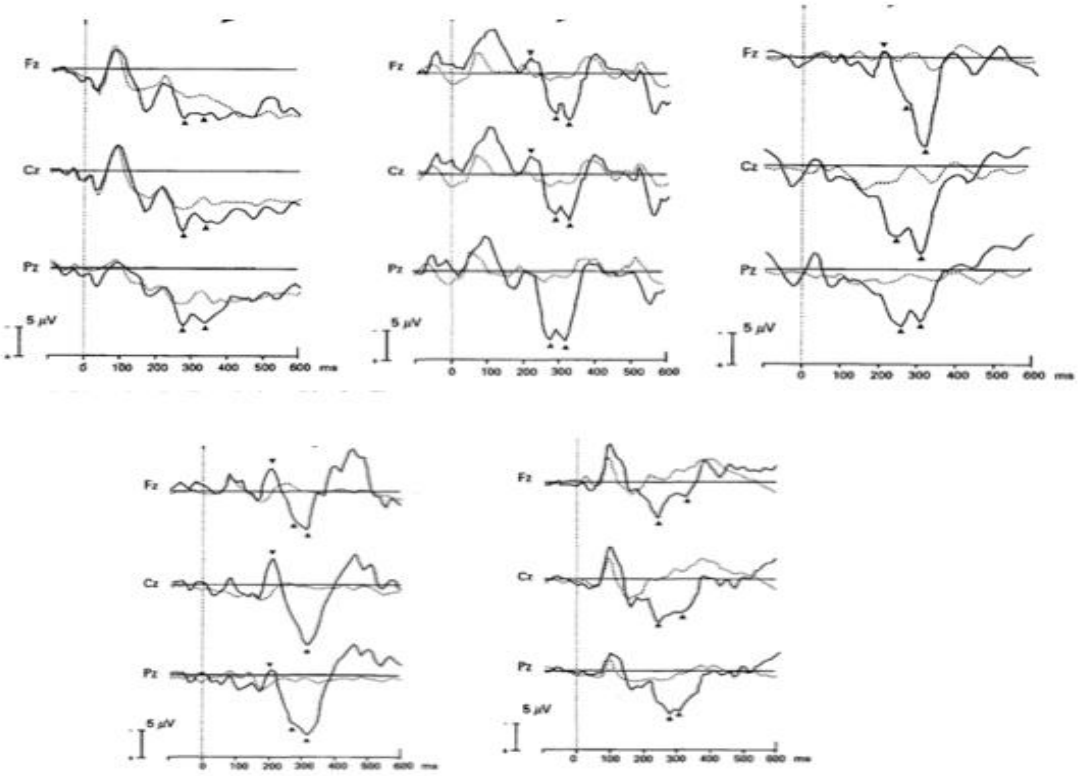


Figure 3.10 P3b Effect obtained in an oddball experiment with auditory stimuli by contrasting ERPs elicited by targets and standard stimuli. Results, displayed negative up, are shown from five participants and indicate that the P3b effect is highly reliable at the individual level (Adapted from Lembreghts et al., 1995).

3.4.3 Inter-species Reliability

Consistently with claims that a perspective that the P3b is a very reliable ERP effect, ERPs morphologically similar to a P3b effect have been measured in non-human animals. Specifically, Wilder, Farley and Starr, (1981) were able to measure the P3b effect in cats, and Arthur & Starr (1985) described the effect in monkeys (see also Glover et al., 1986) – previous experiments describing the component did not require a response from the animal in relation to the discriminative, or target, stimulus and therefore could not be fully considered P3b effects. An experiment by Jodo et al. (1995) investigated the P3b experiment in rats. Experimenters used an oddball paradigm manipulating target probability (30, 50 or 70% of the trials). A large slow deflection in the ERP was detected peaking 400-500ms post-stimulus, while such a deflection was not elicited by the standard tones in all probability conditions. The authors describe the large positivity to be very similar to the one detected in humans and, similarly to the results obtained with human participants, the amplitude of the positive deflection increased as the probability of the target stimulus decreased (see Figure 3.11).

Human studies in which presentation of a stimulus is omitted during a train of regularly occurring stimuli have shown what has been described as the "missing stimulus potential": a positive deflection in the ERP resembling a P3b component (Bullock, 2003). The timing of the missing stimulus potential is a function of time of the first missing stimulus in a train of stimuli. The missing stimulus potential is

therefore defined as an electrophysiological response in absence of external stimulation. A series of studies have shown the missing stimulus potential in a wide variety of species, including invertebrates (Ramón et al., 2001), suggesting commonalities across many species in the processes involved in elicitation of ERPs that are broadly part of the P300 "family".

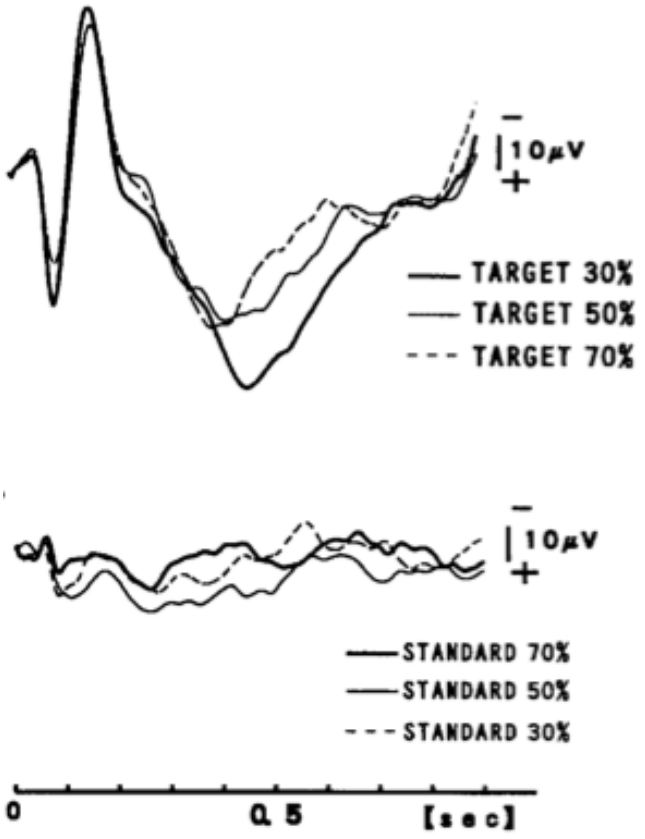


Figure 3.11 Grand average ERPs for 8 rats to the target and standard stimuli at the 3 probability conditions. Data, displayed negative up, shows an effect morphologically compatible with the human P3b (Adapted from Jodo et al., 1995).

3.5 Summary

The P3b represents an interesting example of an effect whose validity is uncertain, but whose reliability is nonetheless strong. The P3b, of the three effects investigated in the current thesis, is the only one whose inter-species reliability has been studied and demonstrated. This effect therefore provides a solid baseline to which results from other components can be compared. Procedural and individual variables influencing the amplitude and latency of the P3b are well known: however the high degree of experimental control over the effect in this case does not translate automatically to clear theoretical understanding. Moreover, insights from source location analyses do not help elucidate what the effect is a measure of, instead pointing to a high degree of complexity. The Left Parietal old/new effect by comparison, discussed in the next chapter, has been accepted as a neural correlate of recollection within dual process theory of recognition memory, but we will describe some evidence questioning this conclusion. The Left Parietal effect's inter-individual reliability, moreover, is not as high as the reliability of the N400 effect and the P3b effect.

Chapter 4

The Left Parietal Old/New Effect

A late cognitive component investigated in the current thesis is the Left Parietal old/new effect. While the inter-laboratory reliability of the N400 and P3b has been previously assessed, the inter-laboratory reliability of the Left Parietal effect has yet to be directly investigated. Moreover, similarly to the other two effects considered in the current thesis questions remain about the effect's validity, specifically about the relation between the Left Parietal effect and the P3b effect. The purpose of the current chapter is to describe factors influencing the Left Parietal effect, with the goal of reviewing its validity and reliability, and thus providing a complete background for the experimental work carried out in the current thesis.

4.1 What is the Left Parietal effect?

Recognition memory is supported, according to dual process theories, by the two distinct processes of recollection and familiarity, and ERP signatures have been identified and associated with both (for reviews see Friedman & Johnson, 2000; Allan, Wilding & Rugg, 1998; Donaldson, Allan & Wilding, 2002). ERP correlates of recognition memory are obtained by contrasting correctly recognized old items (Hits)

to correctly classified new items (Correct Rejections). Typically ERPs to Hits are more positive than ERPs to Correct Rejections in a variety of time windows, starting from 300ms post stimulus to approximately 700ms post stimulus, with the scalp distribution of the positivity varying over time. This positivity, comprising different topographic patterns, is typically described as the "Old/New effect".

The ERP correlate of recollection, known as the Left Parietal effect (see Figure 4.1), consists of one part of the positivity for correctly recognized old items compared to correctly recognized new items occurring typically between 500-700ms post-stimulus, distributed maximally over left parietal sites. This Left Parietal effect is thought to reflect remembering of a specific episode, often including contextual details, such as the place and the time a specific object has been encountered before. The effect, whose parietal distribution is not always left sided (see for example Mecklinger, 2000), has been found with different kinds of stimulus materials, including words and pictures (Duarte et al., 2004; Schloerscheidt & Rugg, 1997; 2004; Ranganath & Paller, 2000).

Historically, the Left Parietal effect has been first described as a repetition effect (e.g. Rugg & Doyle, 1994) and later has been re-interpreted in relation to the process of recollection (e.g. Wilding, 2000; Schloerscheidt & Rugg, 2004; Smith, Dolan & Rugg, 2004). The idea that the effect was simply a correlate of repetition was ruled out as

studies did not find the effect elicited by old items incorrectly classified as new (misses). Moreover the effect was also never reported to be elicited by new items incorrectly classified as old (false alarms) showing that the effect is not just a correlate of making an 'old' response (Rugg and Doyle, 1992; Sanquist et al., 1980).

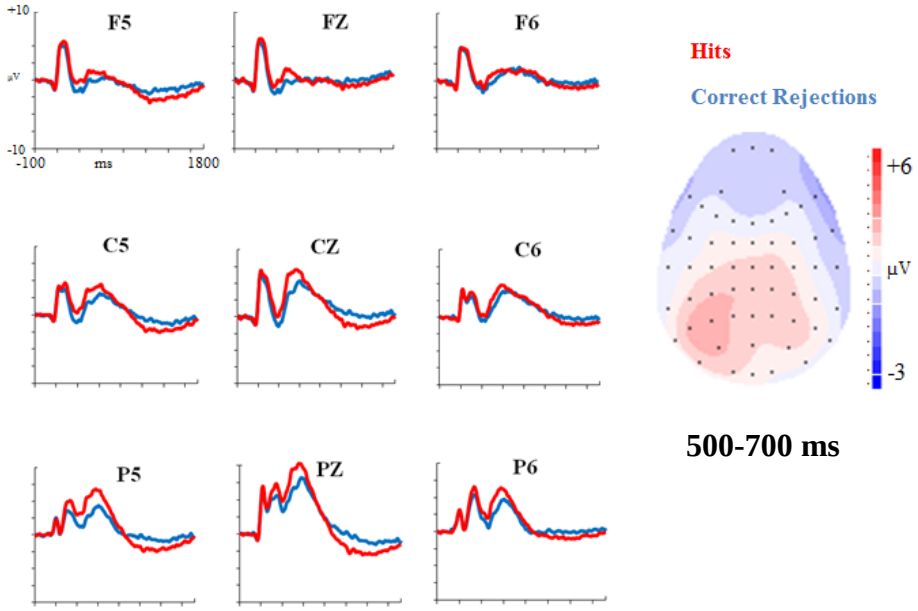


Figure 4.1 Example Left Parietal effect obtained in a recognition memory experiment with visual verbal stimuli by contrasting ERPs elicited by correctly classified old (Hits) and new (Correct Rejections) items. The waveforms and the topographic map on the right show the classic parietal distribution of the effect, maximal in the left hemisphere, in the 500-700ms time window (Adapted from Chapter 5).

4.2 Factors influencing the Left Parietal effect

4.2.1 Size of the Left Parietal Effect

Experiments involving a source judgment task (e.g. Wilding & Rugg, 1996; Senkfor & Van Petten, 1998; Trott, Friedman, Ritter & Fabiani, 1997) show that the effect's amplitude increases as a function of the amount of contextual information remembered at test. Typically a source task involves recognizing an item as "old", and then remembering some contextual details relative to the study trial. For example, remembering that a specific word had appeared in the top-left corner of the screen. Results typically show the size of the effect to be proportional to the amount of contextual information remembered at test (Figure 4.2), and the same results have been found with source tasks involving, for example, the modality in which the stimuli were presented at study (Wilding, Doyle & Rugg, 1995) or the gender specificity of the voice speaking at study (Wilding & Rugg, 1996).

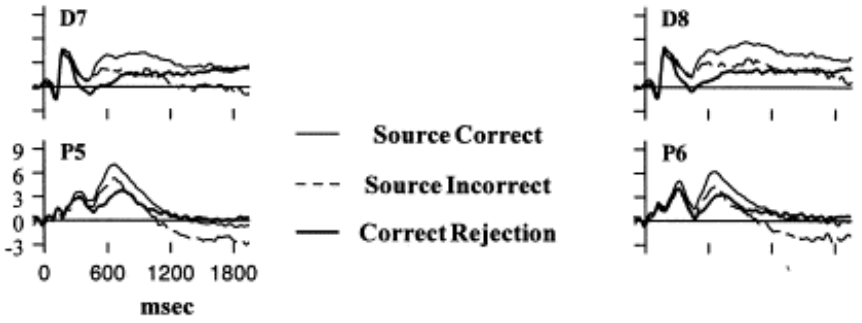


Figure 4.2 Example Left Parietal Effect obtained in a recognition memory experiment with correct and incorrect source judgments. The size of the old/new difference increases as a function of the amount of source information remembered (Adapted from Wilding, 1999).

The size of the Left Parietal effect has also been manipulated in associative recognition experiments, in which word pairs are presented at study and then are either presented again intact at test or are presented in recombined, or rearranged, pairs (thereby creating pairs that were not presented during study). In this context the amplitude of the Left Parietal effect is typically found to be larger for intact compared to rearranged pairs (e.g. Rugg et al., 1996; Rugg et al., 1998). Importantly associative recognition studies, from a behavioural perspective, are traditionally considered to selectively engage recollection (e.g. Hockley, 1992; Yonelinas, 1997).

Studies manipulating depth of processing have also shown an effect on the size of the neural correlate of recollection. The amplitude of the Left Parietal difference was in fact found to increase as a function of depth of processing (e.g. Paller & Kutas, 1992). Moreover, recognition memory studies involving remember-know judgments, initially carried out by Smith (1993), typically show the effect to be larger[4] in trials where the participants judges to be "remembering" the specific episode as compared to trials in which the participant affirms to "know" that the item has been encountered in the study phase (e.g. Vilberg, Moosavi & Rugg, 2006; Mark & Rugg, 1998; Curran,

[4] Although recollection and remembering are procedurally defined by using source tasks and remember-know judgments, recollection does not necessarily involve remembering contextual details. It is in fact theoretically possible to recollect seeing a specific item without recollecting contextual information.

2004). In addition the Left Parietal effect is typically elicited during an explicit memory test, but has been shown to disappear if the behavioural task during the test phase involves implicit memory retrieval (Rugg et al., 1998) and to be more positive for Hits than for False Alarms, but only in poor performers and not in good performers (Curran, Schacter, Johnson & Spinks, 2001). Overall, therefore, evidence from several procedures points to the observation that the size of the Left Parietal effect increases as the amount of information remembered from the study episode increases. The next section will review the Left Parietal effect's validity, and specifically how the conceptual label of "recollection" allows the effect to be dissociated from other data explained by the conceptual label of "familiarity", both from an electrophysiological and a neuroanatomical perspective.

4.3 Validity of the Left Parietal Effect

4.3.1 Dissociation between the Left Parietal and the Bilateral Frontal Effect

The Left Parietal Effect has been dissociated from another, early, old/new effect named the early Bilateral Frontal Effect, already described in Chapter 3 when discussing the N400's validity (see Chapters 8 & 9 for an example of this dissociation provided in the current experimental work). The Bilateral Frontal old/new effect, shown in Figure 4.3, is a positivity in the ERPs occurring between 300-500ms post-stimulus for correctly recognized old items compared to correctly classified new items (e.g. Curran & Cleary, 2003), widely considered to be a neural correlate of familiarity-

based remembering[5]. Familiarity-based remembering represents a form of episodic memory where an object is recognized as having been seen before, but with a lack of recollection of the remembered episode.

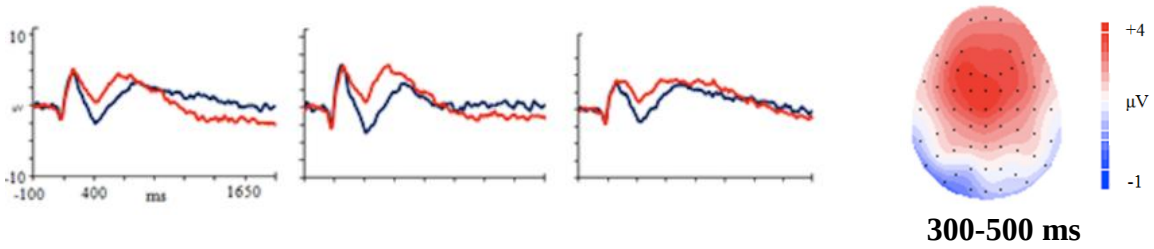


Figure 4.3 Waveforms and topographic map showing the early Bilateral Frontal effect. ERPs are shown for Hits (red lines) and Correct Rejections (blue lines). Waveforms are shown for three fronto-central electrodes (FC5, FCZ, FC6). The topographic map on the right shows the distribution of the old/new effect in the 300-500ms time window (Adapted from Chapter 9).

The Bilateral Frontal effect was initially considered to be insensitive to depth of processing manipulations (Rugg et al., 1998), leading for the first time to the hypothesis that the effect may be dissociable from the Left Parietal effect and represent a neural correlate of familiarity. Later evidence, however, showed familiarity memory to be sensitive to depth of processing manipulations (e.g. Yonelinas et al., 1998). Stronger evidence in favour of a dissociation between the Bilateral Frontal effect and

[5] The proposed interpretation that the early bilateral frontal effect indexes familiarity has been questioned. Other proposed interpretations of the bilateral-frontal effect involve the conceptual priming hypothesis (e.g. Yovel & Paller, 2004) and a novelty detection mechanism (Tsivilis, Otten & Rugg, 2001). The general consensus seems, however, to be oriented towards the familiarity interpretation (e.g. Bridson et al., 2006; Rugg & Curran, 2007).

the Left Parietal effect comes from experiments showing the early correlate of recognition, but not the later Left-Parietal effect, present for both Hits and False Alarms (e.g. items incorrectly classified as old). Specifically, Curran (2000) presented words in one form during study (e.g. *frog*) and then reversed in plurality during test (*frogs*); the early Bilateral Frontal effect, but not the Left Parietal effect, was present at test both with old items and with lures (items whose plurality had been reversed), denoting the fact that familiarity is at least in part influenced by the similarity of the item between study and test. This similarity does not have to be physical as the same pattern has been shown with mirror-reversed pictures (Curran & Cleary, 2003). This pattern of results suggests a clear dissociation between the Left Parietal effect and the Bilateral Frontal effect and, provided the two effects are valid measures of recollection and familiarity (but see Chapters 5 & 10), a dissociation between the two processes involved in episodic recognition.

4.3.1.1 Neuroanatomy and Validity of Measures of Recollection

From a neuroanatomical perspective, and consistent with the dissociation described at the ERP level, familiarity and recollection are generally considered to be supported by separate structures within the medial temporal lobes. Specifically, recollection is thought to involve Hippocampal activity and familiarity is considered to be supported by the Perirhinal Cortex (e.g. Eichenbaum, Yonelinas & Ranganath, 2007; Yonelinas et al., 2005).

The hippocampus' high internal connectivity allows it to play a fundamental role in the pattern completion activity, considered to be a prerequisite for successful recollection (e.g. Montaldi & Mayes, 2011). For instance, in an experiment involving a source judgment task the stimulation presented during the test phase is typically a subset of the stimulation that had been presented during study, and hippocampus-mediated pattern completion allows that subset of the original stimulation to elicit additional neural responses, leading to neural activation that more closely corresponds to the neural response that had occurred during study. The phenomenological counterpart of this process is conscious recollection (e.g. Meiser & Sattler, 2007).

Even though the hippocampus appears to have a fundamental role in supporting recollection, another area, the left inferior parietal lobe has been shown in fMRI studies to be involved in recollection (Wagner et al., 2005). It is therefore probable that the left inferior parietal cortical areas comprise the neural generators responsible for the Left Parietal effect, particularly given that cortical areas are more likely than subcortical structures (such as the hippocampus) to elicit scalp potentials such as ERPs. By contrast, evidence suggests that familiarity is supported by the perirhinal cortex[6] (e.g. Haskins et al., 2008; Holscher, Rolls & Xiang, 2003), strengthening the idea that the two processes can be neuroanatomically dissociated.

[6] The perirhinal cortex is a polymodal-polysensory associative cortex receiving stimulation from different modalities (e.g. visual and auditory) sensitive to complex forms of stimulation. The perirhinal cortex is located in the ventral visual stream and receives inputs from all other

There is in fact clear evidence that the perirhinal cortex is sensitive to recency and familiarity of stimuli (e.g. Fahy, Riches & Brown, 1993), leading to the possibility that the perirhinal cortex supports object processing that involves temporal but not spatial information. This sensitivity to the temporal dimension in responding to objects fits well with the characteristics of familiarity, but could also be characterized as a sensitivity to contextual information – which fits the definition of recollection equally well. Within the memory literature, therefore, a distinction is drawn between intrinsic and extrinsic context. From this perspective one argue that recency, familiarity and novelty are types of information on the temporal dimension that refers to a single object and are not therefore, in themselves, the same kind of contextual information typically recollected in source memory tasks, where the relevant contextual information appears to be of the extra-item kind.

As mentioned above, the Perirhinal cortex is located in the ventral portion of the visual stream, considered to be the "what" or the "object" pathway (i.e. involved in the processing of stimulus features) as compared to the parietal portion of the visual stream considered to be the "where" or "spatial" pathway, involved in processing of

---

higher-order neocortical fields from each modality, and is therefore in a perfect position to have important associative functions (i.e. the function served by the perirhinal cortex may be dependent on its connections more than on its specific internal anatomy). These associative functions appear to be important specifically in object identification, especially when to identify an object it is important to integrate polysensory and polymodal information (Murray & Bussey, 1999).

the spatial context in which objects are immersed (Mishkin, Ungerleider & Macko, 1983). It is therefore not surprising that the Perirhinal cortex involvement in perception and memory appears to be limited to specific object features and does not involve broader contextual or spatial information.

Some researchers (e.g. Squire, Wixted & Clark, 2007) have however argued against the neuroanatomical dissociation between recollection and familiarity. Theoretically the Hippocampus is in the ideal neuroanatomical position to be involved both in familiarity and in recollection: it receives stimulation regarding both item and context. On this point Wais, Squire & Wixted (2011) have suggested that the hippocampus may be involved in both familiarity and recollection, an idea that they investigated using fMRI during a source memory task. Specifically the authors compared trials in which the source was correctly retrieved compared to trials in which the source was not retrieved, and by equating confidence strength across the two kinds of trials the authors suggest that they are able to avoid a common confound in source judgment experiments where memory strength is typically not matched across successful and unsuccessful source retrieval attempts. The authors did find similar hippocampal activity across successful and unsuccessful source retrieval attempts, and in both cases hippocampal activity was more pronounced compared to forgotten items. Differential activation, higher for successful than unsuccessful source retrievals, was however found in the pre-frontal cortex. The authors suggest that the trials where the source was successfully retrieved are trials in which recollection is occurring, and the trials in

which the source was not retrieved are trials where familiarity is occurring. Given similar hippocampal activation in both kinds of trials, they suggest hippocampal involvement in both processes.

A problem with this interpretation (as suggested by Montaldi and Mayes, 2011) is the assumption that unsuccessful source retrievals constitute a case of "pure" familiarity, uncontaminated by recollection. While the specific contextual details necessary to perform adequately in the source judgment task were not retrieved, it is difficult to rule out the possibility that other contextual information has been retrieved, and in general it is impossible to rule out that item recollection has occurred. Certainly, this is a confound inherent in all source memory experiments and must be kept in mind even when memory strength is equated. In another study (Kirwan, Wixted & Squire, 2008) the authors propose the idea that medial temporal lobe activation, regardless of the fact that it involves the hippocampus or the perirhinal cortex, is correlated to subsequent memory strength, while pre-frontal cortex activation is predictive of subsequent recollection.

While it is reasonable from a neuroanatomical perspective to support the idea that the hippocampus may be involved in both familiarity and recollection, it is not immediately evident how the perirhinal cortex, given its position and internal structure, could be involved in recollection. The perirhinal cortex in fact appears to lack the

structural organization to support pattern completion, considered to be fundamental prerequisite of the process of recollection. While the perirhinal cortex is involved in associations (Murray & Bussey, 1999), the associations integrated by the perirhinal cortex appear to be relative to different features of a specific object, independently from spatial/contextual information.

Evidence from lesion studies appears also to point towards the hypothesis that the hippocampus and the perirhinal cortex support different processes. For instance the Left Parietal effect is diminished or not present in patients with hippocampal damage (e.g. Mecklinger et al., 1998), while the Bilateral Frontal effect has been measured in Alzheimer's patients with hippocampal atrophy (Tendolkar, Doyle & Rugg, 1999). Moreover in recognition memory studies selective hippocampal damage has been shown to produce a recollection-specific deficit while leaving unaffected familiarity (e.g. Mayes et al., 2002; Aggleton et al., 2005; Düzel et al., 2001). At the same time, lesions involving both the hippocampus and the perirhinal cortex have been shown to produce a deficit in both recollection and familiarity (e.g. Yonelinas et al., 2002).

One alternative to the idea that there is a recollection-familiarity division of labour within the medial temporal lobe is based on the hypothesis that the Hippocampus supports a "strong" form of memory with regards to the studied episode, while the perirhinal cortex supports a "weak" form of memory. However, there is strong

evidence against this interpretation from a clinical case study (Bowles et al., 2007) involving a patient whose portion of the anterior medial temporal lobe had been removed including the perirhinal cortex, while leaving intact the Hippocampus. This patient exhibited an impairment in familiarity while leaving recollection intact, thereby providing evidence in favor of both dual process theories of recognition memory and a division of labour based on the recollection-familiarity dichotomy within medial temporal lobe structures.

In general neuroanatomical evidence is consistent with the idea that the Left Parietal effect and the Bilateral Frontal effect, considered as measures of recollection and familiarity memory, are supported by distinct brain circuitry. Summarizing, the fact that the Left Parietal effect appears to be independent from the Bilateral Frontal effect is overall consistent with the available neuroanatomical evidence. In the next section we ask if the Left Parietal effect is also independent from another effect with overlapping time-course: the P3b effect (described in Chapter 3).

4.3.2 The Left Parietal Effect and the P3b

The P3b has a centro-parietal distribution over the scalp and peaks between 300 and 800ms post stimulus presentation. There is, therefore, an overlap between the P3b and the Left Parietal effect both in time course and scalp distribution (see also Chapters 3, 6 & 7). Moreover, given the fact that both effects reflect large parietal positivities, the

Left Parietal effect has often been considered as closely related to the P3b. The Left-Parietal old/new effect has in fact been described as the "P300 old/new difference" (Johnson, 1995) and the "P600 old/new effect" (Curran, 1999; Rugg & Doyle, 1992) and has been considered to co-occur with the P3b (Bentin & McCarthy, 1994; Spencer, Vila Abad, & Donchin, 2000). From this perspective the relative positivity of correctly recognized old (Hits) compared to new (Correct Rejections) items may be due to the relatively lower subjective probability of Hits yielding a "target" effect (see also Chapter 3; Neville et al., 1986). This target effect has also been proposed to emerge when the test item matches an episodic memory trace. The positivity for Hits may therefore represent matching instead of recognition, as matching judgments are associated with a positivity compared to mismatches (Squires et al. 1973).

The discussion about the putative independence between the Left Parietal effect and the P3 effect is clearly important in investigating the validity of the two effects. In fact, if the two effects are shown to be related then a number of possibilities arises. For instance: is the Left Parietal effect to be considered a part of the P3 family and, if so, would it be correct to describe the P300 family as sensitive to memory in broad terms? Is the P300 effect actually reflective of the memory demands of the task – even in the simple oddball paradigm typically used to measure the P3b, what the participant is doing is responding differentially to stimuli presented repeatedly.

An analysis of the memory and oddball paradigm suggests that the difference between the two procedures and definitions appears largely to be quantitatively related to the number of repetitions involved. According to this perspective the Left Parietal effect is not elicited by incorrectly classified old items, or misses, simply because these stimuli are not attended to and encoded in the first place, making it hard to rule out entirely the possibility that the Left Parietal Effect indexes repetition.

There are a number of ways in which memory and probability sensitivity could be separated experimentally. For example if the topography of the Parietal old/new effect is invariant to different procedures and modalities, one would in fact expect to see a Left-Parietal effect obtained by contrasting the second correctly discriminated target presentation compared to the first one, including therefore the typical oddball paradigm used to elicit a P3b effect. Moreover, if the Left Parietal effect is exclusively sensitive to recollection, there are no theoretical reasons to believe that the relative probability of old (Hits) and new (Correct Rejections) items in the test phase of a recognition memory experiment should have an influence on the size of the ERP correlate of recollection. We investigated directly this experimental question in Chapter 7.

4.4 Reliability and Validity of the Left Parietal Effect

Inter-laboratory reliability of the Left Parietal effect has not been directly investigated, as far as we are aware, therefore the results presented in Chapter 5 are novel within the ERP literature. However, inter-individual reliability of the Left Parietal effect has been directly investigated on a large group of participants (MacLeod & Donaldson, 2011), finding a majority of participants showing the Left Parietal effect, but a minority of subjects (32 over 122) not displaying the effect (see Figure 4.4). MacLeod and Donaldson conclude that "changes in the size of the Left Parietal effect do not reflect difference in memory performance", as the subgroups showing different electrophysiological patterns did not differ behaviourally in their sensitivity, response bias or reaction time.

In terms of the validity of the effect, the independence of the electrophysiological pattern from all behavioural variables of interest shown by MacLeod and Donaldson puts into question the role of the Left Parietal effect as a neural correlate of recollection. Assuming that the behavioural performance in the old/new recognition task implemented by MacLeod and Donaldson is not entirely based on familiarity memory, there should be in fact a relationship between the size of the Left Parietal effect and recognition performance. This problematic lack of relationship between the Left Parietal effect and relevant behavioural variables is further discussed in Chapters 5 & 10.

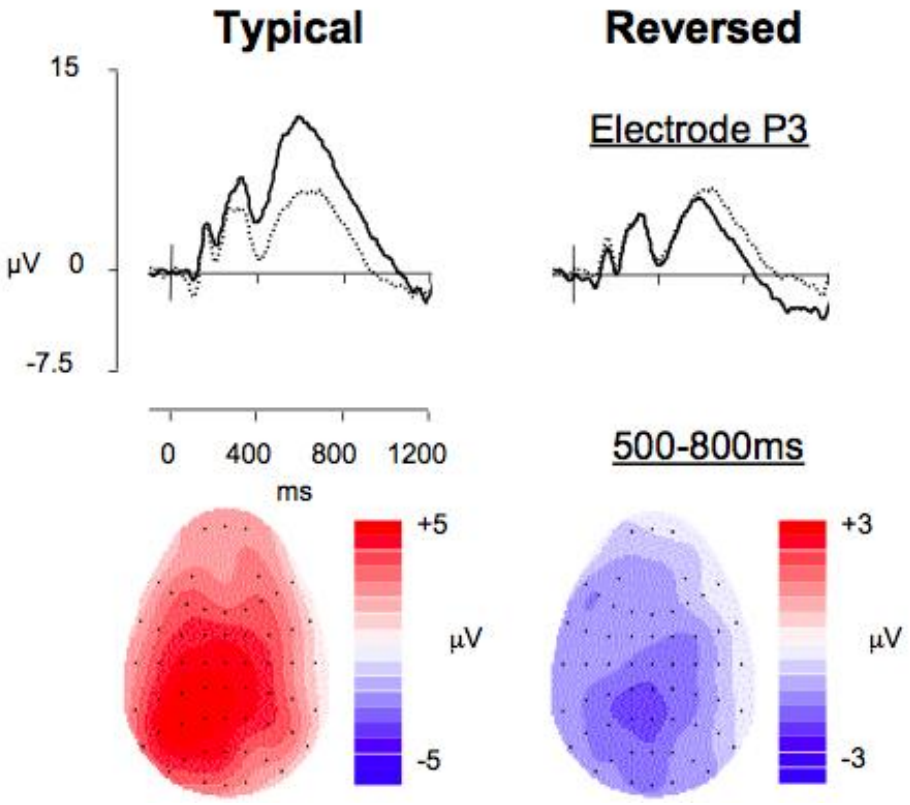


Figure 4.4 Waveforms and topographic maps showing the Left Parietal effect from two subgroups of participants from a pool of 122 subjects. The data on the left show a group displaying the typical Left Parietal effect (N=58); on the right a group showing a reversed pattern, a parietal negativity (N=32). Groups do not differ behaviourally in their sensitivity, response bias and reaction time.

4.5 Summary

The Left Parietal effect is considered to be an index of recollection within dual process theories of recognition memory, as shown by the fact that its size increases as the amount of remembered information increases. The Left Parietal effect is a measure of recollection, but not familiarity memory: the parietal old/new effect has been in fact dissociated from the Bilateral Frontal effect, a neural correlate of familiarity memory. However, some researchers consider the putative correlate of recollection to belong to the P300 'family'. Inter-laboratory reliability of the Left Parietal effect has not been directly assessed in the previous literature, therefore the results of the reliability analysis presented in Chapter 5 constitute a novel contribution. There is some evidence however pointing to the fact that the Left Parietal effect has a relatively weak inter-individual reliability and validity, since it has been shown that the size and polarity of the effect appear to be unrelated to several behavioural parameters measured during a recognition performance. The next Chapter presents results of an inter-laboratory and inter-individual reliability analysis carried out for all three experimental effects of interests considered in the current thesis.

Chapter 5

Reliability Assessment

As mentioned in the Introduction and in Chapter 1, brain activity as measured by the EEG has a high degree of variability in the single subject and across subjects, and it is important to understand the factors controlling this variability and at the same time to have precise measurement tools yielding the smallest possible measurement error. Since reproducibility and internal consistency are different but equally important aspects of reliability, in the current assessment we investigated both reliability across laboratories and inter-individual reliability of the N400, the P3b and the Left Parietal effect, three of the most important effects in the ERP literature considered to involve linguistic, attentional and memory processes, with the two-folded purpose of a) assessing the precision of measurement tools used in this form of neuroimaging, and b) of investigating inter-individual reliability across experimental effects.

5.1 Reliability

5.1.1 Reliability across Laboratories

When assessing reliability of ERPs across laboratories there are many technical variables that can potentially influence the outcome of such an assessment. The present

study was conducted to verify if reproducible results can be obtained across different laboratories using the same experimental procedure, but different technical equipment. The study was carried out across two ERP research laboratories in Scotland, one located in Aberdeen and the other located in Stirling, having different data acquisition systems (BioSemi in Aberdeen and Neuroscan in Stirling - see methods section for details). Importantly, the data processing steps were kept constant across laboratories and so any detected difference across laboratories would have to be due to differences in the experimental apparati or differences across the two pools of participants.

The BioSemi and the Neuroscan acquisition systems differ in many perspectives. For instance, BioSemi ActiveTwo uses electrodes that integrate the first stage of amplification into the Ag-AgCl electrode, allowing theoretically very low noise in the measurement at the electrode level, without skin preparation. By contrast, Neuroscan's electrodes do not have any amplification at the electrode level and therefore require skin preparation to obtain the required impedance levels. Another important difference across the two systems is that in the BioSemi system the conventional ground electrode, used in the Neuroscan system, is replaced with two separate electrodes: a Common Sense Mode (CSM) active electrode and a Driven Right Leg (DRL) passive electrode (see also Methods section). These two electrodes form a feedback loop that allows the average potential of the experimental participant to be as close as possible to the reference voltage of the analogue to digital box, yielding 40 dB extra CMRR

(Common Mode Rejection Ratio) at 50 Hz, where a high CMRR is an important factor in achieving a higher signal-to-noise ratio (Huhta & Webster, 1973).

An important difference across laboratories to be taken into account is that data in Aberdeen were recorded in DC (Direct Current) mode (the default mode for the BioSemi system), while in Stirling data were recorded in AC (Alternating Current) mode. Many ERP laboratories prefer using AC rather than DC amplifiers because they tend to be easy to calibrate and generally yield more stable EEG compared to a DC system. An AC circuit functions in fact as an analogue filter, attenuating and phase shifting the input voltage based on the amplifier's time constant (e.g. Gasser et al., 1982; Elbert & Rockstroh, 1980). By comparison a DC recording is considered to be a form of "true recording", as the AC amplifier's time constant can potentially lead to a distortion of low frequency ERP components. While a DC amplifier does not exclude any low frequencies, and has the advantages of capturing slow activity, it also has the disadvantages of being more susceptible to drift artifacts (Hennighausen et al., 1993).

As the ERP components involved in the present reliability investigation do not belong to the slow component category the difference in amplification modality should not yield detectable discrepancies across laboratories, but nonetheless it is an important factor to be taken into account when investigating consistency of results across facilities collecting electrophysiological data. Overall, the current assessment will

clarify whether or not the technical differences present across laboratories are relevant when measuring ERP effects that are clearly established in the neuroscientific literature.

5.1.2 Inter-individual Reliability

Inter-individual variation, selection and retention of genetic, behavioural and neural information have been described as fundamental factors in allowing species to be adaptive within a potentially changing environment (Donahoe, 2003). From a statistical perspective however, variation, selection and retention in a population of individuals can be described in terms of changes in "signal-to-noise" over time (i.e. how a distribution's mean and standard deviation vary over time as a function of environmental feedback). Inter-individual variability will in turn determine the degree of inter-individual reliability of experimental effects: the higher the degree of variability across individuals, the lower the degree of inter-individual reliability.

Reliability of results across individuals is especially important in behavioural and neuroscientific research where the measured variables typically have a high degree of variability (Yarkoni & Braver, 2010). Measurements across individuals in psychological research have in fact shown important individual differences in cognitive, emotional, social and perceptual functioning and this person-to-person variation seems to increase with age (MacDonald et al., 2006). To describe inter-

individual variability in neural activity, behavioural variables such as accuracy (Callicott et al., 1999; Gray, Chabris, & Braver, 2003) and reaction time (Rypma, Berger, & D'Esposito, 2002; Rypma & D'Esposito, 1999; Schaefer et al., 2006; Wager, Sylvester et al., 2005) have been used as predictors of brain activation.

In practice the results of between-subjects individual difference analysis and within subject analysis have often been found to converge (Gray et al., 2003; Lee et al., 2006). Nonetheless, there are cases in the literature in which within subject results are conflicting with individual difference analysis. For example the Left Ventrolateral Prefrontal Cortex (VLPFC) is considered to support resolution of proactive interference (Jonides & Nee, 2006), but individuals who are better at resolving proactive interference show decreased VLPFC activation than individuals who are worse (Nee, Jonides, & Berman, 2007). Discrepancies between the group level and the individual level of analysis point to a higher variability, or decreased reliability, across individuals compared to examples of consistencies between the individual and the group levels. In the ERP literature, as described in Chapters 1-4, studies of reliability were typically focused on the reliability of ERP effects across laboratories and within laboratory, and when interindividual variability was investigated (e.g. Pekkonen et al., 1995) it was not investigated across effects. To our knowledge, interindividual reliability of ERPs has yet to be investigated within the same pool of participants on a range of established effects representing different cognitive functions.

5.2 Methods

5.2.1 Participants – Aberdeen

Thirty-two (11 male) right-handed native English speakers participated for course credit. Participants mean age was 19.5 years (range 18-24) and all reported normal or corrected to normal vision with no history of neurological disorders. Informed consent procedures were approved by the Psychology ethics committee at the University of Aberdeen.

5.2.2 ERP Recording Parameters and Analysis - Aberdeen

EEG was recorded using a Biosemi Active-Two amplifier system (Biosemi, Amsterdam, Netherlands) from 64 locations based on the International 10-20 system (Jasper, 1958). Electrodes, placed in an elastic cap, were active Ag–AgCl and two additional electrodes named "Driven Right Leg" and "Common Mode Sense" were used as ground and online reference (www.biosemi.com/faq/cms&drl.htm; see also Metting Van Rijn, Peper, & Grimbergen, 1990, 1991). All channels were re-referenced offline to averaged mastoids reference. The EEG was sampled at a 512Hz rate and downsampled offline to 250Hz. Vertical and horizontal EOG were recorded from pairs of electrodes placed above and below the left eye, and on the outer canthi, to allow ocular artifact reduction. Electrode offsets were kept between ±25 mV.

Data was processed using Neuroscan Edit 4.3 (www.neuroscan.com). EEG was band pass filtered between 40 and 0.1Hz, and segmented into 2040ms epochs, starting 104ms before stimulus onset. Waveforms were baseline corrected and smoothed over a 5-point kernel. Ocular artifacts were removed using linear regression (Semlitsch et al., 1986), and trials were excluded if drift exceeded ±75 μV, or if in any point during the epoch activity exceeded ±100 μV. The mean number of trials contributing to ERPs in each condition for the N400 effect were: Unrelated 80.31, Related 80.06; for the P3b effect: Standard 248.31, Target 34.46; for the Left Parietal effect: Hits 55.18, Correct Rejections 55.9. Statistical analyses were performed on mean voltage data relative to the pre-stimulus baseline period, using repeated measures ANOVA. The Geisser–Greenhouse correction for nonsphericity of data was applied as appropriate and corrected df and F values are reported.

5.2.3 Participants – Stirling

Thirty-two (16 male) right-handed native English speakers participated for payment (£5 an hour). Participants mean age was 20.1 years (range 18-24) and all reported normal or corrected to normal vision with no history of neurological disorders. Informed consent procedures were approved by the Psychology ethics committee at the University of Stirling.

5.2.4 ERP Recording Parameters and Analysis - Stirling

EEG was recorded using a Synamps^2 amplifier and Acquire 4.3 software (Neuromedical supplies; www.neuroscan.com). Data was sampled from 62 extended 10-20 (Jasper, 1958) scalp sites using Ag–AgCl electrodes embedded in an elasticised cap (Quickcaps, Neuromedical Supplies; www.neuroscan.com). All channels were referenced to an electrode placed between CZ and CPZ and then re-referenced offline to averaged mastoids reference. Vertical and horizontal EOG were recorded from pairs of electrodes placed above and below the left eye and on the outer canthi to allow ocular artifact reduction. Impedances were maintained below 5kΩ. The data were digitised at a rate of 250Hz and band pass filtered during recording between 40 and 0.1Hz. The mean number of trials contributing to ERPs in each condition for the N400 effect were: Unrelated 96.59, Related 97.18; for the P3b effect: Standard 310.25, Target 44.78; for the Left Parietal effect: Hits 68.03, Correct Rejections 69.59. Data processing and analysis followed the same criteria used in processing the data collected in Aberdeen.

5.2.5 Reliability Analysis Parameters

The 58 electrodes common to both acquisition systems were FP1, FP2, FPZ, AF3, AF4, FZ, F1, F2, F3, F4, F5, F6, F7, F8, FCZ, FC1, FC2, FC3, FC4, FC5, FC6, FT7, FT8, CZ, C1, C2, C3, C4, C5, C6, T7, T8, CPZ, CP1, CP2, CP3, CP4, CP5, CP6, TP7, TP8, PZ, P1, P2, P3, P4, P5, P6, P7, P8, POZ, PO3, PO4, PO7, PO8, OZ, O1, O2, and reliability analyses were conducted on a subset of those electrodes representing all

locations and superior and inferior sites from frontal to parietal areas(F1, F2, F5, F6, FC1, FC2, FC5, FC6, C1, C2, C5, C6, CP1, CP2, CP5, CP6, P1, P2, P5, P6). Consistently with the existing literature (e.g. Duncan et al., 2009; Rugg & Curran, 2007; Alexander et al., 1994) the N400 effect was analyzed in the 300-500ms time-window; the P3b effect in the 275-400ms time-window and the Left Parietal effect in the 500-700ms time-window. Analysis of the Left Parietal effect was performed on correctly recognized old (Hits) and new (Correct Rejections) items.

To investigate reliability across laboratories a comparison of behavioural variables was first conducted for each effect. Electrophysiologically, the ERP effects of interest were statistically characterized first separately for each of the laboratories, investigating the statistical significance of the difference across experimental conditions (unrelated-related for the N400; standard-target for the P3b and hits-correct rejections for the Left Parietal Effect) and its distribution across scalp sites. The next step comprised directly investigating possible differences across laboratories by statistically comparing difference waves. After the assessments of reliability across laboratories were carried out, inter-individual reliability was investigated by pooling results from both laboratories and calculating for each effect a) the proportion of individuals showing the effect, b) the signal to noise ratio, c) cronbach alpha and d) split-half *r*, all considered to be measures of reliability and internal consistency of results (Cronbach, 1951; Kaplan & Saccuzzo, 2001; Yarkoni & Braver, 2010).

5.3 N400 Effect

5.3.1 Methods

Two hundred and four word pairs were created taken from the MRC Psycholinguistic Database (www.eat.rl.ac.uk). The words were divided into two experimental conditions: word pairs with no association and word pairs with high association (see Table 5.1 for examples). Association ratings were taken from the Edinburgh Association Thesaurus (Kiss et al., 1973) a word production norm indexing the strength of associative links between words in terms of the probability that a specific word will come to mind in association with another one.

Unrelated	**High Association**
Gesture - Heaven	*Nursery - Rhyme*
Corn - Really	*Lean - Meat*
Hawk - Movie	*Cherry - Tree*
Majestic - Trunk	*Spark - Plug*
Interview - Week	*Camel - Hump*
Mirror - Thumb	*Capital - City*
Parade - Slice	*Crystal - Ball*
Widow - Painter	*Atom - Bomb*
Sweep - Ugly	*Bread - Butter*
Soap - Coin	*Horror - Film*

Table 5.1 Examples of word pairs across experimental conditions.

While the degree of association between words was manipulated, semantic distance was kept statistically constant across experimental conditions. Semantic distance was indexed through a semantic space model, which assesses numerically how interchangeable a specific word is with other words within a context that is provided by a large language corpus. The psychological validity of the interchangeability index has been shown in studies (Huettig & Altmann, 2005; Huettig et al., 2006) demonstrating that interchangeability measures behaved similarly to other indices of semantic relatedness, including empirical indices of feature overlap (Cree & McRae, 2003). Word frequency (assessed using the Kucera and Francis frequency norms, 1967), word length and imagability (assessed using the MRC psycholinguistic database and the Cortese and Fugett norms, 2004) of the individual words within each pair were also statistically matched across conditions assuring that the degree of association would be the independent variable of interest.

The experiment involved presentation of the 204 experimental word pairs. ERPs were recorded while participants were performing a judgement of relatedness task. Two words (prime and target) were presented, separated by a stimulus onset asynchrony of 800ms. Each word was presented visually using a white uppercase 18-point Courier New font against a black background.

Participants were instructed to read the first word, then wait for the second word, read it, and then wait for a question appearing on the screen asking them either "RELATED?" or "UNRELATED?". Participants were instructed to say "Yes" or "No" by pressing the extreme left and right hand button using a 5 button response-box (the mapping of responses to buttons was counterbalanced across participants). Presentation of the question "Related" or "Unrelated" following each pair was randomized. It is important that participants do not know what to press when the target is presented so that a P3b component elicited after the target can be avoided. The P3b is a very large component and it would most likely overshadow the smaller N400. By having participants making a choice not after the target but after the question it is possible to elicit and record a "pure" N400 not contaminated by P3b (Hill et al., 2005).

Each trial began with a fixation cross (+) presented in the centre of the screen for 700 ms, followed by the prime, presented for 150ms. Each prime was then followed by a blank screen for 650ms. The target was then displayed for 1000ms. After a delay of 200ms the question would appear and stay on the screen until the participant had responded; it would disappear after 2 seconds if no response was made. Following the response a new trial began with a fixation cross.

5.3.2 Results

5.3.2.1 Behavioural Comparison across Laboratories

A repeated measures ANOVA was performed on reaction times to targets using a within subject factor of condition (unrelated, high association) and a between subjects factor of Laboratory (Stirling, Aberdeen) yielding a main effect of condition [$F(1, 62) = 178.38$; $p < .001$] but no differences across laboratories [$F(1, 62) = .70$; $p = .405$], showing that reaction times to highly associated targets were quicker than reaction times to unrelated targets, and that the resulting priming effect did not differ across laboratories.

5.3.2.2 N400 effect - Stirling Laboratory

The N400 ERP effect measured at the laboratory in Stirling was investigated with an initial ANOVA with factors of Condition (unrelated-related), Location (frontal, fronto-central, central, centro-parietal, parietal) and Site (superior: sites 1 & 2; inferior: sites 5 & 6), yielding a main effect of Condition [$F(1, 31) = 141.42$; $p < .001$], a significant Condition x Location interaction [$F(1.192, 36.947) = 14.79$; $p < .001$], a significant Condition x Site interaction [$F(1, 31) = 114.57$; $p < .001$], and a significant Condition x Location x Site interaction [$F(1.965, 60.93) = 6.28$; $p < .004$]. Follow up ANOVAs on each separate location revealed the effect to be significant at all locations [Frontal: ($F(1, 31) = 80.02$; $p < .001$); Fronto-Central: $F(1, 31) = 106.74$; $p < .001$, Central: $F(1, 31) = 138.3$; $p < .001$; Centro-Parietal: $F(1, 31) = 169.83$; $p < .001$; Parietal: $F(1, 31) = 163.77$; $p < .001$]. Overall these results show a broadly distributed effect, with a

centro-parietal maximum, larger at sites closer to the midline, as can be seen from Figures 5.1 and 5.2.

5.3.2.3 N400 effect – Aberdeen Laboratory

The same ANOVA performed on the N400 data from the Stirling laboratory was also performed on the Aberdeen results. The analysis yielded a main effect of Condition [$F(1, 31) = 106.57$; $p < .001$], a significant Condition x Location interaction [$F(1.545, 47.89) = 12.05$; $p < .001$] and a significant Condition x Site interaction [$F(1, 31) = 43.51$; $p < .001$]. Follow up ANOVAs on each separate location revealed the effect to be significant at all locations [Frontal: ($F(1, 31) = 59.25$; $p < .001$); Fronto-Central: $F(1, 31) = 80.57$; $p < .001$, Central: $F(1, 31) = 116.07$; $p < .001$; Centro-Parietal: $F(1, 31) = 120.57$; $p < .001$; Parietal: $F(1, 31) = 118.50$; $p < .001$]. Consistently with the results from the Stirling Laboratory (see Figure 5.2) these results show an effect with a centro-parietal maximum, broadly distributed and larger at sites closer to the midline.

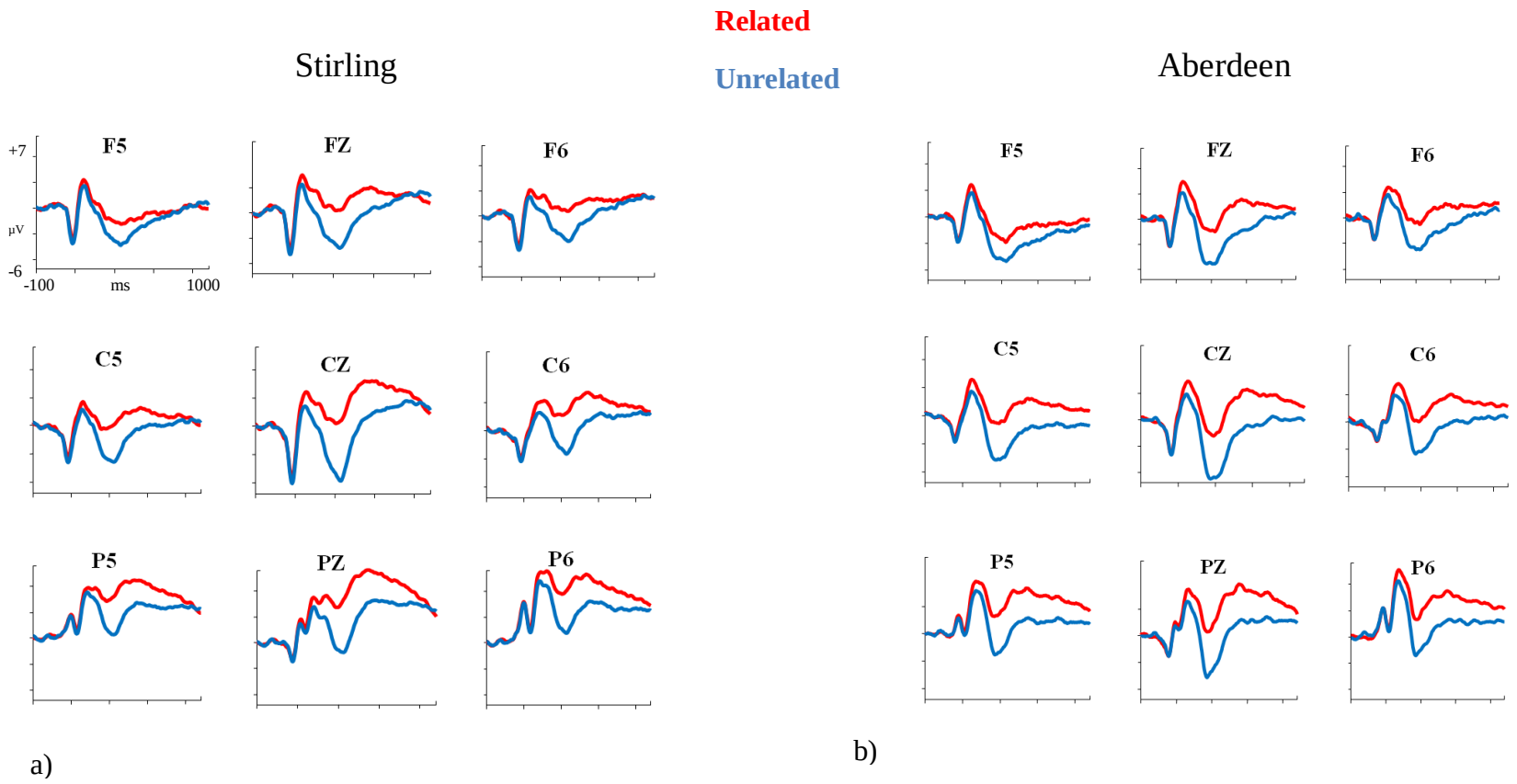


Figure 5.1 Comparison across laboratories of the N400 effect. Panel a) shows grand average waveforms of the effect relative to the Stirling Laboratory; Panel b) shows grand average waveforms effect measured at the laboratory located in Aberdeen. Nine electrodes are shown for each laboratory from frontal to parietal locations; data is displayed positive up.

5.3.2.4 N400 Effect – Comparison across Laboratories

After characterizing the effect in each of the laboratories, a direct comparison across laboratories was carried out using difference waves, by means of an ANOVA with the same factors used in the initial analyses and an additional between subjects factor (Laboratories: Stirling, Aberdeen). This analysis did not yield any significant differences across laboratories. To further investigate possible differences at the single electrode spatial resolution a between subjects ANOVA with a factor of Laboratory was carried out for each individual electrode in the analysis. As Figure 5.2 and Table 5.2 show, the size of the effect did not differ across laboratories significantly at any of the electrodes. Overall, therefore, the results suggest a statistically reliable N400 effect was present in both laboratories, and no significant differences were detected across laboratories.

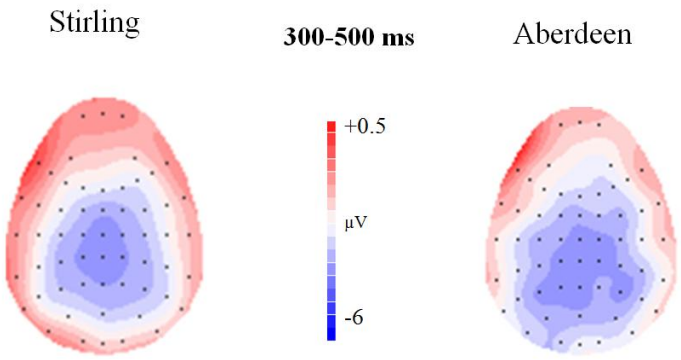


Figure 5.2 Topographic maps showing the N400 effects elicited in the inter-laboratory reliability comparison across Stirling and Aberdeen. In both cases the distribution of the effects has a clear centro-parietal maximum.

Site	F	*p*
F5	1.19	.279
F1	.04	.831
F2	.00	.973
F6	.00	.959
FC5	.24	.621
FC1	.00	.980
FC2	.15	.696
FC6	.24	.621
C5	2.1	.151
C1	.03	.848
C2	.02	.878
C6	.00	.993
CP5	.73	.395
CP1	.00	.998
CP2	.01	.895
CP6	.76	.387
P5	1.4	.241
P1	.23	.629
P2	.00	.949
P6	.17	.676

Table 5.2 Across laboratories comparison of the N400 effect at the single electrode spatial resolution. For each electrode in the analysis the F and the *p* values are reported.

5.4 P3b Effect

5.4.1 Methods

ERPs were elicited by randomized presentation of binaural auditory stimuli (600Hz and 1600Hz). Duration of the stimuli was 80ms and there was an inter-stimulus interval of 1.5s. One of the two stimuli was presented 12.5% of the trials, and the other

the 87.5% of the trials. Participants were instructed to press the central button of a five-button response box after hearing the infrequent, or "target", stimulus and the use of left vs. right hand in responding to targets was counterbalanced across participants. Moreover, having a high or low pitch target stimulus was also counterbalanced across participants to ensure the P3b effect would not be confounded by the physical features of the stimuli.

5.4.2 Results

5.4.3 Behavioural Comparison

Accuracy in the oddball task was 99.18% for participants in Aberdeen and 99.81% for participants in Stirling. Mean reaction time to targets was 294.94ms in Aberdeen and 273.88ms in Stirling. Reaction time data to targets were found not to differ statistically across laboratories [$F(1, 62) = 1.32$; $p = .254$].

5.4.4 P3b Effect – Stirling Laboratory

The P3b effect measured at the Stirling laboratory was investigated by means of an initial ANOVA with factors of Condition (standard-target), Location (frontal, fronto-central, central, centro-parietal, parietal) and Site (superior: sites 1 & 2; inferior: sites 5 & 6). The analysis yielded a main effect of Condition [$F(1, 31) = 210.424$; $p < .001$], a significant Condition x Location interaction [$F(1.216, 37.688) = 53.76$; $p < .001$], a significant Condition x Site interaction [$F(1, 31) = 78.71$; $p < .001$], and a significant

Condition x Location x Site interaction [F(1.744, 54.060) = 10.03; $p < .001$]. Follow up ANOVAs on each separate location revealed the effect to be significant at all locations [Frontal: (F(1, 31) = 70.63; $p < .001$); Fronto-Central: F(1, 31) = 115.51; $p < .001$, Central: F(1, 31) = 175.14; $p < .001$; Centro-Parietal: F(1, 31) = 266.07; $p < .001$; Parietal: F(1, 31) = 309.54; $p < .001$]. Overall these results show a broadly distributed effect, maximal over parietal and centro-parietal areas and larger at sites closer to the midline.

5.4.5 P3b Effect – Aberdeen Laboratory

The same ANOVA performed on the data from the Stirling laboratory was also performed on the P3b results from the Aberdeen laboratory. The analysis yielded a main effect of Condition [F(1, 31) = 99.47; $p < .001$], a significant Condition x Location interaction [F(1.440, 44.627) = 72.86; $p < .001$], a significant Condition x Site interaction [F(1, 31) = 41.17; $p < .001$], and a significant Condition x Location x Site interaction [F(2.835, 87.883) = 2.78; $p < .05$]. Follow up ANOVAs on each separate location revealed the effect to be significant at all locations [Frontal: (F(1, 31) = 42.69; $p < .001$); Fronto-Central: F(1, 31) = 63.48; $p < .001$; Central: F(1, 31) = 89.88; $p < .001$; Centro-Parietal: F(1, 31) = 120.73; $p < .001$; Parietal: F(1, 31) = 147.79; $p < .001$]. These results show an effect maximal over Parietal and Centro-Parietal areas, broadly distributed effect and larger at sites closer to the midline, consistently with the topographic distribution found in the ERP laboratory in Stirling.

5.4.6 P3b Effect – Comparison across Laboratories

After characterizing the effect in each of the laboratories, a direct comparison (see Figures 5.3 and 5.4) across laboratories was carried out using difference waves, employing by an ANOVA with the same factors used in the initial analyses and an additional between subjects factor (Laboratories: Stirling, Aberdeen). The analysis did not yield any significant differences across laboratories. To further investigate possible differences another between subjects ANOVA with a factor of Laboratory (Stirling, Aberdeen) was carried out for each individual electrode in the analysis, yielding the results shown in Table 5.3. The two effects were found not to differ across laboratories at the single electrode spatial resolution. Overall the results reveal a set of P3b effects that are consistent both with the previous literature and with each other across laboratories.

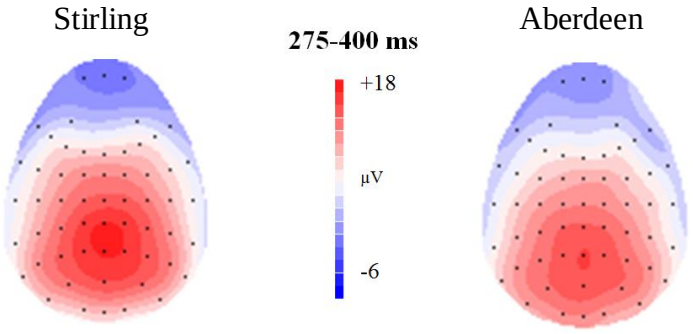


Figure 5.3 Topographic maps showing the P3b effects elicited in the inter-laboratory reliability comparison across Stirling and Aberdeen. In both cases the distribution of the effects has a clear parietal maximum.

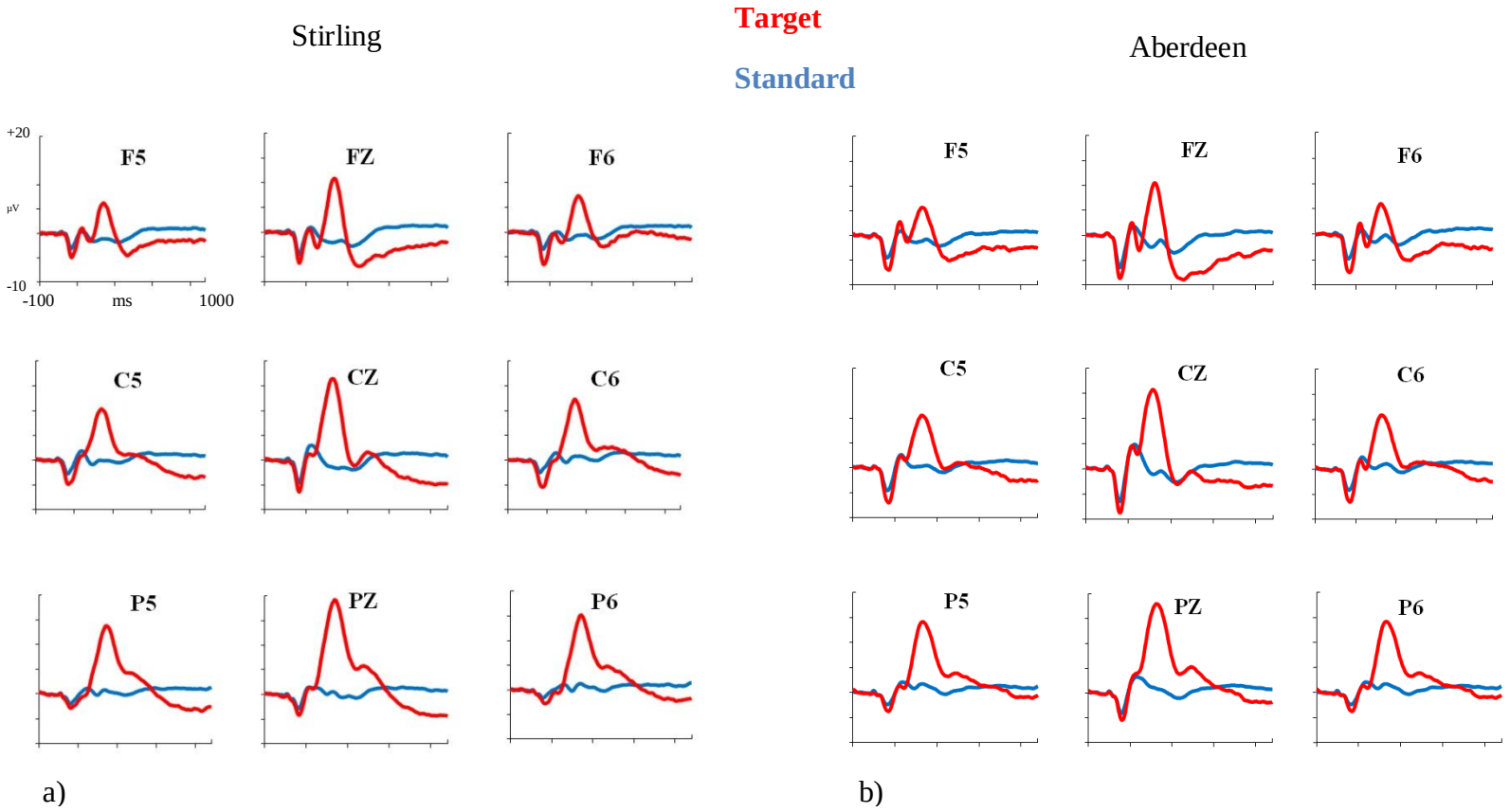


Figure 5.4 Comparison across laboratories of the P3b effect. Panel A shows grand average waveforms and topographic distribution of the effect relative to the Stirling Laboratory; Panel B shows grand average waveforms and topographic distribution of the effect elicited at the Aberdeen Laboratory. Nine electrodes are shown for each laboratory from frontal to parietal locations; data is displayed positive up.

Site	F	Sig.
F5	.68	.412
F1	.67	.415
F6	1.89	.173
F2	1.06	.307
FC5	1.93	.169
FC1	1.59	.212
FC6	2.41	.125
FC2	1.14	.289
C5	.26	.610
C1	1.33	.253
C6	1.06	.307
C2	2.07	.154
CP5	.33	.568
CP1	1.64	.205
CP6	2.83	.097
CP2	2.85	.096
P5	.22	.641
P1	1.27	.263
P6	.90	.346
P2	1.69	.198

Table 5.3 Comparison of the P3b effect across laboratories at the single electrode spatial resolution. For each electrode in the analysis are reported the F and the *p* values.

5.5 Left Parietal Effect

5.5.1 Methods

Stimuli consisted of 176 words presented visually taken from the MRC Psycholinguistic Database. Mean word frequency (and standard deviation) was 13.79 (10.25) counts per million, and word length ranged between 3 and 9 letters. The experiment was divided into four study-test blocks. During each study phase 22 words

were shown and participants judged if the words referred to living or non-living objects. In each test phase 44 words were shown, half of them old and half of them new, while participants performed an old/new recognition task. Across participants each word served equally frequently as an old or new item. For the study phase each trial began with a fixation cross presented for 2100ms, followed by the experimental stimulus for 300ms. The stimulus was followed by a blank screen during which the participant performed the living/non-living judgement. Each test phase trial started with a fixation cross presented for 2100ms, followed by the stimulus for 300ms and by a blank screen for 2700ms. During the blank screen participants performed the old/new recognition task by pressing the extreme left and right buttons of a 5 button response box. Mapping of old and new responses to buttons was counterbalanced across participants.

5.5.2 Results

5.5.2.1 Behavioural Comparison across Laboratories

Behavioural consistency across laboratories was investigated by comparing a measure of discriminability called 'sensitivity' (Snodgrass and Corwin, 1988), computed by subtracting the probability of committing a False Alarm from the probability of making a Hit. The ANOVA did not yield a significant result [$F(1, 62) = 2.30$; $p = .134$]. Moreover response bias, the tendency of participants to be more conservative or liberal in choosing "old" during the recognition memory test was analysed to assess possible differences across laboratories. The ANOVA did not yield a significant result

[F(1, 62) = .02; p = .880]. Additionally, reaction time data to Hits [F(1, 62) = .34; p = .559] and Correct Rejections [F(1, 62) = .11; p = .741] were also found not to differ statistically across laboratories.

5.5.2.2 Left Parietal Effect – Stirling Laboratory

The ERP effect was investigated statistically with an initial ANOVA, employing factors of Condition (Hits, Correct Rejections), Location (Frontal, Fronto-Central, Central, Centro-Parietal, Parietal and Parietal-Occipital), Hemisphere (Left, Right) and Site (superior: sites 1 & 2, PO3, PO4; inferior: sites 5 & 6, PO7, PO8). The Hemisphere factor and the PO electrodes were introduced to best characterize the typical parietal and asymmetrical nature of the Left Parietal effect. The ANOVA yielded a significant effect of Condition [F(1, 31) = 28.34; p < .001], a significant Condition x Location interaction [F(1.220, 37.817) = 6.07; p < .02], a significant Condition x Site interaction [F(1, 31) = 8.51; p < .008], and a significant Condition x Location x Site interaction [F(2.620, 81.216) = 6.38; p < .002].

Follow up ANOVAs on each location found the effect to be significant at all locations [Frontal: (F(1, 31) = 10.70; p < .004); Fronto-Central: F(1, 31) = 18.11; p < .001, Central: F(1, 31) = 27.64; p < .001; Centro-Parietal: F(1, 31) = 28.84; p < .001; Parietal: F(1, 31) = 25.09; p < .001; Parietal-Occipital: F(1, 31) = 24.35; p < .001]. A subsidiary analysis focused on parietal locations (Cp, P & PO) found the parietal effect

to be larger on the left hemisphere compared to the right hemisphere, as reflected by a significant Condition x Hemisphere interaction [$F(1, 31) = 4.59$; $p < .05$]. Overall these results reflect a broadly distributed effect that is statistically largest over left-parietal sites.

5.5.2.2 Left Parietal Effect – Aberdeen Laboratory

The effect was investigated statistically with the same ANOVA performed on the data from the Stirling laboratory. The ANOVA yielded a significant effect of Condition [$F(1, 31) = 27.95$; $p < .001$], a significant Condition x Location x Site interaction [$F(3.23, 100.11) = 3.62$; $p < .02$] and a significant Condition x Hemisphere interaction [$F(1, 31) = 6.48$; $p < .02$]. Follow up ANOVAs on each location found the effect to be significant at all locations [Frontal: ($F(1, 31) = 10.73$; $p < .004$); Fronto-Central: $F(1, 31) = 14.75$; $p < .002$; Central: $F(1, 31) = 32.44$; $p < .001$; Centro-Parietal: $F(1, 31) = 35.53$; $p < .001$; Parietal: $F(1, 31) = 28.53$; $p < .001$; Parietal-Occipital: $F(1, 31) = 23.91$; $p < .001$]. A subsidiary analysis focused on parietal locations (Cp, P & PO) found the parietal effect to be larger on the left hemisphere compared to the right hemisphere, as reflected by a significant Condition x Hemisphere interaction [$F(1, 31) = 5.32$; $p < .03$]. Overall these results reflect a broadly distributed effect largest over the left hemisphere particularly at parietal electrodes.

5.5.2.3 Left Parietal Effect – Comparison across Laboratories

After characterizing the effect in each of the laboratories, a direct comparison across laboratories (see Figures 5.5 and 5.6) was carried out using difference waves, by means of an ANOVA with the same factors used in the initial analyses and an additional between subjects factor (Laboratories: Stirling, Aberdeen). The analysis did not yield significant differences across laboratories. To further investigate possible differences another between subjects ANOVA (with a factor of Laboratory: Stirling, Aberdeen) was carried out at the single electrode spatial resolution. As Table 5.4 shows, the size of the effect did not differ across laboratories significantly at any of the electrodes.

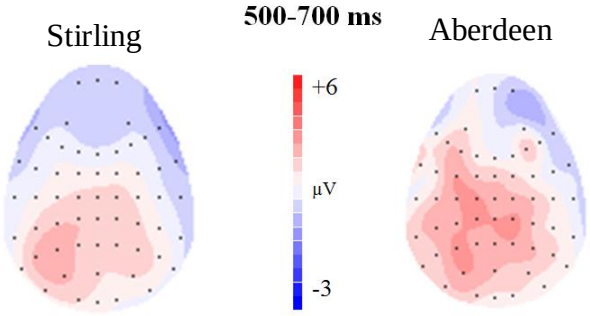


Figure 5.5 Topographic maps showing the Left Parietal effects elicited in the inter-laboratory reliability comparison across Stirling and Aberdeen. In both cases the distribution of the effects has parietal maximum, and the distribution of the effect is slightly broader over the left hemisphere for the effect measured in the Aberdeen laboratory.

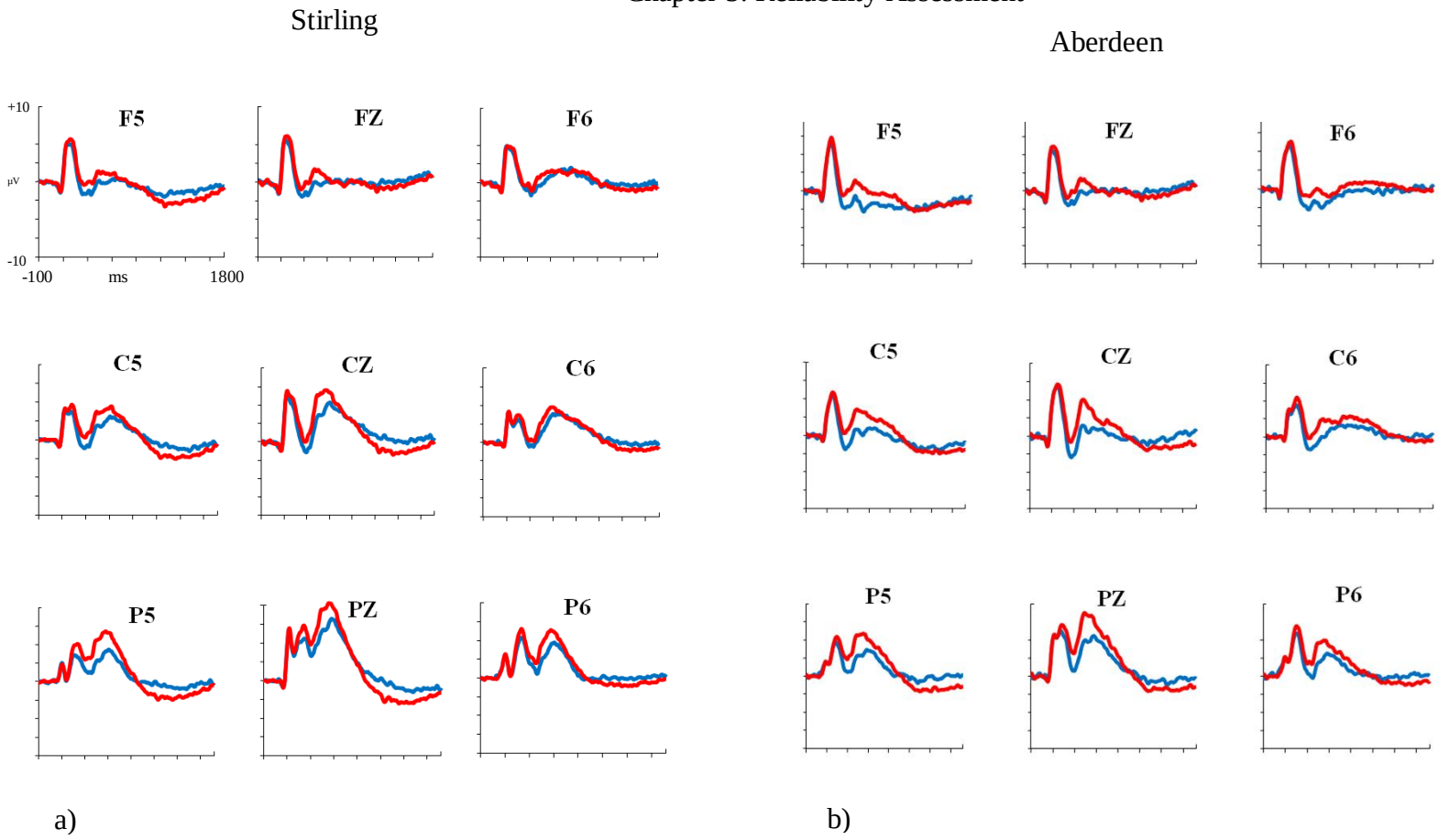


Figure 5.6 Comparison across laboratories of the Left Parietal effect. Panel a) shows grand average waveforms and topographic distribution of the effect relative to the Stirling Laboratory; Panel b) shows grand average waveforms and topographic distribution of the effect relative to the Aberdeen Laboratory. Nine electrodes are shown for each laboratory from frontal to parietal locations.

Site	F	Sig.
F5	3.72	.058
F1	.69	.407
F2	.36	.546
F2	.06	.799
FC5	1.62	.208
FC1	1.04	.310
FC6	.00	.965
FC2	.13	.718
C5	1.98	.164
C1	2.32	.133
C6	.55	.460
C2	.14	.704
CP5	.69	.407
CP1	.76	.386
CP6	.06	.795
CP2	1.00	.319
P5	.31	.576
P1	.16	.689
P6	.01	.900
P2	.80	.372
PO7	.08	.770
PO3	.20	.655
PO8	.02	.885
PO4	.00	.996

Table 5.4 Between subjects comparison across laboratories of the Left Parietal effect at the single electrode spatial resolution. For each electrode in the analysis the F and the *p* values are reported.

5.6 Inter-individual Reliability

After revealing that the elicited experimental effects were consistent both with the previous literature and across laboratories, an important consideration regards the overall inter-individual reliability of the ERP effects. As the variability of an effect across participants decreases, reliability measures such as the signal-to-noise ratio will increase. Conversely, as the inter-individual variability of the effect increases, its

signal-to-noise ratio will decrease. Consistency of results across participants was investigated by pooling results from both laboratories and calculating for each effect a) the proportion of individuals showing the effect, b) the signal-to-noise ratio, c) cronbach alpha and d) split-half *r*. Histograms in Figure 5.7 show inter-individual variability of the effects, measured over a set of electrodes where the effects were maximal (CZ, CPZ, PZ for the N400 effect; CP1, CP3, CP5 for the Left Parietal effect; CZ, CPZ, PZ for the P3b effect). The number within each bar represents the number of participants showing an effect of that magnitude, and the magnitude is indicated on the x axis.

It is worthwhile noting that in the case of the N400 all the participants showed the effect and in the case of the P3b one participant did not show the effect, whereas in the case of the Left Parietal effect eleven participants did not show the effect, suggesting that the N400 and P3b effect have an overall higher level of inter-individual reliability. The results of the Left Parietal effect inter-individual reliability analysis are compatible with the corresponding data collected by MacLeod and Donaldson (2011), previously discussed in Chapter 4 and further discussed in Chapter 10.

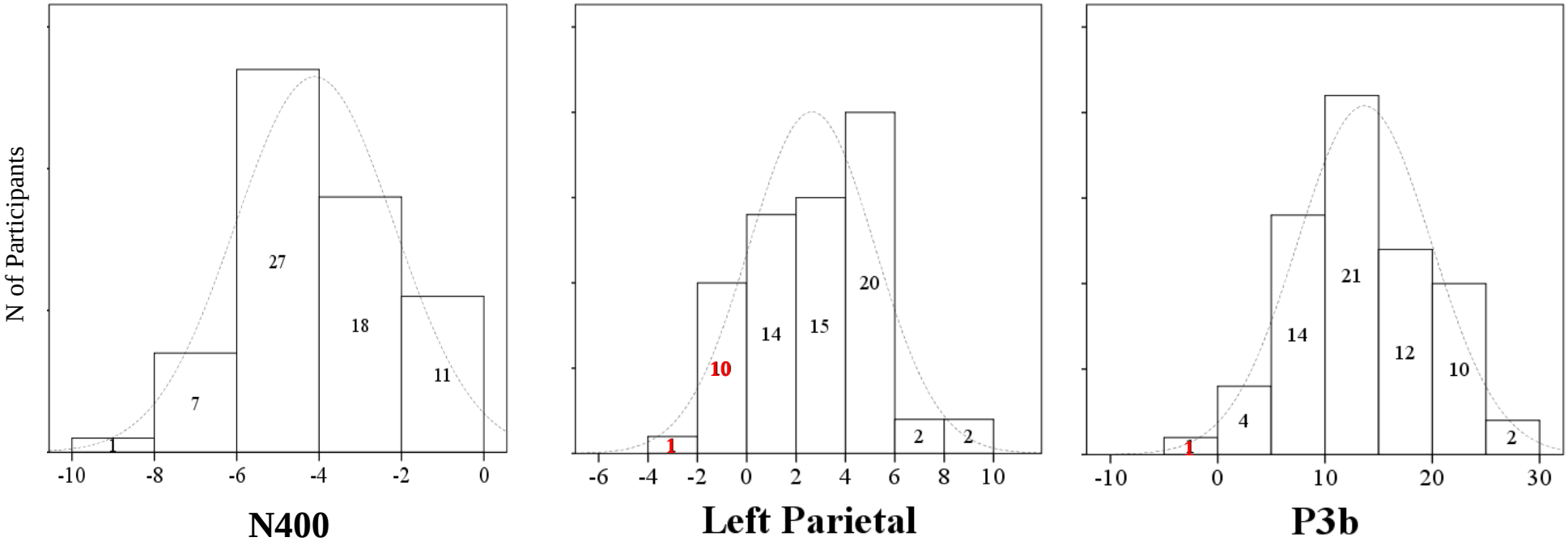


Figure 5.7 Histograms representing the distribution of the magnitude of each effect across participants. The number within each bar represents the number of participants showing an effect of that magnitude. Red numbers represent participants not showing the effect. All participants displayed a N400 effect; 11 participants did not display a Left Parietal effect and one participant did not display the P3b effect. Values on the x axis are expressed in microvolts.

Mean amplitude (and standard deviations) across all participants are reported for each effect in Table 5.5. The table also shows the signal-to-noise ratio for each of the effect, calculated (e.g. Lütkenhöner, 1995) as the average signal power (mean) divided by average noise power (standard deviation). Note that even though the P3b effect has a much larger magnitude than the N400, the signal-to-noise ratio for the two effects is similar, showing that a higher absolute magnitude does not imply a higher signal-to-noise ratio.

	Mean	**Std. Dev.**	**SNR**	**Cronbach** α	**Split-Half** r
N400	-4.1	1.92	2.13	.97	.98
Left Parietal	2.64	2.54	1.03	.86	.89
P3b	13.67	6.26	2.18	.98	.99

Table 5.5 For each investigated effect are reported the mean, standard deviation, signal to noise ratio, Cronbach α and Split-Half r.

Internal consistency of results was also assessed for each effect by calculating Cronbach's α, a widely used measure of reliability (Cronbach, 1951) sensitive to how closely related a set of individual results are as a group. Typically, Cronbach's alpha gets higher when the inter-correlations among individual values increase. For the N400 and the P3b effects very high internal consistency of results was found (α = .97; α = .98, respectively) across the 64 participants, while for the Left Parietal effect internal consistency – although not as high as the other effects – was still found to be at high levels (α = .86). Split-half reliability measures (Kaplan & Saccuzzo, 2001) found

similar results (N400: r = .98; P3b: r = .99; Left Parietal: r = .89). By convention, reliability coefficients of .8 are considered adequate in most domains of psychological research, and coefficients of .9 or more are generally considered high (Yarkoni & Braver, 2010). These results are consistent with the signal-to-noise values and with the proportion of the sample showing each effect, leading to the overall conclusion that all three effects can be considered reliable at the group level, albeit with the N400 and the P3b exhibiting a higher degree of reliability than the Left Parietal effect.

The levels of inter-individual variability relative to the P3b and N400 point to their reliability both at the group and at the individual level, while the Left Parietal effect appears to be reliable only at the group level as there is a portion of participants not showing the effect. To investigate if the subset of participants not showing the Left Parietal effect was doing so because of a comparatively poor performance, a comparison of relevant behavioural variables, sensitivity and response bias, was carried out between subjects showing the effect and subjects not showing the effect. The ANOVA did not yield significant differences [sensitivity: $F(1, 62) = 1.36$; p = .247; response bias: $F(1, 62) = .01$; p = .901] suggesting that behavioural variables are not responsible for the absence of the effect, therefore confirming the discrepancy between the individual and the group level described for the Left Parietal effect (see Table 5.6).

The observed lack of behavioural differences between the participants showing the Left Parietal effect and the participants not showing the effect is consistent with the results described in Chapter 4 by MacLeod and Donaldson (2011), showing, within a large group of participants (N=122), that the proportion of participants showing a 'negative' Left Parietal effect (i.e. an effect opposite in polarity compared to the one typically observed) did not display a different behavioural pattern compared to the majority of participants showing the typical parietal old/new positivity.

Behavioural Indices	**F**	**Sig.**
Response Bias	.016	.901
Sensitivity	1.364	.247
RT Hits	.197	.658
RT CRs	.527	.471

Table 5.6 Lack of behavioural differences in response Bias, Sensitivity and reaction Times for Hits and Correct Rejections between the participants showing the Left Parietal effect and the participants not showing the effect.

5.7 Discussion

The results of the reliability assessment of the P3b, N400 and Left Parietal Effect point to two main conclusions. The first is that all three of the effects investigated yielded reliable results, both behaviourally and electrophysiologically, across laboratories. The

shape of the waveforms and the topographic distribution of the effects were in fact consistent across laboratories and, importantly, the elicited effects were strictly consistent with descriptions in the respective literatures. This conclusion is important because it shows how the specific laboratories involved in the study are equipped with apparati capable of similarly capturing a range of ERP effects that reflect different cognitive functions and time windows, allowing data-pooling across laboratories with important consequences for future collaborative research.

The other important conclusion is that the Left Parietal effect, compared to the P3b and the N400, has a higher degree of inter-individual variability, as shown by reliability indices. This may be due to genetic variability across individuals or may be a sign of differential effects of experience-dependent plasticity across individuals, as brain structures are known to be modified as a consequence of the specific environmental variables influencing the individual's behaviour. Genetic and environmental variables may interact in generating a higher degree of inter-individual variability, and - in the case of the Left Parietal Effect - perhaps the use of different encoding and recollecting strategies may play a role in determining a higher degree of inter-individual variability compared to the P3b and the N400 effect.

It is important to acknowledge however that reliability indices for the Left Parietal effect, even though lower than reliability indices for the N400 and the P3b, are still

high enough to consider the effect robust at the group level. Since research in cognitive neuroscience typically relies on within-subject and between subjects experimental designs involving a relatively large number of participants, the degree of inter-individual variability seen in the Left Parietal effect should only have negligible consequences. Nevertheless, if the Left Parietal effect is to become a reliable measure of recollection memory at the single subject resolution (and be used in clinical and forensic settings), then progress needs to be made in terms of understanding the factors that contribute to its measured inter-individual variability.

From a validity perspective, however, the lack of difference in behavioural pattern between the participants showing the Left parietal positivity and the participants not showing the Left Parietal positivity is problematic. Validation of indices of episodic memory needs to rely on a reliable relationship between the effect and a behavioural dependent variable. As described in Chapter 4, the size of the Left Parietal effect is considered to reflect the amount of information retrieved, and as such there should be a difference in sensitivity performance across the group showing the parietal positivity and the group not showing the positivity. The lack of difference across those groups shown in the current Chapter and in the study performed by MacLeod and Donaldson (2011) described in Chapter 4 suggests that perhaps a more specific measure of behavioural recollection is needed to validate the Left Parietal effect (i.e. a source memory task instead of generic sensitivity), as the strongest evidence in favor of the idea that the Left Parietal effect indexes episodic recollection comes in fact from

source memory studies. It is possible however that in the current study and in Macleod and Donaldson's study the proportion of participants not showing the effect was able to perform adequately in the recognition test not by remembering but by knowing they had seen the old items before (i.e. using the process of familiarity and not recollection; see Chapter 4 for a review of the two processes in relation to ERP effects and Chapter 10 for further discussion on the Left Parietal effect's validity).

Chapter 6

The Left Parietal Effect and the P3b Pt. 1: A Correlational Study

When validating the P3b effect and the Left Parietal effect, it is essential to investigate if the two effects are independent from each other (discriminant validity, see Introduction) or if there is a degree of overlap between the two effects. Ideally the P3b effect and the Left Parietal effect should be entirely independent to be considered as highly precise measurement tools of attention and memory. But as we saw in Chapters 3-4 there is some evidence suggesting that the variables measured by the two effects may be overlapping. In the experiment described in the current chapter we therefore investigated directly this possibility by conducting a correlational study with a large number of participants (N = 64) to detect possible correlations across the effects. If common processes are present between the two effects, such a correlational investigation should be sensitive enough to detect them. Importantly, the N400 effect was also measured within the same participants providing a direct example of discriminant validity.

6.1 Introduction

The Left Parietal effect, considered to be an electrophysiological correlate of recollection in recognition memory experiments (see Chapter 4), consists of an enhanced positivity of ERPs elicited by correctly recognized old items (Hits) compared to correctly classified new items (Correct Rejections). The difference between Hits and Correct Rejections is typically maximal in a time-window between 500 and 700ms post-stimulus presentation, and the effect is distributed parietally with a maximum in the left hemisphere (e.g. Rugg & Curran, 2007).

The P3b effect, on the other hand, is typically elicited in an oddball paradigm, where the participant is instructed to respond to the targets but not to the standard stimuli (Polich, 2007; see Chapter 3). The P3b effect consists of a large positive deflection elicited by target stimuli compared to standard stimuli. The size of the P3b effect is a function of the relative probability of target and standard stimuli, and as the relative probability of targets decreases the difference in amplitude between ERPs to target and standard stimuli increases (see p. 88; Duncan-Johnson & Donchin, 1982; Squires et al., 1976). Importantly, even when the objective probability of target and standard stimuli is equal, ERPs to targets are still more positive than ERPs to standard stimuli, indicating that the P3b is sensitive to the targetness value, or task-relevance, of the presented stimuli, possibly due to the lower subjective probability of target items compared to non-targets (see Chapter 3 and Figure 6.1).

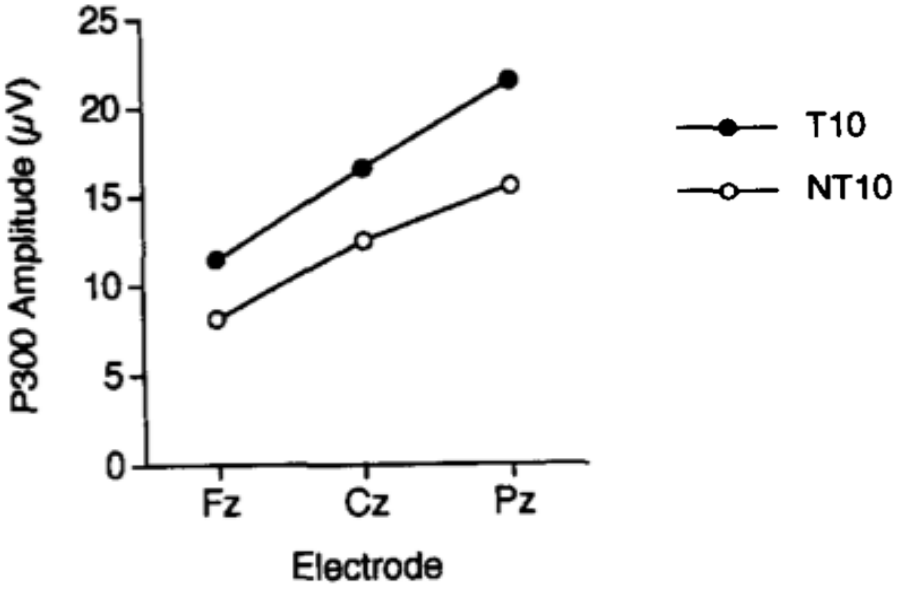


Figure 6.1. The Figure shows amplitude of the P3b effect while manipulating task relevance of stimuli. Specifically, the two lines represent mean amplitude of targets and non-targets while keeping probability of presentation constant at 10%. Mean amplitude is higher for targets compared to non-targets (Adapted from Katayama & Polich, 1996).

As discussed in Chapters 3 and 4, the P3b has a parietal distribution over the scalp, and, depending on the experimental procedure and modality involved, it may peak between 300 and 800ms post stimulus presentation. Peak latency depends in fact on the amount of time required to categorize the stimulus (Kutas, McCarthy & Donchin, 1977; McCarthy & Donchin, 1981) and while for simple auditory discriminations it typically peaks around 300ms post stimulus, for complex tasks it may peak after 400-800ms or later (see Donchin, 1981; Pritchard, 1981). There is therefore an overlap

between the P3b and the Left Parietal effect in their time course and scalp distribution. Historically, the fact that in some experiments P3b amplitude was larger to items part of an original memory set, compared to non-members (similarly to the difference observed between target and non-target items in a P3b experiment), contributed to descriptions in the psychophysiological literature of the Left Parietal effect as a subset of the P3b effect (Andreassi, 2006). The Left-Parietal old/new effect has also been considered to co-occur with the P3b (Bentin & McCarthy, 1994; Spencer, Vila Abad, & Donchin, 2000) and, as mentioned in Chapter 5, has also been described as the "P300 old/new difference" (Johnson, 1995) and the "P600 old/new effect" (Curran, 1999; Rugg & Doyle, 1992). Andreassi (2006) observes that "the P300 represents an efficient way to study recognition memory because it is reliably larger to previously learned materials than to new information" (p. 199).

Andreassi's observation is potentially justified by the possibility that old items in a recognition memory paradigm may have greater targetness value compared to new items, considered that instructions typically emphasize detection of old items. This target effect may be due to the target-nontarget categorization influencing the subjective probability of stimuli, specifically lowering the subjective probability of old items and therefore increasing their ERP amplitude. Similarly, Karis et al. (1984) have also proposed that the enhanced positivity for Hits in recognition memory paradigms may be partially due to a P300 "target effect". This target effect is proposed to be the outcome of the test item matching an episodic memory trace, compared to a test item

not matching a memory trace, and the enhanced positivity for Hits may reflect matching in general rather than recognition, as suggested by the fact that matching judgments are typically associated with an enhanced positivity compared to mismatching judgments. For instance, the closer the match of a stimulus to a template, the larger and earlier the P300 was found to be by Squires et al. (1973).

The independence of the Left Parietal effect from the P3b effect has been questioned directly by Spencer et al. (2000). The authors argued specifically that the relative positivity found in ERP recognition memory experiments involving a remember/know procedure (e.g. Smith, 1993; see Chapter 3), was not due to a specific effect representing the mnemonic process of recollection. Instead Spencer et al. suggested that the component measured by Smith (1993) was a P300 and the remember/know putative mnemonic modulation was due to differences in P300 jittering across remember and know conditions, due to the fact that "remember" decisions were reached with a more consistent latency compared to "know" decisions. The authors therefore considered the interpretation that the Left Parietal effect is a specific correlate of recollection independent from the P3b to be inaccurate, at least within the constraints of a remember/know procedure. However some other evidence (Herron et al., 2003), described in detail in Chapter 7, suggests that the Left Parietal effect and the P3b constitute independent effects.

It is apparent that in the ERP literature there is no consensus regarding the relationship between P3b and the Left Parietal effect. In the current experiment we investigated directly the potential relationship between the P3b and the Left Parietal by eliciting the two effects in a group of sixty-four participants and examining correlations between the effects. If the two effects are entirely independent no significant correlations are expected; on the other hand if some processes are shared, then significant correlations may point to commonalities. Importantly we also collected an N400 effect to provide a neutral term of comparison within the correlational analysis.

6.2 Methods

6.2.1 Participants, ERP recording parameters and experimental procedure

Sixty-four (27 male), thirty-two from Aberdeen and thirty-two from Stirling, right-handed native English speakers participated for course credit (Aberdeen) or for payment of £5 an hour (Stirling). Participants mean age was 19.8 years (range 18-24) and all reported normal or corrected to normal vision with no history of neurological disorders. Informed consent procedures were approved by the psychology ethics committee at the University of Aberdeen and at the University of Stirling. Data analysed in the current chapter correspond to the ERPs described in the reliability analyses presented in Chapter 5; ERP recording parameters and experimental procedures match therefore to the ones presented in Chapter 5. Correlational analyses were conducted on chains of electrodes where the effects were maximal (CZ, CPZ, PZ

for the N400 effect; CP1, CP3, CP5 for the Left Parietal effect; CZ, CPZ, PZ for the P3b effect). These regions of interests correspond to descriptions in the literature of typical distribution of the effects: centro-parietal distribution for the P3b and N400 and left parietal distribution for the Left Parietal effect (e.g. Rugg & Curran, 2007; Duncan et al., 2009).

6.3 Results

Results presented in Chapter 5 show that the effects' time-course and topographic distribution was consistent with the previous literature and, importantly, that there were no significant differences in the effects of interest across the two laboratories where the study was carried out. A correlational analysis was then conducted between the Left Parietal effect and the P3b effect. The relationship between mean amplitudes of the Left Parietal effect and the P3b effect is presented in Figure 6.2. As can be seen from the graph, a significant correlation was found between the Left Parietal and the P3b effect (p <.05). Further correlations were calculated between the P3b effect and the N400 effect and between the Left Parietal effect and the N400 effect. These correlations served the purpose of having a term of comparison in the current correlational analysis, as no significant correlations between the P3b and the N400 and between the Left Parietal effect and the N400 are theoretically expected.

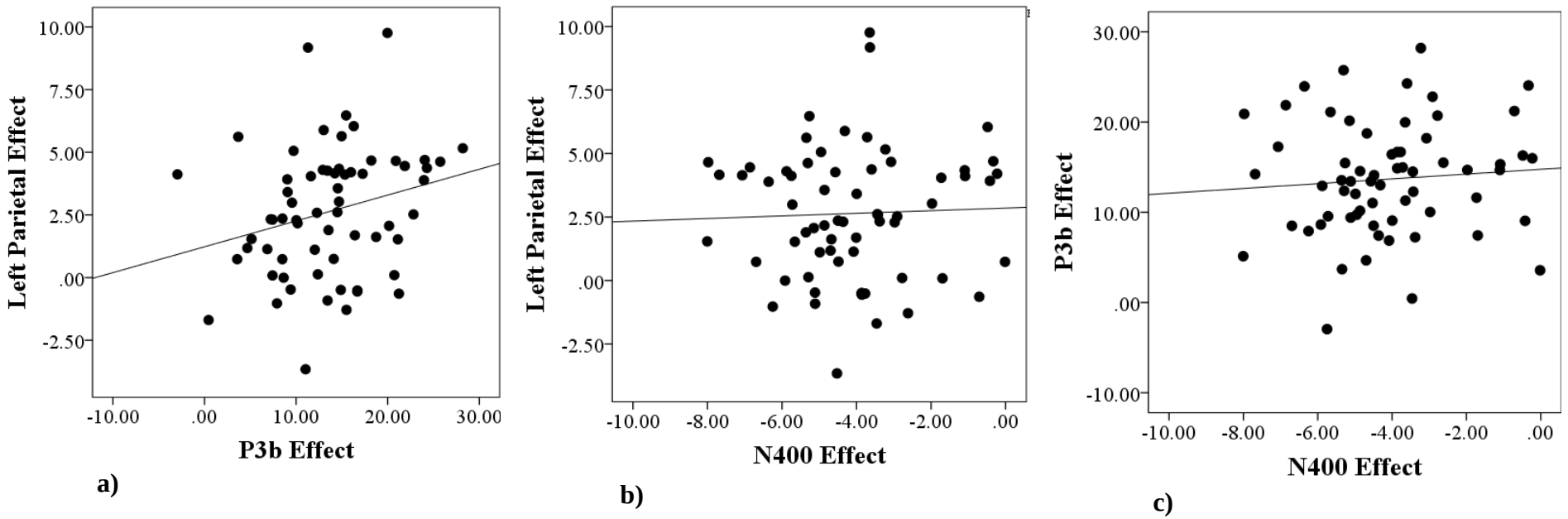


Figure 6.2 The Figure shows (a) the significant correlation between mean amplitude of the P3b Effect and the Left Parietal effect, (b) the absence of correlation between the N400 effect and the Left Parietal effect and (c) the absence of correlation between the N400 effect and the P3b effect. All values are expressed in microvolts.

Results in Figure 6.2 show an absence of significant correlations between the P3b effect and the N400 effect and between the Left Parietal effect and the N400 effect. Overall the analyses conducted show a significant correlation between the Left Parietal effect and the P3b effect, and an absence of significant correlations between the Left Parietal effect and the N400 effect and between the P3b and the N400 effect. Having assessed a significant correlation between the P3b and the Left Parietal effect, further correlations were run between the P3b effect and Hits and between the P3b effect and Correct Rejections. Significant correlations were found between the P3b effect and Hits and between the P3b effect and Correct Rejections (Figure 6.3, see Table 6.1 for all correlational results).

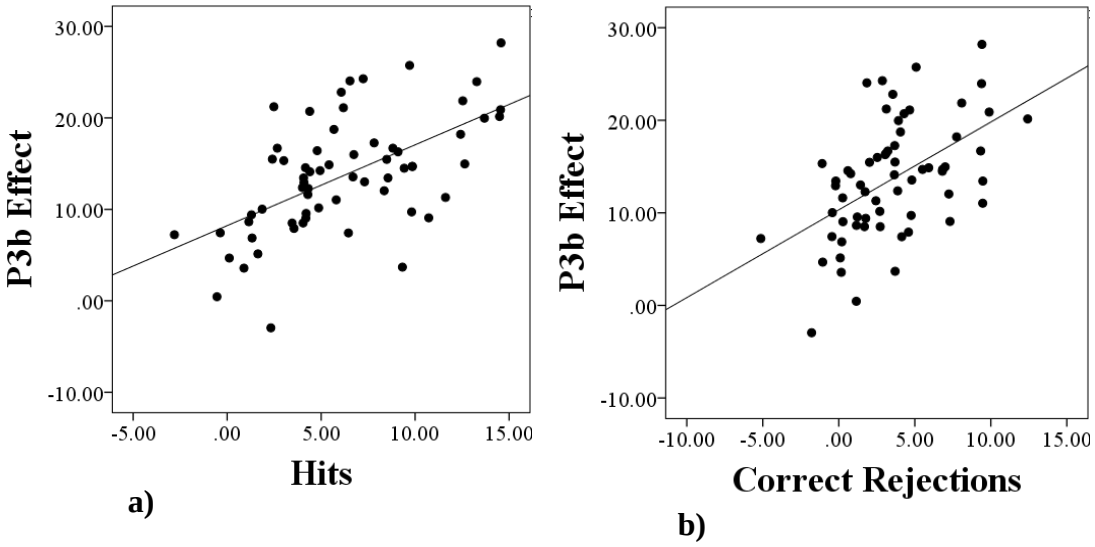


Figure 6.3 The Figure shows a) the significant correlation between mean amplitude of the P3b Effect and mean amplitude of Hits and b) between the mean amplitude of the P3b Effect and the mean amplitude of Correct Rejections. All values are expressed in microvolts.

Correlations						
		Left Parietal	**Hits**	**Correct Rejections**	**P3b**	**N400**
Left Parietal	Pearson	1	.567	-.062	.253	.039
	Sig.		<.01	.629	<.05	.760
Hits	Pearson		1	.787	.582	-.126
	Sig.			<.01	<.01	.320
Correct Rejections	Pearson			1	.515	-.182
	Sig.				<.01	.150
P3b	Pearson				1	.082
	Sig.					.521
N400	Pearson					1
	Sig.					

Table 6.1 The table shows Pearson Correlation coefficients and significance values for the correlational analysis involving the P3b effect, the Left Parietal effect (including Hits and Correct Rejections) and the N400 effect.

6.4 Discussion

A straightforward interpretation of the current results based on the suggestion by Hillyard, Squires, Bauer, and Lindsay (1971) is that since signal detection is occurring both in P3b and Left Parietal experiments, the commonalities seen across the two effects may reflect the signal detection component common to both procedures. In other words, both P3b and Left Parietal experiments could be considered variations of the same signal detection procedure since in both cases the effect is obtained by contrasting ERPs to Hits (targets) to ERPs to Correct Rejections (standards). Specifically in an auditory detection experiment Hillyard, Squires, Bauer, and Lindsay (1971) examined ERPs for the four outcomes in a signal detection task, finding that the P3b wave was evoked only by hits, but not by misses, false alarms or correct rejections. Moreover, the size of the P3b component was found to increase in amplitude with increased detectability of the signal.

Another possible interpretation for the significant correlation found between the P3b and the Left Parietal Effect is, as mentioned in the introduction, that in a recognition memory task old items have higher targetness value compared to new items, as memory tests typically tend to emphasize detection of old items compared to rejection of new items. As the P3b is sensitive to the targetness value of stimuli, the measured relationship between the two effects in the current experiment may reflect precisely a target processing function necessary to perform adequately in both tasks. Moreover,

even in preparations in which probability of stimuli is kept constant (as in the Left Parietal experimental paradigm used in the current experiment) the targetness effect may be due to the perceived lower *subjective* probability of targets. As mentioned in Chapter 3, Mecklinger and Ullsperger (1993) performed a study in which the stimuli, five words, were equally probable. They found that any word, when instructed as the target, had higher P300 amplitude, leading Rosenfeld et al. (2005) to propose that stimulus categorization (and therefore target vs. non-target categorization) plays an important role in determining subjective probability and therefore in influencing P3b amplitude. The correlation between P3b and Left Parietal effect found in the current experiment may therefore be due to the fact that in this kind of recognition memory experiment participants are explicitly instructed to detect old items, and they therefore operate an explicit target vs. non-target categorization leading to a lower subjective probability for old compared to new items.

If it is true, as suggested by the current correlational analysis, that the targetness effect may be due to the perceived lower *subjective* probability of targets, a straightforward way to investigate the nature of the relationship would be to carry out an *objective* probability manipulation during a recognition memory test. Such manipulation would involve the relative probability of correctly classified old and new items. The P3b is in fact very sensitive to the probability of target items and if the Left Parietal effect is influenced by P3b-like probability effects, a strong probability manipulation should yield some control over the size of the memory effect. Specifically, in an experimental

condition with low probability Hits and high probability Correct Rejections, the size of the Left Parietal effect should be larger compared to a condition in which the relative probability of Hits is larger than the probability of Correct Rejections. The following chapter describes precisely such a manipulation.

6.5 Summary

A consensus has not been reached in the ERP literature regarding the relationship between the P3b Effect and the Left Parietal Effect. If there is a relationship between the two effects a correlational analysis with a large number of participants comparing the two effects should be sensitive enough to detect it. We carried out such analysis and found a significant correlation between the Left Parietal effect and the P3b effect but, importantly, not between the Left Parietal effect and the N400 effect and the P3b effect and the N400 effect. These results may be due to a target effect for old items in the recognition memory experiment, possibly caused by a lower perceived subjective probability. Following up on the correlational analysis, the next chapter will address directly the relationship between the Left Parietal effect and the P3b effect by manipulating the objective relative probability of Hits and Correct Rejections in a recognition memory test. Since P3b amplitude is very sensitive to the relative probability of standard and target stimuli, we hypothesize that if the Left Parietal effect

is sensitive to probability a manipulation of the relative probability of Hits and Correct Rejections should yield differences in the size of the Left Parietal effect.

Chapter 7

The Left Parietal Effect and the P3b Pt. II:

A Probability Study

There is uncertainty in the ERP literature regarding how the Left Parietal effect and the P3b effect represent "pure" measures of memory and attentional processes, respectively. The idea that the two effects may be measuring overlapping processes is implicitly present in the literature (see Chapters 3, 4 & 6), and is confirmed by results presented in Chapter 6. The experiment presented in the current chapter follows up on those results and investigates directly if the Left Parietal effect and the P3b effect are measuring overlapping processes. If they are, then the two effects cannot be considered "pure" measures of attention and memory, and perhaps there is a "contamination" across effects in measuring the two functions.

7.1 Introduction

The correlational evidence presented in Chapter 6 points to overlapping processes between the P3b effect and the Left Parietal effect, and the significant correlation found may be due to a target effect, perhaps due to the lower subjective probability of old items compared to new items. A direct way to investigate the relationship between the P3b effect and the Left Parietal effect is to carry out an objective probability manipulation within a recognition memory paradigm. Typically in recognition memory experiments the relative probability of correctly recognized old items (Hits) and correctly classified new items (Correct Rejections) is kept equal, but if we hypothesize that the P3b effect and the Left Parietal effect "behave" similarly under analogous manipulations a clear prediction (see Figure 7.1) can be made about the way the Left Parietal effect should be influenced by probability changes.

If the relative probability of Hits is lower than the relative probability of Correct Rejections the size of the effect should be larger compared to a condition in which the relative probability of Hits is larger than the relative probability of Correct Rejections. The mean amplitude of Hits, already typically more positive than the mean amplitude of Correct Rejections, should in fact become even more positive as Hits probability decreases. Conversely the mean amplitude of Correct Rejections, already typically more negative than the mean amplitude of Hits, should become even more negative as Correct Rejections probability increases.

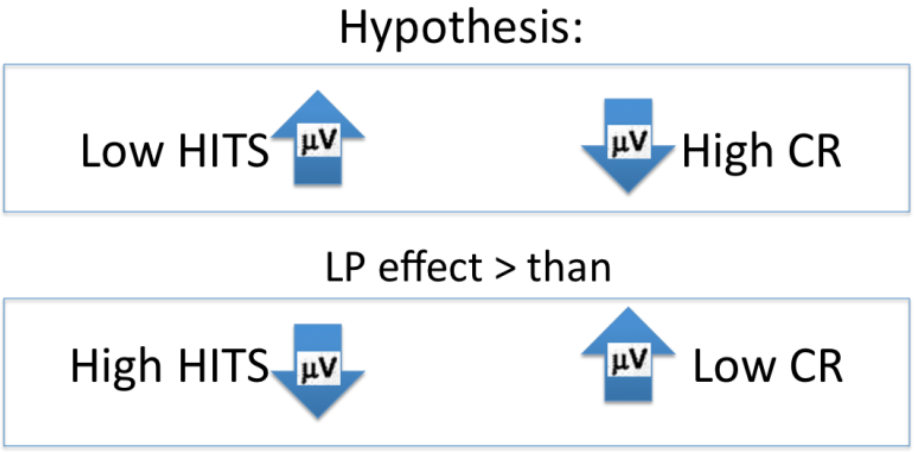


Figure 7.1 The Figure shows the experimental hypothesis relative to the current experiment. If the Left Parietal effect and the P3b effect behave similarly under equivalent manipulations, the size of the Left Parietal should be larger in an experimental condition in which the probability of Hits is low and the probability of Correct Rejections is high, compared to an experimental condition in which the probability of Hits is high and the probability of correct rejections is low.

The effect of probability on the Left Parietal effect was first assessed by Smith and Guster (1993) in a recognition memory experiment in which either old or new items worked as infrequent target items. The Parietal old/new effect was observed regardless of the fact that the infrequent target item was old or new, but a limitation of that study was the very limited stimulus set (10 stimuli) making it hard for those results to be generalized to the typical recognition memory experiment, where stimuli are not repeated multiple times at test. Friedman (1990) also manipulated the probability of old and new items (33/66 ratio), finding no effect of probability on the old/new effect. However, the paradigm chosen by the experimenter - continuous recognition - makes it hard to rule out the possibility that probability would have an

effect within the canonical study-test paradigm. Herron et al. (2003) also investigated the role of probability on the Left Parietal effect, using a probability ratio of 25/75. Herron et al. also did not find the probability of old and new items to affect the Left Parietal effect in a statistically significant fashion; however a trend towards the hypothesis described in Figure 7.1 can be inferred from their ERPs (see Figure 7.2). Overall, the null results described so far could be due to the choice of relatively weak probability manipulations. By observing Figure 7.3 it should in fact be apparent that to show a clear P3b probability effect between target conditions with different probabilities a 70/30 ratio manipulation may not be sufficient, while a 90/10 ratio manipulation should unequivocally yield a probability effect if there was one.

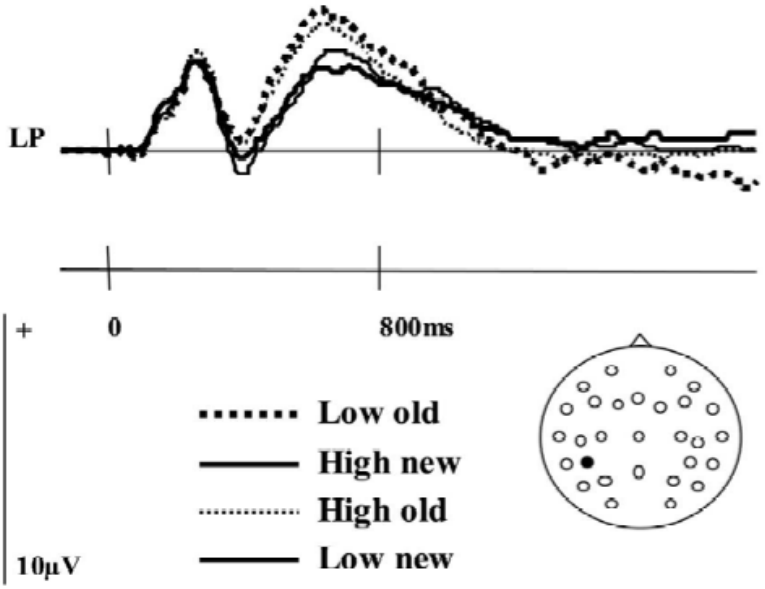


Figure 7.2 The Figure shows the experimental results of the study carried out by Herron et al. (2003). ERPs show a trend for low probability conditions to be higher in amplitude compared to high probability conditions, consistently with the hypothesis described in Figure 8.1. (Adapted from Herron et al., 2003).

In the current experiment we therefore chose a strong probability manipulation (90/10 ratio). If the Left Parietal effect is sensitive to probability in a similar way to the P3b effect, then we would expect the Low Probability Hits - High Probability Correct Rejections condition to yield a larger Left Parietal effect compared to the High Probability Hits - Low Probability Correct Rejections condition.

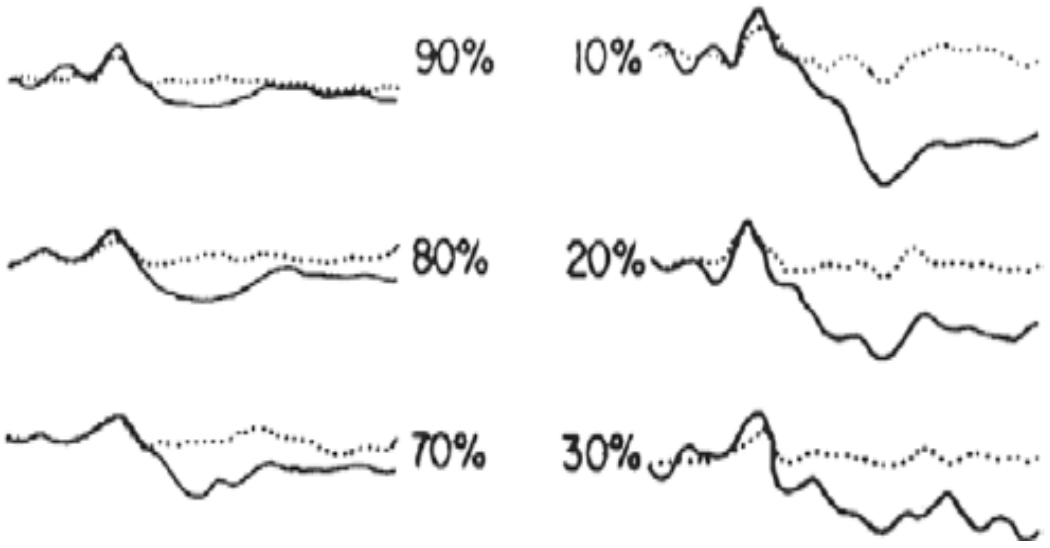


Figure 7.3 The Figure shows sensitivity of target conditions within a P3b experiment to different probability levels. The 90/10 ratio contrast at the top of the figure shows a clear effect of the probability manipulation compared to the 70/30 ratio shown at the bottom. (Adapted from Duncan-Johnson and Donchin, 1977).

7.2 Methods

7.2.1 Participants

Forty-one right-handed native English speakers participated for payment (£7.50 an hour). Data from nine participants was discarded due to poor behavioural performance. Of the remaining thirty-two participants[7], twenty-four (eleven male) had more than sixteen trials in all critical experimental conditions and were included in the reported analyses. Participants' mean age was 19 years (range 18-25) and all reported normal or corrected to normal vision with no history of neurological disorders. Informed consent procedures were approved by the Psychology Ethics Committee at the University of Stirling.

7.2.2 Materials and Procedure

Stimuli consisted of 1008 words taken from the MRC Psycholinguistic Database, word length ranging between 4 and 9 letters. The experiment was divided into four study-test blocks. During each study phase 162 words were shown and participants judged if the words referred to living or non-living objects. In each test phase 180 words were shown, 10% (18) of them new and 90% (162) old in A blocks and 10% (18) of them old and 90% (162) of them new in B blocks, with alternating A and B blocks, while

[7] These thirty-two participants correspond to the subjects who also took part in the N400 experiment described in Chapter 8. Order of experiments was counterbalanced across participants: half of the participants started with the experiment described in the current chapter and half of the participants started with the experiment described in Chapter 8.

participants performed an old/new recognition task. For the study phase each trial began with a fixation cross presented for 2100ms, followed by the experimental stimulus for 300ms. The stimulus was followed by a blank screen lasting 1500ms during which the participant performed the living/non-living judgement. Each test phase started with a fixation cross presented for 2100ms followed by the stimulus for 300ms and by a blank screen for 2700ms. During the blank screen participants performed the old/new recognition task by pressing the extreme left and right buttons of a 5 button response box. Mapping of old and new responses to buttons was counterbalanced across participants.

7.2.4 ERP Recording Parameters

ERP Recording parameters correspond to section 5.4.4 in Chapter 5. The mean number (all conditions >16) of trials contributing to ERPs in each condition were: Low Hits 20.34, High Hits 202.66, Low Correct Rejections 23.64, High Correct Rejections 188.37. The Left Parietal effect was investigated within the 500-800ms time window (as compared to the 500-700ms time window analyzed in the other Chapters) to allow carrying out a direct comparison with the correspondent experiment by Herron et al. (2003).

7.3 Results

7.3.1 Behavioural Results

Performance during the recognition memory task was assessed via a measure of discriminability called 'sensitivity' (Snodgrass and Corwin, 1988), computed by subtracting the probability of committing a false alarm from the probability of making a hit. A repeated measures ANOVA was performed to assess differences in sensitivity across conditions. No significant differences were found across conditions [$F(1, 23) = .2$; $p = .659$], as clear from Figure 7.4.

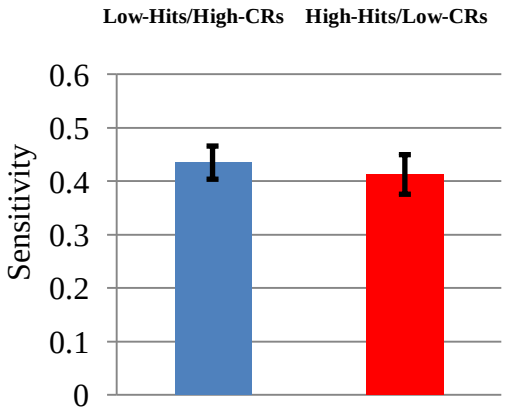


Figure 7.4 Behavioural performance during the recognition test. Sensitivity did not differ significantly across experimental conditions.

Additionally response bias - the tendency of participants to be more liberal or conservative in choosing "old" during the test phase of the recognition experiment - was also assessed. Previous behavioural research (Ratcliff et al., 1992) in recognition memory experiments involving a probability manipulation of old and new items has in

fact shown a more liberal response bias in the High-Hits/Low-CRs condition (compared to Low-Hits/High-Correct Rejections). As expected the ANOVA yielded a significant difference (see Figure 7.5) across conditions [$F(1, 31) = 6.95$; $p < .02$].

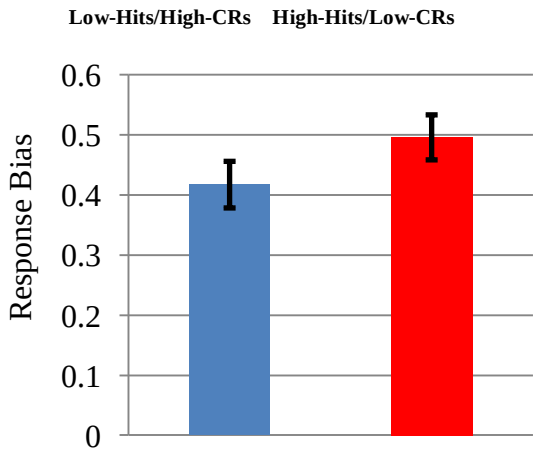


Figure 7.5 Behavioural performance during the recognition test. Response bias differed significantly across conditions; a more liberal response bias was found for the High-Hits/Low-CRs condition.

7.3.2 ERP Results

Grand average waveforms for the two experimental conditions are shown in Figure 7.6. The Low-Hits/High-CRs condition shows a positivity for Hits compared to Correct Rejections maximal over parietal sites and lasting approximately until 800ms post stimulus presentation. For the High-Hits/Low-CRs condition the positivity of Hits compared to Correct Rejections appears to be reduced. For each experimental condition, the effect was investigated statistically with an initial ANOVA with factors

of Old/New (Hits, Correct Rejections), Location (Frontal, Fronto-Central, Central, Centro-Parietal, Parietal and Parietal-Occipital), Hemisphere (Left, Right) and Site (superior: sites 1 & 2, PO3, PO4; inferior: sites 5 & 6, PO7, PO8).

For the Low-Hits/High-CRs condition the initial ANOVA yielded a significant Old/New effect [$F(1, 23) = 17.67$; $p<.001$], a significant Old/New x Location x Hemisphere interaction [$F(1.33, 30.66) = 10.95$; $p <.002$], a significant Old/New x Site interaction [$F(1, 23) = 41.06$; $p < .001$] and a significant Old/New x Location x Site interaction [$F(1.991, 45.79) = 15.29$; $p < .001$]. A follow up ANOVA focused on parietal sites [P1, P5, P2, P6, PO3, PO7, PO4, PO8] yielded a significant Old/New effect [$F(1, 23) = 13.84$; $p<.001$], a significant Old/New x Hemisphere interaction [$F(1, 23) = 6.65$; $p<.02$] and a significant Old/New x Site interaction [$F(1.742, 40.07) = 18.59$; $p<.001$]. Overall these analyses show a relative positivity for Hits compared to Correct Rejections maximally distributed over left parietal electrodes.

For the High-Hits/Low-CRs condition the initial ANOVA did not yield significant effects [all *p*s>.321]. Follow up ANOVAs focused on parietal sites [P1, P5, P2, P6, PO3, PO7, PO4, PO8] did not yield significant results [all *p*s>.207]. Overall these analyses show the lack of a significant Left Parietal effect in the High-Hits/Low-CRs condition. To assess directly differences across experimental conditions the size of the Left Parietal effect was compared statistically across the Low-Hits/High-CRs and the

High-Hits/Low-CRs conditions in the same left parietal electrodes analyzed in Chapter 6 [CP5, CP3, CP1], yielding a significant effect of Condition [$F(1, 23) = 12.44$; $p < .003$], showing that the size of the Left Parietal effect was larger for the Low-Hits/High-CRs condition compared to the High-Hits/Low-CRs condition (See Figures 7.6 and 7.7).

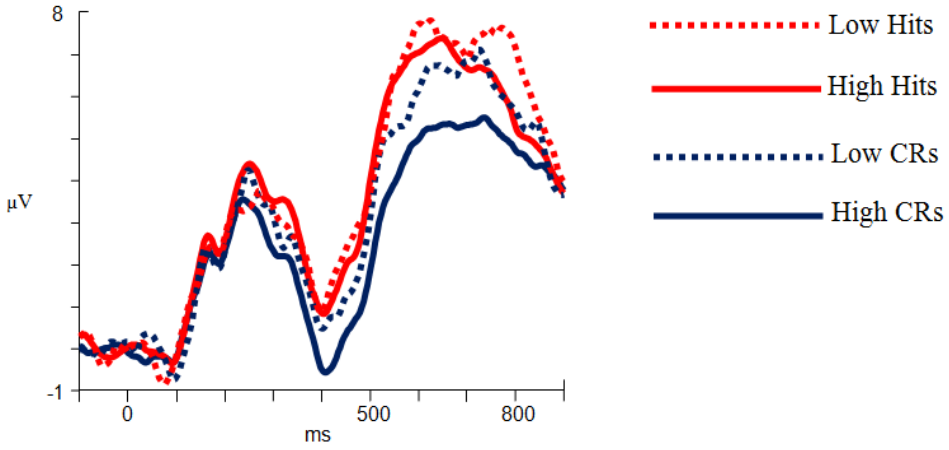


Figure 7.6 The Figure shows Hits and Correct rejections across levels of probability at the left parietal electrode P3. Compared to the results by Herron et al. (2003) shown in Figure 7.2 the figure shows that the current probability manipulation was effective in yielding low probability conditions to be higher in amplitude than to high probability conditions, consistently with the hypothesis described in Figure 7.1.

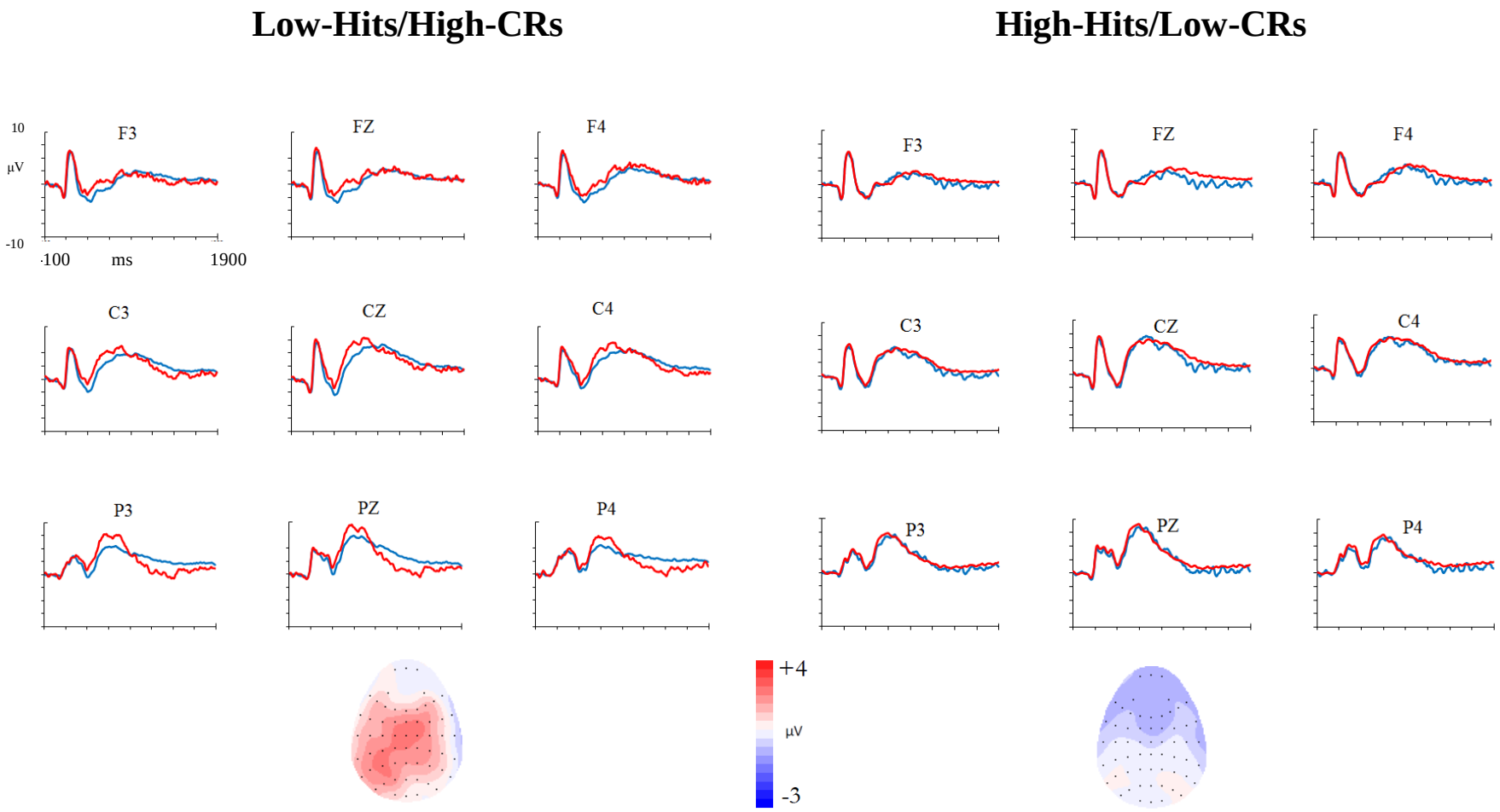


Figure 7.7 ERPs relative to the Low-Hits/High-CRs condition (Panel A) compared to the High-Hits/Low-CRs condition (Panel B). In both panels, Hits are shown in red and Correct Rejections are shown in Blue. Topographic maps show a Left Parietal distribution of the effect (500-800ms) evident only for the Low-Hits/High-CRs condition.

7.4 Discussion

The results presented in the current chapter show that when the relative probability of old and new items differs objectively, such that Hits are relatively infrequent and Correct Rejections are frequent, then the Left Parietal effect is detectable. But when Hits are frequent and Correct Rejections are infrequent, the Left Parietal effect disappears. Differently from what proposed by Herron et al. (2003) ERP probability effects as detected by the P3b *can be* confounds on ERP memory retrieval effects as measured by the Left Parietal effect, as the former spatio-temporally overlap with the latter. In other words, probability can trigger positivities that mask neural activity reflecting memory retrieval (see also Chapter 10 for further discussion). These results are consistent with the results presented in Chapter 6 showing a significant correlation between the P3b and the Left Parietal effect, plausibly due to a target effect for old items due to a lower subjective probability.

The observed pattern of results suggests that previous similar experiments (e.g. Herron et al., 2003) did not yield significant results because they did not use a strong enough probability manipulation. Moreover, the absence of a significant difference in response bias across conditions in Herron et al.'s (2003) study, at odds with the existing behavioural research on the topic (e.g. Ratcliff et al., 1992), points to the overall inadequacy of the chosen probability manipulation. Our results suggest instead that, if the carried out probability manipulation is strong enough, differences in response bias

will be detected across conditions and the size of the Left Parietal effect will be sensitive to the probability manipulation.

Behaviourally, the absence of differences in discrimination performance across conditions may be explained with the fact that while a common memory process was activated and constant across conditions, the subset of (attentional) neural processes influenced by probability was independently manipulated. This interpretation is consistent with a fMRI recognition memory experiment (Herron et al., 2004) in which the relative probability of old and new items was manipulated similarly to Herron et al. (2003). The fMRI study showed that while a group of brain regions showed greater activity elicited by correctly classified old compared to new items, independently of probability, another group of regions responded accordingly to the probability manipulation. The regions showing greater activity for old compared to new items independently from probability are possibly the ones responsible for the mnemonic portion of recognition performance.

The Left Parietal effect may therefore be confounded, because of temporal overlap, by neural generators affected by probability manipulations. But the fact that a Left Parietal *negativity* (an effect equal in size but opposite in polarity) was not produced by the High-Hits/Low-CRs condition, as would be expected if the Left Parietal effect was identical to the P3b effect, together with the absence of differences in behavioural

sensitivity across conditions, suggests that the Left Parietal effect also reflects memory processing independent from neural processing sensitive to probability. These results overall point to the fact that ERP recollection effects can be confounded by overlapping probability related P3b effects.

The fact that attentional processes sensitive to probability appear to overlap and confound a recognition memory performance is not surprising considered that participants need to be able to discriminate the stimuli and act accordingly. But while discriminating the stimuli is a fundamental prerequisite in recognition memory, the participant must also be able to remember if that specific stimulus has been shown during the study phase or not. Indeed it could be argued that a recognition memory experiment is a complex version of a simple oddball paradigm in which the participant to perform well has to remember many stimuli instead of only two stimuli (leading to stronger memory activation compared to the simple oddball). Conversely, it could be said that the oddball procedure requires a relatively simple form of recognition memory compared to a typical recognition memory experiment.

Hypothesizing that the probability-sensitive attentional processes manipulated successfully in the current experiment are constant across oddball and recognition memory procedures, the difference between oddball and recognition procedures, at

least as reflected by ERPs, may be due to the quantitative "memory load" involved in performing adequately in the two procedures.

From a neuroanatomical perspective repeated stimulation is known to determine a decreased hippocampal activity over trials (e.g. Ries et al., 2008). Given the large number of repetitions of both target and standard stimuli in an oddball experiment compared to the typical very low amount of repetitions in recognition memory experiments, it is plausible that the hippocampal disengagement present in the oddball paradigm is not matched in recognition experiments. During the test phase of a recognition memory experiment in fact typically half of the stimuli are seen for the first time in the experiment and the other half is seen for the second time, possibly leading to an overall higher recollection-related hippocampal activation compared to the oddball paradigm characterized by overlearning.

Another possible interpretation (further discussed in Chapter 10) is that the P3b and the Left Parietal effect reflect the same probability-sensitive neural signal. This would fit with the idea that old items are more positive in amplitude because they have a lower subjective probability compared to new items, due to their task relevance and targetness (see Chapters 3 & 6). In the High-Hits/Low-CRs condition effects due to subjective and objective probability might have cancelled each other, leading to the disappearance of the effect. While the lower *subjective* probability for old items

(categorized as targets in a recognition memory experiment) would cause amplitude of Hits to be higher than amplitude of Correct Rejections (as it happens typically when objective probability of old and new items is matched), the lower *objective* probability for Correct Rejections would cause the amplitude of Hits to be lower than the amplitude of Correct Rejections, leading to the subjective and objective probability effects to cancel each other and for the Left Parietal effect to disappear. This interpretation would tie parsimoniously together the P3b and the Left Parietal effect as a single probability-sensitive phenomenon, and would also explain the lack of validity for the Left Parietal effect described in Chapter 5 and further described in Chapter 10. Section 10.3 will propose possible future research meant to test which of the two proposed interpretations more accurately describes the observed data.

7.5 Summary

The results presented in the current chapter suggest, together with the evidence presented in Chapter 6, that there are common processes shared by the P3b effect and the Left Parietal effect. A possibility is that both effects involve attentional activation sensitive to probability of stimuli and that the two effects differ in the amount of memory activation engaged. The memory load of recognition experiments is typically much higher than the memory load present in oddball experiments, where the same few stimuli are presented repeatedly throughout the experiment, yielding perhaps a stronger recollection-related hippocampal activity. From a validity perspective the Left

Parietal and the P3b effect can be said, based on the current results, to overlap with each other, being both sensitive to attentional and memory processes. If this interpretation is correct, neither the P3b effect nor the Left Parietal effect can be considered a "pure" measure of attention or memory. Another interpretation is that the P3b and the Left Parietal effect reflect the same probability-sensitive phenomenon, old items having a more positive amplitude because they have a lower subjective probability compared to new items, due to their task relevance and targetness.

Chapter 8

Validity of the N400 Pt. I: Semantic or Association Relationships?

In the process of assessing the validity of the N400 effect it is important to question if the dominant views on what the effect is a measure of are accurate. In Chapter 2 we reviewed the previous literature and described how the interpretation of the effect has been essentially the same since the early experiments, an interpretation based on the idea of semantic mismatch that puts the effect strictly into a linguistic domain. The effect is currently considered to be a neural correlate of language processing, in spite of a series of experiments that either put into question that kind of specificity or dilute the definition of what is "semantic" to a point in which one wonders about its usefulness. When a definition does not yield clear criteria for exclusion, such that an element can be left out of a category defined in a specific way, then it is hard to falsify any hypothesis based on such a definition. In other words, it is not very useful to say that the N400 effect is a measure of semantic relationships if one is unable to say what is *not* a semantic relationship. Many definitions of semantics have been given, most of them very broad or circular. In the current experiment, designed to investigate what the N400 is a measure of, we adopted a definition of semantic relationships based on the

concept of interchangeability of words within a specific linguistic context. After having defined what we mean by semantic relationship, we also defined association relationships as the likelihood that hearing a specific word will bring to mind another word. Based on previous evidence (Rhodes & Donaldson, 2008) we had reason to think that the N400 effect may be sensitive to associations rather than semantic relationships, and we therefore created a manipulation to assess if the N400 effect is sensitive to association relationships when semantic relationships are held constant. We used the described norms to parametrically vary the strength of association between words within word-pairs, while holding constant their degree of semantic congruency. This manipulation allowed us to compare N400s elicited by unrelated prime-target word pairs with N400s generated by related prime-target word pairs of either low or high degrees of association.

In the current chapter we show that even when semantic relationships are held constant, N400 modulations can still be observed if prime-target stimuli differ in the strength of their associative relationship. Larger N400 effects occurred in fact for highly associated versus lowly associated pairs despite the fact that no differences in terms of semantic congruency existed between pairs belonging to the highly and lowly associated conditions. These findings are important in investigating the validity of the N400, because they demonstrate that the N400 is modulated by associative relationships independently of semantics and help refining current interpretations on what the N400 is a measure of, suggesting that the effect is highly sensitive to

association relationships even in absence of semantic differences, casting a doubt over the current dominant interpretation of the N400. The current results suggest that the N400 effect indexes a general process, not confined to the linguistic domain, sensitive to the contiguity of distinct elements within one's past experience. The experiment presented in the current Chapter also allowed assessing within-laboratory reliability, by comparing the N400 effect obtained by the participants taking part into the current study with the N400 effect measured in the N400 experiment described in Chapter 5 (Stirling Laboratory).

8.1 Introduction

The N400 Event-Related Potential (ERP) component is one of the most widely studied neurophysiological effects in the cognitive neuroscience literature (see Chapter 2; Kutas & Federmeier, 2011). First discovered in studies of language processing (Kutas & Hillyard, 1980), N400 modulations are typically evoked when a mismatch occurs between a stimulus and its preceding context. It is generally accepted that the mismatch responsible for the N400 effect reflects meaning-based processing (Bentin et al., 1995; Federmeier & Laszlo, 2009; Heinze at al., 1998; Kutas & Hillyard, 1984; Kutas et al., 1984; Kutas & Federmeier, 2011; Luck et al., 1996), but the specific functions involved remain unclear. Here, we review the distinction between associative and semantic types of relationship, which has been investigated within the cognitive literature on priming but has been essentially ignored within the N400 literature. This

leads us to hypothesize that the N400 could be sensitive to associative relationships, independently of semantics, and we provide new evidence that this is the case, based on prior proposals from Rhodes and Donaldson (2008) who suggested that the N400 may be sensitive to experience-dependent associative relationships and not semantic relationships.

Associative relationships in language depend on contiguity, i.e. how often two words occur together in a specific order. Thus, the definition of associative relationships does not depend on the structural content (Anderson & Charles, 1977) of verbal stimuli: any two words can be associated with each other as long as one word tends to follow the other in everyday usage (Kiss et al., 1973). In practice, the contiguity between words in language that causes individuals to learn their associative relationship can happen for many reasons. Sometimes the reason is that there are overlapping features in (the referents of) words that co-occur together. It is the presence of such featural overlap constitutes one basis for a semantic relationship – i.e. a relationship that exists independent of any associative relationship. So for example, distributed models of semantic memory (e.g. see Kawamoto, 1993; Masson, 1995; Moss et al., 1994) typically define semantic relationships in terms of the presence of overlapping features. By this definition, the words *pig* and *dog* are semantically related because their referents share the common features of *four legs, a tail, ears, etc*. According to this view, the way semantic relationships are organized is dependent on the similarity of overlapping features of the referred objects.

Another way to define semantic relationships is based on the how interchangeable words are within a specific linguistic context. Interchangeability (Huettig et al., 2006) has the advantage of being a more comprehensive index of semantic relationships than measures of feature overlap (which are typically limited to indexing concrete objects). Words can be interchangeable within a linguistic context because they share physical features, but often the overlap is of a conceptual kind without apparent shared physical features (e.g. god and divine conceptually overlap but it is not clear what physical features would be overlapping since the referents do not exist). Interchangeability provides therefore an index of semantic relatedness both in presence and in absence of physical shared features.

The distinction between associative and semantic relationships is reflected by differences in how each kind of relationship is measured. Indices of semantic relationships are inherently bi-directional, whereas associations are not – two words may have very different forward and backward associations (e.g., bar-mars compared to mars-bar). Associative relationships are also defined in terms of the likelihood that a word will evoke, or bring to mind, another word (i.e., "presentation of stimulus A increases the chance of response B"). For example, reading "*traffic"* leads to the response "*jam"* (Postman & Keppel, 1970). Unlike semantic features, however, associative relationships are not constrained to linguistic stimuli. Logically, any response to a stimulus can lead to another response, regardless of the nature of the stimulus. Importantly, associative relationships are defined empirically (experientially)

and not *a-priori*. The experimenter does not decide which two words are associated with each other and which are not: rather, databases such as the Edinburgh Association Thesaurus (Kiss et al., 1973) have been created by presenting a word to a large number of participants and then asking them what other word came to mind.

Neuropsychological studies have clearly dissociated semantic and association relationships in patients with Alzheimer's (Glosser & Friedman, 1991) and in children with reading disabilities (Nation & Snowling, 1999). Similarly, within the behavioural literature on priming, associative and semantic relationships have also been shown to exert independent effects. Priming experiments typically show behavioural facilitation (decreases in reaction time) after the presentation of a target word (*butter*) preceded by a related prime (*bread*), as compared to an unrelated prime (*chair*). Experimentally, priming can be obtained for semantic relationships alone (McRae & Boisvert, 1998; Perea & Rosa, 2002) and for associative relationships alone (Ferrand & New, 2003; Perea et al., 1997; Williams, 1996). In a recent meta-analytic review Lucas (2000) reveals that the effect size of associative priming is larger than for semantic priming; moreover the effect was also enhanced (associative "boost") for word-pairs that shared both associative and semantic relationships as compared to semantic relationships alone (see also Moss, Ostrin, et al., 1995).

The distinction between associative and semantic relationships has not, however, been made as clearly within N400 research (though see Koivisto and Revonsuo, 2001). Consequently, previous ERP studies have either not controlled for the associations between words, or more commonly have failed to distinguish between associative and semantic relationships (e.g., Federmeier & Kutas, 1999; Heinze et al., 1998; Kuonios & Holcomb, 1992; ; Kutas & Hillyard, 1980, 1984; Kutas, 1993; Kutas & Iragui, 1998; Luck et al., 1996; Neville et al., 1986). Moreover, in N400 experiments with sentences a semantic mismatch is thought to be more predictive of the N400 effect than the fit of the specific word within the sentence itself (Federmeier & Kutas, 1999). Despite the ubiquity of the semantic mismatch view of the N400 effect there are existing data that appear contradictory or at least difficult to account for. For example, Nieuwland & Van Berkum (2006) suggest that the N400 modulation can in fact be entirely context-dependent, based on the finding that N400 effects following the final word of a sentence can be modulated by the content of a paragraph read prior to reading the sentence itself. Nieuwland & Van Berkum's results suggest that the N400 effect is not dependent on long-term memory category structure per se.

To our knowledge, the distinction between associative and semantic relationships has been examined empirically in only one prior study. Rhodes and Donaldson (2008) investigated the effect of varying associative and semantic relationships on N400 modulations evoked by visually presented pairs of words. Using unrelated word pairs as a baseline (e.g. alarm-cloud), Rhodes and Donaldson observed N400 modulations

only when word pairs were associatively related (e.g. traffic-jam), or associatively and semantically related (e.g. lemon-orange), but not when they were only semantically related (e.g. cereal-bread). These findings are important because they throw light upon the nature of the mechanism reflected by the N400, and in particular they suggest that a key factor is not the existence of a semantic relationship per se, but rather the presence of an associative relationship between stimuli.

In the current experiment, we test the associative N400 hypothesis (Rhodes and Donaldson, 2008) using a parametric manipulation of associative relationships. If the processes reflected by the N400 are indeed sensitive to associative relationships, it should be possible to modulate their activity by controlling the strength of this relationship between cue–target pairs within a typical N400 paradigm. In particular, if the processes reflected by the N400 are specifically sensitive to associative relationships, we should be able to observe a modulation of the effect even if we hold the degree of semantic relatedness constant across conditions.

8.2 Methods

8.2.1 Participants and materials

Thirty-two (13 male) right-handed native English speakers participated for payment (£7.50 an hour). Participants mean age was 19 years (range 18-25) and all reported

normal or corrected to normal vision with no history of neurological disorders. Informed consent procedures were approved by the Psychology Ethics Committee at the University of Stirling. Three hundred and six word pairs were created (3 to 11 letters in length) taken from the MRC Psycholinguistic Database (www.eat.rl.ac.uk). The words were divided into three experimental conditions: Unrelated word pairs, word pairs with Low Association and word pairs with High Association. The Unrelated and High Association conditions correspond to the ones described in the N400 experiment presented in Chapter 5 (Section 5.3.1). A Low association condition was added in the current experiment to investigate the possibility that increasing degrees of association would modulate the N400 effect while keeping semantic relatedness constant. Table 8.1 summarises the associative differences, as well as other controlled factors, between the stimuli in each condition.

Compound word meaning was assessed according to the Collins English Dictionary online (www.collinsdictionary.com/dictionary/english/) to make sure proportion of word-pairs having compound word meaning would be constant across the low and high association conditions. In the unrelated condition no word-pairs had compound word meaning. The percentage of word-pairs having compound word meaning was 24% for the low association condition and 30% for the high association condition. Importantly, the proportion of word-pairs having compound word meaning did not differ statistically across the low and the high association conditions [χ^2(1, N= 204)

=.609; p=.435]. The experimental procedure corresponds to the one described in the N400 experiment presented in Chapter 5 (Section 5.3.1).

	Unrelated	Low	High	Significance
Association	.000 (0)	.068 (.003)	.357 (.012)	$p < .00001$
Semantic Distance	.28 (.01)	.28 (.015)	.29 (.016)	$p > .05$
Word Frequency 1	33.5 (4.5)	32.1 (3.5)	32.1 (8.2)	$p > .05$
Word Frequency 2	45.9 (6.3)	54.8 (7.3)	62.8 (8.6)	$p > .05$
Word Length 1	5.34 (.15)	5.4 (.16)	5.3 (.14)	$p > .05$
Word Length 2	5.13 (.14)	5.15 (.15)	4.79 (.14)	$p > .05$
Imagability 1	514.6 (9.9)	502.2(10.3)	502.7(10.4)	$p > .05$
Imagability 2	510.8 (10.6)	513.0 (9.5)	533.3 (9.9)	$p > .05$

Table 8.1 Degree of association between words within word pairs was manipulated while keeping constant all other relevant parameters. Values reported are means (and standard error of the mean).

8.2.2 ERP Recording parameters

EEG was recorded according to the parameters described in Section 5.4.4. The mean number of trials (all conditions >16) contributing to ERPs in each condition were: unrelated 92.71, low association 92.68; high association 92.37.

8.3 Results

8.3.1 Behavioural Results

Reaction time data for the judgement of relatedness task were analysed conducting an ANOVA with a factor of degree of association (3 levels: unrelated, low, high). The analysis yielded a significant result [$F(2, 62) = 72.3$; $p < .001$] and follow up pairwise comparisons (Bonferroni corrected) showed all experimental conditions to differ significantly from each other (all *p*s < .001). Reaction times were longest for the unrelated condition and shortest for the high association condition, with low associations in between.

Participants judgments of relatedness yielded the following outcome (results are mean and standard deviation, where 1 = related and 5 = unrelated): high association = 1.54 (.35); low association 1.85(.37); unrelated 4.1(.42). An ANOVA with a factor of level of association (unrelated, low, high) found a significant difference across conditions [$F(2, 62) = 429.6$; $p < .001$] and Bonferroni corrected pairwise comparisons found all three conditions to differ from each other significantly (all ps < .001).

8.3.2 ERP Results

Grand average ERP waveforms are shown in Figure 8.1. Relative to the unrelated baseline condition both the low and the high association conditions exhibit a clear

modulation of the N400 component, starting around 300ms post stimulus. Figure 8.2 illustrates the topographic distribution of the N400 effects (based on unrelated minus high and unrelated minus low difference waveforms) during the classic 300-500ms N400 time window. As the topographic maps make clear, both the high and the low association conditions elicited an N400 effect consistent with the previous literature (e.g. Duncan et al., 2009). Following previous studies (e.g. Kutas & Hillyard, 1984; Van Berkum et al., 2003) statistical analyses were performed on data from the 300-500ms time window, using ANOVA with factors of relationship type (unrelated, low, high), hemisphere (left, right), site (superior: sites 1 & 2; inferior: sites 5 & 6), and location (Frontal, Fronto-Central, Central, Centro-Parietal, Parietal).

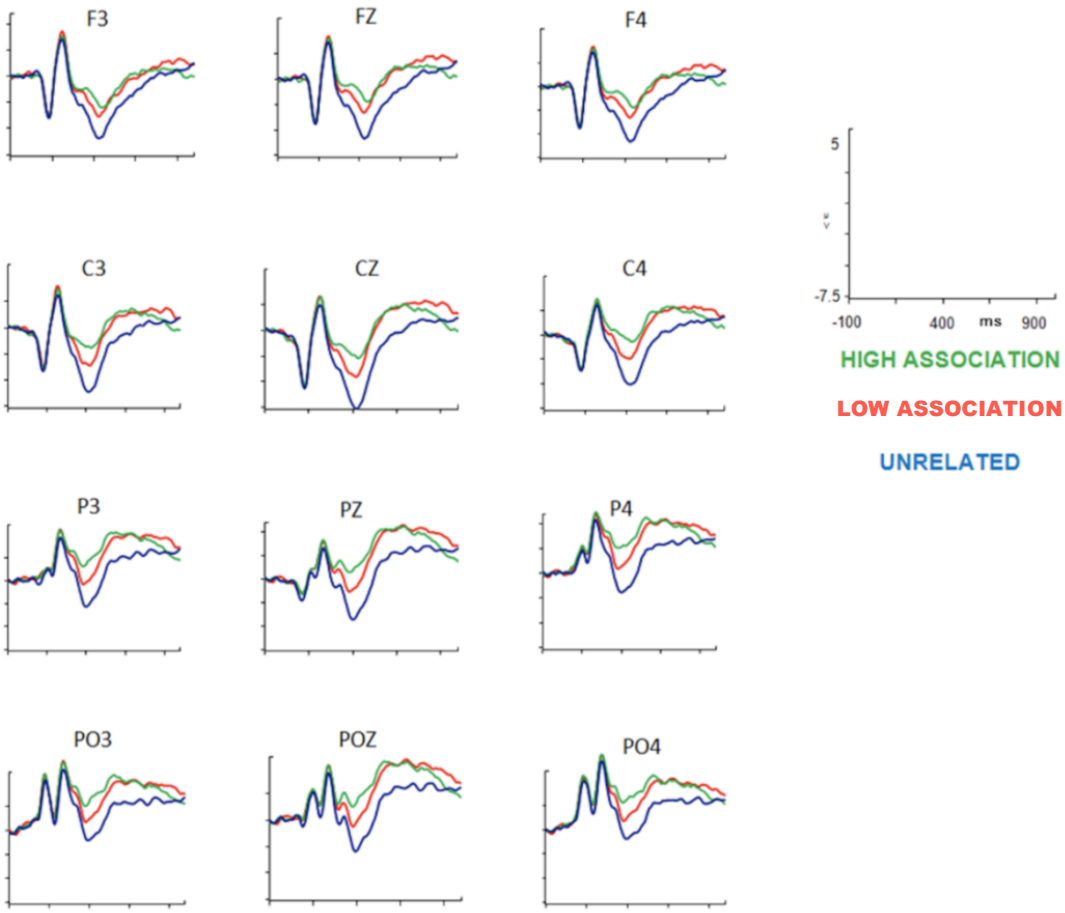


Figure 8.1 Grand average ERPs for the unrelated, low and high association word-pairs, shown from pre-stimulus to 1000ms. Twelve electrodes are shown across frontal, central, parietal and parietal-occipital scalp locations. Waveforms show a modulation of the N400 effect with the size of the effect directly proportional to the degree of association.

The ANOVA revealed a main effect of Relationship [$F(1.43, 44.34) = 48.43$; $p < .001$]. A significant Relationship x Site interaction [$F(1.44, 44.91) = 22.99$; $p < .001$] was also present, reflecting the fact that the differences were larger at midline than inferior electrodes. In addition, results revealed a significant Relationship x Location interaction [$F(2.37, 73.56) = 7.17$; $p < .001$]. Subsidiary ANOVAs were conducted on each of the five locations, finding an effect of relationship type at each location [Frontal: ($F(1.63, 50.66) = 33.47$; $p < .001$); Fronto-Central: $F(1.44, 44.88) = 39.59$; $p < .001$, Central: $F(1.50, 46.53) = 46.04$; $p < .001$; Centro-Parietal: $F(1.51, 47.02) = 48.65$; $p < .001$; Parietal: $F(1.62, 50.38) = 46.56$; $p < .001$]. Importantly, Bonferroni corrected pairwise comparisons showed all three relationship types to differ from each other significantly at all locations (all ps $< .008$), except for at the frontal location, where low and high did not differ significantly.

Overall these analyses reflect a reduced negativity, with a centro-parietal maximum, for both the low and the high association word pairs compared to unrelated word pairs. But the critical finding for the associative N400 hypothesis is that ERPs to low association word pairs were significantly more negative than ERPs to highly associated word pairs, confirming the graded N400 pattern evident across Figures 8.1 and 8.2.

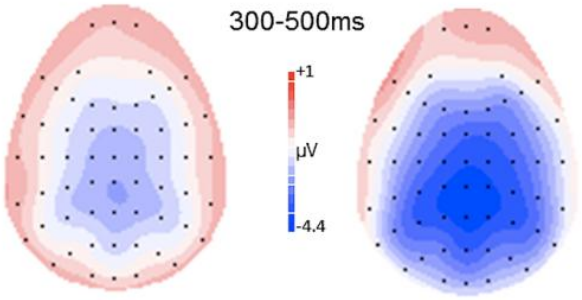


Figure 8.2 Topographic maps showing the distribution of the N400 effect obtained by subtracting the low (topographic map on the left) and the high (topographic map on the right) association conditions from the unrelated condition. The scale bar indicates the size of the N400 effect in microvolts.

8.3.2.1 Topographic Analyses

Topographic analyses were performed on difference waveforms (unrelated minus low and unrelated minus high) using rescaled data (McCarthy & Wood, 1985). ANOVA was used to assess differences across experimental conditions in the scalp distribution of the N400 effect, employing factors of condition (low, high), hemisphere (left, right), site (superior: sites 1 & 2; inferior: sites 5 & 6), and location (Frontal, Fronto-Central, Central, Centro-Parietal, Parietal). Results revealed no main effect of condition or interactions involving the condition factor, suggesting no differences in the neural generators of the N400 in the low and high associative conditions.

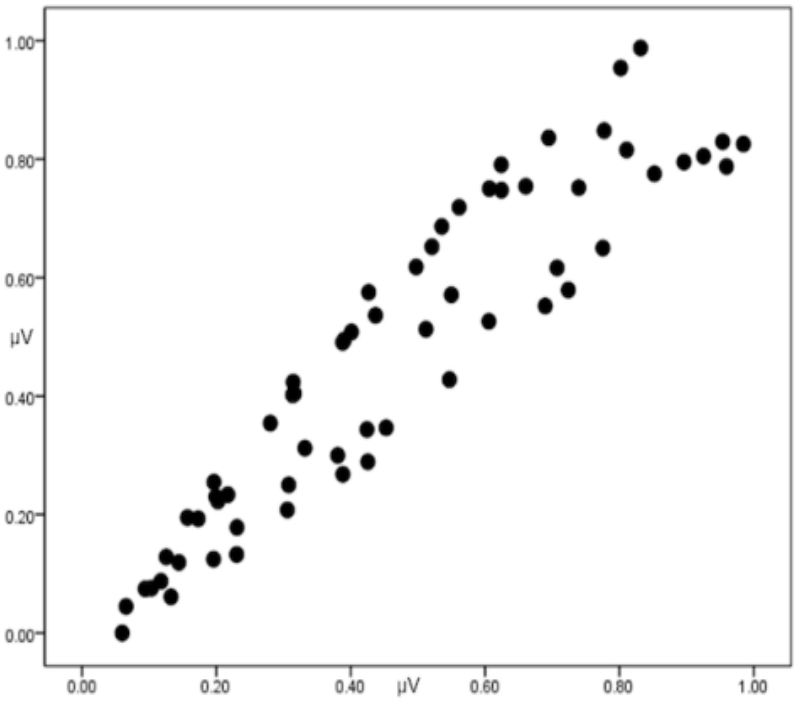


Figure 8.3 Correlation of mean amplitude within the 300-500ms time window relative to the high (x axis) and low (y axis) association conditions, subtracted from the unrelated condition and rescaled according to McCarthy & Wood (1985). Each data point reflects a single electrode location. The linear correlation confirms high topographic similarity across conditions shown in Figure 8.2.

Additionally, the rescaled results for all the 62 electrodes were used to investigate topographic similarity via a Pearson product-moment correlation analysis. The mean amplitude over the 300-500ms interval was obtained for each electrode (averaged across participants), within each experimental condition (unrelated minus low and unrelated minus high), and these values were compared across conditions (see Figure

8.3). This analysis revealed a significant positive correlation between the high and low condition N400 effects ($r = .93$; r^2 linear = .86; $n = 62$; $p < .001$) that emphasises the tight topographic similarity in N400 effects across conditions. Importantly, even when difference waves were not calculated (therefore excluding the unrelated condition from the analysis) the correlation between the low and the high association condition was still found to be significant [$p < .001$].

8.3.2.2 Within Laboratory Reliability

To provide additional elements to the reliability analysis described in Chapter 5, we compared the N400 results collected in Stirling in the reliability across laboratories reliability experiment (Chapter 5) with the N400 results collected in the same laboratory in the experiment described in the current Chapter. The N400 experiment described in the current Chapter had three experimental conditions (no association, low association and high association), and to allow the current within laboratory comparison only the no association and the high association conditions were considered, as they correspond to the unrelated and high association conditions described in the N400 preparation presented in Chapter 5.

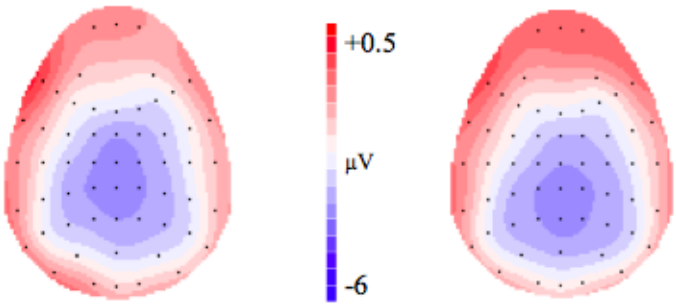


Figure 8.4 Topographic maps showing the N400 effects elicited during Experiment 1 (left) and Experiment 2 (right). In both cases the distribution of the effects has a clear centro-parietal maximum.

Topographic maps shown in Figure 8.4 show the effect's distribution across experiments. Possible differences were investigated via a repeated measures ANOVA on difference waves, using within subjects factors of Location (Frontal, Fronto-Central, Central, Centro-Parietal and Parietal), Site (superior: sites 1 & 2; inferior: sites 5 & 6) and a between subjects factor of Experiment (Experiment 1, Experiment 2). The analysis did not yield significant results involving the Experiment factor. To investigate differences at the single electrode spatial resolution, a between subjects ANOVA with a factor of Experiment was run on each of the electrodes used in the analysis. Results are shown in Table 8.2, revealing no statistical differences in the size of the N400 effect at any electrode within the 300-500ms time window. Overall the within laboratory reliability analysis shows reliable results consistent with the inter-laboratory reliability analysis described in Chapter 5.

Site	F	Sig.
F5	.04	.831
F1	.05	.815
F2	.16	.684
F6	.34	.561
FC5	.13	.715
FC1	.26	.609
FC2	.08	.774
FC6	.05	.809
C5	.14	.702
C1	.17	.679
C2	.03	.851
C6	.04	.842
CP5	.00	.953
CP1	.02	.884
CP2	.00	.983
CP6	.05	.816
P5	.21	.646
P1	.04	.830
P2	.04	.832
P6	.07	.790

Table 8.2 Results at the single electrode spatial resolution of the between subjects comparison relative to the within laboratory N400 comparison. For each electrode in the analysis are reported the F and the *p* values.

8.4 Discussion

We investigated whether the N400 effect is modulated by changes in associative strength, reflecting sensitivity to differences in contiguity of distinct stimuli within one's past experience. We employed a cue-target priming procedure, and we manipulated the degree of association between the cue and the target word while keeping their semantic relatedness constant. Behaviourally we found that participants were able to clearly discriminate between levels of association and also found robust priming effects, with reaction times to targets modulated by the degree of association. N400 effects, obtained by subtracting the high and the low association conditions from the unrelated condition in ERPs to targets, were found to be maximal over centro-parietal regions from 300-500ms post-stimulus. Critically, the N400 effect was graded in size, being largest for targets primed by highly related words. Overall, these findings suggest that the degree of association between words can modulate N400 generators, even when the degree of semantic relatedness between words does not differ across conditions. In short, the present findings support the associative N400 hypothesis (Rhodes & Donaldson, 2008), and underline the importance of experientially formed associations for the generation of the N400.

Besides the results of the current experiment and of Rhodes & Donaldson (2008), experiments demonstrating N400 effects elicited by phonological mismatches are particularly difficult for a semantic account to accommodate (e.g., see Perrin et al.,

2003). In addition, previous work using arithmetical statements (Niedeggen et al., 1999a; 1999b) point towards the inadequacy of an account of the N400 based exclusively on semantic relationships. Niedeggen et al. (1999a; 1999b) showed participants stimuli such as "7x4", followed either by a correct target ("28") or by an incorrect target ("26"), and observed N400 modulations by contrasting ERPs evoked by the correct versus incorrect targets. Whilst a semantic interpretation of such effects is not readily apparent, an association-based interpretation readily explains the results. Participants have a long history of saying "28" after they read or hear "7x4", whereas a "26" after a "7x4" constitutes a clear associative mismatch given previous experience.

More broadly, the alternative 'associative mismatch' account is attractive because it allows links to be forged with the wider stimulus equivalence literature which defines "meaning" as the by-product of intra-experimentally created associations among novel stimuli (Barnes Holmes et al., 2005). A number of studies have found N400 effects using intra-experimentally created associations (Haimson et al., 2009; and see also Barnes Holmes et al., 2005), using trigrams (SIG, BEH, POR) and nonrepresentational forms (e.g. abstract black and white shapes considered to be difficult to name). These studies have measured the N400 during the development of arbitrary associations among stimuli, showing that the effect emerges as a function of the training procedure. For example, Haimson and colleagues found that during the first 60 training trials no N400 effect was detected, while during the last 60 trials there was a measured N400 effect. Overall, the fact that the N400 has been measured with trigrams,

nonrepresentational forms and numbers, as well as verbal stimuli, with extra and intra-experimentally created associations, serves to emphasise the generality of the associative mechanism that it may reflect.

The current study emphasizes that the N400 is sensitive to how often two stimuli were presented contiguously within an individual's past experience. In addition, the associative account also suggests that the temporal dynamics of one's experience may be important for the processes revealed by the N400. It is well known that particular temporal patterns of stimulation are important for the acquisition of associations, based on findings from many different levels of analysis. For example at the synaptic level close temporal proximity in the occurrence of neuronal responses is fundamental for the induction of long-term potentiation (e.g. Gustaffson et al., 1987; Levy & Stewart, 1983; Gustaffson et al., 1987), the mechanism that strengthens synaptic associations. Behaviourally, the significance of temporal contiguity can also be seen in associations created through sensory preconditioning paradigms (e.g. Rescorla, 1980), where repeated pairings can be sufficient in establishing relationships between otherwise arbitrary unrelated stimuli.

Temporal contiguity is also an important factor for priming. If associated prime-target stimuli are presented sequentially, a facilitating effect will be measured in decreased reaction times after presentation of the target stimulus; but an interposition of

unrelated items between the two associated ones has been shown to decrease this facilitating effect (Ratcliff & McKoon, 1981). Some evidence of sensitivity to such timing parameters does exist from prior ERP experiments showing that the presence of an intervening word between a prime and a target disrupts the N400 effect (Deacon et al., 1998). Similarly, language comprehension studies (using auditory garden path sentences, e.g., I took off my shirt and tie) have shown that the N400 effect is reduced by the introduction of either silence (MacGregor et al., 2010) or disfluency (Corley et al., 2007), both of which may be viewed as primarily disrupting temporal contiguity. We would argue that these prior findings are naturally accommodated within the associative account of the N400.

Finally, we would point out that the associative account provides a useful way to operationalize the term "meaning". When we speak of a "meaningful" association, or a meaningful sentence, we tend to refer to an association or a sentence consistent with our previous experience. "traffic-jam" or "speech-therapy" are meaningful word pairs because we have seen or heard the words comprising the pair many times together. Presentation of sentences with anomalous endings, such as *I drink my milk with cream and dog,* are not consistent with our previous experience, and we may therefore consider such sentences "meaningless". However, even one repetition of a "meaningless" sentence will attenuate the N400 component measured after the final word, showing that one exposure to that specific association makes it less anomalous (Besson et al., 1992). From this perspective the N400 effect does not reflect the

transient activation of semantic knowledge. Rather, the N400 may reflect the acquisition of meaning via associations formed and maintained by the contiguity of distinct elements within one's experience.

Results presented in Section 8.3.2.2 strengthen the idea that the N400 effect is highly reliable, showing within laboratory reliability results consistent with the inter-laboratory reliability results described in Chapter 5. What does, however, the experiment presented in the current Chapter suggest with regards to the validity of the N400 effect? Does the N400 measure what it is supposed to be measuring? Starting from the perspective that the N400 measures strictly semantic relationships, then it could be argued, based on Rhodes and Donaldson (2008) and the current results that the N400 is not a valid measure of semantic relationships. On the other hand if the N400 is re-defined as a measure of a process sensitive to association relationships, not limited to the linguistic domain, then it can be concluded that the N400 appears to be a valid measure of such a process. To rule out the possibility that the N400 is indeed constrained to the linguistic domain it would be important to test if the effect can be measured, using arbitrary intra-experimentally created associations, with non-human species. Other ERP effects such as the P3b have been measured in non-human species (see Chapter 3) and a direct investigation of the N400 effect in non-human species has yet to be carried out. If the effect is somehow directly related to language intended as an ability typical of humans, then it should not be possible to measure the effect in non-human species. If, on the other hand, the effect is measured in non-human species

than it would be further proof that it may be a reflection of a general process sensitive to contiguity-based associations.

8.5 Summary

The results presented in the current Chapter point towards the need to redefine what the N400 is a measure of. It appears in fact that the N400 could be a measure of a process sensitive to contiguity-based association relationships and not to semantic relationships. Moreover the results presented in the current Chapter also allowed assessing within-laboratory reliability by comparing N400 effects carried out across two different experiments. Overall, while the reliability of the effect appears to be high, the validity of the effect might have to be redefined. If the effects is considered as a measure of semantic relationships, then its validity - given the current results - cannot be considered as high. If the effect is however considered as a measure of association relationships, then it could be considered as highly valid.

Chapter 9

Investigating the Validity of the N400 Pt. 2: Are the N400 and the Bilateral Frontal Effect indexing the same process?

9.1 Introduction

In Chapter 8 we investigated how the N400 effect behaves when participants are exposed to varying degrees of associations while keeping semantic relationships constant across conditions. The experiment was carried out to investigate the possibility that the effect may reflect a contiguity-based process sensitive to associations, and the results appeared to offer a new perspective on what the N400 is a measure of. The possibility that the N400 represents a measure of association relationships is not the only validity-related issue yet to be resolved. Voss and Federmeier (2011) have in fact recently proposed that the N400 and the Bilateral Frontal Effect (also described as FN400), a frontally distributed old/new effect occurring in the same time-window as the N400 effect, may actually reflect the same underlying process. Voss and Federmeier propose that both effects reflect semantic

processing, specifically that the Bilateral Frontal effect reflects semantic processing occurring during an old/new recognition procedure.

Even if the N400 does not reflect semantic processing, as we have proposed in Chapters 2 & 8, the assertion that the N400 and the Bilateral Frontal effect reflect the same phenomenon warrants a direct investigation because, if that was the case, a large number of studies in the ERP recognition memory literature would have to be reinterpreted from a N400 perspective. To investigate directly the possibility that the N400 and the Bilateral Frontal effect are a measure of the same phenomenon, in the current chapter we describe an old/new recognition experiment, using as the same low and high association word-pairs described in Chapter 8, designed to assess if the putative old/new effect behaves similarly or differently compared to the N400. More specifically, the current experiment relies on an associative recognition procedure to investigate the early Bilateral Frontal effect as a function of association relationships.

As described in Chapter 4, associative recognition (Rhodes & Donaldson, 2007; see also Opitz & Cornell, 2006) requires discrimination between word pairs that are intact (i.e. the same as at study) or rearranged (i.e. recombined into new pairings), compared to a baseline of correctly rejected new pairs (i.e., unstudied). Within the theoretical framework of dual process theory (see Chapter 4) associative recognition was traditionally thought to rely solely on recollection (e.g. Hockley, 1992; Yonelinas,

1997) and early ERP studies (e.g., Donaldson & Rugg, 1998; 1999; Jager et al., 2006) revealed clear Left Parietal old/new effects consistent with this view. More recently, however, ERP studies have demonstrated that associative recognition can engage familiarity in some circumstances. In particular Rhodes and Donaldson (2007) examined recognition of associatively related pairs ("Traffic-Jam") compared to unrelated pairs ("Carpet-Razor"), using free association norms to generate these two classes of stimuli. They found that while all word pairs elicited the left parietal correlate of recollection, only associated pairs elicited the Bilateral Frontal effect.

The experiment presented in the current chapter not only offers the possibility to investigate if the N400 and the Bilateral Frontal effect behave similarly or differently to word-pairs with varying degrees of association. As an interesting corollary, investigating how the Bilateral Frontal effect varies as a function of association relationships allows in fact potentially to gain new information on the nature of the early old/new effect. If the notion that the effect reflects a measure of familiarity memory (see Chapters 2 & 4) is true, the current experiment allows asking whether a change in the strength of association between words systematically influences the familiarity their pairing engenders during recognition – as indexed by the Bilateral Frontal old/new effect.

As described above, in their study Rhodes and Donaldson (2007) examined associative recognition using unrelated (0 association) and moderately associated (.206) word

pairs, finding the Bilateral Frontal old/new effect for associated word pairs only. The current experiment examines associative recognition using low (.068) and high (.357) levels of association (the same values used in the N400 experiment described in Chapter 8), allowing to compare the Bilateral Frontal effect with the N400 and to examine the effect of increasing associative strength on familiarity. This manipulation from low to high associative strength could lead to either an enhancement or a reduction in the size of the bilateral frontal effect.

On the basis of Rhodes and Donaldson's (2007) existing data we predicted that increasing levels of association could enhance familiarity. This prediction is illustrated in Figure 9.1A, which extrapolates from existing data points in Rhodes and Donaldson (2007). If the Bilateral Frontal effect behaved according to this prediction, then it would be consistent with the N400 results described in Chapter 8, where the size of the N400 effect increased as the degree of association increased. A second possibility is that familiarity will decrease as a function of associative strength (as illustrated in Figure 9.1B). This view is predicated on the assumption that the strength of the familiarity signal generated within the context of the experiment is calculated relative to one's pre-experimental exposure to the pair, i.e. to its baseline familiarity (for a recent discussion of different forms of familiarity, including relative familiarity, see Coane et al., 2011). By definition highly associated pairs have a higher baseline level of pre-experimental familiarity than low associated pairs, therefore relative familiarity would be stronger during recognition of low vs. high associative pairs. If this is the

case, the bilateral frontal effect may be larger in magnitude when elicited during the associative recognition of low vs. high associative strength pairs. Moreover, if the Bilateral Frontal effect behaved according to this prediction, then it would be inconsistent with the N400 results described in Chapter 8, where the size of the N400 effect increased as the degree of association increased, suggesting, contrary to what suggested by Voss and Federmeier (2011), that the N400 and the Bilateral Frontal effect are not the same phenomenon. In sum, the primary aim of the experiment presented in the current chapter is to investigate if the Bilateral Frontal effect behaves similarly or differently compared to the N400 effect in reaction to the same degrees of associations. As a secondary aim, the experiment allows exploring the nature of the Bilateral-Frontal old/new effect interpreted as a familiarity signal contributing to associative recognition.

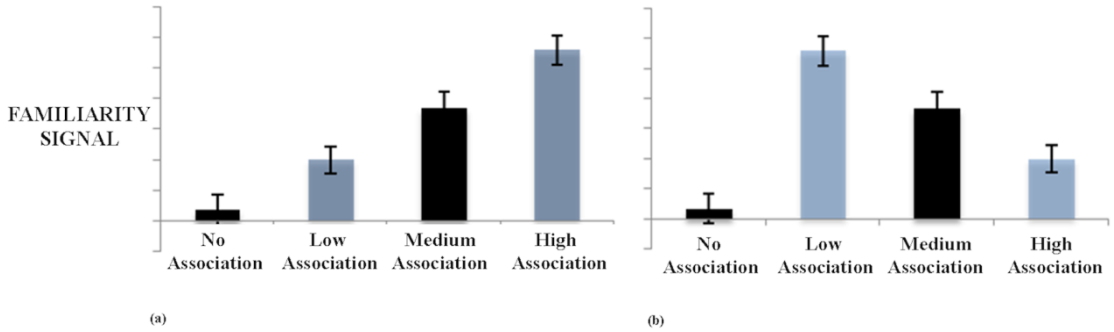


Figure 9.1 Competing predictions for the relationship between associative strength and the size of the familiarity signal during associative recognition. Black bars show existing data points from Rhodes and Donaldson (2007). Grey bars depict two contrasting hypotheses. Panel a) illustrates the 'baseline familiarity' view, whereby increasing associative strength leads to stronger familiarity. Panel b) illustrates the 'relative familiarity' view, whereby increasing associative strength, acting as an index of one's prior exposure to the pairing, leads to weaker familiarity.

9.2 Methods

9.2.1 Participants and Materials

Twenty-four (16 female) right-handed native English speakers participated for payment (£5 an hour). Participants' mean age was 21 years (range 18-30) and all reported normal or corrected to normal vision with no history of neurological disorders. Informed consent procedures were approved by the Psychology Ethics Committee at the University of Stirling. Three hundred and six word pairs were created (3 to 11 letters in length) taken from the MRC Psycholinguistic Database (www.eat.rl.ac.uk). The words were divided into two experimental conditions: word pairs with low association and word pairs with high association, according to the same criteria presented in Chapters 5 & 8; note that the high and low association stimuli were randomly intermixed during study and test phases, such that participants were unaware of the conditions.

9.2.2 Procedure, ERP recording Parameters and Analysis

Word pairs were presented visually (one above the other, in central vision) using a white uppercase 18-point Courier New font against a black background. The experiment was divided into 17 study-test blocks. Study blocks comprised 12 word-pairs. Test blocks comprised 18 word-pairs, 6 of which were the same as presented at study (intact), 6 were in a different pairing from study (rearranged), and 6 were entirely new. Study and test lists were rotated across participants to avoid item effects.

At study, participants were instructed to read and remember each word-pair.

Each trial began with a fixation cross (+), presented in the centre of the screen for 1000 ms, followed by the word-pair for 1500 ms, and a further blank screen for 1250ms. After each study block an associative recognition memory test was performed. Test trials began with a 1000 ms fixation cross, followed by the word-pair for 2000 ms and a 1750 ms blank screen. Participants were asked to respond with either an intact, rearranged or new judgement, using a 5-button response-box. All participants made "Rearranged" responses using the middle button; rearranged pairs were not of primary interest and behavioural and ERP data are therefore not analysed further; their inclusion was however important to force participants to respond "intact" only when they remembered the specific relationship between members of a word-pair, not just that both words in the pair were old. "Intact" and "New" responses were made using the extreme left and right hand buttons, and the mapping of responses to buttons was counterbalanced across participants.

EEG was recorded according to the parameters described in section 6.4.4. ERPs were formed (time-locked to the onset of stimuli at test) for correct responses to intact and new pairs, allowing old/new differences to be examined as a function of associative strength. Both intact and new pairs were separated based on strength of association: low-association intact and new pairs comprised the low-association condition and

high-association intact and new pairs comprised the high-association condition. Trials were excluded if drift exceeded ±55 μV, or if in any point during the epoch activity exceeded ±100 μV. The mean number of trials (all conditions >16) contributing to ERPs was: low association intact 24.5; low association correct rejections 27.29; high association intact 24.79; high association correct rejections 27.83. ANOVAs were conducted on twenty-four electrodes divided into four channels groups: left anterior (FP1, AF3, F7, F5, F3, F1), right anterior (FP2, AF4, F8, F6, F4, F2), left posterior (CP3, CP1, P3, P1, PO5, PO3) and right posterior (CP4, CP2, P4, P2, PO6, PO4).

9.3 Results

9.3.1 Behavioural Results

Mean accuracy (and standard deviation) for intact pairs was .79(.12) for the low association condition and .82(.08) for the high association condition; for new pairs .91(.1) for the low association condition and .91(.09) for the high association condition. These data were analysed using repeated measures ANOVA with factors of association (low, high) and response (intact, new). A significant main effect of response [$F(1, 23) = 16.3$; $p < .001$] reflects participants' greater accuracy at rejecting new pairs than recognizing intact old pairs, independent of associative strength. By contrast there was no main effect of association, or association x response interaction [$F(1,23) = 1.16$; $p = .293$; $F(1,23) = .83$; $p = .371$], suggesting that associative strength did not influence overall levels of discrimination.

9.3.2 ERP Results

The grand average ERPs elicited by low association word-pairs are shown in Figure 9.2A. The waveforms diverge about 200ms post-stimulus onset, with the ERPs for intact pairs becoming more positive than correct rejections, a difference maximal over frontal sites. Positive activity is also observed over parietal sites for intact in comparison to correct rejections (see Figures 9.2A and 9.2B). This parietal positivity emerges around 500ms and is maximal over left-parietal sites for both low and high association word-pairs.

Consistently with the previous literature data were divided into time windows of 300-500 and 500-700ms for analyses related to the Bilateral Frontal and the Left Parietal old/new effects, respectively. Choice of the 300-500 time window also allows directly comparing the Bilateral Frontal effect described in the current chapter with the N400 effect described in Chapter 8. Figure 9.3 illustrates the topographic distribution of the old/new effects (based on intact minus correct rejection difference waveforms) during time windows that capture the ERP correlates of familiarity and recollection. The data were analysed using ANOVA, initially conducted separately for low association and high association to characterise the old/new effects for each condition, before carrying out comparisons across conditions.

9.3.2.1 Bilateral Frontal old/new effect

Analysis employed ANOVA with factors of Response (Intact, New), Hemisphere (Left, Right) and Location (Anterior, Posterior). For the low association condition analyses revealed a main effect of Response [$F(1,23) = 31.02$; $p < .001$] and a significant Response x Location interaction [$F(1,23) = 4.81$; $p < .04$], showing the effect to be larger at the anterior compared to the posterior location. Follow up analysis focused on the anterior location found an effect of Response [$F(1,23) = 27.07$; $p < .001$] and, consistently with the typical distribution of the bilateral frontal effect, no response x hemisphere interaction [$F(1,23) = .002$; $p = .96$]. ANOVA examining the high association condition found a significant main effect of Response [$F(1,23) = 7.02$; $p < .02$] but no Response x Location interaction effects or interactions [$F(1,23) = .14$; $p = .170$]. Follow up analysis on the anterior location found a marginally significant effect of Response [$F(1,23) = 4.09$; $p = .055$] and no Response x Hemisphere interaction [$F(1,23) = 1.17$; $p = .28$].

A magnitude analysis was performed using data from the anterior channels groups with factors of Condition (Low Association, High Association), Response (Intact, New) and Hemisphere (Left, Right) to assess directly differences in the size of the Bilateral Frontal old/new effect across experimental conditions. This ANOVA revealed a significant Condition x Response interaction [$F(1,23) = 4.5$; $p < .05$], showing the larger magnitude of the effect for the low compared to the high association condition.

9.3.2.2 Left Parietal old/new effect

As can be seen in Figures 9.2 and 9.3, both the low and high association conditions appear to exhibit left parietal old/new effects. Consistent with previous literature (e.g. Curran, 2004) the left parietal effect was examined by focusing on two posterior channels groups, using ANOVA with factors of Response (Intact, New) and Hemisphere (Left, Right). For the low association condition ANOVA revealed a significant effect of Response [$F(1,23) = 26.89$; $p < .001$] and a Response x Hemisphere interaction [$F(1,23) = 7.86$; $p < .02$], showing the effect to be larger over the left than right hemisphere. Analysis of the high association condition also revealed a significant effect of Response [$F(1,23) = 16.34$; $p < .002$], and a Response x Hemisphere interaction [$F(1,23) = 6.39$; $p < .02$] showing again the effect to be larger over the left than right hemisphere.

A magnitude analysis with factors of condition (Low Association, High Association), response (Intact, New) was then carried out using data from the left posterior channel group, to assess possible differences in the size of the left parietal old/new effect across experimental conditions. This ANOVA revealed no significant condition x response interaction [$F(1,23) = 1.19$; $p = .286$] suggesting that the size of the left parietal effect was equivalent across conditions.

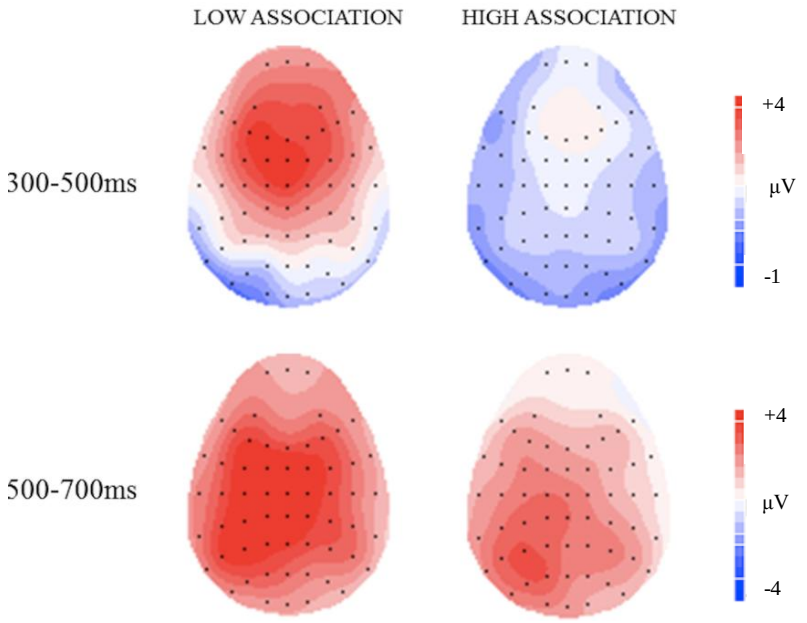


Figure 9.2 Topographic maps showing the distribution of the old/new effects in the low and high association conditions separately for early (300-500ms) and late (500-700ms) time windows.

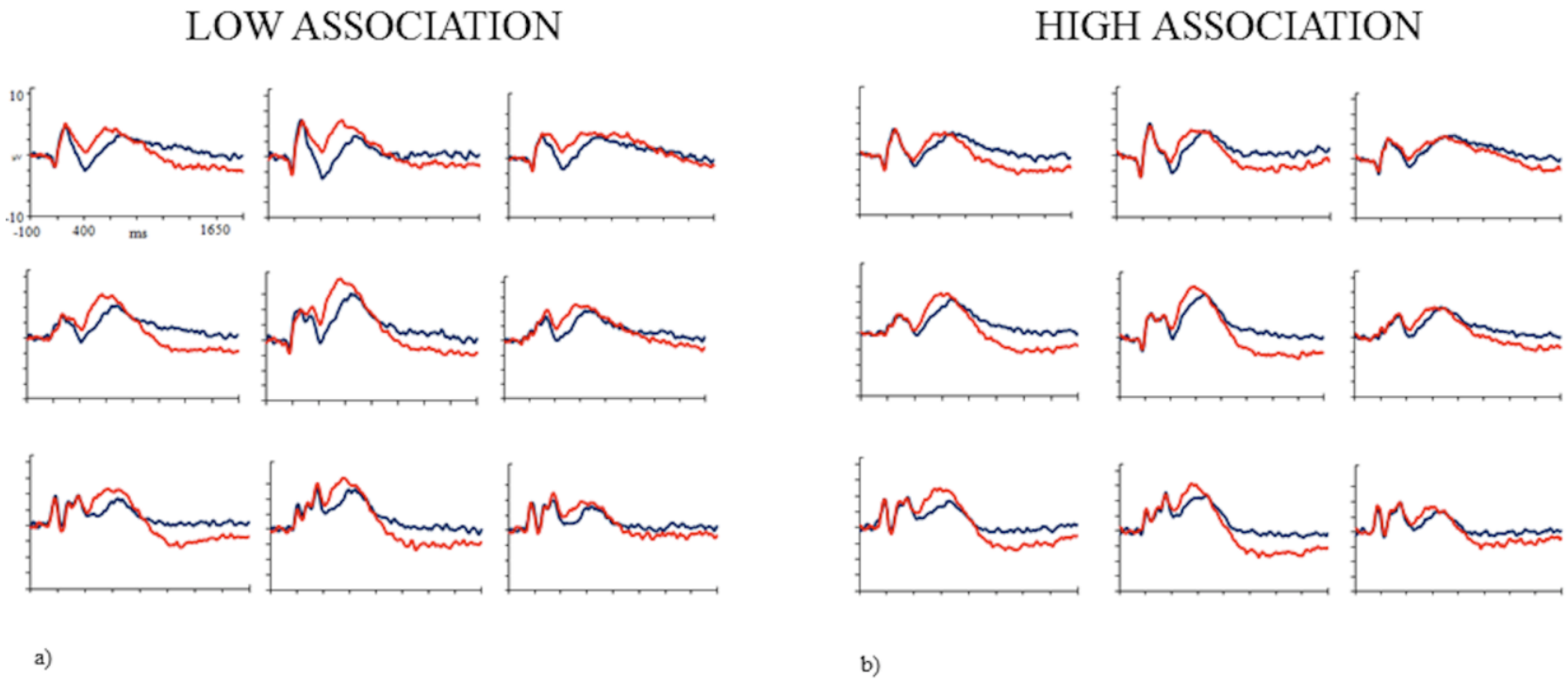


Figure 9.3 ERPs for low (Panel a) and high (Panel b) association word-pairs, shown time locked to stimulus onset, for the recognised intact pairs (red lines) and rejected new pairs (blue lines). Waveforms are shown for nine electrodes (FC5, FCZ, FC6, CP5, CPZ, CP6, PO5, POZ, PO6), from frontal to parietal sites, in each experimental condition.

9.4 Discussion

The current experiment allowed comparing the Bilateral Frontal effect to the N400 effect as described in Chapter 8 by using the same stimulus set and experimental conditions, and it also gave insight on the nature of the familiarity signal involved in associative recognition memory. The observed pattern of results, taken together with results from Chapter 8, suggests that the Bilateral Frontal effect behaves differently compared to the N400 effect, whose size was larger for stimuli with high levels of associative strength (see Figure 9.4 and 9.5). As clear from Figure 9.5, the two effects not only display opposite patterns as a response to increasing degree of association, but also appear to show a different distribution of the effect, centro-parietal for the N400 effect and fronto-central for the Bilateral Frontal effect.

While the opposite pattern of the N400 effect and the Bilateral Frontal effect as a function of degree of association is most likely related to the fact that the effects reflect different processes, the difference in distribution may be due to the fact that the two procedures required different SOAs. While in the N400 priming procedure there was an SOA of 800ms between prime and target stimuli, in the Bilateral Frontal experiment the SOA was 0ms, as required by the associative recognition procedure. From the existing data therefore it cannot be suggested that the observed distributional differences are due to differences in the underlying neural generators, as the SOA has

been shown to be an important variable in determining the timing and distribution of the N400 effect (Anderson & Holcomb, 1995).

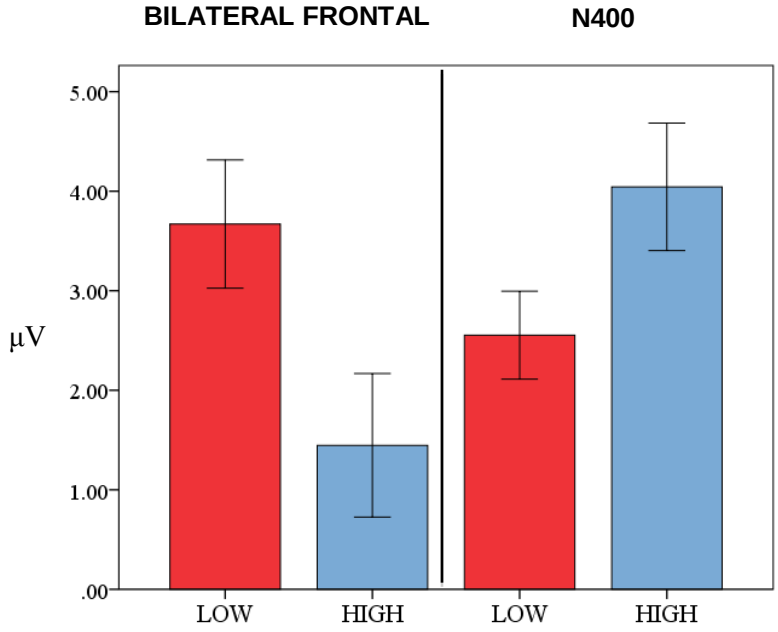


Figure 9.4 Bar graphs show the size (in microvolts) of the Bilateral Frontal effect (current Chapter) and the N400 effect (Chapter 8) at electrode Cz within the 300-500ms time-window. The two effects behave differently to low and high degrees of association relationships. The size of the Bilateral Frontal effect decreases as the degree of association increases, while the size of the N400 effect increases as the degree of association increases.

As discussed in Chapter 2, Voss and Federmeier (2011) have carried out a within participants topographical comparison between the N400 effect and the Bilateral Frontal effect. The authors did not find any topographical differences across the two

effects. It has to be noted however that Voss and Federmeier did not describe a statistically well-characterized distribution for either effect. While in the N400 studies presented in the current thesis (Chapters 5 & 8) and for the Bilateral Frontal effect presented in the current Chapter we were able to topographically characterize the effects via significant condition by location interactions, yielding statistical proof for the typical centro-parietal distribution of the N400 effect and the frontal distribution of the Bilateral Frontal effect (or FN400), Voss and Federmeier found in both cases broadly distributed effects not varying statistically across electrode locations. It is therefore not surprising that the topographic analysis carried out in their study did not yield significant differences. The same topographic analysis would have to be repeated when the two effects are characterized more precisely than a broad positivity. Until then, such a null result has to be interpreted with caution.

The difference in the way the two effects behave in relation to association relationships is moreover hard to reconcile with the idea that the N400 and the Bilateral Frontal effect are indistinguishable. As Figure 9.4 and 9.5 show, the size of the N400 effect increases as the degree of association increases (Unrelated minus Low Association < Unrelated minus High Association), while the size of the Bilateral Frontal effect decreases as the degree of association increases (Low Association Hits > High Association Hits). If the same process was underlying both ERP effects, it would be plausible to expect the effects to react in the same direction, not opposite directions, to varying degrees of association. We instead suggest that the opposite pattern observed

across effects warrants different interpretations as the two effects appear to be measuring different phenomena. In Chapters 2 & 8 we have suggested an interpretation of the N400 effect based on results indicating sensitivity to association relationships. In the following section we provide, within dual process theory of recognition memory, an interpretation of the Bilateral Frontal effect based on the possibility that the effect reflects a form of relative familiarity.

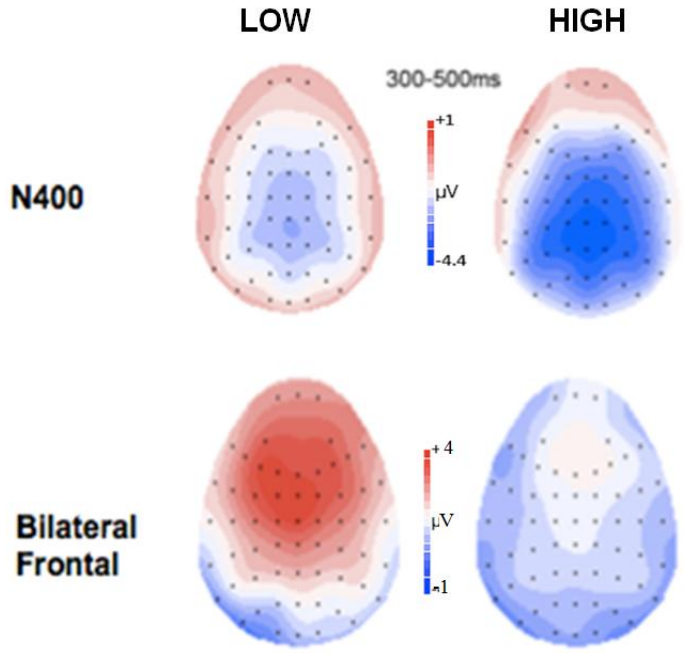


Figure 9.5 Topographic maps showing how the N400 effect and the Bilateral Frontal effect behave differently to the same degrees of association relationships. The size of the N400 effect increases as the degree of association increases (Unrelated minus Low Association < Unrelated minus High Association), while the size of the Bilateral Frontal effect decreases as the degree of association increases (Low Association Hits minus CRs > High Association Hits minus CRs).

The data presented in the current Chapter suggest that a relative familiarity signal (Coane et al., 2011) is generated by word-pairs during associative recognition, and that associative strength has selective effects on neurophysiological correlates of familiarity and does not alter recollective processing, at least so far as it is indexed by ERP old/new effects. It is worth pointing out here that behaviourally, participants were well able to recognise the stimuli, with equivalent levels of performance for the low and high association conditions. One might therefore consider the recognition data to be inconsistent with the claim that familiarity contributed more to performance in one case than the other. However, while overall recognition rates are a function of recollection and familiarity (Yonelinas, 2001), the way in which the processes combine to support behaviour is not yet known (e.g. Cohen et al., 2008). In essence, no 'process pure' measure exists to directly assess familiarity, which is why we used the ERP old/new effects to index retrieval processing instead.

A more pertinent issue, however, is the nature of the mechanisms that are indexed by the Bilateral Frontal old/new effect, because the familiarity interpretation has not attracted unanimous support. Specifically, some authors have argued that the effect could be a correlate of changes in conceptual fluency due to priming (e.g. Voss & Paller, 2004; Paller et al., 2007), while others have argued that the effect reflects neither familiarity nor priming (De Chastelaine et al., 2009). However, our findings, along with other recent results which indicate that the Bilateral Frontal effect is graded according to familiarity strength, (Yu and Rugg, 2010) add to existing evidence

difficult to reconcile with these contrasting interpretations (Groh-Bordin et al., 2006; Stenberg et al., 2009). In what follows below, we therefore utilize the prevalent view that the bilateral frontal effect is a neural correlate of familiarity (e.g. Curran, 2000; for review see Rugg and Curran, 2007).

Our data clearly rule out the first of our two predictions; i.e., that increases in associative strength lead to monotonic increases in familiarity. Instead, our data, along with previous findings (Rhodes & Donaldson, 2007) fit well with operational definitions of familiarity as a relative signal (Coane et al., 2011; Mandler, 1980; Rugg et al., 1995). By definition our high association pairings have a greater amount of pre-experimental exposure, such that the experimental presentation should elicit a relatively small increase in familiarity. Conversely, the encounter with a low association pair during the memory test should produce a relatively large increase in familiarity compared to pre-experimental 'baseline' levels. As Coane et al. (2011) make clear, stimuli with a lower degree of pre-experimental exposure receive a relatively greater boost in familiarity from a recent presentation compared to stimuli with a higher degree of pre-experimental exposure. Thus, the current findings extend those of Rhodes and Donaldson (2007), demonstrating that since the bilateral frontal old/new effect indexes relative familiarity, as the degree of pre-experimental exposure increases the frontal old/new effect can decrease.

In the study by De Chastelaine et al. (2009) noted above, it was reported that the frontal effect does not increase in size with repeated intra-experimental exposure to single item stimuli. Within a multiple study-test repetition paradigm (in which old items were constantly repeated and new items were replaced at each study-test repetition) they found that the bilateral frontal effect decreased with repetitions of old items. The topography of their old/new effects also shifted gradually from frontal to parietal across the four test phases, suggesting an increased reliance upon recollection.

In effect, De Chastelaine et al. therefore demonstrate that changes in intra-experimental exposure lead to a disappearance of the Bilateral Frontal effect, and we would argue that this is broadly consistent with the effect being a correlate of familiarity assessed relative to one's level of exposure to a stimulus. If this alternative interpretation is valid, our findings along with those from the study by De Chastelaine et al (2009) indicate that the bilateral frontal effect is more pronounced when familiarity is evoked by more novel stimuli. Furthermore, our present findings (and see Rhodes and Donaldson, 2007) suggest that a common relative familiarity signal is evoked during both item recognition and associative recognition.

It is worth pointing out that the present findings fit well with neural accounts of familiarity that stress the experience-dependent plasticity of brain areas generating the signal. One of the important features of the inferior temporal circuitry that supports

familiarity is the repetition sensitivity which allows sharpening of representations (Brown & Aggleton, 2001). In particular, repetition sensitive neurons in the perirhinal cortex are known to respond differentially to novelty (Xiang & Brown, 1998) such that stimuli with more pre-experimental exposure are less sensitive to repetition. Our data suggest that such differences in prior exposure may be captured by the numerical indices of associative strength that we used to form the low and high associative strength pairs.

9.5 Summary

Results presented in the current Chapter suggest that the N400 effect and the Bilateral Frontal effect are not reflecting the same neural phenomena, as the effects show opposite patterns in reaction to the same degrees of association relationships. We therefore propose different interpretations for the two effects, and while an interpretation of the N400 effect based on a general process sensitive to contiguity-based association relationships has been described in Chapters 2 & 8, here we interpreted the pattern of Bilateral Frontal effect's results within dual process theory of recognition memory as measure of relative familiarity. The following Chapter summarizes all the results and theoretical implications proposed in the current thesis.

Chapter 10

General Discussion

Results presented in the current thesis showed that all measured effects were consistent with the time course, morphology and topography described in the respective literatures. The effects were found to be reliable across laboratories at the group level and the P3b and the N400 effects were also found to be highly reliable at the single participant level. Regarding the effects' validity, results presented in Chapters 6 & 7 point to the fact that P3b probability effects may overlap with the Left Parietal effect, especially when the relative probability of old and new items is not matched. This finding is highly relevant in assessing the Left Parietal effect's validity: when the probability of old and new items is not matched the effect may disappear while the person *is* recollecting.

The N400 effect was found to be independent from attentional processes as reflected by the P3b, and from episodic recollection as indexed by the Left Parietal effect.

Having established the independence of the N400 effect from the other two sub-domains investigated in the current thesis, we proceeded to investigate if the effect is a valid measure of what it is typically considered to index, i.e. semantic relationships (Chapter 8). When we discovered that the effect is sensitive to associative relationships in absence of semantic differences we used this sensitivity of the N400 to associative relationships to investigate the independence of the N400 effect from another effect occurring within the same time window – the Bilateral Frontal effect, typically studied by memory researchers. Results of Chapters 8 & 9 taken together suggest that the N400 effect is a valid measure of associative relationships, independent from both semantic memory and the episodic memory process of familiarity. The following sections will summarize the results and elaborate on the theoretical interpretations presented in the current thesis for each experimental effect considered.

10.1 The P3b

Results from Chapter 5 show a high degree of reliability for the P3b effect both at the group and at the individual level, with only one participant (from sixty-four) not showing the effect (see Figure 10.1). Together with the evidence discussed in Section 3.4.3 showing a P3b-like effect in several non-human species, the P3b, among the three effects considered in the current thesis, might be considered overall the most reliable. The N400 effect in fact showed a high degree of reliability both at the group and individual level (see Section 10.4), but its inter-species reliability has not yet been

explored. One might ask: why is inter-species reliability important in an overall evaluation of a neurophysiological experimental effect? A key reason is that consistency across species is important in establishing the generality of a process. Some of the most important processes discovered in psychology (e.g. operant selection) have been measured in a large number of species. From this perspective the P3b represents a neurophysiological effect with strong evolutionary foundations, representing processes (perhaps due to convergent evolution) common among many species. The fact that the processes indexed by the P3b are not completely understood, as described in Chapter 3, that it is not agreed upon *yet* what the effect is a measure of, represents a temporary limitation on the current conceptualization on its validity.

In the current work we are able to add a contribution to understanding what the P3b is a measure of, as the P3b amplitude appears not to be independent from Left Parietal effect's amplitude (as described in Chapters 6, 7 and in Section 10.3). In essence the P3b effect either overlaps with the Left Parietal effect during the same time window, making the effects difficult to separate, or the two effects share common sensitivity to subjective and objective probability. This latter interpretation leaves open the possibility that the P3b and the Left Parietal effect may actually be the same probability-sensitive phenomenon emerging in different ERP sub-fields (see Section 10.3).

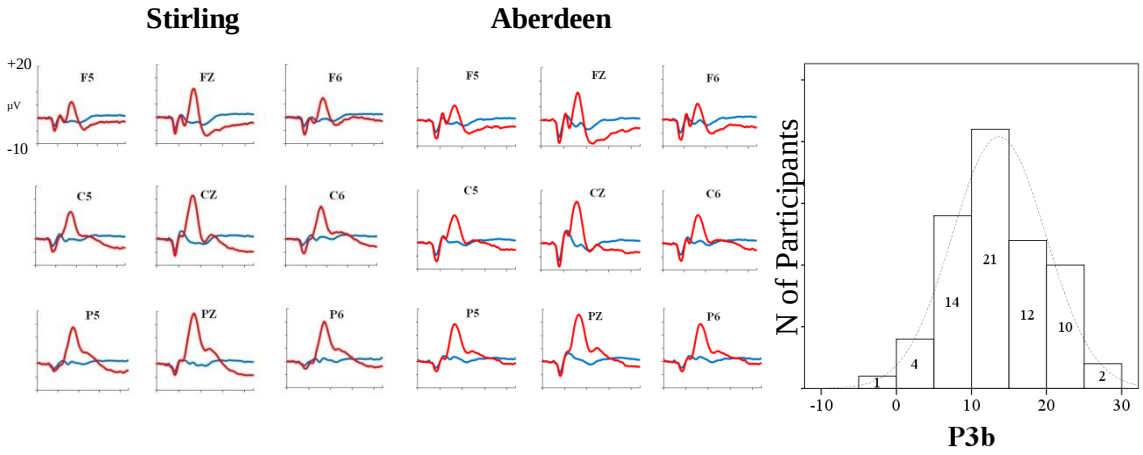
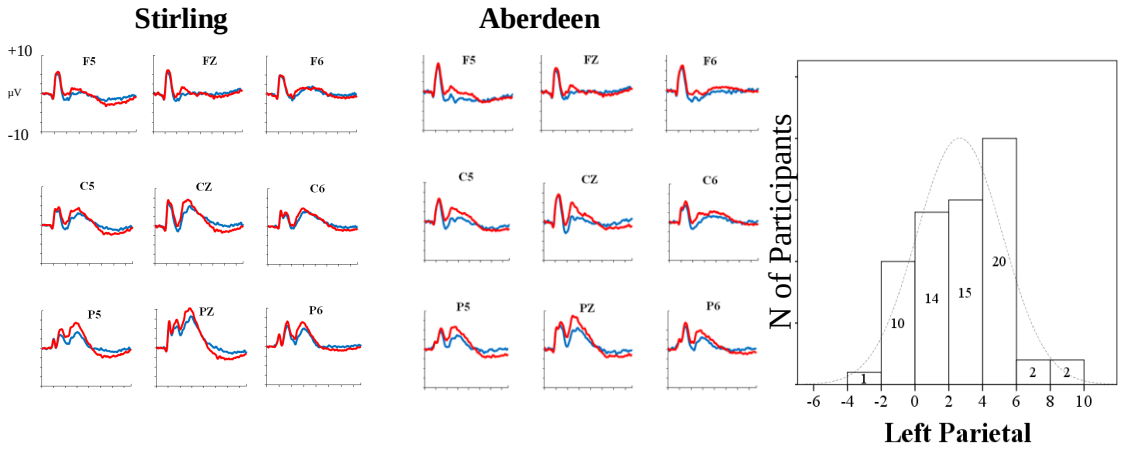


Figure 10.1 The graph shows a) inter-laboratory and b) inter-individual reliability of the P3b effect. The waveforms on the left (showing the target condition in red and the standard condition in blue, from 100ms pre-stimulus to 1000ms post stimulus) show the similarity of the effect across laboratories. The histogram on the right shows a normal distribution of the size of the effect across participants, with only one participant over sixty-four not showing the P3b effect. Data shown in the histogram is relative to the 275-400ms time-window post stimulus presentation (Adapted from Chapter 5).

10.2 The Left Parietal effect

The Left Parietal effect, while reliable at the group level, was not found to be as reliable as the P3b effect at the individual level, with eleven participants (from sixty-four) not showing the effect (see Figure 10.2). While this result does not constitute a limit within the constraints of a typical cognitive neuroscience experiment, it does represents a limit for the putative correlate of recollection when entering applied and clinical settings, where single-subject reliability is a basic prerequisite. The results

presented in Chapter 5 show that, compared to the N400 effect and the P3b effect the Left Parietal effect tends to display a larger degree of inter-individual variability – a finding that is compatible with MacLeod and Donaldson's (2011) results described in Chapter 4. A full explanation of the lack of inter-individual reliability clearly requires further experimentation, and may be related to either different strategies adopted by individuals during the recognition memory experiment, or perhaps to differences in the folding of parts of the cerebral cortex involved in eliciting the Left Parietal effect.



a) b)

Figure 10.2 The graph shows a) inter-laboratory and b) inter-individual reliability of the Left Parietal effect. The waveforms on the left (showing Hits in red and Correct Rejections in blue, from 100ms pre-stimulus to 1800ms post stimulus) show the similarity of the effect across laboratories, while the histogram on the right shows the distribution of the size of the effect across participants, with eleven participants over sixty-four not showing the Left Parietal effect. Data is relative to the 500-700ms time-window post stimulus presentation (Adapted from Chapter 5).

As mentioned in Chapter 5, from a validity perspective the absence of difference in behavioural pattern between the participants showing the Left Parietal effect and the participants not showing the effect is problematic, because validation of indices of episodic memory relies on a relationship between the ERP effect and a behavioural dependent variable considered to index the process of recollection. As the size of the Left Parietal effect is considered to reflect the amount of information retrieved there should be a measurable difference in sensitivity performance across participants showing the Left Parietal effect and participants not showing the effect. As described in Chapter 5 perhaps a more specific measure of behavioural recollection, such as source memory performance, would be needed to validate the Left Parietal effect. Theoretically, at least, it is possible that in the results presented in Chapter 5 and in Macleod and Donaldson's study the subgroup of participants not showing the effect was performing via the process of familiarity and not recollection.

Even if there is a possibility that the participants not showing the Left parietal effect were able to display equivalent behavioural sensitivity by using a familiarity process, it has to be noted that all other behavioural parameters (response bias and reaction times for both Hits and Correct Rejections) measured during the recognition memory task did not come close to differ significantly across the participants showing the Left Parietal effect compared to the subjects not showing the effect, once again consistent with the results reported by MacLeod and Donaldson (2011). These sets of results are overall problematic for the Left Parietal's effect validity because they show an

independence of all measured behavioural variables from the electrophysiological variable of interest.

The results presented in Chapter 7 also contribute to the idea that the Left Parietal effect is weakly related to behavioural indices of episodic memory. Results show that the size of the Left Parietal effect is sensitive to the relative probability of old and new items, pointing to the important suggestion (validity wise) that the Left Parietal effect's capability of indexing recollective processes may disappear when the relative probability of old and new items is not matched. Participants in the experiment described in Chapter 7 were behaviourally able to perform well and discriminate between old and new items in all experimental conditions, but the Left Parietal effect was only present when the probability of old items was lower than the probability of new items (see Figure 10.3).

From a methodological and clinical perspective these results, together with the reliability results, suggest that before the Left Parietal effect can be used in clinical and applied settings as a valid measure of recollection further experimentation is required at the basic research level. One important step to be carried out would be to systematically study the sub-group of participants that typically do not show a Left Parietal effect under different kinds of experimental procedures and stimulus materials. If a participant does not show the effect with a typical study-test recognition paradigm,

would the effect instead be measurable under other circumstances such as a continuous recognition memory procedure? Or does the effect appear when participants perform a task that necessarily requires recollection, such as source memory? And is the effect absent when participants recollect other kinds of stimulus material?

If the effect is measurable when performing some memory tests but not others, and with some kinds of stimulus materials but not others, then the effect's validity could be refined more specifically as a function of the specific procedures and materials. If, on the other hand, some participants do not show the effect under *any* circumstances, then those participants could be studied via MRI to investigate if a specific difference in the way their cerebral cortex folds may be causing significant differences in the way dipoles are oriented in generating the Left Parietal effect. Until it is clearly understood why some individuals do not show the effect it is not possible, for instance, to say that an individual is not recollecting based on an absence of Left Parietal effect, as the individual may be recollecting but may be part of the sub-group of individuals that typically do not show the Left Parietal effect.

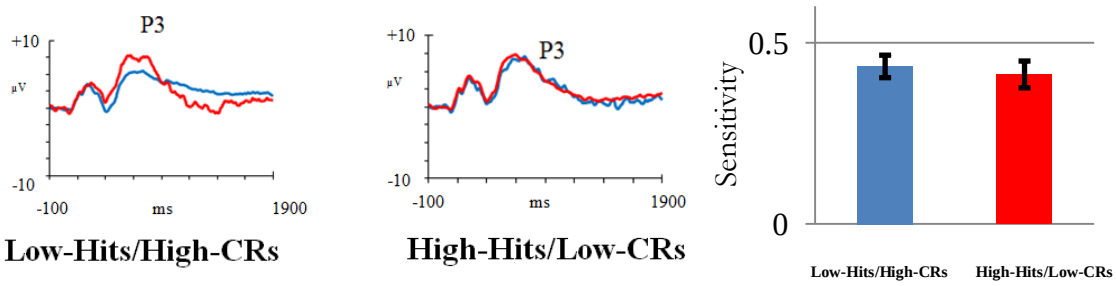


Figure 10.3 Results from Chapter 7 show how the size of the Left Parietal effect is sensitive to the relative probability of old and new items, and specifically how the effect disappears when the probability of old items is higher than the probability of new items. Conversely, the bar graph on the right shows an absence of difference in behavioural sensitivity across probability conditions (Adapted from Chapter 7).

In summary, the current investigation found the Left Parietal effect to be reliable at the group level but not at the single participant level. The reliability results for the Left Parietal effect appear to be relatively weak compared to the corresponding results for the P3b and the N400 effect. From a validity perspective the results of the current work presented in Chapters 5 and 7, together with the evidence described by MacLeod and Donaldson (2011) lead to doubts about the validity of the Left Parietal effect as a measure of episodic recollection, as there does not appear to be a clear relationship between the electrophysiological putative measure of recollection and correspondent behavioural measures.

10.3 The P3b and the Left Parietal effect

Results presented in Chapter 6 show correlational evidence suggesting a relationship between the Left Parietal effect and the P3b effect, but not between the Left Parietal effect and the N400 or the P3b effect and the N400. This relationship may be due to a target effect for old compared to new items, driven by the lower subjective probability of old items (Rosenfeld et al., 2005). The relationship between the Left Parietal effect and the P3b effect was further investigated in Chapter 7 via an objective probability manipulation applied during a recognition memory test. As the P3b effect is known to be very sensitive to the relative probability of standard and target stimuli, the relative probability of Hits and Correct Rejections was manipulated, potentially introducing to a difference in the size of the Left Parietal effect, if indeed it was sensitive to probability similarly to the P3b.

Results, shown in Figure 10.4, revealed a sensitivity of the Left Parietal effect to probability consistent with the typical behavior of the P3b under probability manipulations. One interpretation of these results illustrated in Figure 10.5 is that the memory effect typically seen in the Left Parietal effect was still present in the High-Hits/Low-CRs condition but was attenuated (to the point of disappearance) by a counter-acting, probability sensitive, P3b effect. This possibility is suggested by the absence of difference in sensitivity performance across conditions and by the fact that in the High Hits/Low Correct Rejection condition the Left Parietal effect was not

reversed into a negativity. According to this interpretation the P3b effect simply acts as a confound when measuring the temporally overlapping Left Parietal effect.

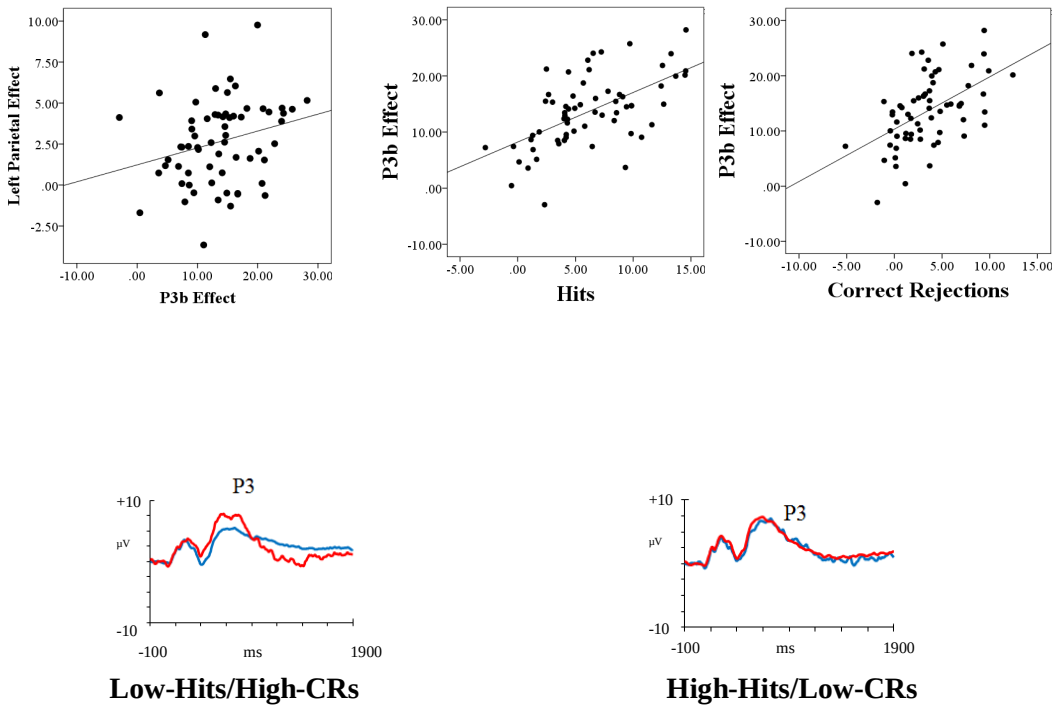


Figure 10.4 Summary of results from Chapters 6 & 7. The correlations at the top show the significant relationship found within 64 participants between the P3b effect and the Left Parietal effect, and also between the P3b and Hits and the P3b and Correct Rejections (all values are expressed in microvolts). The waveforms at the bottom show the Left Parietal effect's sensitivity to the relative probability of old and new items within a recognition memory paradigm. Specifically, the key result is the Left Parietal effect's disappearance when new items have low probability and old items have high probability.

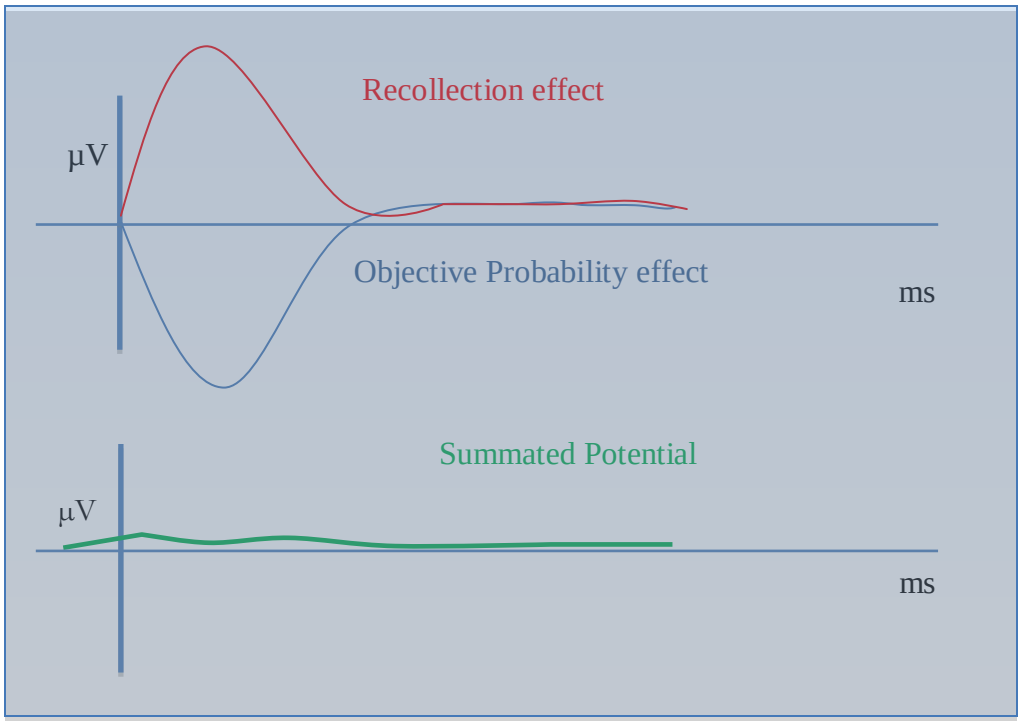


Figure 10.5 Schematic of an interpretation of the results from the the High-Hits/Low-CRs condition from Chapter 7. The recollection effect typically seen in the Left Parietal effect is still present, but is attenuated by a counter-acting P3b effect sensitive to the objective probability of old and new items in the recognition experiment.

Another possible interpretation (cf. Figure 10.6) is that the P3b and the Left Parietal effect both reflect the same probability-sensitive phenomenon. If this is the case, the relative positivity for old items seen in the typical recognition memory test may be due to the lower subjective probability of old items, which are effectively targets in a recognition test. The results of the High-Hits/Low-CRs condition presented in Chapter 7 could then be explained in terms of the objective probability effect working against

the typically seen subjective probability/target effect, leading to the cancellation of the Left Parietal effect.

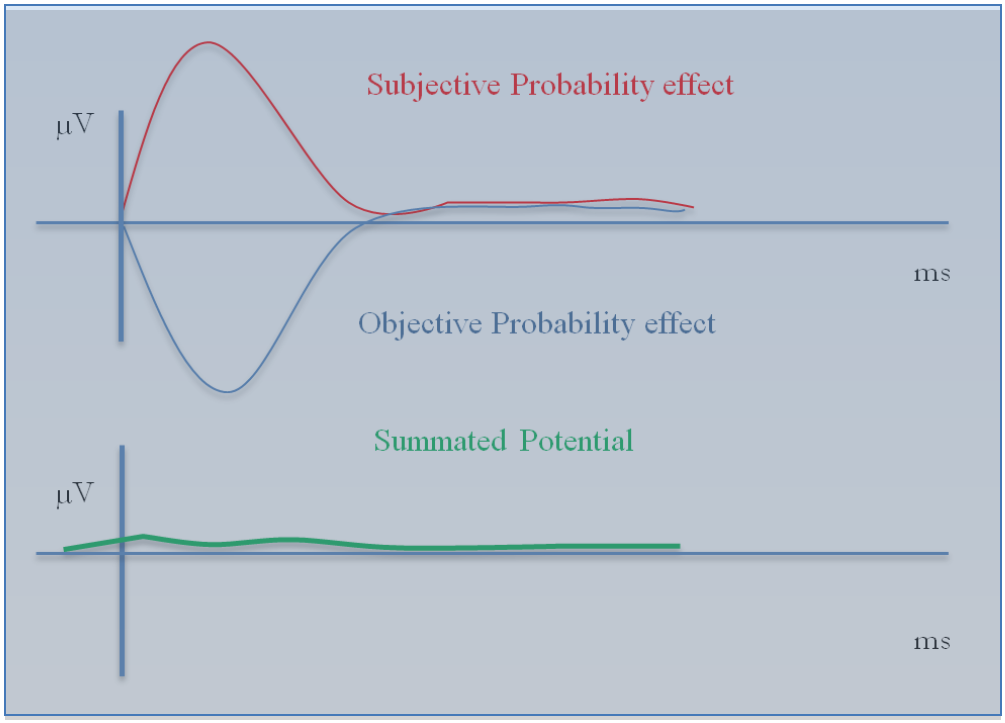


Figure 10.6 Schematic of an interpretation of the results from the the High-Hits/Low-CRs condition from Chapter 7. The Left Parietal effect, due to the lower subjective probability of old items perceived as target items, is still present but attenuated by a counter-acting effect sensitive to the objective probability of old and new items in the recognition experiment.

The first interpretation proposed, that in the High-Hits/Low-CRs condition the P3b probability effect counteracted/confounded the recollection memory effect, is conservative in that it does not question the *status quo* of the Left Parietal effect as an

index of recollection. The second interpretation instead opens the possibility that what we call "P3b effect" and "Left Parietal effect" may actually be the same probability-sensitive phenomenon emerging in different subfields of research. To rule out this option a possible experiment would be a "novelty detection" experiment, identical to the typical old/new recognition experiment, in which participants would still be required to recollect to perform adequately in the task, except where the emphasis is put on the detection of new items instead of the detection of old items. If the second interpretation proposed is correct, and the relative positivity for old items in recognition memory experiments is actually due to a subjective-probability-driven target effect, then correctly classified new items should yield a relative positivity compared to old items.

Moreover, if the second interpretation is correct, the typical results seen in a source memory task, in which the ERPs to correctly recognized old items whose source is remembered (Hit-Hits) are more positive than the ERPs to correctly recognized old items without source retrieval (Hit-Misses), may be due to the fact that Hit-Hits have a higher targetness value, and lower subjective (and perhaps objective) probability than Hit-Misses, in a procedure that emphasizes detection of old items and especially remembering contextual details relative to the study episode. This interpretation would reconcile the discrepancies observed in the current thesis and in MacLeod and Donaldson (2011) between behavioural and electrophysiological results, assuming that, for example, the participants displaying a ‘negative’ Left Parietal effect are

behaviourally engaged in detecting new items instead of old items. They are still required to recollect to discriminate between old and new items, hence the same behavioural pattern, but if their 'targets' are the new items then the reversed Left Parietal pattern described by MacLeod and Donaldson (2011) would be expected.

10.4 N400 Effect

The N400 effect was found to be highly reliable both at the group and at the single participant level (see Figure 10.7). In fact, all participants in the inter-laboratory experiment described in Chapter 5 displayed an N400 effect. This result encourages the possibility of using the N400 effect in clinical and applied work. However, the fact that the effect has not been clearly measured in non-human species constitutes a limitation in assessing the generality of the process indexed by the effect, especially if (as suggested in Chapters 2 & 8) it appears that the process indexed by the N400 effect is sensitive to contiguity-based associative relationships (as associative learning is seen amongst a large number of species).

We have investigated the N400's validity in three different ways. First, in Chapter 5 we saw that the size of the N400 effect did not correlate with the size of the P3b or the Left Parietal effect, suggesting an independence (discriminant validity) of the N400 compared to the other two effects of interest. In Chapter 8 we directly investigated

what the N400 is a measure of, by showing that the effect can be elicited by varying degrees of association even when keeping semantic relatedness constant, suggesting that the effect may be sensitive to associative relationships even in the absence of any semantic manipulation (see Figure 10.8).

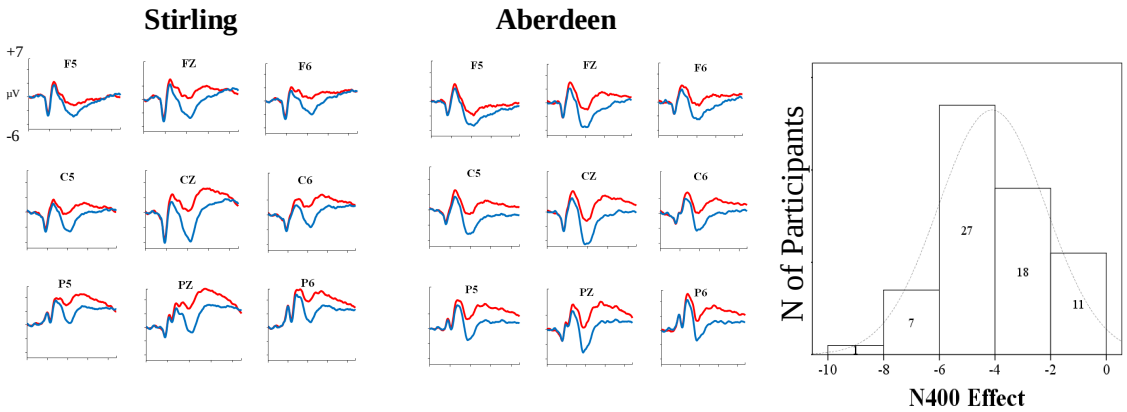


Figure 10.7 The graph shows a) inter-laboratory and b) inter-individual reliability of the N400 effect. The waveforms on the left (showing ERPs to related targets in red and to unrelated targets in blue, from 100 ms pre-stimulus to 1100 ms post stimulus) show the similarity of the effect across laboratories, while the histogram on the right shows a normal distribution of the size of the effect across participants, with all sixty-four participants showing the N400 effect. Data is relative to the 300-500ms time-window post stimulus presentation (Adapted from Chapter 5).

The results provided in Chapter 8 do not prove conclusively that the N400 effect is modulated *exclusively* by association relationships. While the results show that associative relationships clearly modulate the N400 effect in absence of semantic differences, they do not show that semantic differences *do not* modulate the N400

effect. However, as the results of another study (Rhodes & Donaldson, 2008) have shown the N400 effect to be modulated by association and not by semantic relationships, we feel the interpretation provided in the current thesis of the N400 effect as a measure of a general process sensitive to contiguity-based association relationships is justified.

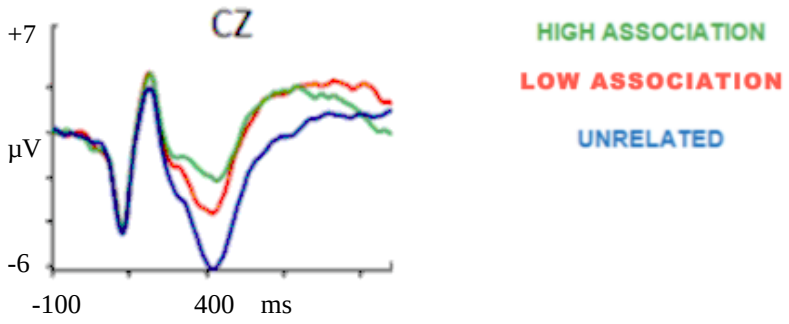


Figure 10.8 Grand average ERPs for the unrelated, low and high association word-pairs, shown from pre-stimulus to 1000ms at electrode Cz. Waveforms show a modulation of the N400 effect with the size of the effect directly proportional to the degree of association (Adapted from Chapter 8).

The results presented in Chapter 8, taken together with the results of Rhodes and Donaldson (2008) point to the idea that there might have been a confound in the previous ERP literature. That is, due to the fact that the associative and semantic dimensions were not investigated independently, leading to the possibly premature conclusion that the N400 is an index of semantic processing. In answering the

important question in a validity investigation: "What is the N400 a measure of?" we can now add the strong suggestion that the effect indexes associative relationships.

Together with experimental evidence, there are also theoretical reasons for considering an alternative to the semantic interpretation of the N400 effect. It has been proposed (e.g. Sidman, 1994) that linguistic capabilities are based on the human ability to learn associations that were not explicitly trained or reinforced. This view receives support from results in the stimulus equivalence literature, which shows that human participants can easily learn "untrained" relationships. For instance, after learning XY and YZ, via a matching to sample procedure, a number of other relationships "emerge" such as YX and ZY – also known as symmetrical relationships – and XZ and ZX, known as transitive and equivalence relationships, respectively (see Figure 10.9).

The emergence of the non-trained relationships has so far been seen in humans, but not in non-human organisms (although see Schusterman & Kastak, 1993), leading to the possible interpretation that perhaps human language is in itself defined by the ability to continuously learn associations that were not explicitly reinforced. This ability could be supported at the neural level by the number of polymodal and polysensory associative areas present in the human brain, compared to the brain of other species (Donahoe & Palmer, 1994). If the theory proposed by Sidman is accurate, it would lead to a direct prediction of an N400 effect being observed by contrasting ERPs

elicited by emergent (untrained) associated stimuli and ERPs elicited by stimuli that are not associated with one another.

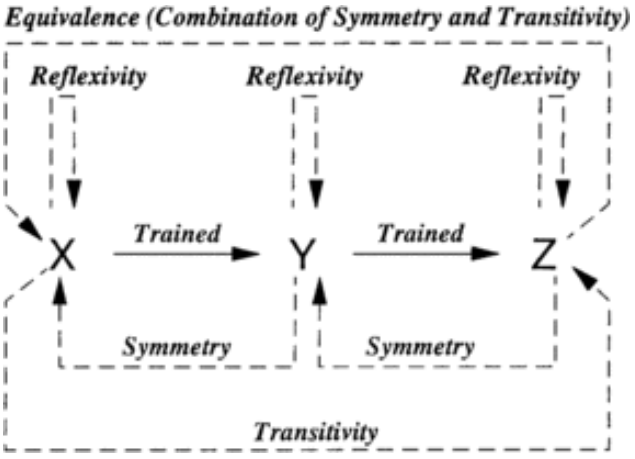


Figure 10.9 The graph shows development of untrained associative relationships (ZY, YX, XZ, ZX) as a function of trained associative relationships (XY, YZ) via a matching to sample procedure. Sidman has proposed that linguistic abilities may be develop as a function of the ability to learn untrained associative relationships (Adapted from Hayes & Hayes, 1992).

If the N400 effect does reflect a general process sensitive to contiguity-based associations, future research could further investigate how such associations can be created intra-experimentally with a variety of "meaningless" stimuli. As a first step, research might investigate N400 ‘development’ in directly trained associations. For example, experimental questions could involve a precise measurement of the

development (over time) of the N400 effect via a matching to sample procedure (e.g. How many training trials does it take for a reliable N400 effect to develop?). The matching to sample procedure could also be used to assess if an N400-like effect develops in non-human animals, because variants of the matching to sample procedure are widely used in experiments with non-humans. If the effect can be observed and experimentally controlled in non-human animals using arbitrary and meaningless stimuli, then it would be difficult to still describe the N400 effect as a neural correlate of language and semantic processing, unless language and semantic processing are then considered to be faculties extended to other species.

If the N400 effect is not shown to be present in other species, then it may reflect a contiguity-based associative process restricted to human beings, perhaps because of the large amount of polysensory and polymodal associative cortices present in humans but not in other animals. Future research could then focus on human research on the behavior of the N400 in the development of untrained, emergent, relationships which so far have been clearly measured only in humans. If the N400 effect is not measurable in non-human animals, an interesting parallel may be drawn with the fact that equivalence relationships appear to be found uniquely in human beings.

Regardless of whether the N400 is uniquely human, the results of the present thesis do clearly rule out one current interpretation of the N400 effect. Namely the results show

that the N400 and the Bilateral Frontal effect do not index the same underlying phenomenon, contrary to some perspectives present in the literature (Voss & Federmeier, 2011). Taken together the results presented in Chapter 8 and 9 suggest that the N400 is independent from the Bilateral Frontal old/new effect. While in the results presented in Chapter 8 higher levels of association lead to an increase in the size of the N400 effect, the results of the experiment presented in Chapter 9 - carried out with the same stimuli as the one presented in Chapter 8 - showed the opposite pattern of results (see Figure 10.10).

While results presented in Chapter 8 suggest that the N400 may be a measure of associative relationships, data shown in Chapter 9 point to the interpretation that the Bilateral Frontal effect appears to be a measure of relative familiarity, suggesting a separation of the associative domain from the memory domain within the 300-500ms post stimulus time window. From this perspective, Chapter 9 helped refine what the N400 is a measure of by excluding the possibility that it is a mnemonic measure of familiarity. This result is interesting because it leads to a dissociation between the component and the effect. The N400 component (i.e. peak) in itself cannot be considered as reflective of a specific brain function, without also assessing how differences in amplitude (i.e. effects) are influenced by different procedures. Compared to the results obtained in the current thesis, showing the N400 effect and the Bilateral Frontal effect to behave differently in relation to degrees of association, the

results presented by Voss & Federmeier represent a null finding as they were not able to find differences between the two effects.

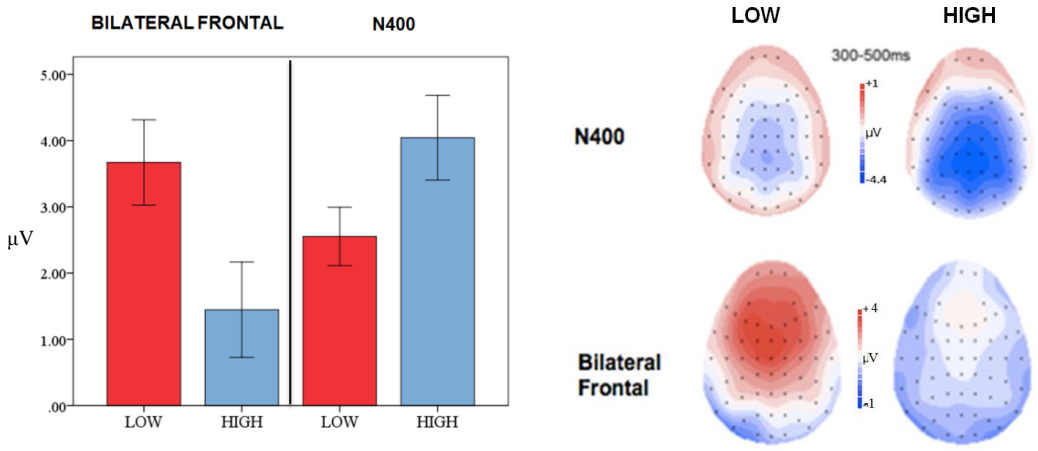


Figure 10.10 Bar graphs on the left show the size of the Bilateral Frontal effect (Chapter 9) and the N400 effect (Chapter 8) at electrode Cz. The two effects behave differently to low and high degrees of association relationships. The size of the Bilateral Frontal effect decreases as the degree of association increases, while the size of the N400 effect increases as the degree of association increases. The same data are shown in topographic form on the right, adapted from Chapters 8 & 9.

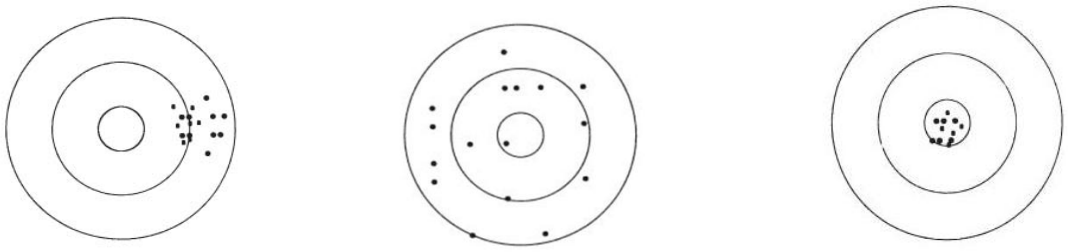
Summarizing, results presented in Chapter 8 suggest that the N400 effect, consistently with previous research (Rhodes & Donaldson, 2008), appears to be closely related to a learning process sensitive to contiguity-based association relationships. Importantly, the results described in Chapters 8 & 9 taken together rule out the possibility that the N400 effect is a measure of familiarity memory. The N400 effect and the Bilateral Frontal effect were in fact found to show opposite patterns in reaction to the same

degrees of associative relationships. Finally, even though prominent N400 researchers (e.g. Kutas & Federmeier, 2011) present the thirty years of N400 research concluding that the effect reflects semantic/meaning processing, we believe interpreting the effect as a reflection of semantic processing represents a circular argument (the N400 is defined as meaning processing and meaning processing is determined by the presence or absence of the N400). Defining the N400 effect in terms of which procedural variables produce an N400 effect, especially when intraexperimentally creating associations between meaningless stimuli, would instead constitute, we believe, a more useful alternative to operationally define the N400 phenomenon and, perhaps, 'meaning' itself.

10.5 Conclusion

The P3b effect, according to the literature and the inter-laboratory and inter-individual reliability analysis presented in the current thesis, is a highly reliable effect. The high degree of experimental control over the effect is however not paired with an equivalently good theoretical understanding of what the effect actually measures. Moreover, the strong sensitivity of the P3b effect to subjective and objective probability manipulations may create a confound within the time window in which the Left Parietal effect is typically measured. The Left Parietal effect is considered to reflect the memory process of recollection, but in the current work we did not find the expected relationship between behavioural measures and the putative

electrophysiological index of recollection. The Left Parietal effect has moreover not been found to be reliable at the individual level and is confounded by probability sensitive attentional processes when the relative probability of old and new items is not matched. The N400 effect on the other hand has been found to be highly reliable and it has been proven to be a valid measure of contiguity-based association relationships. Table 10.1 and Figure 10.11 summarize the reliability and validity of the three investigated electrophysiological effects, based on the previous literature and the results presented in the current thesis.



P3b **Left Parietal** **N400**

Figure 10.11 Visual analogy of the reliability and validity of the effects described in the current thesis, based on Figure 1 from the Introduction. The P3b can be considered as a highly reliable effect, but the large amount of research on the effect carried out so far has not clarified what the effect is measuring, and specifically it is not clear if the P3b constitutes a measure of stimulus categorization independent from response selection processes. The Left Parietal effect, reliable at the group level, is however poorly reliable at the individual level and, within the constraints of the current thesis, unrelated to behavioural indices measured during the recognition task showing poor validity as a measure of of recollection. The N400 effect is highly reliable both at the individual and the group level and appears to be a valid measure of a learning process sensitive to contiguity-based associative relationships.

		N400	P3b	Left Parietal
Reliability	**Group**	Excellent	Excellent	Good
	Single	Excellent	Very Good	Poor
	Inter-species	No	Yes	No
Validity	**What does it measure?**	A learning process sensitive to contiguity-based associations	Probability sensitive categorization process Unclear if P3b is sensitive or not to response selection processes	Source memory studies suggest the effect indexes episodic recollection but evidence from the current thesis and from MacLeod and Donaldson (2011) does not validate such a statement
	It has shown independence from?	1.Semantic Processing 2.Recollection 3.Probability-sensitive attentional processes 4. (Relative) Familiarity	1. A learning process sensitive to contiguity-based associations	1. (Relative) Familiarity 2. A process sensitive to contiguity-based associations
	It has not shown independence from?			Probability sensitive categorization process when probability of old and new items is not matched

Table 10.1 Summary of reliability and validity of the N400 effect, P3b effect and Left Parietal effect based on the previous literature and on the results presented in the current thesis.

References

Aggleton, J.P., & Brown, M.W. (1999). Episodic memory, amnesia and the hippocampal-anterior thalamic axis. *Behavioral Brain Sciences, 22,* 425-444.

Aggleton, J.P., Vann, S.D., Denby, C., Dix, S., & Mayes, A.R. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia, 43,* 1810-1823.

Ainsworth-Darnell, K., Shulman, H.G., & Boland, J.E. (1998). Dissociating brain responses to syntactic and semantic anomalies: Evidence from event-related potentials. *Journal of Memory and Language, 38,* 112-130.

Alexander, J.E., Polich, J., Bloom, F.E., Bauer, L.A., Kuperman, Rohrbaugh, J., Morzorati, S., O'Connor, S.J., Porjesz, B., & Begleiter, H. (1994). P300 from an auditory oddball task: inter-laboratory consistency. *International Journal of Psychophysiology. 17,* 35-46.

Allan, K., Wilding, E. L., & Rugg, M. D. (1998). Electrophysiological evidence for dissociable processes contributing to recollection. *Acta Psychologica, 98,* 231-252.

Alle, H., & Geiger, J. R. P. (2006). Combined analog and action potential coding in hippocampal mossy fibers, *Science, 311,* 1290-1293.

Allison, T., Wood, C. C., & McCarthy, G. (1986). The central nervous system. In M.G.H., Coles, E., Donchin, & S. W. Porges (Eds.), *Psychophysiology: Systems, processes and applications* (p. 5-26). London, UK: Guildford Press.

Anderson, J. M., & Charles, J., (1977). *Phonological structure and the history of English*. Amsterdam, Netherlands: North-Holland.

Andreassi, J. L. (2006). *Psychophysiology: Human behavior and physiological response* (4th ed.). Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Anthony, B.J. (1985). In the blink of an eye: Implications of reflex modification for information processing. In: P.K., Ackles, J.R., Jennings, & M.G.H., Coles, (Eds). *Advances In Psychophysiology* (Vol.1. p. 167-218). Greenwich, CT: JAI Press.

Ardal, S., Donald, M. W., Meuter, R., Muldrew, S., & Luce, M. (1990). Brain responses to semantic incongruity in bilinguals. *Brain and Language, 39,* 187-205.

Arthur, D.L., & Starr, A. (1985). Task-relevant late positive component of the auditory event-related potential in monkeys resembles P300 in humans. *Science, 223,* 186-188.

Aston-Jones, G., Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *Journal of Neuroscience, 14,* 4467-4480.

Bahramali, H., Gordon, E., Li, W.M., Rennie, C., Wright, J., & Meares, R. (1998). Fast and slow reaction times and associated ERPs in patients with schizophrenia and controls. *International Journal of Neuroscience, 95*, 155-165.

Barnes-Holmes, D., Staunton, C., Whelan, R., Barnes-Holmes, Y., Commins, S., Walsh, D., Stewart, I., Smeets, P. M., & Dymond, S. (2005). Derived stimulus relations, semantic priming, and event-related potentials: Testing a behavioral theory of semantic networks. *Journal of the Experimental Analysis of Behavior, 84,* 417-433.

Barrett, S. E., & Rugg, M. D. (1989). Event-related potentials and the semantic matching of faces. *Neuropsychologia, 27,* 913-922.

Basar, E., Basar-Eroglu, C., Karakaş, S., & Schurmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. *International Journal of Psychophysiology, 39,* 241-248.

Begleiter,H., & Porjesz, B. (1995). Neurophysiological phenotypic factors in the development of alcoholism. In: H., Begleiter, & B., Kissin, (Eds.), *The Genetics of Alcoholism* (pp. 269-293). New York, NY: Oxford University Press.

Begleiter, H., Porjesz, B., Chou, C.L., & Aunon, J.I. (1983). P3 and stimulus incentive values. *Psychophysiology, 20,* 95-101.

Behme, C., & Deacon, S. H. (2008). Language learning in infancy: Does the empirical evidence support a domain specific language acquisition device? *Philosophical Psychology, 21,* 641-671.

Bentin, S., & McCarthy, G. (1994). The effects of immediate stimulus repetition on reaction time and event-related potentials in tasks of different complexity. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 20,* 130-149.

Bentin, S., Kutas, M., & Hillyard, S.A. (1995). Semantic processing and memory for attended and unattended words in dichotic listening: Behavioral and electrophysiological evidence. *Journal of Experimental Psychology: Human Perception and Performance, 21,* 54-67.

Bentin, S., Kutas, M., & Hillyard, S.A. (1993). Electrophysiological evidence for task effects on semantic priming in auditory word processing. *Psychophysiology, 30,* 161-169.

Berger, H. (1969). On the electroencephalogram of man. *Electroencephalography and Clinical Neurophysiology, 28,* 37-74.

Bertrand, O., Perrin, F., & Pernier, J. (1985). A theoretical justification of the average reference in topographic evoked potential studies. *Electroencephalography and Clinical Neurophysiology, 62,* 462-464.

Besson, M., Kutas, M., & Van Petten, C. (1992). An event-related potential (ERP) analysis of semantic congruity and repetition effects in sentences. *Journal of Cognitive Neuroscience., 4,* 132-149.

Bobes, M. A., Valdés-Sosa, M., & Olivares, E. (1994). An ERP study of expectancy violation in face perception. *Brain Cognition, 26,* 1-22.

Boutros, N., Nasrallah, H., Leighty, R., Torello, M., Tueting, P., & Olson, S. (1997). Auditory evoked potentials, clinical vs. research applications. *Psychiatry Research, 69,* 183-195.

Bowles, B., Crupi, C., Mirsattari, S. M., Pigott, S. E., Parrent, A. G., Pruessner, J. C., et al. (2007). Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proceedings of the National Academy of Sciences, 104,* 16382-16387.

Bozat, S., Lambon Ralph, M. A., Patterson, K., Garrard, P., & Hodges, J.R. (2000). Non-verbal semantic impairment in semantic dementia. *Neuropsychologia, 38,* 1207-1215.

Brazier, M.A.B., (1964). Evoked responses recorded from the depths of the human brain. *Annals of the New York Academy of Science, 112,* 33-59.

Bridson, N.C., Fraser, C.S., Herron, J.E., & Wilding, E.L. (2006). Electrophysiological correlates of familiarity in recognition memory and exclusion tasks. *Brain Research, 1114,* 149-160.

Brown, M.W., & Aggleton J.P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Review Neuroscience, 2,* 51-61.

Brualla, J., Romero, M. F., Serrano, M., & Valdizan, J. R. (1998). Auditory event-related potentials to semantic priming during sleep. *Electroencephalography and Clinical Neurophysiology, 108,* 283-290.

Bruder, G.E., Tenke, C. & Stewart, J. (1995). Brain event-related potentials to complex tones in depressed patients: relations to perceptual asymmetry and clinical features. *Psychophysiology, 32,* 373-381.

Brunia, C.H.M., Möcks, J., van den Berg-Lenssen, M., Coelho, M., Coles, M.G.H., Elbert, T., et al. (1989). Correcting ocular artifacts – A comparison of several methods. *Journal of Psychophysiology, 3,* 1-50.

Bullock, T. H. (2003). Have brain dynamics evolved? Should we look for unique dynamics in the sapient species? *Neural Computation, 15,* 2013-2027.

Bussey, T.J., Saksida, L.M., & Murray, E.A. (2002). Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *European Journal of Neuroscience, 15,* 365-374.

Buzsaki, G. (2005). Theta rhythm of navigation: Link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus 15,* 827-840.

Buzsaki, G. (2006). *Rhythms of the Brain.* New York, NY: Oxford University Press.

Cajal, S.R.Y. (1909). *Histologie du systeme nerveux de l'homme et des vertébrés*. Paris: Maloine.

Callicott, J. H., Mattay, V. S., Bertolino, A., Finn, K., Coppola, R., Frank, J.A., et al. (1999). Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cerebral Cortex, 9,* 20-26.

Capitani, E., Laiacona, M., Mahon, B., & Caramazza, A. (2003). What are the facts of semantic category-specific deficits? A critical review of the clinical evidence. *Cognitive Neuropsychology, 20,* 213-261.

Chao, L. L., Nielsen-Bohlman, L., & Knight, R. T. (1995). Auditory event-related potentials dissociate early and late memory processes. *Electroencephalography & Clinical Neurophysiology, 96,* 157-168.

Chatrian, G. E., Lettich, E., & Nelson, P. L. (1985). Ten percent electrode system for topographic studies of spontaneous and evoked EEG activity. *American Journal of EEG Technology, 25,* 83-92.

Chiu, P., Ambady, N., & Deldin, P. (2004). Contingent negative variation to emotional in- and out-group stimuli differentiates high- and low-prejudiced individuals. *Journal of Cognitive Neuroscience, 16,* 1830-1839.

Chomsky, N. (1965). *Aspects of the Theory of Syntax*. Cambridge, MA: MIT Press.

Chomsky, N. (1975). Recent contributions to the theory of innate ideas. In S.P., Stich (Ed.), *Innate ideas.* Berkeley, CA: University of California Press.

Coane, J.H., Balota, D.A., Dolan, P.O., & Jacoby, L.L. (2011). Not all sources of familiarity are created equal: The case of word frequency and repetition in episodic recognition. *Memory and Cognition, 39,* 791-805.

Cohen, A. L., Rotello, C. M., & Macmillan, N. A. (2008). Evaluating models of remember–know judgments: Complexity, mimicry, and discriminability. *Psychonomic Bulletin & Review, 15,* 906-926.

Collins, A. M., & Loftus, E. F. (1975). A spreading activation theory of semantic processing. *Psychological Review, 82,* 407-428.

Combs, L.A., & Polich, J. (2006). P3a from auditory white noise stimuli. *Clinical Neurophysiology, 117,* 1106-1112.

Comerchero, M.D., & Polich, J. (1999). P3a and P3b from typical auditory and visual stimuli. *Clinical Neurophysiology, 110,* 24-30.

Connolly, J.F., & D'Arcy, R.C.N. (2000). Innovations in neuropsychological assessment using event related brain potentials. *International Journal of Psychophysiology,37,* 31-47.

Conroy, M.A., & Polich, J. (2007). Normative variation of P3a and P3b from a large sample (N = 120): Gender, topography, and response time. *Journal of Psychophysiology, 21,* 22-32.

Corley, M., MacGregor, L.J., & Donaldson, D.I. (2007). It's the way that you, er, say it: hesitations in speech affect language comprehension. *Cognition, 105,* 658-668.

Cortese, M., & Fugett, A. (2004). Imageability ratings for 3000 monosyllabic words. *Behavioral methods and research, instrumentation, and computers, 36,* 384-387.

Courchesne, E., Hillyard, S., & Galambos, R. (1975). Stimulus novelty, task relevance and the visual evoked potential in man. *Electroencephalography and Clinical Neurophysiology, 39,*131-143.

Courchesne, E. (1990). Chronology of postnatal human brain development: Event-related potential, positron tomography, myelinogenesis, and synaptogenesis. In: J., Rohrbaugh, R., Parasuraman, & R., Johnson, (Eds.), *Event-Related Brain Potentials: Basic Issues and Applications* (pp. 210-241). New York, NY: Oxford University Press.

Cowell, R. A., Bussey, J., & Saskida, L.M. (2010). Components of Recognition Memory: Dissociable Cognitive Processes or Just Differences in Representational Complexity? *Hippocampus, 20,*1245-1262.

Croft, R.J., & Barry, R.J. (2000). Removal of ocular artefact from the EEG: a review. *Neurophysiologie Clinique, 30,* 5-19.

Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika, 16,* 297-334.

Curran, T. (1999). The electrophysiology of incidental and intentional retrieval: ERP old/new effects in lexical decision and recognition memory. *Neuropsychologia, 37,* 771-785.

Curran, T. (2000). Brain potentials of recollection and familiarity. *Memory and Cognition, 28,* 923-938.

Curran, T. (2004). Effects of attention and confidence on the hypothesized ERP correlates of recollection and familiarity. *Neuropsychologia, 42,* 1088-1106.

Curran, T., & Cleary, A.M. (2003). Using ERPs to dissociate recollection from familiarity in picture recognition. *Cognitive Brain Research, 15,* 191-205.

Curran, T., & Doyle, J. (2011). Picture Superiority Doubly Dissociates the ERP Correlates of Recollection and Familiarity. *Journal of Cognitive Neuroscience, 23,* 1247-1262.

Curran, T., & Hancock, J. (2007). The FN400 indexes familiarity based recognition of faces. *Neuroimage, 36,* 464-471.

Curran, T., Schacter, D. L., Johnson, M. K., & Spinks, R. (2001). Brain potentials reflect behavioral differences in true and false recognition. *Journal of Cognitive Neuroscience, 13*, 201-216.

D'Arcy, R.C.N., Service, E., Connolly, J.F. & Hawco, C.S. (2005). The influence of increased working memory load on semantic neural systems: a high-resolution event-related brain potential study. *Cognitive Brain Research, 22*, 177-191.

Danker, J. F., Hwang, G. M., Gauthier, L., Geller, A., Kahana, M. J., & Sekuler, R. (2008). Characterizing the ERP old-new effect in a short term memory task. *Psychophysiology, 45*, 784-793.

De Chastelaine, M., Friedman, D., Cycowicz, Y.M., & Horton, C. (2009). Effects of multiple study-test repetition on the neural correlates of recognition memory: ERPs dissociate remembering and knowing. *Psychophysiology, 46*, 86-99.

De Pascalis, V., Varriale, V., & Matteoli, A. (2007). Intelligence and P3 components of the event-related potential elicited during an auditory discrimination task with masking. *Intelligence, 36*, 35-47.

Deacon, D., Hewitt, S., & Tamny, T. (1998). Event-related potential indices of semantic priming following an unrelated intervening item. *Cognitive Brain Research, 6*, 219-225.

Deacon, D., & Shelley-Tremblay J. (2000). How automatically is meaning accessed: a review of the effects of attention on semantic processing, *Frontiers in Bioscience, 5*, 82-94.

Dien, J. (1998). Issues in the application of the average reference: review, critiques, and recommendations. *Behavior Research Methods Instruments & Computers, 30*, 34-43.

Dien, J., & Santuzzi, A. M. (2005). Application of repeated measure ANOVA to high-density ERP dataset: a review and tutorial. T. C. Handy (Ed.), *Event-Related Potentials: A Methods Handbook.* Cambridge, MA: MIT Press.

Donahoe, J. W., & Palmer, D. C. (1994). *Learning and complex behavior*. Boston, MA: Allyn and Bacon.

Donahoe, J. W. (2003) Selectionism. In K. Lattal & P.Chase (Eds.), *Behavior theory and philosophy* (pp.103–128). Dordrecht, Netherlands: Kluwer Academic Publishers.

Donaldson, D. I., & Curran, T. (2007). Letter to the editor. *NeuroImage, 36*, 288-289.

Donaldson, D. I., & Rugg, M. D. (1998). Recognition memory for new associations: Electrophysiological evidence for the role of recollection. *Neuropsychologia, 36*, 377-395.

Donaldson, D. I., & Rugg, M. D. (1999). Event-related potential studies of associative recognition and recall: Electrophysiological evidence for context dependent retrieval processes. *Cognitive Brain Research, 8*, 1-16.

Donaldson, D.I., Allan, K., & Wilding, E.L. (2002). Electrophysiological investigations of explicit memory retrieval. In E.L. Wilding, A. Parker, & T. Bussey (Eds.), *The Cognitive Neurosciences*. London, UK: Psychology Press.

Donchin, E., & Lindsley, D.B. (1966). Average evoked potentials and reaction times to visual stimuli. *Electroencephalography and clinical Neurophysiology, 20*, 217-223.

Donchin, E. (1981). Surprise!…. Surprise? *Psychophysiology, 18*, 493-513.

Donchin, E., & Coles, M.G.H. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences, 11*, 357-374.

Doyle, D. J., & Hyde, M. L. (1981). Analogue and digital filtering of auditory brainstem potentials. *Scandinavian Audiology, 10*, 81-89.

Duarte, A., Ranganath, C., Winward, L., Hayward, D., & Knight, R.T. (2004). Dissociable neural correlates for familiarity and recollection during the encoding and retrieval of pictures. *Cognitive Brain Research, 18,* 255-272.

Duncan-Johnson, C.C., & Donchin, E. (1977). Effects of a priori and sequential probability of stimuli on event-related potential. *Psychophysiology, 14,* 95.

Duncan-Johnson, C.C., & Donchin, E. (1977). On quantifying surprise: The variation of event-related potentials with subjective probability. *Psychophysiology, 14*, 456-467.

Duncan-Johnson, C. C. (1981). P300 latency: a new metric of information processing. *Psychophysiology, 18,* 207-215.

Duncan-Johnson, C. C., & Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. *Biological Psychology, 14,* 1-52.

Duncan-Johnson, C.C., Morihisa, J.M., Fawcett, R.W., & Kirch, D.G. (1987). P300 in schizophrenia: State or trait marker? *Psychopharmacology Bulletin, 23,* 497-501.

Duncan-Johnson, C. C., Barry R. J., Connolly J. F., Fischer C., Michie P. T., Näätänen R., Polich J., Reinvang, I., & Van Petten C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology, 120,* 1883-1908.

Düzel, E., Vargha-Khadem, F., Heinze, H.J., & Mishkin, M. (2001). Brain activity evidence for recognition without recollection after early hippocampal damage. *Proceedings of the National Academy of Science, 98,* 8101-8106.

Edwards, J., Wesnes, K., Warburton, D., & Gale, A. (1985). Evidence of more rapid stimulus evaluation following cigarette smoking. *Addictive Behaviors, 10,* 1l3-126.

Eichenbaum, H. (2000). A cortical-hippocampal system for declarative memory. *Nature Reviews Neuroscience, 12,* 41-50.

Eichenbaum, H., Yonelinas, A.P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Reviews Neuroscience, 30,* 123-152.

Elbert, T., & Rockstroh, B. (1980). Some remarks on the development of a standardized time constant. *Psychophysiology, 17,* 504-505.

Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S.Y., & Engel, S. A. (2000). Remembering episodes: a selective role for the hippocampus during retrieval. *Nature Reviews Neuroscience*, 3, 1149-1152.

Fabiani, M., Friedman, D., & Cheng, J. (1998). Individual differences in P3 scalp distribution in older adults, and their relationship to frontal lobe function. *Psychophysiology, 35,* 698-708.

Fahy, F.L., Riches, I.P., & Brown, M.W. (1993) Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex. *Experimental Brain Research, 96,* 457-472.

Falkenstein, M., Hohnsbein, J., & Hoormann, J. (1994). Time pressure effects on late components of the event related potential. *Journal of Psychophysiology, 8,* 22-30.

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1990). Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In C. Brunia, A. Gaillard, & A. Kok (Eds.), *Psychophysiological brain research* (pp. 192-195). Tilburg, the Netherlands: Tilburg University Press.

Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology, 51*, 87-107.

Fanselow, M.S., & Poulos, A.M. (2005). The neuroscience of mammalian associative learning. *Annual Review of Psychology, 56*, 207-234.

Federmeier, K.D., & Kutas, M. (1999). A rose by any other name: Long term memory structure and sentence processing. *Journal of Memory and Language, 41*, 469-495.

Federmeier, K.D., & Laszlo, S. (2009). Time for meaning: electrophysiology provides insights into the dynamics of representation and processing in semantic memory. In B.H., Ross (Ed.) *The Psychology of Learning and Motivation*, (pp. 1–44). San Diego,CA: Elsevier.

Fell, J., Dietl, T., Grunwald, T., Kurthen, M., Klaver, P., Trautner, P., et al. (2004). Neural bases of cognitive ERPs: More than phase reset. *Journal of Cognitive Neuroscience, 16*, 1595-1604.

Ferrand, L., & New, B., 2003. Semantic and associative priming in the mental lexicon. In P., Bonin (Ed.), *Mental lexicon: Some words to talk about words* (pp. 25-43). Hauppauge, NY: Nova Science Publisher.

Fischler, I.S., Bloom, P.A., Childers, D.G., Roucos, S.E., & Perry, N.W. (1983). Brain potentials related to stages of sentence verification. *Psychophysiology, 20*, 400-409.

Fischler, I.S., Childers, D.G., Achariyapaopan, T., & Perry, N.W. (1985). Brain potentials during sentence verification: Automatic aspects of comprehension. *Biological Psychology, 21*, 83-105.

Fjell, A.M., Walhovd, K.B., Fischl, B., & Reinvang, I. (2007). Cognitive function, P3a/P3b brain potentials, and cortical thickness in aging. *Human. Brain Mapping, 28*, 1098-1116.

Friedman, D. (1990). ERPs during continuous recognition memory for words. *Biological Psychology, 30*, 61-87.

Friedman, D., & Simpson, G. (1994). ERP amplitude and scalp distribution to target and novel events: effects of temporal order in young, middle-age, and older adults. *Cognitive Brain Research, 2*, 49-63.

Friedman, D., & Johnson, R., Jr. (2000). Event-Related Potential (ERP) studies of memory encoding and retrieval: a selective review. *Microscopy Research & Technique, 51*, 6-28.

Friedrich, M., & Friederici, A.D. (2004). N400-like semantic incongruity effect in 19-month-olds: Processing known words in picture contexts. *Journal of Cognitive Neuroscience, 16*, 1465-1477.

Fujimichi, R., Naya, Y., Koyano, K.W., Takeda, M., Takeuchi, D., & Miyashita, Y. (2010). Unitized representation of paired objects in area 35 of the macaque perirhinal cortex. *European Journal of Neuroscience, 32*, 659-667.

Ganis, G., & Kutas, M. (2003). An electrophysiological study of scene effects on object identification. *Cognitive Brain Research, 16*, 123-144.

Ganis, G., Kutas, M., & Sereno, M. I. (1996). The search for "common sense": An electrophysiological study of the comprehension of words and pictures in reading. *Journal of Cognitive Neuroscience, 8*, 89-106.

Gasser, T., Bacher, P., & Steinberg, H. (1985). Test–retest reliability of spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology, 60*, 312-319.

Gasser, T., Kneip, A., & Verleger, R. (1982). Modification of the EEG time constant by digital filtering. *Psychophysiology, 19*, 237-240.

Gehring, W.J.(1992).The error-related negativity: Evidence for a neural mechanism for error-related processing. Unpublished doctoral dissertation, University of Illinois at Urbana–Champaign.

Geisler, C.D., & Gerstein, G.L. (1961). The surface EEG in relation to its sources. *Electroencephalography and Clinical Neurophysiology*, *13*, 927-934.

Gevins, A.S. (1990). Analysis of multiple lead data. J.W., Rohbraugh, R., Parasuraman, & J.R., Johnson (Eds.), *Event-Related Brain Potentials* (pp. 44-56). New York, NY: Oxford University Press.

Giuliodori, M., & Zuccolilli, G. (2004). Postsynaptic potential summation and action potential initiation: function following form, *Advances in Physiology Education, 28*, 79-80.

Glickstein, M. (2006). Golgi and Cajal: The neuron doctrine and the 100th anniversary of the 1906 Nobel Prize, *Current Biology, 16*, 147-151.

Glosser, G., & Friedman, E. B. (1991). Lexical but not semantic priming in Alzheimer's disease. *Psychology and Aging, 6,* 522-527.

Glover, A.A., Onofrj, M.C., Ghilardi, M.F., & Bodis–Wollner, I. (1986). P300-like potentials in the normal monkey using classical conditioning and an auditory "oddball" paradigm. *Electroencephalography and Clinical Neurophysiology, 65*, 231-235.

Gonsalvez, C.J., & Polich, J. (2002). P300 amplitude is determined by target-to-target interval. *Psychophysiology, 39,* 388-396.

Graham, F. K., & Hackley, S.A. (1991). Passive and active attention to input. In J. R., Jennings & M.G. H., Coles, (Eds.), *Handbook of cognitive psychophysiology: Central and autonomic nervous system approaches* (pp. 251–356). New York, NY: John Wiley and Sons Ltd.

Gray, J. R., Chabris, C. F., & Braver, T. S. (2003). Neural mechanisms of general fluid intelligence. *Nature Neuroscience, 6*, 316-322.

Green, M.F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry, 67*, 3-8.

Grunwald, T., Beck, H., Lehnertz, K., Blümcke I., Pezer, N., Kutas, M., Kurthen, M., Karakas, H. M., Van Roost, D., Wiestler, O. D., & Elger, C. E. (1999). Limbic P300s in temporal lobe epilepsy with and without Ammon's horn sclerosis. *European Journal of Neuroscience, 11,* 1899-1906.

Grunwald, T., Lehnertz, K., Heinze, H. J., Helmstaedter, C., & Elger, C. E. (1998). Verbal novelty detection within the human hippocampus proper. *Proceedings of the National Academy of Sciences, U.S.A., 95,* 3193-3197.

Gunter, T.C., Jackson, J.L. & Mulder, G. (1995). Language, memory, and aging: an electrophysiological exploration of the N400 during the reading of memory- demanding sentences. *Psychophysiology, 32,* 215-229.

Gustafsson, B., Wigstrom, H., Abraham, W.C., & Huang, Y.Y. (1987). Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. *Journal of Neuroscience, 7,* 774-780.

Hagoort, P., Brown, C. M., & Swaab, T. Y. (1996). Lexical-semantic event-related potential effects in patients with left hemisphere lesions and aphasia, and patients with right hemisphere lesions without aphasia, *Brain, 119,* 627-649.

Haimson, B., Wilkinson, K. M., Rosenquist, C., Ouimet, C., & McIlvane, W. J. (2009). Electrophysiological Correlates of Stimulus Equivalence Processes. *Journal of the Experimental Analysis of Behavior, 92,* 245-256.

Halgren, E., Baudena, P., Clarke, J.M., Heit, G., Marinkovic, K., Devaux, B., Vignal, J. P., & Biraben, A. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral, and posterior temporal lobe. *Electroencephalography and Clinical Neurophysiology, 94*, 229-250.

Halgren, E., Marinkovic, K., & Chauvel, P. (1998). Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalography and Clinical Neurophysiology, 106*, 156-164.

Halgren, E., Squires, N., Wilson, C., Rohbraugh, J., Bab, T., & Crandall, P. (1980). Endogenous potentials in the human hippocampal formation and amygdala by infrequent events. *Science, 210,* 803-805.

Harlow, I.M., MacKenzie, G., & Donaldson, D.I. (2010). *Journal of Experimental Psychology: Learning, Memory and Cognition*, 36, 1381-1388.

Haskins, A.L., Yonelinas, A.P., Quamme, J.R., & Ranganath, C. (2008). Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron, 59,* 554-560.

Hayes, S. C., & Hayes, L. J. (1992). Verbal relations and the evolution of behavior analysis. *American Psychologist, 47,* 1383-1395.

Heinze, H. J., Muente, T. F., & Kutas, M. (1998). Context effects in a category verification task as assessed by event-related brain potential (ERP) measures. *Biological Psychology, 47,* 121-135.

Helmholtz, H. (1853) Ueber einige gesetze der vertheilung elektrischer strome in korperlichen leitern, mit anwendung auf die thierischelektrischen versuche. *Annalen der Physik und Chemie, 89,* 211-233, 353-377.

Hennessey F., J., Verfaellie, M., & Giovanello, K.S. (2010) Neural correlates of familiarity-based associative retrieval, *Neuropsychologia, 48*, 3019-3025.

Hennighausen, E., Heil, M., & Rösler, F. (1993). A correction method for DC drift artifacts. *Electroencephalography and Clinical Neurophysiology, 86*, 199-204.

Herron, J. E., Quayle, A. H., & Rugg, M. D. (2003). Probability effects on event-related potential correlates of recognition memory. *Cognitive Brain Research, 16*, 66-73.

Herron, J.E., & Rugg, M. D. (2004) Probability effects on the neural correlates of retrieval success: An fMRI study. *Neuroimage 21*, 302-310.

Hill, H., Ott, F., & Weisbrod, M. (2005). SOA-dependent N400 and P300 semantic priming effects using pseudoword primes and a delayed lexical decision. *International Journal of Psychophysiology, 56,* 209-221.

Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science, 182,* 177-180.

Hillyard, S. A., Squires, K. C., Bauer, J. W., & Lindsay, P. H. (1971). Evoked potential correlates of auditory signal detection. *Science, 172,* 1357-1360.

Hockley, W.E. (1992). Item versus associative information: Further comparisons of forgetting rates. *Journal of Experimental Psychology: Learning, Memory and Cognition, 18,* 1321-1330.

Hohnsbein, J., Falkenstein, M., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. I. Simple and choice reaction tasks. *Electroencephalography and Clinical Neurophysiology, 78,* 438-446.

Holcomb, P. J. (1993). Semantic priming and stimulus degradation: implications for the role of the N400 in language processing. *Psychophysiology, 30,* 47-61.

Holcomb, P. J., & Neville, H. (1990). Auditory and visual semantic priming in lexical decision: A comparison using event-related brain potentials. *Language and Cognitive Processes, 4,* 281-312.

Holcomb, P. J., & Neville, H. J. (1991). Natural speech processing: An analysis using event-related potentials. *Psychobiology, 19,* 286-300.

Holcomb, P. J., Coffey, S. A., & Neville, H. J. (1992). Visual and auditory sentence processing: A developmental analysis using event-related brain potentials. *Developmental Neuropsychology, 8,* 203-241.

Holm, A., Rantaaho, P.O., Sallinen, M., Karjalainen, P.A., & Müller, K. (2006). Relationship of P300 single-trial responses with reaction time and preceding stimulus sequence. *International Journal of Psychophysiology, 61,* 244-252.

Holscher, C., Rolls, E. T., & Xiang, J. (2003). Perirhinal cortex neuronal activity related to long-term familiarity memory in the macaque. *European Journal of Neuroscience, 18,* 2037-2046.

Huettig, F., & Altmann, G. T. M. (2005). Word meaning and the control of eye fixation: semantic competitor effects and the visual world paradigm. *Cognition, 96,* 23-32.

Huettig, F., Quinlan, P. T., McDonald, S. A., & Altmann, G. T. M. (2006). Models of high-dimensional semantic space predict language mediated eye movements in the visual world. *Acta Psychologica., 121,* 65-80.

Huhta, J. C., & J. G. Webster (1973). 60-Hz interference in electrocardiography. *IEEE Transactions Biomedical Engineering, 20,* 91-101.

Jacoby, L.L. (1991). A process dissociation framework: Separating automatic from intentional uses of memory. *Journal of Memory and Language, 30,* 513-541.

Jäger, T., Mecklinger, A., & Kipp, K.H. (2006). Intra- and inter-item associations doubly dissociate the electrophysiological correlates of familiarity and recollection. *Neuron, 52,* 535-545.

Jasper, H. (1958). The Ten Twenty System of the International Federation. *Electroencephalography and Clinical Neurophysiology, 10,* 37-75.

Jentzsch, I., & Sommer, W. (2001). Sequence-sensitive subcomponents of P300: Topographical analyses and dipole source localization. *Psychophysiology, 38,* 607-621.

Jodo, E., Takeuchi, S., & Kayama, Y. (1995). P3b-like potential of rats recorded in an active discrimination task. *Electroencephalography and Clinical Neurophysiology, 96,* 555-560

Johansson, M., Mecklinger, A., & Treese, A.C. (2004). Recognition memory for emotional and neutral faces: an event-related potential study. *Journal of Cognitive Neuroscience, 16,* 1840-1853.

Johnson, R. (1986). A triarchic model of P300 amplitude. *Psychophysiology, 23,* 367-384.

Johnson, R. (1988). The amplitude of the P300 component of the event-related potentials: Review and synthesis. In: P., Ackles J., Jennings, & M.G.H., Coles, (Eds.), *Advances in psychophysiology. 2.* (pp. 69-137). Greenwich, CT: JAI Press, Inc.

Johnson, R. (1993). On the neural generators of the P300 component of the event- related potential. *Psychophysiology, 30,* 90-97.

Johnson, R. J. (1995). Event-related potential insights into the neurobiology of memory systems. In F. Boller & J. Grafman (Eds.), *Handbook of neuropsychology* (Vol. 10, pp. 135-163). Amsterdam, Netherlands: Elsevier.

Jonides, J., & Nee, D. E. (2006). Brain mechanisms of proactive interference in working memory. *Neuroscience, 139,* 181-193.

Kan, S.H. (2002). *Metrics and Models in Software Quality Engineering*. Cambridge, MA: Addison-Wesley Publishing Company.

Kaplan, R. M., & Saccuzzo, D. (2001). Psychological testing: Principles, applications, and issues (5th ed.). Pacific Grove, CA: Wadsworth.

Karis, D., Fabiani, M., & Donchin, E. (1984). "P300" and memory: Individual differences in the von Restorff effect. *Cognitive Psychology, 16,* 177-216.

Katayama, J., & Polich, J. (1996). P300 from one-, two-, and three-stimulus auditory paradigms. *International Journal of Psychophysiology, 23*, 33-40.

Katayama, J., & Polich, J. (1996). P300, probability, and the three-tone paradigm. *Electroencephalography and clinical Neurophysiology, 100,* 555-562.

Kawamoto, A. H. (1993). Nonlinear dynamics in the resolution of lexical ambiguity: A parallel distributed processing account. *Journal of Memory and Language, 32*, 474-516.

Kerlinger, F. (1986). *Foundations of behavioral research* (3rd ed.). Orlando, FL: Harcourt Brace Jovanovich.

Kirwan, C.B., Wixted, J.T. & Squire, L.R. (2008). Activity in the medial temporal lobe predicts memory strength, whereas activity in the prefrontal cortex predicts recollection. *The Journal of Neuroscience, 28,* 10541-10548.

Kiss, G.R., Armstrong, C., Milroy, R., & Piper, J. (1973). An associative thesaurus of English and its computer analysis. In A.J., Aitken, R.W., Bailey, & N., Hamilton-Smith, (Eds.), *The Computer and Literary Studies*. Edinburgh, UK: University Press.

Klimesch, W., Doppelmayr, A., Yonelinas, A. O., Kroll, N. E. A., Lazara, M., & Rohm, D. (2001). Theta synchronization during episodic retrieval: Neural correlates of conscious awareness. *Cognitive Brain Research, 12,* 33-38.

Knight, R. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography and Clinical Neurophysiology, 59,* 9-20.

Knight, R. (1990). Neural mechanisms of event-related potentials from human lesion studies. In: J., Rohbraugh, , R., Parasuraman, & R., Johnson, (Eds.), *Event-Related Brain Potentials: Basic Issues and Applications* (pp. 3-18). New York, NY: Oxford University Press.

Knight, R. (1997). Distributed cortical network for visual attention. *Journal of Cognitive Neuroscience, 9,* 75-91.

Knight, R., Grabowecky, M., & Scabini, D. (1995). Role of human prefrontal cortex in attention control. *Advances in Neurology, 66,* 21-34.

Koivisto, M., & Revonsuo, A. (2001). Cognitive representations underling the N400 priming effect. *Cognitive Brain Research, 12,* 467-490.

Kok, A. (1988). Overlap between P300 and movement related potentials: a response to Verlager. *Biological Psychology, 27,* 51-58.

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology, 38,* 557-577.

Koles, Z.J. (1998). Trends in EEG source localization. *Electroencephalography and Clinical Neurophysiology, 106,* 127-137.

Kramer, A.F., Wickens, C.D., & Donchin, E. (1985). Processing of stimulus properties: evidence for dual-task integrality. *Journal of Experimental Psychology: Human Perception and Performance, 11,* 393-408.

Kucera, H., & Francis, W.N. (1967). *Computational analysis of present-day American English.* Providence, RI: Brown University Press.

Kuonios, J., & Holcomb, P. J. (1992). Structure and process in semantic memory: Evidence from event-related brain potentials and reaction times. *Journal of Experimental Psychology: General, 121,* 459-479.

Kuperman, S., Porjesz, B., Arndt, S., Bauer, L., Begleiter, H., Cizadlo, T., O'Connor, S., & Rohrbaugh, J. (1995). Multi-center N400 ERP consistency using a primed and unprimed word paradigm, *Electroencephalography and Clinical Neurophysiology, 94,* 462-470.

Kutas, M., McCarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation. *Science, 197,* 792-795.

Kutas, M., & Hillyard, S.A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science,* 207, 203-205.

Kutas, M., & Hillyard, S.A. (1983). Event-related brain potentials to grammatical errors and semantic anomalies. *Memory and Cognition, 11,* 539-550.

Kutas, M., & Hillyard, S.A. (1984). Brain potentials reflect word expectancy and semantic association during reading. *Nature, 307,* 161-163.

Kutas, M., Lindamood, T.E., & Hillyard, S.A. (1984). Word expectancy and event-related brain potentials during sentence processing. In S., Kornblum, & J. Requin (Eds.) *Preparatory States and Processes* (pp. 217–37). Hillsdale, NJ: Erlbaum.

Kutas, M. (1987). Event-related brain potentials (ERPs) elicited during rapid serial visual presentation of congruous and incongruous sentences. In: R., Johnson, Jr., J.W., Rohrbaugh & R., Parasuraman (Eds.), Current Trends in Event-Related Brain Potential Research, *Electroencephalography and Clinical Neurophysiology, Supplement. 40,* 406-411.

Kutas, M., Neville, H. J., & Holcomb, P. J. (1987). A preliminary comparison of the N400 response to semantic anomalies during reading, listening, and signing. *Electroencephalography and Clinical Neurophysiology, Supplement 39*, 325-330.

Kutas, M., Van Petten, C., & Besson, M. (1988). Event-related potential asymmetries during the reading of sentences. *Electroencephography and Clinical Neurophysiology, 69*, 218-233.

Kutas, M., & Dale, A. (1997). Electrical and magnetic readings of mental functions. In M.D., Rugg, (Ed.) *Cognitive Neuroscience Studies in Cognition* (pp. 197-241). Cambridge, MA: MIT Press.

Kutas, M., & Iragui, V. (1998). The N400 in a semantic categorization task across 6 decades. *Electroencephography and Clinical Neurophysiology, 108*, 456-471.

Kutas, M., & Federmeier, K.D. (2000). Electrophysiology reveals semantic memory use in language comprehension. *Trends in Cognitive Science, 4*, 463-470.

Kutas, M., & Federmeier, K., D. (2011). Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). *Annual Review of Psychology, 62*, 621-647.

Laszlo, S., & Federmeier, K. D. (2008). Minding the Ps, queues, and PXQs: Uniformity of semantic processing across multiple stimulus types. *Psychophysiology, 45*, 458-466.

Leahy, R.M., Mosher, J.C., Spencer, M.E., Huang, M.X., & Lewine, J.D. (1998). A study of dipole localization accuracy for MEG and EEG using a human skull phantom. *Electroencephalography and Clinical Neurophysiology, 107*, 159-173.

Lee, K. H., Choi, Y. Y., Gray, J. R., Cho, S. H., Chae, J. H., Lee, S., et al. (2006). Neural correlates of superior intelligence: Stronger recruitment of posterior parietal cortex. *NeuroImage, 29*, 578-586.

Lembreghts, M., Crasson, M., El Ahmadi, A., & Timsit-Berthier, M.(1995). Etude de la variabilité interindividuelle des potentiels évoqués auditifs exogènes et endogènes en condition d'attention volontaire. *Clinical Neurophysiology, 25*, 203-223.

Levy, W.B., & Stewart O. (1979). Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. *Neuroscience, 8*, 791-797.

Lins, O.G., Picton, T., Berg, P., & Scherg, M. (1993). Ocular artifacts in EEG and event-related potentials I: Scalp topography. *Brain Topography, 6*, 51-63.

Lucas, M. (2000). Semantic priming without association: A meta-analytic review. *Psychonomic Bulletin Review, 7*, 618-630.

Luck, S. J. (2005). *An Introduction to the event-related potential technique*. Cambridge: MIT press.

Luck, S. J., Vogel, E. K., & Shapiro, K. L. (1996). Word meanings can be accessed but not reported during the attentional blink. *Nature, 383*, 616-618.

Lütkenhöner, B., Pantev, C., Grunwald, A., & Menninghaus, E. (1995). Source-space projection of single trials of the auditory evoked field. In: C., Baumgartner, L., Deeke, G., Stroink & S.J., Williamson (Eds.), *Biomagnetism: Fundamental Research and Clinical Applications* (pp. 347–351). Amsterdam, Netherlands: Elsevier Science Publishers.

MacDonald, S.W., Nyberg, L., & Backman, L. (2006) Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. *Trends in Neuroscience, 29*, 474-480.

MacGregor, L.J., Corley, M., & Donaldson, D.I. (2010). Listening to the sound of silence: Investigating the consequences of disfluent silent pauses in speech for listeners. *Neuropsychologia, 48*, 3982-3992.

MacLeod, A.C., & Donaldson, D.I. (2011). Does brain activity provide a reliable biomarker for episodic memory retrieval? Poster presented at the 5th International Conference on Memory - University of York, UK.

Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychological Review, 87*, 252-271.

Marchand, Y., D'Arcy, R.C.N., & Connolly, J.F. (2002). Linking neurophysiological and neuropsychological measures for aphasia assessment. *Clinical Neurophysiology, 113*, 1715-1722.

Mark, R.E., & Rugg, M.D. (1998). Age effects on brain activity associated with episodic memory retrieval: An electrophysiological study. *Brain, 121*, 861-873.

Masson, M. E. J. (1995). A distributed memory model of semantic priming. *Journal of Experimental Psychology: Learning, Memory and Cognition, 21*, 3-23.

Mattson, M.P., & Kater, S.B. (1989). Excitatory and inhibitory neurotransmitters in the generation and degeneration of hippocampal neuroarchitecture, *Brain Research, 478*, 337-348.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Hunkin, N. M., & Roberts, N. (2002). Relative sparing of item recognition memory in a patient with adult-onset damage limited to the hippocampus. *Hippocampus, 12*, 325-340.

Mayes, A., Montaldi, D., & Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Sciences, 11*, 126-135.

McCarley, R.W., Shenton, M., O'Donnell, B. et al., (1993). Auditory P300 abnormalities and left posterior superior temporal gyrus volume reductions in schizophrenia. *Archive of General Psychiatry, 50*, 190-197.

McCarthy, G., & Donchin, E. (1981). A metric for thought: a comparison of P300 latency and reaction time. *Science, 211*, 77-80.

McCarthy, G., & Wood, C. C. (1985). Scalp distributions of event-related potentials: An ambiguity associated with analysis of variance models. *Electroencephalography and Clinical Neurophysiology, 61*, S226-S227.

McCarthy, G., Wood, C., Williamson, P., & Spencer, D. (1989). Task-dependent field potentials in human hippocampal formation. *Journal of Neuroscience, 9*, 4253-4266.

McCarthy, G., & Nobre, A.C. (1993) Modulation of semantic processing by spatial selective attention. *Electroencephography and Clinical Neurophysiology, 88*, 210-219.

McCarthy, G., Nobre, A. C., Bentin, S., & Spencer, D. D. (1995). Language-related field potentials in the anterior–medial temporal lobe: I. Intracranial distribution and neural generators. *Journal of Neuroscience, 15*, 1080-1089.

McCarthy, G., Luby, M., Gore, J., & Goldman-Rakic, P. (1997). Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *Journal of Neurophysiology, 77*, 1630-1634.

McDonald, S. (2006). Semantic space model demo. Retrieved from http://www.iccs.inf.ed.ac.uk/smcdonal/semantic_space_model.html.

McRae, K., & Boisvert, S. (1998). Automatic semantic similarity priming. *Journal of Experimental Psychology: Learning, Memory and Cognition, 24,* 558-572.

Mecklinger, A. (2000). Interfacing mind and brain: a neurocognitive model of recognition memory. *Psychophysiology, 37,* 565-582.

Mecklinger, A., & Ullsperger, P. (1993). P3 varies with stimulus categorization rather than probability. *Electroencephalography and Clinical Neurophysiology, 86,* 395-407.

Mecklinger, A., Von Cramon, D.Y., & Cramon, G.M.V. (1998). Event-related potential evidence for a specific recognition memory deficit in adult survivors of cerebral hypoxia. *Brain, 121,* 1919-1935.

Meiser, T., & Sattler, C.(2007). Boundaries of the relation between conscious recollection and source memory for perceptual details. *Conscious Cognition, 16,* 189-210.

Mertens, R., & Polich J. (1997). P300 from a single-stimulus paradigm: passive versus active tasks and stimulus modality. *Electroencephalography and Clinical Neurophysiology, 104,* 488-497.

Metting Van Rijn, A.C., Peper, A., & Grimbergen, C.A. (1990). High quality recording of bioelectric events. I: Interference reduction, theory and practice. *Medical & Biological Engineering and Computing, 28,* 389-397.

Metting Van Rijn, A.C., Peper, A., & Grimbergen, C.A. (1991). High quality recording of bioelectric events. II: A low noise low-power multichannel amplifier design. *Medical & Biological Engineering and Computing 29,* 433-440.

Milberg, W., Blumstein, S.E., & Dworetzky, B. (1987). Processing of lexical ambiguities in aphasia. *Brain and Language, 31,* 138-150.

Miller, G.A., Lutzenberger, W. & Elbert, T. (1991). The linked-reference issue in EEG and ERP recording. *Journal of Psychophysiology, 5,* 273-276.

Mills, D.L., Plunkett, K., Prat, C., & Schafer, G. (2005). Watching the infant brain learn words: Effects of vocabulary size and experience. *Cognitive Development, 20,* 19-31.

Miltner, W., Larbig, W., & Braun, C. (1986). Biofeedback of visual evoked potentials. *International Journal of Neuroscience, 29,* 291-303.

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: Two cortical pathways. *Trends in Neuroscience, 6,* 414-417.

Montaldi, D., & Mayes, A.R. (2011). Familiarity, recollection and medial temporal lobe function: an unresolved issue. *Trends in Cognitive Science, 15,* 339-340.

Morth, J.P., Pedersen, B.P., Toustrup-Jensen, M.S., Sorensen, T.L., Petersen, J., Andersen, J.P., Vilsen, B., & Nissen, P. (2007). Crystal structure of the sodium–potassium pump. *Nature, 450,* 1043-1049.

Moss, H. E., Hare, M. L., Day, P., & Tyler, L. K. (1994). A distributed memory model of the associative boost in semantic priming. *Connection Science, 6,* 413-427.

Moss, H. E., Ostrin, R. K., Tyler, L. K., & Marslen-Wilson, W. D. (1995). Accessing different types of lexical semantic information: Evidence from priming. *Journal of Experimental Psychology: Learning, Memory and Cognition, 21,* 863-883.

Murray, E.A., & Bussey, T.J. (1999). Perceptual-mnemonic functions of the perirhinal cortex. *Trends in Cognitive Science, 3,* 142-151.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical Neurophysiology, 118*, 2544-2590.

Nation, K., & Snowling, M. J. (1999). Developmental differences in sensitivity to semantic relations among good and poor comprehenders: Evidence from semantic priming. *Cognition*, 70, B1–B13.

Nee, D. E., Jonides, J., & Berman, M. G. (2007). Neural mechanisms of proactive interference-resolution. *Neuroimage, 38*, 740-751.

Neely, J. H. (1991). Semantic priming effects in visual word recognition: A selective review of current findings and theories. In D., Besner & G., Humphreys (Eds.), *Basic processes in reading: Visual word recognition* (pp. 264-336). Hillsdale, NJ: Erlbaum.

Neville, H. J., Kutas, M., Chesney, G. & Schmidt, A. (1986). Event related brain potentials during initial encoding and subsequent recognition memory of congruous and incongruous words. *Journal of Memory and Language, 25,* 75-92.

Niedeggen, M., & Rœsler, F. (1999a). N400 effects reflect activation spread during retrieval of arithmetic facts. *Psychological. Science, 10,* 271-276.

Niedeggen, M., Rœsler, F., & Jost, K. (1999b). Processing of incongruous mental calculation problems: evidence for an arithmetic N400 effect. *Psychophysiology, 36,* 307-324.

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychological Bulletin, 131,* 510-532.

Nieuwland, M. S., & Van Berkum, J. J. A. (2006). When peanuts fall in love: N400 evidence for the power of discourse. *Journal of Cognitive Neuroscience, 18,* 1098-1111

Nigam, A., Hoffman, J. E., & Simons, R. F. (1992). N400 and semantic anomaly with pictures and words. *Journal of Cognitive Neuroscience, 4,* 15-22.

Nobre, A. C., & McCarthy, G. (1995). Language-related Field potentials in the anterior-medial temporal lobe: II. Effects of word type and semantic priming. *Journal of Neuroscience, 15,* 1090-1098.

Nobre, A. C., Allison, T., & McCarthy, G. (1994). Word recognition in the human inferior temporal lobe. *Nature, 372,* 260-263.

Olichney, J., Van Petten, C., Paller, K., Salmon, D., Iragui, V., & Kutas, M. (2000). Word repetition in amnesia: electrophysiological evidence of spared and impaired memory. *Brain, 123,* 1948-1963.

Oostenveld, R., & Praamstra P. (2001). The five percent electrode system for high-resolution EEG and ERP measurements. *Clinical Neurophysiology, 112,* 713-719.

Opitz, B., & Cornell, S. (2006). Contribution of Familiarity and Recollection to Associative Recognition Memory: Insights from Event-related Potentials. *Journal of Cognitive Neuroscience, 18,* 1595-1605.

Osselton, J.W. (1965). Acquisition of EEG data by bipolar, unipolar and average reference methods: a theoretical comparison. *Electroencephalography and Clinical Neurophysiology, 19,* 527-528.

Palay, S. L. (1956). Synapses in the central nervous system. *Journal of Biophysical and Biochemical Cytology*, 2, 193-202.

Paller, K. A., & Kutas, M. (1992). Brain potentials during memory retrieval provide neurophysiological support for the distinction between conscious recollection and priming. *Journal of Cognitive Neuroscience, 4*, 375-391.

Paller, K. A., Voss, J. L., & Boehm, S. G. (2007). Validating neural correlates of familiarity. *Trends in Cognitive Sciences, 11*, 243-250.

Pekkonen, E., Rinne, T., & Naatanen, R. (1995). Variability and replicability of the mismatch negativity. *Electroencephalography and Clinical Neurophysiology, 96*, 546-554.

Perea, M., & Rosa, E. (2002). The effects of associative and semantic priming in the lexical decision task. *Psychological Research, 66*, 180-194.

Perea, M., Gotor, A., & Nacher, M. J. (1997). Efectos de facilitation associativa vs. semantica con una breve asincronia estimular senaltest. [Associative and semantic priming effects at a very brief stimulus onset asynchrony]. *Psicothema, 9*, 509-517.

Perrin, F., & Garcia-Larrea, L. (2003). Modulation of the N400 potential during auditory phonological/semantic interaction. *Cognitive Brain Research*, 17, 36-47.

Perrin, F., García-Larrea, L., Mauguière, F., & Bastuji, H. (1999). A differential brain response to the subject's own name persists during sleep. *Clinical Neurophysiology, 110*, 2153-2164.

Perry, N.W. (1966). Signal versus noise in evoked potential. *Science*, 153, 1022.

Picton, T.W., Bentin, S., Berg, P., Donchin, E., Hillyard, S.A., Johnson, Jr., R, Miller, G.A., Ritter, W., Ruchkin, D.S., Rugg, M.D., & Taylor, M.J. (2000). Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*, 37, 127-152.

Polich J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*, 2128-2148.

Polich, J., & Comerchero, M.D. (2003). P3a from visual stimuli: typicality, task, and topography. *Brain Topography, 15*, 141-52.

Polich, J., & Squire, L. (1993). P300 from amnesic patients with bilateral hippocampal lesions. *Electroencephalography and Clinical Neurophysiology, 86*, 408-417.

Polich, J., & Pitzer, A. (1999). P300 in early Alzheimer's disease: Oddball task difficulty and modality effects. In: G., Comi, C.H., Lucking, J., Kimura, & R.M., Rossini, (Eds.), *Clinical Neurophysiology: From Receptors to Perception, EEG Supplement* (pp. 281-287). Amsterdam, Netherlands: Elsevier.

Porjesz, B., & Begleiter, H. (1990). Event-related potentials in individuals at risk for alcoholism. *Alcohol, 7*, 465-469.

Postman, L., & Keppel, G. (1970). *Norms of word association*. New York, NY: Academic Press.

Price, G.W., Michie, P.T., Johnston, J., Innes-Brown, H., Kent, A., & Clissa, P. (2006) A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia. *Biological Psychiatry, 60*, 1-10.

Pritchard, W. (1981). Psychophysiology of P300. *Psychological Bulletin, 89*, 506-540.

Pritchard, W.S. (1986). Cognitive event-related potential correlates of schizophrenia. *Psychological Bulletin, 100,* 43-66.

Quamme, J.R., Yonelinas, A.P., & Norman, K.A. (2007). The effect of unitization on associative recognition in amnesia. *Hippocampus, 17,* 192-200.

Ragot, R., & Fiori, N. (1994). Mental processing during reactions toward and away from a stimulus: an ERP analysis of auditory congruence and S-R compatibility. *Psychophysiology, 31,* 439-446.

Ramón, F., Hernández, O. H., & Bullock, T. H. (2001). Event-related potentials in a invertebrate: Crayfish emit 'omitted stimulus potentials'. *Journal of Experimental Biology, 204,* 4291-4300.

Ranganath, C., & Rainer, G. (2003). Neural mechanisms for detecting and remembering novel events. *Nature Review Neuroscience, 4,* 193-202.

Ranganath, C., & Paller, K.A. (2000). Neural correlates of memory retrieval and evaluation. *Cognitive Brain Research, 9,* 209-222.

Ratcliff, R., & McKoon, G. (1981). Does activation really spread?, *Psychological Review, 88,* 385-408.

Ratcliff, R., Sheu, C.F., & Gronlund, S.D. (1992). Testing global memory models using ROC curves. *Psychological Review, 99,* 518-535.

Ravden, D., & Polich, J. (1998). Habituation of P300 from visual stimuli. *International Journal of Psychophysiology, 30,* 359-365.

Rescorla, R.A. (1980). Simultaneous and successive associations in sensory preconditioning. *Journal of Experimental Psychology: Animal Behavior Processes, 6,* 207-216.

Rhodes, S. M., & Donaldson, D. I. (2007). Electrophysiological evidence for the influence of unitization on the processes engaged during episodic retrieval: Enhancing familiarity based remembering. *Neuropsychologia, 45,* 412-424.

Rhodes, S. M., & Donaldson, D. I. (2008). Association and not semantic relationships elicit the N400 effect: Electrophysiological evidence from an explicit language comprehension task. *Psychophysiology, 45,* 50-59.

Rhodes, S.M., & Donaldson, D.I. (2008). Electrophysiological evidence for the effect of interactive imagery on episodic memory: Encouraging familiarity for non-unitized stimuli during associative recognition. *Neuroimage,* 39, 873-884.

Ries, M.L., Carlsson, C.M., Rowley, H.A., Sager, M.A., Gleason, C.E., Asthana, S., et al. (2008). Magnetic resonance imaging characterization of brain structure and function in mild cognitive impairment: a review. *Journal of American Geriatric Society, 56,* 920-934.

Roberts, L.E., Rau, H., Lutzenberger, W., & Birbaumer, N. (1994). Mapping P300 waves onto inhibition: Go/no-go discrimination. *Electroencephalography and Clinical Neurophysiology, 92,* 44-55.

Roger, M., & Galand, G. (1981). Operant conditioning of visual evoked potentials in man. *Psychophysiology, 18,* 477-482.

Rosenfeld, J. P., Biroschak, J. R., Kleschen, M. J., & Smith, K. M. (2005). Subjective and objective probability effects on P300 amplitude revisited. *Psychophysiology, 42,* 356-359.

Rugg, M. D. (1990). Event-related brain potentials dissociate repetition effects of high- and low-frequency words. *Memory and Cognition, 18,* 367-379.

Rugg, M. D., Mark, R. E., Walla, P., Schloerscheidt, A. M., Birch, C. S., & Allan, K. (1998). Dissociation of the neural correlates of implicit and explicit memory. *Nature, 392,* 595-598.

Rugg, M. D., Schloerscheidt, A. M., Doyle, M. C. , Cox, C. J. C., & Patching, G. R. (1996). Event-related potentials and the recollection of associative information. *Cognitive Brain Research, 4,* 297-304.

Rugg, M.D. & Curran, T. (2007). Event-related potentials and recognition memory. *Trends in Cognitive Sciences,* 11, 251-257.

Rugg, M.D. & Doyle, M.C. (1992). Event-related potentials and recognition memory for low-frequency and high-frequency words. *Journal of Cognitive Neuroscience, 4,* 69-79.

Rugg, M.D., Cox, C.J.C., Doyle, M.C., & Wells, T. (1995). Event-related potentials and the recollection of low and high frequency words. *Neuropsychologia,* 33, 471-484.

Rugg, M.D., & Doyle, M.C. (1994). Event-related potentials and stimulus repetition in direct and indirect tests of memory. In: H.J., Heinze, T., Munte, G.R., Mangun (Eds.), *Cognitive Electrophysiology* (pp. 124-148). Boston, MA: Birkhauser.

Rugg, M.D. (1995). Event-related potentials studies of human memory. In M.D., Rugg & M.G.H., Coles (Eds.). *Electrophysiology of Mind: Event-Related Brain Potentials and cognition* (Vol. 15, pp. 132-170). New York, NY: Oxford University Press.

Rypma, B., & D'Esposito, M. (1999). The roles of prefrontal brain regions in components of working memory: effects of memory load and individual differences. *Proceedings of the National Academy of Sciences, 96,* 6558-6563.

Rypma, B., Berger, J. S., & D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *Journal of Cognitive Neuroscience, 14,* 721-731.

Salisbury, D., Squires, N.K., Ibel, S., & Maloney, T. (1992). Auditory event related potentials during stage 2 NREM sleep in humans. *Journal of Sleep Research, 1,* 251-257.

Salisbury, D.F., Rutherford, B., Shenton, M.E., & McCarley, R.W. (2001). Button-pressing affects P300 amplitude and scalp topography. *Clinical Neurophysiology, 112,* 1676-1684.

Sanquist, T.F., Rohrbaugh, J.W., Syndulko, K., & Lindsley, D.B. (1980). Electrocortical signs of levels of processing: perceptual analysis and recognition memory. *Psychophysiology, 16,* 568-576.

Schaefer, A., Braver, T. S., Reynolds, J. R., Burgess, G. C., Yarkoni, T., & Gray, J. R. (2006). Individual differences in amygdala activity predict response speed during working memory. *Journal of Neuroscience, 26,* 10120-10128.

Schloerscheidt, A.M., & Rugg, M.D. (1997). Recognition memory for words and pictures: an event-related potential study. *NeuroReport, 8,* 3281-3285.

Schloerscheidt, A.M., & Rugg, M.D. (2004). The impact of change in stimulus format on the electrophysiological indices of recognition. *Neuropsychologia, 42,* 451-466.

Schoenle, P. W., & Witzke, W. (2004). How vegetative is the vegetative state? *Neurorehabilitation, 19,* 329-334.

Schusterman, R. J., & Kastak, D. (1993). A California sea lion (Zalophus californianus) is capable of forming equivalence relations. *The Psychological Record, 43,* 823-839.

Sculthorpe, L.D., Stelmack, R.M., & Campbell, K.B. (2009). Mental ability and the effect of pattern violation discrimination on P300 and mismatch negativity. *Intelligence, 37,* 405-411.

Segalowitz, S., & Barnes, K. (1993). The reliability of ERP components in the auditory oddball paradigm. *Psychophysiology,* 30, 451-459.

Segalowitz, S., Santesso, D., Murphy, T., Homan, D., Chantziantoniou, D., & Khan, S. (2010). Retest reliability of medial frontal negativities during performance monitoring. *Psychophysiology, 47,* 260-270.

Semlitsch, H. V., Anderer, P., Schuster, P., & Presslich, O. (1986). A solution for reliable and valid reduction of ocular artefacts applied to the P300 ERP. *Psychophysiology*, 23, 695-703.

Senkfor, A.J., & Van Petten, C. (1998). Who said what? An event-related potential investigation of source and item memory. *Journal of Experimental Psychology: Learning Memory & Cognition, 24,* 1005-1025.

Sidman, M. (1960). *Tactics of scientific research*. NewYork, NY: Basic Books.

Sidman, M. (1994). *Equivalence relations and behavior: A research story.* Boston, MA: Authors Cooperative.

Simons, R.F., Graham, F.K., Miles, M.A., & Chen, X. (2001). On the relationship of P3a and the novelty-P3. *Biological Psychology, 56,* 207-218.

Smith, A.P.R., Dolan, R.J., & Rugg, M.D. (2004). Event-related potential correlates of the retrieval of emotional and nonemotional context. *Journal of Cognitive Neuroscience 16,* 760-775.

Smith, M. E., Stapleton, J. M., & Halgren, E. (1986). Human medial temporal lobe potentials evoked in memory and language tasks. *Electroencephalography and Clinical Neurophysiology, 63,* 145-159.

Smith, M.E. (1993). Neurophysiological manifestations of recollective experience during recognition memory judgments. *Journal of Cognitive Neuroscience*, 5, 1-13.

Smith, M.E., & Guster, K. (1993) Decomposition of recognition memory event-related potentials yields target, repetition, and retrieval effects. *Electroencephalography and Clinical Neurophysiology, 86,* 335-343.

Smulders, F.T.Y., Kok, A., Kenemans, J. L., & Bashore, T.R. (1995). The temporal selectivity of additive factors effects on the reaction process revealed in ERP component latencies. *Acta Psychologica, 90,* 97-109.

Snodgrass, J.G., & Corwin, J. (1988). Pragmatics of measuring recognition memory: applications to dementia and amnesia. *Journal of Experimental Psychology: General, 117,* 34-50.

Soderling, T.R., & Derkach, V.A. (2000). Postsynaptic protein phosphorylation and LTP. *Trends in Neuroscience, 23,* 75-80.

Sommer, W. (1987). Operant conditioning of P300. *Psychophysiology, 24,* 612.

Sommer, W., & Schweinberger, S. (1992) Operant conditioning of P300. *Biological Psychology, 33,* 37-49.

Spencer, K. M., Vila Abad, E., & Donchin, E. (2000). On the search for the neurophysiological manifestation of recollective experience. *Psychophysiology, 37,* 494-506.

Spencer, K.M., Dien, J., & Donchin E. A. (1999). Componential analysis of the ERP elicited by novel events using a dense electrode array. *Psychophysiology, 36,* 409-414.

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: A new perspective. *Nature Reviews Neuroscience, 8,* 872-883.

Squires, K. C., Hillyard, S. A. & Lindsay, P. H. (1973). Cortical potentials evoked by confirming and disconfirming feed-back following an auditory discrimination. *Perception Psychophysics, 13,* 25-31.

Squires, K. C., Wickens, C., Squires, N. K., & Donchin, E. (1976). The effect of stimulus sequence on the waveform of the cortical event-related potential. *Science, 193*, 1142-1146.

Squires, N., Squires, K.C. & Hillyard, S. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalography and Clinical Neurophysiology, 38,* 387-401.

Srinivasan, R., Tucker, D.M. & Murias, M. (1998). Estimating the spatial nyquist of the human EEG. *Behavior Research Methods Instruments & Computers*, *30*, 8-19.

Stamenov, M.L. (2002). Some features that make mirror neurons and human language faculty unique. In M.L., Stamenov & V., Gallese (Eds.), *Mirror Neurons and the Evolution of Brain and Language* (pp. 249-271). Amsterdam, Netherlands: John Benjamins.

Stenberg, G., Hellman, J., Johansson, M., & Rosén, I. (2009) Familiarity or Conceptual Priming: Event-related Potentials in Name Recognition. *Journal of Cognitive Neuroscience, 21,* 447-460.

Sutton, S., Braren, M., Zubin, J., & John, E. (1965). Evoked potential correlates of stimulus uncertainty. *Science, 150,* 1187-1188.

Swartz, B.E., & Goldensohn, E.S. (1998). Timeline of the history of EEG and associated fields. *Electroencephalography and Clinical Neurophysiology, 106,* 173-176.

Tello, C., De Moraes, C., Prata, T., Derr, P., Patel, J., Siegfried, J., et al. (2010). Repeatability of short-duration transient visual evoked potentials in normal subjects. *Documenta Ophthalmologica, 120,* 219-228.

Tendolkar, I., Doyle, M.C., & Rugg, M.D. (1999). An event-related potential study of retroactive interference in memory. *NeuroReport, 8,* 501-506.

Teplan, M. (2002). Fundamentals of EEG measurement, *Measurement Science Review, 2,* 1-11.

Tervaniemi, M., Maury, S., & Naatanen, R. (1994). Neural representations of abstract stimulus features in the human brain as reflected by the mismatch negativity. *NeuroReport,* 5, 844-846.

Trenkwalder, C., & Winkelmann, J. (2003) Pathophysiology of the restless legs syndrome. In: S., Chokroverty W.A., Hening, & A.S.,Walters, (Eds.), *Sleep and movement disorders* (pp. 322–332). Philadelphia, PA: Butterworth/Henemann.

Trott, C.T., Friedman, D., Ritter, W., & Fabiani, M. (1997). Item and source memory: differential age effects revealed by event-related potentials. *NeuroReport, 8,* 3373-3378.

Tsivilis, D., Otten, L., & Rugg, M.D. (2001). Context effects on the neural correlates of recognition memory: an electrophysiological study. *Neuron, 31,* 497-505.

Tucker, D.M. (1993). Spatial sampling of head electrical fields: the geodesic sensor net. *Electroencephalography & Clinical Neurophysiology, 87,* 154-163.

Urbach, T. P., & Kutas, M. (2002). The intractability of scaling scalp distributions to infer neuroelectric sources. *Psychophysiology, 39,* 791-808.

Van Berkum, J. J. A., Zwitserlood, P., Brown, C. M., & Hagoort, P. (2003). When and how do listeners relate a sentence to the wider discourse? Evidence from the N400 effect. *Cognitive Brain Research, 17,* 701-718.

Van Petten, C., & Kutas, M. (1991). Electrophysiological evidence for the flexibility of lexical processing. In G.B.,Simpson (Ed.), *Understanding Word and Sentence* (pp. 129-174). Amsterdam, Netherlands: North-Holland Press.

Van Petten, C., & Rheinfelder H. (1995). Conceptual relationships between spoken words and environmental sounds: Event-related brain potential measures. *Neuropsychologia, 33,* 485-508.

Van Petten, C. M., & Kutas, M. (1990). Interactions between sentence context and word frequency in event-related brain potentials. *Memory and Cognition, 18,* 380-393.

Van Petten, C. M., Kutas, M., Kluender, R., Mitchiner, M., & McIsaac, H. (1991). Fractionating the word repetition effect with event-related potentials. *Journal of Cognitive Neuroscience, 3,* 131-150.

Van Petten, C. M., Weckerly, J., McIsaac, H.K., & Kutas, M. (1997). Working memory capacity dissociates lexical and sentential context effects. *Psychological Science, 8,* 238-242.

Van Petten, C. M., & Luka, B.J. (2006) Neural localization of semantic context effects in electromagnetic and hemodynamic studies. *Brain and Language, 97,* 279-293.

Verleger, R. (1997). On the utility of P3 latency as an index of mental chronometry. *Psychophysiology, 34,* 131-156.

Verleger, R., Heide, W., Butt, C., & Kompf, D. (1994). Reduction of P3b in patients with temporo–parietal lesions. *Cognitive Brain Research, 2,* 103-116.

Verleger, R., Jaśkowskis, P., & Wascher, E. (2005). Evidence for an integrative role of P3b in linking reaction to perception. *Journal of Psychophysiology, 19,* 150-150.

Vilberg, K.L., Moosavi, R.F., & Rugg, M.D. (2006). The relationship between electrophysiological correlates of recollection and amount of information retrieved. *Brain Research, 1122,* 161-170.

Vilberg, K.L., & Rugg, M.D. (2009). Functional significance of retrieval-related activity in lateral parietal cortex: evidence from fMRI and ERPs. *Human Brain Mapping, 30,* 1490-1501.

Voss, J. L., & Federmeier, K. D. (2011). FN400 potentials are functionally identical to N400 potentials and reflect semantic processing during recognition testing. *Psychophysiology, 48,* 532-546.

Voss, J.L., & Paller, K.A. (2006). Fluent conceptual processing and explicit memory for faces are electrophysiologically distinct. *Journal of Neuroscience, 26,* 926-933.

Wager, T. D., Sylvester, C. Y. C., Lacey, S. C., Nee, D. E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *Neuroimage, 27,* 323-340.

Wagner, A.D., Shannon, B.J., Kahn, I., & Buckner, R.L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Science, 9,* 445-453.

Wais, P.E., Squire, L.R., & Wixted, J.T. (2010). In search of recollection and familiarity signals in the hippocampus. *Journal of Cognitive Neuroscience, 22,* 109-123.

Wickens, C., Kramer, A., Vanasse, L., & Donchin E. (1983). Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science, 221,* 1080-1082.

Wilder, M. B., Farley, G. R., & Starr, A. (1981). Endogenous late positive component of the evoked potential in cats corresponding to P300 in humans. *Science, 211,* 605-607.

Wilding, E. L. (1999). Separating retrieval strategies from retrieval success: An event-related potential study of source memory. *Neuropsychologia, 37,* 441-454.

Wilding, E. L. (2006). The practice of rescaling scalp-recorded event-related potentials. *Biological Psychology, 72,* 325-332.

Wilding, E. L., & Rugg, M. D. (1996). An event-related potential study of recognition memory with and without retrieval of source. *Brain, 119,* 889-905.

Wilding, E.L. (2000). In what way does the parietal ERP old/new effect index recollection? *International Journal of Psychophysiology, 35,* 81-87.

Wilding, E.L., Doyle, M.C., & Rugg, M.D. (1995). Recognition memory with and without retrieval of context: an event-related potential study. *Neuropsychologia, 33,* 743-767.

Williams, J. N. (1996). Is automatic priming semantic? *European Journal of Cognitive Psychology, 22,* 139-151.

Wixted, J.T. (2007). Dual-process theory and signal-detection theory of recognition memory. *Psychological Review, 114,* 152-176.

Wood, C.C., & Allison, T. (1981). Interpretation of evoked-potentials: a neurophysiological perspective. *Canadian Journal of Psychology, 35,* 113-135.

Word Association Thesaurus (n.d.). Edinburgh Association Thesarus, MRC Psycholinguistic database. Available at http://www.eat.rl.ac.uk

Xiang, J. Z., & Brown, M. W. (1998). Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology, 37,* 657-676.

Yamaguchi, S., & Knight, R. (1991). Age effects on the P300 to novel somatosensory stimuli. *Electroencephalography and Clinical Neurophysiology, 78,* 297-301.

Yarkoni, T., & Braver, T.S. (2010). Cognitive neuroscience approaches to individual differences in working memory and executive control: conceptual and methodological issues. In A.,Gruszka, G., Matthews, & B., Szymura (Eds.), *Handbook of individual differences in cognition: Attention, memory and executive control.* New York, NY: Springer.

Yonelinas, A. P. (1997). Recognition memory ROCs for item and associative information: The contribution of recollection and familiarity. *Memory and Cognition, 25,* 747-763.

Yonelinas, A. P. (2001). Consciousness, control, and confidence: The 3 Cs of recognition memory. *Journal of Experimental Psychology: General, 130,* 361-379.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *Journal of Memory and Language, 46,* 441-517.

Yonelinas, A. P., Kroll, N. E. A., Dobbins, I. G., & Soltani, M. (1999). Recognition memory for faces: When familiarity supports associative recognition judgments. *Psychonomic Bulletin and Review, 6*, 654-661.

Yonelinas, A. P., Kroll, N. E. A., Dobbins, I., Lazzara, M., & Knight, R. T. (1998). Recollection and familiarity deficits in amnesia: Convergence of remember know, process dissociation, and Receiver-Operating-Characteristic data. *Neuropsychology, 12*, 323-339.

Yonelinas, A.P. (2001). Components of episodic memory: the contribution of recollection and familiarity. *Philosophical Transcripts of the Royal Society of London, Biological Sciences, 356*, 1363-1374.

Yonelinas, A.P., Aly, M., Wang, W. C., & Koen, J.D. (2010). Recollection and familiarity: Examining controversial assumptions and new directions, *Hippocampus, 20*, 1178-1194.

Yonelinas, A.P., Kroll, N.E., Quamme, J.R., Lazzara, M.M., Sauve, M.J., Widaman, K.F., & Knight, R.T. (2002). *Nature Neuroscience, 5*, 1236-1241.

Yonelinas, A.P., Otten, L.J., Shaw, K.N., & Rugg, M.D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *The Journal of Neuroscience, 25*, 3002-3008.

Yovel, G., & Paller, K.A. (2004). The neural basis of the butcher-on-the-bus phenomenon: when a face seems familiar but is not remembered. *NeuroImage, 21*, 789-800.

Yu, S. S., & Rugg, M. D. (2010) Dissociation of the electrophysiological correlates of familiarity strength and item repetition. *Brain Research*, 1320, 74-84.

Zurif, E.B., Caramazza, A., Myerson, R., & Galvin J. (1974). Semantic feature representations for normal and aphasic language. *Brain and Language, 1*, 167-187.