SINGLE-TRIALS ANALYSIS OF EVENT-RELATED POTENTIALS

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To my family:

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Abstract

Single-trial analysis of event-related potentials

It is a common practice to study the dynamics of sensory and cognitive processes using event-related potentials (ERPs) measured by placing electrodes on the scalp. These ERPs are very small in comparison with the on-going electroencephalogram (EEG) and are barely visible in the individual trials. Therefore, most ERP research relies on the identification of different waves after averaging several presentations of the same stimulus pattern. Although ensemble averaging improves the signal-to-noise-ratio, it implies a loss of information related to variations between the single-trials.

In this thesis, I present an automatic denoising method based on the wavelet transform to obtain single-trial evoked potentials. The method is based on the interand intra-scale variability of the wavelet coefficients and their deviations from baseline values. The performance of the method is tested with simulated ERPs and with real visual and auditory ERPs. For the simulated data the method gives a significant improvement in the visualisation of single-trial ERPs as well as in the estimation of their amplitudes and latencies in comparison with the standard denoising technique (Donoho's thresholding) and in comparison with the noisy single-trials. For the real data, the proposed method helps the identification of single-trial ERPs, providing a simple, automatic and fast tool that allows the study of single-trial responses and their correlations with behaviour.

We used our proposed denoising algorithm to study the amplitude modulation of the ERP responses to the flashes of faces and to investigate whether the ERP responses in a visual and an auditory oddball paradigm were due to phase-resetting of on-going EEG (phase-resetting model) or due to additive neural responses adding to the background EEG in response to the stimulus presentation (additive model).

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Contents

		Abstract		
		Acknowledgments		
		Publications	V	
		Poster Presentations	V	
		Table of Contents	/I	
List of Figures			Х	
		Abbreviations	XI	
1	Bac	ckground	. 2	
	1.1	Electroencephalography (EEG)	. 2	
	1.2	EEG recordings	2	
	1.2.	.1 Electrodes	. 3	
	1.2.	.2 Analogue to digital conversion	. 4	
	1.2.	.3 Sources of Artefacts in the EEG recordings	5	
	1.3	Event-related potentials (ERPs)	.7	
	1.3.	.1 Visual evoked potentials (VEPs)	8	
	1	.3.1.1 Pattern reversal visual evoked potential (PRVEP)	8	
	1.3.	.2 Auditory evoked potentials1	10	
	1.3.	.3 Somatosensory evoked potentials (SEPs)1	12	
	1.3.	.4 ERPs in cognitive neuroscience 1	13	
	1.4	Oddball paradigm1	13	
	1.4.	.1 P3 and cognition1	14	
	1.5	Neural basis of ERP generation1	17	
	1.6	Organisation of the thesis1	17	
2	Wa	velet transform1	19	
	2.1	Background and history1	19	
	2.2	Uncertainty principle2	20	
	2.3	Continuous wavelet transform2	21	
	2.4	Discrete wavelet transform2	23	
	2.5	Multiresolution approximation and filter banks2	24	
	2.6	Wavelet Families	28	
		,	VI	

	2.7	Wa	velet Denoising	. 31
3	Au	toma	atic denoising of single-trial event-related Potentials	. 34
	3.1	Bac	kground	. 34
	3.2	Mat	erials and methods	. 36
	3.2	.1	Real data recording	. 36
	3	.2.1.	1 Visual oddball paradigm	. 36
	3	.2.1.	2 Auditory oddball paradigm	. 37
	3.2	.2	Synthetic data	. 38
	3.3	Wa	velet denoising	. 40
	3.3	.1	Donoho's denoising implementation	. 40
	3.3	.2	Neighbouring and Zerotrees (NZT) denoising	. 41
	3	.3.2.	1 Denoising using neighbour coefficients and level dependency	. 42
	3	.3.2.	2 Zerotrees denoising	. 43
	3.3	.3	Denoising of ERPs	. 44
	3.3	.4	Summary of the NZT algorithm	. 47
	3.4	Res	sults	. 47
	3.4	.1	Simulated data	. 47
	3.4	.2	Real data	. 49
	3.5	Dis	cussion	. 55
4	Sin	gle-	trial analysis of conscious face perception	. 59
	4.1	Bac	kground	. 59
	4.2	Mat	erials and methods	. 61
	4.2	.1	EEG recordings	. 61
	4.2	.2	Stimuli	. 61
	4.2	.3	Paradigm	. 62
	4.2	.4	ERP analysis	. 64
	4.2	.5	Single-trial ERP analysis	. 65
	4.3	Res	sults	. 66
	4.3	.1	Average ERP analysis	. 66
	4.3	.2	Single-trial analysis	. 67
	4.4	Dis	cussion	. 70

5 A	meth	od to evaluate the presence of phase-resetting and additive is in the generation of ERPs	73	
5.1	Intro	oduction		
5.2	Mat	Materials and methods		
5.2	5.2.1 Simulation of the additive model			
5.2	2.2	Simulation of the phase-resetting model		
5.3	Ехр	erimental set up and empirical data		
5.4	Des	cription of the method	79	
5.4	4.1	Estimation of the single-trial ERP latencies		
5.4	4.2	Aligning of the single-trial latencies	82	
5.4	4.3	Quantification of phase-resetting	82	
5.5	Res	sults		
5.5	5.1	Simulated data		
5.5	5.2	Real data		
į	5.5.2.	1 Real VEPs		
į	5.5.2.	2 Real AEPs		
į	5.5.2.	3 Baseline controls		
5.6	5.6 Discussion			
6 Ge	enera	I discussion and conclusion	100	
6.1	Ger	neral discussion	100	
6.1	1.1	Automatic denoising of single-trial event-related potentials	100	
6.1	1.2	Single-trial analysis of conscious face perception	103	
6.1	1.3	Neural basis of ERP generation	104	
6.2	Ger	neral conclusion	106	
7 Bi	bliog	raphy	109	

List of Figures

Figure 1.1 The international 10-20 electrode placements.	4
Figure 1.2 EEG traces	6
Figure 1.3 Blink artifact.	6
Figure 1.4 Single-trials ERPs.	8
Figure 1.5 Major components of average VEP and AEP	11
Figure 1.6 Responses to non-target VEPs at different scalp locations.	16
Figure 1.7 Responses to target VEP.	16
Figure 2.1 Time-frequency boxes of STFT and WT.	22
Figure 2.2 Continuous wavelet transform (CWT).	23
Figure 2.3 Multiresolution decomposition and reconstruction.	27
Figure 2.4 ERP Multiresolution decomposition and reconstruction.	27
Figure 2.5 Wavelet functions	29
Figure 2.6 B-Spline (3.15) wavelet filters.	29
Figure 2.7 B-Spline (3.15) filter coefficients.	30
Figure 2.8 Hard and soft Thresholding	32
Figure 3.1 EEG recording in the NeuroEngineering Lab	37
Figure 3.2 Simulated ERP	39
Figure 3.3 Parent-children dependency in the Zerotrees denoising algorithm	44
Figure 3.4 Wavelet decomposition and denoising using Donoho's method and the	
NZT algorithm.	46
Figure 3.5 RMS error.	48
Figure 3.6 Error in the estimation of ERP components.	50
Figure 3.7 Automatic wavelet denoising of a visual ERP recorded from a left occipit (O1) location	tal 52
Figure 3.8 Automatic wavelet denoising of an auditory ERP recorded from a centra	1
location (Cz).	53
Figure 3.9 Performance of Donoho's (blue) and NZT (red) denoising methods with	
real average evoked potentials.	54
Figure 4.1 Structure of a trial	63
Figure 4.2 Neural correlates of conscious versus unconscious face perception	67
Figure 4.3 Decoding the subjects' report with single-trial ERPs	68
Figure 4.4 Single-trial analysis of ERPs.	70
Figure 5.1 Ringing effect introduced by digital filtering	74
Figure 5.2 Simulated VEPs based on the additive and oscillation models	79
Figure 5.3 Average simulated ERPs before and after correcting the latency jitter	81
Figure 5.4 Automatic wavelet denoising of an average VEP simulated based on the	Э
additive model	84

Figure 5.5 Automatic wavelet denoising of an average VEP simulated based on th	e
phase-resetting model	84
Figure 5.6 The PR values for the simulated ERPs	86
Figure 5.7 Automatic wavelet denoising of an average VEP recorded from O1	
electrode.	. 88
Figure 5.8 Automatic wavelet denoising of an average AEP recorded from Cz	
electrode.	. 88
Figure 5.9 Latency-corrected averages of real VEP and AEP.	90
Figure 5.10 The PR values for the real and simulated ERPs	.91
Figure 5.11 Latency-corrected averages in the baseline of real VEP and AEP	93
Figure 5.12 The PR values for the real ERPs, baselines and simulated ERPs	94

Abbreviations

ADC	Analogue to Digital Converter
AEP	Auditory Evoked Potential
BSAEP	Brain Steam Auditory Evoked Potential
СМТ	Continuous Wavelet Transform
DWT	Discrete Wavelet Transform
EEG	Electroencephalogram
EP	Evoked Potential
ERF	Event-Related Field
ERP	Event-Related Potentials
ICA	Independent Component Analysis
IWT	Inverse Wavelet Transform
MEG	Magnetoencephalography
NZT	Neighbouring and ZeroTrees
PRVEP	Pattern Reversal Visual Evoked Potential
RMS	Root Mean Square
SEP	Somatosensory Evoked Potential
SNR	Signal to Noise Ratio
SSVEP	Steady State Visual Evoked Potential
STFT	Short Time Fourier Transform
TVEP	Transient Visual Evoked Potential
VEP	Visual Evoked Potential
WT	Wavelet Transform

Chapter 1

1 Background

1.1 Electroencephalography (EEG)

In 1875, Caton, a physician practicing in Liverpool, measured the electrical activity in animal brains by recording the current variations in the skull surface of monkeys and rabbits. He reported distinct current changes which increased during sleep and stopped after death. About fifty years after Caton's report of his discovery, at the British Medical Association in Edinburgh, Hans Berger recorded the electrical activity in the human brain by placing electrodes on the scalp. He published this observation in 1929 and he called this electrical activity Electroencephalogram (EEG). Berger's findings weren't accepted by neurophysiologists of his time, until Lord Edgar Adrian (a respected physiologist at the University of Cambridge) among others confirmed his findings. Since then, the EEG has been used in scientific and clinical applications such as diagnosis of epilepsy, tumours, stroke, coma and brain death. Moreover, it is also used to study sleep disorders as well as brain sensory and cognitive processing non-invasively in normal subjects.

1.2 EEG recordings

The EEG signal represents a mix up of synchronous activity of many neurons (Freeman, 1975; Lopes da Silva, 2005a) and can be recorded by placing electrodes on the human scalp based on the so-called international 10-20 system (Jasper, 1958). The international 10-20 system is a standard method to describe the placement of the scalp electrodes for recording EEG signals. This system is based on the correspondence between the location of the electrodes and the underlying area of the cerebral cortex. Numbers "10" and "20" refer to the fact that the

electrodes are placed at 10% or 20% of the measured distance from nasion (the point between the forehead and the nose) to inion (the lowest point of the skull from the back of the head) and from right to left preauricular (the bony indentations in front of ears). The electrode placements are labelled by a letter followed by a number. The letter refers to the lobe in which the electrode is placed. The letters F, T, C, P, and O stand for Frontal, Temporal, Central, Parietal and Occipital lobe respectively (there is no Central lobe and C is just used for identification purposes). The letter Z is defined for the electrode locations in the midline. The number refers to the hemisphere location. Odd numbers are used for the left hemisphere electrode positions, while even numbers for the right hemisphere ones. A schematic of the international 10-20 electrodes placement for the human EEG recording is shown in Figure 1.1.

EEG data is recorded as the voltage difference between an electrode and a reference site (monoploar or referential recordings) or the voltage difference between two electrodes (bipolar recordings). In monopolar recording the reference site can be a neutral electrode (an electrode with little or no brain activity, e.g. at the earlobes) or can be the average of all the electrodes (Reilly, 2005).

1.2.1 Electrodes

To record non-invasively the electrical activity of the human brain an electrode cap with 32, 64 or 128 electrode holders can be used to place the electrodes over the scalp in accordance with the international 10-20 system (Jasper, 1958). In this work, we used 64 silver-silver chloride (Ag/AgCl) active electrodes, each of which containing a preamplifier with high input and low output impedances.



Figure 1.1 The international 10-20 electrode placements. The numbers refer to the hemisphere location. Odd numbers are used for electrodes in the left hemisphere, even numbers for the ones in the right hemisphere and Z or zero indicates the midline electrodes. Front of the head is up.

To improve the connections, conductive gel is inserted between the electrodes and the surface of the scalp.

1.2.2 Analogue to digital conversion

The EEG signals collected continuously by the active electrodes over time are converted to digital signals in order to be stored and processed by computers. This process is accomplished by using analogue-to-digital converters (ADC). To ensure that the frequency content of the recorded EEG signal is limited, an anti-aliasing filter needs to be added before the ADC. The anti-aliasing filter is a low pass filter which restricts the frequency range of the recorded signal to be less than the half of the sampling rate. According to the Nyquist theorem, the sampling rate of the ADC should be at least twice the highest frequency of interest of the EEG signal, ensuring that the critical contents of the EEG recordings are preserved. Therefore, the cut-off frequency of the anti-aliasing filter should be less than half of the sampling rate. Figure 1.2 illustrates 3 seconds of EEG traces recorded with 64 active electrodes.

1.2.3 Sources of Artefacts in the EEG recordings

There are several sources of artefacts that can contaminate the EEG signals, including eye movements, blinks and muscle activities. In most cases these artefacts are very large compared to the EEG data and the brain signals are buried under these large artefacts. Eye movements and blink artefacts are the result of the electrical gradient (the difference in electrical charge) of the eyes. The eyeball acts like a dipole with positive pole at the front (cornea) and the negative pole at the back of the eye (retina) (Reilly, 2005). When the eyes are stationary, a constant DC voltage is propagated across the scalp which is eliminated by the high pass filter of the recording apparatus. However, when the eyes move, the voltage gradient across the scalp becomes more positive towards the eye movement direction and more negative on the opposite direction (Luck, 2005).

Blinking changes the cornea position and since the cornea is more positive compared to the retina, the electrodes closer to the cornea become more positive (Reilly, 2005) than those further away. Blinking generates a monophasic voltage deflection which lasts for 200 to 400 ms and is especially captured by the electrodes near the eye (Luck, 2005).

Muscle artefacts or electromyogram (EMG) activity are voltages generated by muscle contractions. It is possible to reduce these high frequency artefacts by asking the subject to seat still and relax the muscles closer to the scalp, such as neck, jaw and forehead.



Figure 1.2 EEG traces. 3 seconds EEG signals recorded with 64 electrodes while the subject's eyes are closed (sampling rate 512, maximum frequency 70 Hz).



Figure 1.3 Blink artifact. 3 seconds EEG traces. Eye blinks could be identified by checking the EEG recordings from the frontal electrodes; high amplitude fluctuations in the frontal electrodes that vanish from frontal to occipital sites were considered to be eye blinks (red oval).

Muscles below the neck have negligible effect on the EEG signals since the EMG does not propagate very far (Luck, 2005). Figure 1.3 depicts traces of EEG recordings with the blink artefact. The blink artefacts can be recognized as high amplitude "bell shape" fluctuations in the frontal electrodes that vanish from frontal to occipital lobes. Note that after the recordings, epochs containing these artefacts can be discarded from the data set.

1.3 Event-related potentials (ERPs)

Embedded within the EEG are patterns associated with responses to sensory, cognitive or motor events, which are called event-related potentials (ERPs). ERPs are very small in comparison with the on-going EEG and are barely visible in the individual trials. Therefore, most ERP research relies on the identification of different waves after averaging several presentations of the same stimulus pattern (Dawson, 1954; Lopes da Silva, 2005b).

ERP responses to sensory (visual, auditory or somatosensory) stimulations are called sensory evoked potentials (EPs) (Lopes da Silva, 2005b). Figure 1.4 depicts an example of 20 single-trial EPs (responses to visual stimulations) and the corresponding average ERP recorded on the left occipital electrode (O1). In this figure the vertical line represents the onset time of the stimulus presentation for each trial. Note that the potential changes due to the stimulus presentation are not visible (or barely visible) in the single-trials due to the large amount of the background EEG. However by averaging a large number of trials the background noise will cancel and we will end up with the average of the time-locked ERPs responses. In the following sections brain sensory responses to visual, auditory and somatosensory stimulations are explained in more detail.



Figure 1.4 Single-trials ERPs. 20 trials of ERPs recorded on the left occipital location (up) and the average ERP (bottom). The vertical line indicates the onset time of the stimulus presentation. Note that ERP components are not visible in the single-trials however they are clearly visible in the average signal.

1.3.1 Visual evoked potentials (VEPs)

Brain responses to visual stimuli are called visual evoked potentials (VEPs). Due to their small amplitude, non-invasive VEP recordings were not feasible until the introduction of the ensemble averaging by Dawson (Figure 1.4) (Dawson, 1954). Since then, VEPs have been widely studied non-invasively by recording scalp potentials overlying the visual cortex. The VEPs are elicited by visual patterns such as checkerboard (pattern reversal or pattern onset/offset), by light flashes or by the presentation of other visual stimuli (faces, etc.).

1.3.1.1 Pattern reversal visual evoked potential (PRVEP)

The pattern reversal stimulus consists of a checkerboard pattern with black and white checks (constant mean luminance) which alternatively reverse colour (Celesia and Peachey, 2005; Odom et al., 2004). The important characteristics of the stimuli are the check size, the total field size, the stimulus luminance, the contrast level, the reversal frequency and the number of reversals (Odom et al., 2004). In particular, the VEP waveform depends on the reversal frequency of the stimulus; high reversal frequencies elicit steady-state visual evoked potentials (SSVEPs) while low frequencies elicit transient visual evoked potentials (TVEPs) (Odom et al., 2009). The waveform of the SSVEPs has rapid changes and looks like a sinusoid, while the waveform of the TVEPs has a number of distinct deflections (Celesia and Peachey, 2005; Odom et al., 2009). The term VEP or pattern reversal visual evoked potential (PRVEP) refers to the TVEPs typically elicited with the colour reversals of a checkerboard (Odom et al., 2009).

In general, components of event-related potentials can be separated into two sets: exogenous components that are related to the physical character of a stimulus, and endogenous components that are related to the information content of a stimulus (Sutton et al., 1965; Sutton et al., 1967).

A PRVEP has two main components: P1 and N2. The P1 component is a positive peak at about 100 ms post-stimulus. It is largest at lateral occipital electrode sites with an onset of 60-90 ms and a peak at approximately 90-120 ms post-stimulus. It is sensitive to stimulus parameters such the check size, which variation results in changes in latency and amplitude of the P1 (Kurita-Tashima et al., 1991). The P1 component of the PRVEP is an exogenous component and its amplitude and latency changes with properties of the physical characteristics of the stimuli, such as stimulus luminance, contrast, size of the total field and the check size (Celesia and Peachey, 2005).

The N2 is a negative deflection at about 200 ms after stimulus presentation. It has been claimed that N2 consists of several subcomponents, the earliest one peaks at 100-150 ms post-stimulus at posterior parietal cortex, while the other components peak at 150-200 ms post-stimulus at occipital cortex (Di Russo et al., 2005). Like P1, the amplitude and latency of the N2 can vary when the stimulus parameters are changed. Figure 1.5 illustrates an example of an average VEP elicited by the checkerboard pattern (stimulus duration: 1 s). In this figure the P1 and the N2 responses are marked after the stimulus onset.

VEPs can be used clinically for the identification of a dysfunction along the visual pathway. For example, in 1972 Halliday showed that a delay or an absence of VEPs in response to the pattern reversal stimuli can be used for the detection of optic nerve pathologies such as inflammation of the optic nerve (optic neuritis) (Halliday et al., 1973). Moreover a delay or an absence of VEPs in a patient with evidence of central nerve disorders is used as a hallmark for diagnosing multiple sclerosis (Celesia and Peachey, 2005; Mason, 2004).

1.3.2 Auditory evoked potentials

Brain electrical responses to auditory stimuli can be recorded by presenting click or tone stimuli. Based on their latencies, they are subdivided into three groups: early, middle and late latency AEPs (Davis, 1976; Regan, 1989). Early waves are elicited between 1 and 12 ms following an auditory stimulus, which reflects responses from the brain stem and are called brain stem auditory evoked potentials (BSAEP) (Jewett and Williston, 1971).



Figure 1.5 Major components of average VEP and AEP. For VEP the first positive peak around 100 ms post-stimulus the P1 and the negative component around 200 ms N2 and for AEP the first negative deflection around 100 ms is N1 and the positive peak around 200 ms is P2.

BSAEPs are mainly used for testing the integrity of the auditory pathway especially for infants and uncooperative adults (Mason, 2004; Celesia and Brigell, 2005). Moreover BSAEPs are used during surgery to monitor the function of auditory pathway (Celesia and Brigell, 2005).

Middle waves are evoked between 12 and 50 ms after stimulus onset; this type of evoked potentials is commonly used for testing hearing threshold in infants and children and for identification of malfunction in central auditory pathway (Celesia and Brigell, 2005).

The longer latency waves of the human auditory evoked potentials are elicited 50 ms after stimulus presentation (Celesia and Brigell, 2005). The term auditory evoked potential (AEP) is mostly related to this type of auditory response. AEPs have two main components, the N1 and the P2 which have the highest amplitudes in vertex locations. The N1 arises from different sources in temporal and frontal cortex (Burkard et al., 2006) and has three subcomponents. The earliest one peaks around 75 ms after the stimulus presentation. This component is maximum over frontocentral regions and originates from the auditory cortex (Luck, 2005). The second one peaks at about 100 ms post-stimulus and it is maximum in vertex. The origin of this component is unknown (Luck, 2005). The third one peaks around 150 ms and it has a lateral distribution. This subcomponent originates in the superior temporal gyrus (Luck, 2005). Like the early components of VEPs (P1 and N2) the N1 is exogenous (stimulus-related) and its latency and amplitude change based on the characteristics of the external stimulus (Luck, 2005).

The following positive peak, P2, has a latency of 120-200 ms. It has been suggested to originate from the frontal association cortex and/or auditory association cortex and it is maximum over frontocentral regions (Picton et al., 1974). Like the N1 component, the P2 is an exogenous component.

Although abnormal late latency AEPs were reported in different cases of psychopathologies, these potentials haven't been used in clinical diagnosis because of a large inter and intra-subject variability (Celesia and Brigell, 2005). Figure 1.5 illustrates an example of an AEP elicited by 1000 Hz tones (stimulus duration: 100 ms). In this figure the N1 and the P2 fluctuations are marked after the presentation onset.

1.3.3 Somatosensory evoked potentials (SEPs)

Somatosensory evoked potentials (SEP) are extracted by applying electrical pulses to peripheral nerves such as the median nerve and are recorded from the patient's scalp (somatosensory cortex). The first cortical components of SEP are evoked between 20 to 100 ms post-stimulus followed

by a N1 and a P2 component, evoked about 150 and 200 ms post-stimulus (Luck, 2005; Nuwer, 1998). This type of sensory evoked potential is mainly used for the diagnosis of abnormalities in the somatosensory pathway, such as multiple sclerosis. It is also used for monitoring spinal cord during surgeries, such as scoliosis surgery (Nuwer, 1998; Mauguiere, 2005).

1.3.4 ERPs in cognitive neuroscience

ERPs are also widely used in neuroscience research, given that the amplitude, latency and localisation of different peaks or oscillatory patterns have been correlated to a large variety of sensory and cognitive functions (Feng et al., 2012; Hillyard and Anllo-Vento L., 1998; Jongsma et al., 2005; Jongsma et al., 2012; Polich, 2007; Quian Quiroga et al., 2007; Romero and Polich, 1996; Sambeth et al., 2004a; Sambeth et al., 2004b). Compared to single neuron studies, the gold standard in neuroscience, ERPs and EEGs in general, give only an indirect and noisy measure of the neuronal activity as they are recorded from scalp. The large advantage of ERPs, however, is that, unlike single-cell recordings which are rarely performed in humans (Quian Quiroga et al., 2005; Quian Quiroga et al., 2008a), their recording involves a non-invasive procedure with a relatively simple setup, and therefore, they continue to be one of the preferred tools for studying sensory and cognitive processes in human subjects.

1.4 Oddball paradigm

The oddball paradigm is a sequence of pseudo-randomly intermixed nontarget and target stimuli presented to the subject. The non-target (or standard) stimuli appear more frequently and the target ones appear less often and

unexpectedly. The subject is asked to respond to the target stimuli by pressing a button whenever the target stimulus appears, or by counting the number of target appearances in a session (Duncan-Johnson and Donchin, 1977; Duncan-Johnson and Donchin, 1982; Squires et al., 1975). Target and non-target stimuli in an oddball paradigm can be tones with different frequencies, for AEPs, or figures with different shape or colour, for VEPs (Freeman and Quian Quiroga, 2013). An example of non-target and target VEPs elicited by a checkerboard pattern reversal oddball paradigm is shown in Figure 1.6 and Figure 1.7 respectively. Note the positive deflection around 100 ms and the negative deflection around 200 ms post-stimulus visible in parietal and occipital regions with both target and non-target responses. These relatively shorter latency VEP components are task irrelevant components, meaning that irrespective of whether a target or a non-target stimulus is presented; these responses will be observed (Freeman and Quian Quiroga, 2013). These components are sensory related and have their highest amplitude in the primary visual area. The longer latency positive fluctuation upon target stimuli, the so called P3, is elicited in response to the rare and unexpected stimulus (Sutton et al., 1965). It has been shown that the amplitude of the P3 response depends on the probability of target occurrence; the more improbable the target the larger the P3 elicited by the stimulus (Tueting et al., 1971).

1.4.1 P3 and cognition

P3 is a long latency event-related potential with the largest amplitude at the parietal, central and frontal locations (Hillyard et al., 1976; Vaughan and Ritter, 1970). It is a positive wave occurring 250 to 500 ms (the latency can vary

depending on stimulus modality, task conditions and subject age, etc.) poststimulus (Polich, 2007). Many studies have linked the P3 component to processes involving cognition, attention and memory (Polich, 2007; Donchin, 1978; Karis et al., 1984). P3a and P3b are two distinguishable ERP components in the time range of the P3 which are elicited by unpredictable, infrequent changes in the presented stimuli. However, P3b is only present when the subject attends to the stimuli by either counting the target stimuli or by pressing a key in response to the target appearances (Squires et al., 1975). P3a has its maximum amplitude in the frontal site and it is related to the engagement of attention (Polich, 2007). However P3b is maximal in parietal sites and is associated with the engagement of attention when followed by memory processing (e.g. counting the number of target stimuli) (Polich, 2007).

The latency of the P3 component is directly related to the latency of decision processes and is measured by behavioural reaction times. However its amplitude depends on the probability of the target stimuli and it is also sensitive to the subject's certainty in decision making. The P3 amplitude is larger if the subject devotes more attention and effort to the task while it is smaller when the subject is uncertain in his/her decision of whether the presented stimulus is the target or the non-target (Tueting et al., 1971). Researchers almost always use P3 or P300 to refer to P3b (Luck, 2005).



Figure 1.6 Responses to non-target VEPs at different scalp locations. Note a positive fluctuation around 100 ms (the P1) and a negative deflection around 200 ms (the N2) after the stimulus onset (zero) which varies across the scalp locations and have their highest amplitude in the occipital region. Vertical line indicates the stimulus onset.



Figure 1.7 Responses to target VEP. Note that besides the early components of the VEP, P1 and N2, there is a large positive peak between 400 to 600 ms corresponding to target responses. Vertical line indicates the stimulus onset.

1.5 Neural basis of ERP generation

Although ERPs are one of the most frequently used techniques to obtain brain neural responses to sensory and cognitive processes, there is a large debate about the basis of ERP generation. There are three hypotheses in this regard: the first one states that ERPs arise from fixed-latency and fixed-polarity neural responses adding to the background EEG (Hillyard, 1985; Jervis et al., 1983; Schroeder et al., 1995). The second one sees ERPs as a reorganization of the on-going EEG upon the stimulus presentation (Başar, 1999; Jansen et al., 2003; Makeig et al., 2002; Sayers et al., 1974). The third one states that both above hypotheses partially contribute to generate ERPs (Fell et al., 2004; Fuentemilla et al., 2005; Min et al., 2007).

1.6 Organisation of the thesis

This thesis is organised as follows:

Chapter one gives a brief introduction of EEG and ERP signals and recordings. Chapter two describes the mathematical background of wavelet transform and wavelet denoising.

Chapter three describes the implementation of the denoising ERPs together with the discussion of automatic single-trial ERPs denoising.

Chapters four and five describe the applications of the proposed NZT denoising method in the study of the mechanisms of conscious face perception and the study of the basis of ERP generations.

Chapter six includes the final discussion and conclusion of the thesis.

Chapter 2

2 Wavelet transform

2.1 Background and history

The Fourier transform is one of the most common data processing tools used in the field of signal and image processing. It provides a frequency decomposition of the signal. The Fourier transform represents a signal as a superposition of complex sinusoids of varying frequencies and phases, and the Fourier coefficients of the transformed signal represent the activity at each frequency. The Fourier transform assumes that the signal is stationary (the signal spectrum is not time dependent) however, many real world signals have time-varying features so having time dependent spectra.

The short time Fourier transform (STFT) or windowed Fourier transform is a modification of the Fourier transform for analysing non-stationary signals. It overcomes the Fourier transform's drawback by analysing the signal in pieces using a window function such as Gaussian, and applying the Fourier transform to each piece. In the other words, the STFT multiplies the signal by a window function calculating the Fourier transform as the window is sliding along the time axis. Although the STFT provides information about the time evolution of the different frequencies, it uses a fixed window length. In this regard, the choice of window length is crucial, since short windows lead to good time resolution but poor frequency resolution, while long windows lead to good frequency resolution and poor time resolution (Mallat, 1999). In general, low frequency patterns have a longer duration compared to high frequency patterns. For instance, comparing the P3 component of Figure 1.7 in the O1 electrode site with the P1 component, the P3 has a lower frequency (less that 4 Hz) and spans in a wider time range (about 200 ms) while the P1 has a higher frequency

(about 10 Hz) and spans in a shorter time range (about 30 ms); therefore, it is difficult to find a window length that gives good compromise between time and frequency resolution and that is suitable for both frequencies.

In the late 1970s, Jean Morlet, a geophysical engineer who was analysing seismic data having low frequency components with a long time span and high frequency components with a short time span, came up with the idea of using different window lengths by scaling the original window for the analysis of different frequency bands. In 1980 with the help of A. Grossman, the wavelet transform (WT) and the inverse wavelet transform (IWT) were developed (Graps, 1995; Mallat, 1999). In later years, Mallat developed the idea of multiresolution decomposition to calculate the wavelet transform using a series of low pass and high pass filters.

2.2 Uncertainty principle

The STFT uses a single window with a fixed time interval to analyse all frequencies while, the WT uses long time intervals for analysing low frequencies (high scales) and shorter intervals for high frequencies (low scales). Using long time intervals, increases frequency resolution at the cost of time resolution. On the contrary, using shorter time intervals, increases time resolution at the cost of frequency resolution. There is always a trade-off between time and frequency resolution. Analogous to Heisenberg's uncertainty principle in quantum mechanics, which states that there is a limit to the precision of obtaining position and velocity of a particle at the same time, it is not possible to have arbitrary high resolutions in time and frequency simultaneously (Mallat, 1999).

Considering σ_t as the time uncertainty and σ_w as the frequency uncertainty, the uncertainty principle can be mathematically expressed as:

$$\sigma_t \sigma_w \ge \frac{1}{2} \tag{2.1}$$

The time-frequency localisations of the window function in the STFT and in the WT are represented as Heisenberg boxes, located in the time-frequency plane. The Heisenberg time-frequency boxes for the STFT and the WT are shown in Figure 2.1. It is clear from the figure that the location and the width of the Heisenberg boxes for the WT are variable while they are fixed for the STFT. Thus with the WT it is possible to extract fine details of the signal in the higher frequency scales and coarser details of the signal in the lower frequency scales. Therefore, the WT is a very good candidate to analyse signals having a wide range of frequencies as in the case of EEG signals. For instance, in the case of analysing the PRVEP, the P1 and the N2 with higher frequency scales and the P3 component with lower frequency and wider time span can be analysed in a lower frequency scale.

2.3 Continuous wavelet transform

The continuous wavelet transform (CWT) is formalised as the inner product of a given signal with dilated and translated versions of a wavelet basis function. For a given signal s(t) and a wavelet function $\Psi_{a,b}(t)$ the wavelet transform is defined as:



Figure 2.1 Time-frequency boxes of STFT and WT.

$$S(a,b) = \left\langle s, \psi_{a,b} \right\rangle = \int s(t) \,\psi_{a,b}^*(t) dt \tag{2.2}$$

with

$$\psi_{a,b} = |a|^{\frac{-1}{2}} \psi(\frac{t-b}{a})$$
 (2.3)

Where * denotes complex conjugation, $\psi(t)$ is the mother wavelet or basis function and $a > 0, b \in \mathcal{R}$ are the scale and translation parameters respectively. The translation parameter, b, changes the time localization of the wavelet function while the scaling parameter, a, dilates or compresses the wavelet function (Figure 2.2). The factor $|a|^{\frac{-1}{2}}$ is a normalizing factor (Grossmann and Morlet, 1984). Equation (2.2) can be inverted to reconstruct the original signal s(t).

$$s(t) = \int_{0}^{\infty} \int_{-\infty}^{+\infty} \frac{1}{a^2} S(a,b) \tilde{\psi}_{a,b}(t) \, da \, db$$
(2.4)

where $\tilde{\psi}_{a,b}(t)$ is the dual function of $\psi_{a,b}(t)$.

Continuous Wavelet Transform (CWT)



Figure 2.2 Continuous wavelet transform (CWT). The scaling parameter either stretches or compresses the mother wavelet in each scale. The signal is then filtered at each scale by shifting the wavelet function in time and convolving it with the original signal.

2.4 Discrete wavelet transform

The Discrete wavelet transform (DWT) is obtained by discretising the translation and the scale parameters. One way to do this is by choosing a and

b using a dyadic scale:

$$a_j = 2^j \quad b_{j,k} = 2^j k \quad j,k \in \mathbb{Z}$$
 (2.5)

which gives the dyadic wavelet family $\Psi_{j,k}(t)$:

$$\psi_{j,k}(t) = 2^{-j/2} \psi \ (2^{-j} t - k) \tag{2.6}$$

that forms a basis of the Hilbert space L^2 . The DWT is then defined as the inner product of the signal and the dyadic wavelets of equation (2.6).

2.5 Multiresolution approximation and filter banks

Multiresolution approximation computes an approximation of a given signal at different scales of resolutions. Let us assume that V_j is a subspace of multiresolution approximations of a function $s(t) \in L^2$, in which for:

$$\forall (j,k) \in \mathbb{Z}, \qquad s(t) \in V_j \iff s(t-2^j k) \in V_j$$
(2.7)

$$\forall j \in \mathbb{Z}, \qquad V_j \subset V_{j-1} \tag{2.8}$$

The piece of s(t) in subspace V_j is called $s_j(t)$, and the one in the coarser subspace V_{j-1} is called $s_{j-1}(t)$ and their difference can be obtained as:

$$\Delta s_{j}(t) = s_{j-1}(t) - s_{j}(t)$$
(2.9)

which is the detail at level j. Rewriting (2.9):

$$s_{j-1}(t) = s_j(t) + \Delta s_j(t)$$
 (2.10)

and from the viewpoint of subspaces:

$$V_{j-1} = W_j \oplus V_j \tag{2.11}$$

where \oplus denotes the summation of the subspaces. W_i , the difference between

 $V_{\rm j-1}$ and $V_{\rm j}$, is called the wavelet space. By induction:

$$V_{j} = W_{j+1} \oplus W_{j+2} \oplus \cdots$$
(2.12)

and expanding (2.12):

$$V_{j-1} = \sum_{j \in \mathbb{Z}} W_j$$
 or $V_{j-1} = V_J + \sum_{j=j}^J W_j$ (2.13)

where J > 0 is the coarser scale.

Now let us assume that there is a unique basis for each subspace. The V_j has the basis $\phi (2^j t - k)$, the so called scaling function, and W_j has the basis $\psi (2^j t - k)$, the so called wavelet function. Then, we can obtain the approximation of the function s(t) in the scale j-1 using the scaling and wavelet functions as:

$$s_{j-1}(t) = \sum_{k} s_{j}(t) \phi(2^{-J}t - k) + \sum_{j=1}^{J} \sum_{k} C_{j}(k) \psi_{j,k}(t)$$
(2.14)

where

 $\Delta s_j(t) = \sum_k C_j(k) \psi_{j,k}(t)$ is the detail in scale j and $s_j(t)$ is the approximation of the signal in the scale J. $C_j(k)$ are the wavelet coefficients and can be interpreted as the difference between the successive signal approximations at scales j and j-1.

Mallat showed that for discrete time series, the multiresolution decomposition can also be accomplished by applying filter banks (Mallat, 1999; Strang and Nguyen, 1996). Figure 2.3 shows the two-channel filter bank proposed by Mallat. In the decomposition part of this filter bank, by applying high pass and low pass filters, g and h, the signal splits into two new signals, one with the upper half frequency components and one with the lower half frequency components. This decomposition scheme results in twice as many samples as in the original data. To avoid redundancy, both signals are decimated by a factor of two, which means one of every two samples is removed (down sampling), thus giving the first scale (level) detail D_1 and the first scale approximation A_1 respectively. The decomposition can be iterated
by successively decomposing the approximations in each level, so each level contains a lower resolution of the signal. For a J level decomposition, the signal is decomposed into the D_1 to D_J details and the last approximation A_J . After the decomposition, the number of data points of the last approximation plus all data points of the J levels details is equal to the number of data points of the original signal, thus avoiding redundancy.

In the reconstruction part, a similar procedure is done to reconstruct the original signal. In each level, signals are up sampled (inserting zeros between samples) and then filtered using the reverse filters rg and rh (Mallat, 1999; Mallat, 1989). Figure 2.4 shows an example of the multiresolution decomposition and reconstruction of an average ERP signal. In this figure the upper plot shows the average ERP and the lower left plot illustrates a 5 scales wavelet decomposition. The five scales details are denoted D_1 to D_J and A_J , refers to the final approximation (bottom left). In each scale, the coefficients show how closely the signal matches the wavelet function at that scale. The signal can be then reconstructed in each scale, using the inverse wavelet transform (bottom right).



Figure 2.3 Multiresolution decomposition and reconstruction. h and g are decomposition low and high pass filters, respectively. rh and rg are the reconstruction low and high pass filters respectively. Downward and upward arrows indicate down-sampling and up-sampling respectively.



Figure 2.4 ERP Multiresolution decomposition and reconstruction. Five scales decomposition (bottom left) of an average ERP (top). D_1 to D_5 are the decomposition details and A_5 is the last approximation (the lowest frequency band of the signal). In each scale, the coefficients show how closely the signal matches the wavelet function at that scale. In each scale the signal can be reconstructed using the inverse wavelet transform (bottom right).

2.6 Wavelet Families

The wavelet decomposition of a signal depends on the characteristics of the chosen mother wavelet. One can choose a specific mother wavelet based on the application at hand: Figure 2.5 illustrates four commonly used mother wavelets. The first one is the Haar wavelet. It is orthogonal (its inner product with a Harr wavelet at a different time and scale is zero) and anti-symmetric. It has compact support (has a finite duration in time) and can be used both for the CWT and the DWT. The second one is a Daubechies wavelet. Daubechies wavelets are non-symmetric, orthonormal, smooth and have compact support. Like Haar wavelets they can be used both for the CWT and the DWT (Daubechies, 1992). The third one is a B-Spline wavelet. B-Spline wavelets are anti-symmetric, smooth, not orthogonal and have compact support. They are suitable for both CWT and DWT (Unser, 1997). The last example is the Morlet wavelet. This wavelet is complex (it has a real and an imaginary part), thus providing a complex value that can be used to define an instantaneous phase (Freeman and Quian Quiroga, 2013). Morlet wavelets are symmetric and smooth, but they are not orthogonal and they do not have compact support. Morlet wavelets can only be used with CWT.

Along with the mathematical properties that make a wavelet function suitable for data processing, it is advisable the wavelet function to be used is similar to the patterns of interest in the analysed signal. In this thesis, Quadratic B-Spline wavelet functions were selected for analysing ERPs (Cohen et al., 1992; Quian Quiroga and Garcia, 2003). The B-Spline decomposition and reconstruction filters used in this study are shown in Figure 2.6 along with the filter coefficients listed in Figure 2.7.



Figure 2.5 Wavelet functions. Harr, Daubechies, B-Spline and Morlet (real part) wavelet functions. The wavelet functions were generated using the Matlab function "wavefun".



Figure 2.6 B-Spline (3.15) wavelet filters. h, g are the decomposition low pass and high pass filters while rh and rg are the reconstruction filters respectively.

h	g	rh	rg
0			0
0			0
-0.0001			-0.0001
0.0004			-0.0004
0.0007			0.0007
-0.0031			0.0031
-0.0021			-0.0021
0.0148			-0.0148
0.0031			0.0031
-0.0515			0.0515
0.0031			0.0031
0.1422			-0.1422
-0.0276			-0.0276
-0.3468	-0.176	0.1768	0.3468
0.0469	0.5303	0.5303	0.0469
0.9272	-0.5303	0.5303	-0.9272
0.9272	0.1768	0.1768	0.9272
0.0469			-0.0469
-0.3468			-0.3468
-0.0276			0.0276
0.1422			0.1422
0.0031			-0.0031
-0.0515			-0.0515
0.0031			-0.0031
0.0148			0.0148
-0.0021			0.0021
-0.0031			-0.0031
0.0007			-0.0007
0.0004			0.0004
-0.0001			0.0001
0			0
0			0

Figure 2.7 B-Spline (3.15) filter coefficients. h and g are the decomposition low pass filters while rh and rg are the reconstruction filters respectively.

The nearly optimal time-frequency resolution of B-Spline wavelets along with their shape, which is similar to the evoked responses, makes them a good candidate for wavelet analysis of the ERP signals (Freeman and Quian Quiroga, 2013; Unser et al., 1992; Unser, 1999)

2.7 Wavelet Denoising

If the chosen wavelet function has a shape similar to the patterns of interest in the analysed signal, the number of coefficients correlated with the signal of interest will be small (the decomposition will have a good time-frequency localization), thus the signal can be reconstructed accurately using those coefficients (Strang and Nguyen, 1996). Hence, one could formulate the wavelet denoising problem as recovering the significant coefficients in each scale of the decomposition. Such coefficients could be selected by thresholding (Donoho, 1995). The denoising technique can be summarised as follows:

- Decompose a noisy signal with the discrete wavelet transform to obtain the noisy wavelet coefficients.
- 2. Choose a threshold value T for each level of decomposition, and do hard or soft thresholding.

$$y_{hard}(t) = f(s) = \begin{cases} s(t), & |s(t)| > T \\ 0, & |s(t)| \le T \end{cases}$$
(2.15)

$$y_{soft}(t) = f(s) = \begin{cases} sign(s(t))(|s(t)| - T), & |s(t)| > T \\ 0, & |s(t)| \le T \end{cases}$$
(2.16)

 Reconstruct the signal from the new coefficients using the inverse wavelet transform.

One should calculate the threshold value for each scale of the decomposition (Donoho, 1993; Donoho and Johnstone, 1994; Johnstone and Silverman, 1997). In the case of hard thresholding, coefficients with the absolute value above the threshold should be kept and those less than the threshold should be set to zero, while with soft thresholding coefficients less than the threshold should be set to zero and those above the threshold should

be pulled towards zero by a factor which is proportional to the difference with the threshold (Donoho, 1995). The denoised signal is then obtained by a wavelet reconstruction using the denoised coefficients (Donoho 1995; Donoho 1992). Figure 2.8 shows an example of the hard and soft thresholding of an average VEP. In this example we set the threshold to 1, thus both thresholding techniques removed the values between -1 and 1. However the rest of the values were kept unchanged with the hard thresholding but they were pulled towards zero with the soft thresholding. As it is shown, the soft thresholding changes the amplitude of the ERP components, so in this thesis we used hard thresholding to avoid amplitude changes in ERP peaks



Figure 2.8 Hard and soft Thresholding. The threshold was set to 1. Note that, although soft thresholding is more effective in removing the baseline noise, it reduces the amplitude of the original ERP and smoothes the signal.

Chapter 3

3 Automatic denoising of single-trial event-related Potentials

3.1 Background

ERPs have a very small amplitude compared to the on-going EEG in which they are embedded. By far the most popular technique to enhance the observation of ERPs is by averaging several repetitions of the stimulus (Dawson, 1954; Lopes da Silva, 2005b). However, the drawback of ensemble averaging is that critical information about trial-by-trial changes of the evoked responses is lost. In particular, the conventional approach in the design of an ERP paradigm is to try to avoid these single-trial fluctuations in order to get better average responses. But there are many interesting questions that are in fact related to systematic or unsystematic trial-by-trial variations, such as those related to the study of learning processes (Quian Quiroga et al., 2007). Thus the need to develop algorithms to filter the background EEG activity in order to observe the single-trial evoked responses. For this, the use of Wiener filtering was suggested (Walter, 1968). Wiener filtering minimizes the mean square estimation error of average evoked potentials and could in principle be used to denoise single-trials. However, it is a time-invariant method -i.e. it assumes stationary of the signal- and it does not give optimal results when applied to time-varying transient signals such as ERPs (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000). For the same reason, other standard digital filters are not suitable for the analysis of single-trial ERPs, given that ERPs are a series of waves appearing at different times and with different frequency compositions. To deal with the non-stationary issue, De Weerd and co-workers proposed a time-varying Wiener filter, which, however, couldn't provide a good reconstruction of the signal (De Weerd, 1981; De Weerd and Kap, 1981).

Another set of algorithms to filter the single-trial ERPs use wavelets. The wavelet transform has been used in the analysis of ERPs since the early 1990's (Bartnik et al., 1992; Hanrahan, 1990; Quian Quiroga et al., 2001; Thakor et al., 1993). In particular, Bartnik and co-workers (Bartnik et al., 1992) proposed to use an algorithm based on a wavelet decomposition to extract single-trial auditory evoked potentials from the on-going EEG. This algorithm was unsupervised, but it led to large errors in the estimation of the single-trial ERPs. Following this approach, an ad-hoc wavelet denoising technique was proposed for the identification of the single-trial responses (Quian Quiroga, 2000). Given that ERPs have specific time and frequency localizations, after wavelet decomposition, the idea is to reconstruct the signal using only those coefficients related to the evoked responses (deleting the ones related to the on-going EEG). An analysis with synthetic ERP data showed that this ad-hoc implementation improved the signal to noise ratio of the single-trial responses, as well as the estimation of their latencies and amplitudes (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000). But the main caveat of this method is that it requires a manual selection of the stimulus-related coefficients, using prior knowledge of the time and frequency ranges of the ERPs. This makes the denoising procedure subjective, time consuming and not practical for the analysis of large number of channels (given that the selection of wavelet coefficients is not necessarily the same for the different channels). To overcome problems, in this study we propose an automatic denoising these implementation to visualize the single-trial evoked responses. The method is based on the wavelet transform and it introduces an automatic selection of wavelet coefficients based on the inter- and intra-scale correlation of

neighbouring wavelet coefficients, and how their values deviate from baseline. We show its performance with synthetic ERP data, as well as with real visual and auditory ERPs.

3.2 Materials and methods

3.2.1 Real data recording

Recordings were performed in an electrically shielded chamber in 25 voluntary healthy subjects (18-30 years old). Subjects were seated comfortably in a chair and were asked to remain still and relax while they did a visual and an auditory oddball paradigm (see below). The EEG data was recorded continuously using 64 electrodes placed according to the international 10-20 system, band pass filtered between 0.1Hz and 250Hz and sampled at 512 Hz, using an average reference, Figure 3.1. After the recording, the EEG signals were re-referenced to the average of the left and right mastoids and trials that were contaminated with eye blinks, eye movements and other artefacts were removed manually from each data set. For each trial, one second pre- and one second post-stimulation were stored for further analysis.

3.2.1.1 Visual oddball paradigm

As in previous studies (Quian Quiroga and Schürmann, 1999), pattern visual event-related potentials (PVEPs) were obtained with a checkerboard pattern (side length of checks: 50' visual angle). A sequence with two different stimuli was presented pseudo randomly (N=250 stimuli): the frequent or non-target stimuli were a colour reversal of checks (80% of the stimuli), while the less frequent or target stimuli were colour reversals with a half check



Figure 3.1 EEG recording in the NeuroEngineering Lab

displacement (both horizontal and vertical) of the pattern (20% of the stimuli). Subjects were asked to ignore the non-target stimuli and press a key whenever they saw the target ones. Each pattern reversal was shown for 1 s and the inter stimulus interval varied pseudo-randomly between 2 to 2.2 s. No two target stimuli appeared in succession. Subjects were asked to fixate on a small red circle in the centre of the screen during the recording (Quian Quiroga and Schürmann, 1999; Schürmann et al., 1995).

3.2.1.2 Auditory oddball paradigm

Auditory event-related potentials (AEPs) were obtained with an oddball paradigm, using a sequence with two different tones: non-target stimuli (80%) had a frequency 2000 Hz and target stimuli (20%) a frequency 1000 Hz (Goodin et al., 1978). Subjects were instructed to press a key whenever they heard the target tone and ignore the non-target ones. Each stimulus was presented for 100 ms, the inter stimulus interval varied pseudo randomly between 1.5 and 1.7

s and the reverted pattern lasted for 100 ms. As with the VEP, subjects were asked to gaze on a small red circle in the centre of the screen during the recording to avoid eye movements.

3.2.2 Synthetic data

To evaluate the performance of the proposed algorithm, as in previous works (Quian Quiroga and Garcia, 2003), the typical ERP components obtained with a visual oddball, the P1, N2 and P3, were simulated using three Gaussian functions added to background EEG activity (Figure 3.2). Random fluctuations in the latency of the simulated components were introduced in order to resemble the latency variability across single-trials (ranges, P1: 90-125 ms, N2: 120-155 ms and P3: 400-700 ms). The background EEG activity was taken from the recording of one subject with eyes open fixating on a red circle in the centre of the screen. Thirty single-trials of the noisy ERPs, 2 s each, were generated with different signal to noise ratios (SNR). The SNR was defined as the ratio between the standard deviation of the simulated ERPs and the one of the background EEG activity. Figure 3.2(a) shows the average simulated visual ERP with SNR=1. As with real data (see Figure 3.7(a)), it has a positive peak at about 100 ms post-stimulus, the P1, a negative deflection about 200 ms poststimulus, the N2, and a positive peak at about 400-500 ms after stimulus presentation, the P3 (Quian Quiroga and Schürmann, 1999).



Figure 3.2 Simulated ERP. (a) Average simulated ERPs, with (grey) and without (black) the background "noisy" EEG activity for SNR=1. (b) First 5 out of 30 simulated single-trials.

The performance of the algorithm was quantified by the root mean square error (RMS) of the denoised single-trial ERPs – i.e. the difference between the denoised signal and the simulated ERPs without background EEG – and was compared to the performance obtained with the simulated noisy ERPs – i.e. the difference between the simulated noisy ERPs and the simulated ERPs without noise – and the one obtained using a standard denoising implementation (Donoho, 1993) (see next section). Moreover, given that the most important information to be extracted from a single-trial ERP analysis is typically the amplitude and latency of the single-trial responses, we also quantified the error in the estimation of the single-trial amplitudes and latencies of the ERPs. For this, for each peak in each single-trial, a time window around each component was chosen (P1: 55-155 ms, N2: 95-170 ms, P3: 300-700 ms) and the maximum (or minimum) peak in the corresponding window was identified. The error for each single-trial amplitude (latency) was defined as: $e = \langle |\hat{x}_i - x_i| \rangle_i$, where x_i is the actual and \hat{x}_i is the estimated amplitude (latency) of the simulated ERP component. For each SNR, the statistical difference between the different methods was assessed with pairwise t-tests.

3.3 Wavelet denoising

In this study we used a 5-scale decomposition of the ERPs, obtaining the detail levels D_1 to D_5 and a final approximation A_5 . The lower scales provide information of the high frequency components, while the high scales and the final approximation give the information about the low frequency ones (Figure 3.4).

As in previous works (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000), we used a quadratic B-Spline mother wavelet. B-Splines are very suitable for the analysis of ERPs as they have a similar shape to the ERP waveforms, thus providing an optimal time-frequency resolution – i.e. the evoked responses are localized in a few wavelet coefficients (Quian Quiroga, 2000; Quian Quiroga et al., 2001), thus facilitating the denoising procedure.

3.3.1 Donoho's denoising implementation

The ERP signals contain a mixture of on-going EEG background activity and evoked potentials. For the purpose of denoising the data, we considered the former as the noise to be removed and the latter as the signal of interest to be extracted. Using the wavelet formalism, Donoho and Johnstone proposed a denoising implementation where, for each scale, the wavelet coefficients are selected by thresholding (Donoho, 1993; Johnstone and Silverman, 1997). Following this approach, for each scale j a threshold T_j is calculated as:

$$T_{i} = \sigma_{i} \sqrt{2\log_{e} N} \tag{3.1}$$

Where N is the number of wavelet coefficients and σ_j is an estimation of the standard deviation of the noise for each scale:

$$\sigma_{j} = Median \left\{ \left| S_{j,1} - \overline{S}_{j} \right|, \left| S_{j,2} - \overline{S}_{j} \right|, \dots, \left| S_{j,k} - \overline{S}_{j} \right| \right\} / 0.6745$$
(3.2)

The normalizing factor 0.6745 is introduced to give a value of 1 for a Gaussian signal with unitary standard deviation (Johnstone and Silverman, 1997). Denoising is done by hard thresholding the coefficients of each scale as follows:

$$S_{den}(j,k) = \begin{cases} S(j,k) & \text{if } \left| S_{j,k} \right| > T_j \\ 0 & \text{if } \left| S_{j,k} \right| \le T_j \end{cases}$$
(3.3)

The denoised average ERP is then obtained by doing a wavelet reconstruction from the denoised coefficients. Then, this same set of coefficients can be used to denoise the single-trial data. The rationale of this procedure is that one in principle expects to find the single-trial evoked activity in the same time and frequency ranges of the average evoked responses. However, it should be noted that this does not necessarily need to be the case. For example, there could be some latency jitter in the single-trials that may lead to broader peaks (i.e. lower frequency composition) in the average responses.

3.3.2 Neighbouring and Zerotrees (NZT) denoising

Using Donoho's implementation we found that it is not always possible to separate the ERP from the background EEG (see Figure 3.4). The problem is that with Donoho's method each wavelet coefficient is considered individually, irrespective of the value of other neighbouring coefficients at the same or at the next scales, whereas the patterns of a signal are typically distributed across a set of nearby coefficients; in other words no pattern is localized at one and only one coefficient. It has been proposed that considering the value of nearby coefficients can improve denoising results (Cai and Silverman, 2001; Shapiro, 1993). Our proposed algorithm thus combines two such improvements: the first one is to decide whether each coefficient should be kept or not based not only on its value but also on the value of its closest neighbours in the same scale (Cai and Silverman, 2001); and the second one is to also use information from the decomposition at the higher scales, what is known as Zerotrees denoising (Shapiro, 1993).

3.3.2.1 Denoising using neighbour coefficients and level dependency

We implemented the method by Cai and Silverman (Cai and Silverman, 2001), which incorporates information of neighbouring coefficients in the thresholding process. With this denoising scheme, a coefficient is set to zero if the sum of the squares of the coefficient and its immediate neighbours in the same scale is less than a certain threshold. In particular, given the set of wavelet coefficients $S_{j,k}$, we apply the following thresholding criterion:

$$S_{den}(j,k) = \begin{cases} S(j,k) & \text{if} \quad S_{j,k-1}^2 + S_{j,k}^2 + S_{j,k+1}^2 > T_j^2 \\ 0 & \text{if} \quad S_{j,k-1}^2 + S_{j,k}^2 + S_{j,k+1}^2 \le T_j^2 \end{cases}$$
(3.4)

Following Cai and Silverman (Cai and Silverman, 2001) the threshold for each scale was defined as:

$$T_j^2 = \sigma_j^2 (2\log_e N),$$
 (3.5)

where σ_i was estimated as in equation (3.2).

3.3.2.2 Zerotrees denoising

As a second denoising step, we used the Zerotrees implementation proposed by Shapiro (Shapiro, 1993), which considers the dependency of the current coefficient to its "parent coefficient" in the higher scale. The basic idea of the method is that, except for the final approximation, if a wavelet coefficient is not significant (and should be deleted) with respect to a given threshold, most likely the coefficients in the same time location at the lower levels are also not significant and should be deleted as well. Coefficients of coarser scales are the "parents" and those of the finer scales at the same location are called the "children", so in the case of a 1D multi-resolution decomposition each parent has two children in the finer scale (except for the last detail, which has only 1 child per parent). Then, the basic idea of the zerotree denosing is that if a parent coefficient is removed, all its children should be removed as well. Figure 3.3 illustrates the parent-children dependency in the Zerotrees denoising algorithm. This figure shows a 5 level decomposition of an average VEP. Coefficients in the coarser scales are parents of the coefficients in finer scales. For instance the coefficients in the green circles are the parents of those in the red circles. The coefficient in the last approximation (A_5) has only one "child" in the last detail, D_5 , while the one in the D_5 has two "children" in the D_4 scale.



Figure 3.3 Parent-children dependency in the Zerotrees denoising algorithm. Coefficients of coarser scales are the "parents" (coefficients in the green ovals) of those coefficients in finer scales (coefficients in the red ovals). According to the DWT the number of coefficients in each coarser scale is equal to half of the number of coefficients in the previous finer scale, except for the last approximation (A_5) which has the same number of coefficients as in the last detail (D_5). Therefore each parent has two children in the next finer scale, except for the last approximation. Each parent in the last approximation (A_5) has only one child in the last detail (D_5). Note that based on the Zerotrees denoising algorithm, if the mother is not significant with respect to a given threshold and removed by the thresholding procedure, the children in the finer scales should be deleted as well.

3.3.3 Denoising of ERPs

Compared to the NZT denoising implementations described above, in our case we introduced two modifications for the analysis of ERP signals. First, for the estimation of the thresholds in equation (3.1) and equation (3.5) we used only baseline coefficients (i.e. before stimulus onset). Second, instead of the

total number of wavelet coefficients (N), in both equations we used the number of coefficients in each scale (K), which gave better results.

Figure 3.4 shows the 5 level decomposition of an average visual ERP, and its denoising using Donoho's and the NZT methods. With Donoho's method, each coefficient is considered independently, which, as shown in the figure, it doesn't give an optimal removal of the baseline or a reconstruction of the ERP responses. For example, the coefficients in level D_5 and A_5 highlighted in black correlate with the P1-N2 components, but they are relatively small and are deleted with Donoho's method, thus affecting the shape of these ERP responses. On the contrary, based on the values of neighbouring coefficients and its "parent", these coefficients are kept by the NZT method and the reconstruction of the average ERP looks more accurate. Analogously, the baseline coefficient in D_5 marked in blue is relatively large and it is not deleted by Donoho's method, thus introducing some baseline fluctuations. Given the value of its neighbours in the same scale and the value of its parent in level A_5 , this coefficient was deleted with the NZT method - hence improving the denoising outcome. The performance of these two methods is quantified and compared with synthetic data in the following sections.





Figure 3.4 Wavelet decomposition and denoising using Donoho's method and the NZT algorithm. Note that compared to the NZT, Donoho's method does not completely remove the baseline activity (e.g. the coefficient highlighted with a blue circle) and, it removes coefficients that are correlated with the ERP (e.g. the coefficients highlighted with a black circle). Note that with the NZT, the highlighted coefficient in the baseline is removed, because its parent in the last approximation is not selected by the thresholding criterion. However the highlighted coefficients in the black circles are selected since the combination of each of the coefficients and its neighbours is higher than the threshold. For both methods, the coefficients automatically chosen for denoising are shown in red.

3.3.4 Summary of the NZT algorithm

The automatic single-trial ERPs denoising method proposed here consists of the following steps:

- 1. Construct the average ERP.
- 2. Perform a wavelet decomposition of the average ERP.
- 3. Perform a hard thresholding of the wavelet coefficients using (3.4).
- 4. Apply Zerotrees to the denoised coefficients.
- 5. Reconstruct the denoised average ERP using the denoised coefficients.
- 6. Use the same set of coefficients for the single-trial ERPs.

3.4 Results

3.4.1 Simulated data

To quantify denoising performance, we applied the NZT method to the simulated ERPs and compared its results with those obtained with the standard denoising implementation by Donoho.

The root mean square (RMS) error of the simulated single-trials without denoising, denoised with the NZT method and with Donoho's implementation for different SNR values are depicted in Figure 3.5. For all SNRs both denoising methods significantly improve the single-trial ERPs estimation and except for SNR=0.5, the lowest RMS error is obtained with the NZT method.

The error e in the estimation of the amplitudes and latencies of the three ERP peaks are shown in Figure 3.6(a). Compared to the original signals, with NZT denoising we had a general improvement in the extraction of P1 amplitude and latency (except for the P1 latency with SNR=0.5). On the contrary, in most

cases Donoho's implementation gave errors that were larger than the ones obtained with the original signal. For all SNRs the estimation of the single-trial N2 amplitudes was significantly improved (P<0.05) with the NZT compared to the original data, while differences with Donoho's method were not significant. Both denoising methods improved the N2 latency estimation, except for SNR=0.5, where Donoho's method gave a much larger error than NZT and the original signal. Furthermore, both denoising methods significantly improved the estimation of the single-trial P3 amplitudes (P<0.001) compared to the original data. In general, NZT also gave the best estimation of the single-trial latency of the P3.

Figure 3.6(b) shows the mean percentage improvement in the estimation of the single-trial amplitudes and latencies with Donoho and NZT, averaging across ERP components and SNRs. With the NZT the improvement in the single-trial amplitude and latency estimations was significantly larger than zero (P<0.001, T-test).



Figure 3.5 RMS error. RMS error for the original (not-denoised) single-trials and denoised with Donoho's and the NZT method for different SNR values. Note that in all cases the NZT method gives the lowest RMS errors.

Compared to Donoho's method, NZT gave a better estimation of the amplitudes and latencies of the single-trial ERPs (and this difference was highly significant, with P<0.001 for the amplitude estimations).

Altogether, NZT denoising significantly improved the estimation of the amplitude and latency of the single-trial ERP components and gave a lower RMS error compared to the original (not denoised) signals. The performance of Donoho's method was in general poorer than the one with NZT. In fact, it was more variable and less reliable, as in many cases it introduced systematic errors (e.g. deleting relevant coefficients) that worsened the estimations obtained from the original data without any denoising.

3.4.2 Real data

Next we studied the application of the NZT method to the real VEP and AEP recordings. For the VEPs we studied the response in the occipital (O1) electrode and for the AEPs the central (Cz) electrode. We chose these two sites because they are located close to the primary visual and auditory cortical sensory areas, respectively. For the visual ERPs, (Figure 3.7 (a)) the P1, N2 and P3 are clearly recognizable in the average signal and the NZT denoising removed most of the background EEG activity. The wavelet coefficients selected by the NZT denoising algorithm are shown in Figure 3.7(b) in red. Note that the P1-N2 components are mainly correlated with the coefficients at around 100 ms after stimulation in the scales $D_2 - D_5$. The NZT method also kept the coefficients in level A_5 , which are correlated with the P3.

RMS error of the ERP components



Figure 3.6 Error in the estimation of ERP components. (a) Error in the estimation of the single-trial amplitudes and latencies for the 3 ERP peaks, using the original (not-denoised) data, Donoho's denoising and the NZT implementation. Note that the NZT gives an overall improvement in the estimation of amplitudes and latencies of single-trial ERPs. (b) Average improvement (across ERP components and SNRs) with Donoho and NZT in the estimation of the single-trial amplitude and latency.

NZT

Original

Donoho

NZT

Original

-5

Donoho

Figure 3.7(c) and (d) show the contour plots of the original and denoised single-trials and from these plots it is clear that the denoising algorithm improves the identification of the single-trial ERPs. In particular, in the denoised contour plot the background EEG activity has been largely removed and one can see a yellow/red pattern at about 100ms followed by a blue pattern corresponding to the P1-N2 peaks, and a wider yellow/red pattern at about 400-600 ms corresponding to the P3. In this plot, it is also possible to observe variations in the single-trial responses, or the absence of them in some trials (e.g: the P1 response is absent in trials #11, #12 and #13).

Figure 3.8(a) shows the average target AEP recorded from the Cz electrode. The five scale wavelet decomposition coefficients (in grey) and the denoised coefficients (in red) are shown in Figure 3.8(b). Notice that the N1-P2 components are mainly correlated with the earlier coefficients in the $D_2 - D_5$ details while the P3 component is mostly correlated with the later coefficients in the last approximation A_5 , which were the coefficients automatically chosen by the NZT algorithm. The contour plots of the original and the denoised single-trial ERPs are depicted in Figure 3.8(c) and (d) respectively. From Figure 3.8(c) it is difficult to discriminate the AEP components from the background EEG, while after denoising it is easier to distinguish them (Figure 3.8 (d)). The blue pattern at about 100ms followed by a yellow/red pattern at about 200 ms corresponds to the N1-P2 components and the wider yellow/red pattern between 200 ms to 400 ms corresponds to the P3 component. Notice the variations of the ERP components across the single-trials.



Figure 3.7 Automatic wavelet denoising of a visual ERP recorded from a left occipital (O1) location. (a) Original (grey) and denoised (red) average ERP. (b) Full wavelet decomposition (grey) and wavelet coefficients automatically chosen by the NZT algorithm (red). (c) Contour plot of the original data. (d) Contour plot of the denoised data. Note that the single-trial responses are more clearly identifiable with the denoised data.



Figure 3.8 Automatic wavelet denoising of an auditory ERP recorded from a central location (Cz). (a) Original (grey) and denoised (red) average AEP. (b) Full decomposition (grey) and coefficients chosen with the NZT algorithm (red). Contour plot of the original (c) and denoised (d) data. As in the previous figure, after denoising it is possible to identify and trace the evolution of the single-trial responses.



Figure 3.9 Performance of Donoho's (blue) and NZT (red) denoising methods with real average evoked potentials. The original signals (in grey) correspond to average visual evoked potentials in electrode O1 recorded in 10 subjects (VEP #1-10) and auditory evoked potentials in electrode Cz in 5 subjects (AEP #1-5). Note NZT deletes most of the background activity and improves the visualization of the evoked components, whereas Donoho's method changes the shape of the components (e.g. VEP #2) and does not completely delete the ongoing and baseline activity (e.g. VEP #5).

Figure 3.9 shows the denoising of the real visual and auditory average ERPs for all subjects, using the NZT and Donoho's method. In general, note that the NZT-denoised traces (in red) follow the original signals (in grey) and the method largely gets rid of the ongoing and background activity. In contrast, Donoho's denoising tends to alter the evoked responses (e.g. subjects VEP #1, VEP #2, VEP #3, VEP #9, AEP #1, AEP #2, AEP #4) and it is not so efficient in removing the ongoing and baseline activity.

Figure 3.3, Figure 3.4, Figure 3.7 and Figure 3.8 are the output of a software package for the NZT denoising technique (EP_den) freely available at: <u>http://www2.le.ac.uk/centres/csn/software/ep_den</u>.

3.5 Discussion

Event-related potentials have a very small amplitude compared to the background EEG and are barely visible in the single-trials. By far the most popular technique to enhance the ERPs is by averaging the single-trials (Dawson, 1954; Lopes da Silva, 2005b). However, the averaging technique assumes that single-trial ERPs are very similar while noise sources are unrelated to the stimulus presentations, so that by averaging a large number of trials the random noise cancels out, thus improving the observation of the average ERP. This assumption is not true in reality and the dynamics of ERPs vary from one trial to the next and, by averaging, information related to this variation between trials is lost (Rugg and Coles, 1996). In particular, the conventional approach in the design of an ERP paradigm is to try to avoid these single-trial fluctuations in order to get better defined average responses. However, there are many interesting questions that are in fact related to systematic or unsystematic trial-by-trial variations, such as those related to the study of learning processes (Quian Quiroga et al., 2007; Jongsma et al., 2006). Thus the importance of single-trial analyses and the development of algorithms to filter the background EEG activity in order to observe the single-trial evoked responses.

Single-trial ERPs have been previously detected using a denoising implementation based on discrete wavelet decomposition (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000). The denoising was obtained by manually selecting coefficients correlated with the ERPs in each scale of the decomposition, then setting to zero the uncorrelated coefficients and finally reconstructing the signal from the remaining coefficients. However the manual

selection of coefficients is a very subjective and time consuming task. In this study we improved this approach and presented an automatic denoising method (NZT method) for the extraction of the single-trial ERPs from the noisy background EEG.

The performance of the method was tested with simulated ERPs and with real visual and auditory ERPs. For the synthetic data the performance of the method was compared with a standard denoising technique: Donoho's level dependent thresholding. Compared to the data without denoising and compared also to Donoho's technique, the presented method gave a significant improvement in the observation of single-trial ERPs and also in the estimation of the amplitude and latency of the single-trial responses. For the real data, NZT denoising removed most of the baseline and background EEG activity and improved visualization of the ERPs in single-trials. Most importantly the selection of coefficients was very similar to the one done manually in the previous studies (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000), but in this case the selection was fully automatic.

The presented denoising method overcomes the drawbacks of the timeinvariant approaches such as Wiener filtering, since the wavelet transform matches the varying time-frequency patterns of the different ERP components. Closer to our proposed method, Wang and co-workers applied wavelet transform in order to automatically estimate the single-trial evoked potentials of intracortical recordings by using a Donoho level dependent soft thresholding (Wang et al., 2007). However, there are two drawbacks of this approach: first, the soft thresholding reduces the amplitude of the coefficients and smoothes the reconstructed evoked potentials and second, with Donoho's thresholding is not

always possible to extract ERPs since the amplitudes of the ERPs are of the order of or sometimes smaller than the background EEG. In particular we showed that the NZT method proposed here overcomes this problem by incorporating the information of neighbouring coefficients in the thresholding process, which resulted in a more robust estimation and a better performance.

Chapter 4

4 Single-trial analysis of conscious face perception

4.1 Background

ERP are widely used to study time courses of brain cognitive processes. An example of such processes is the study of visual object categorisation in the human brain and particularly the study of face processing in visual cognition. It is known that when potentials evoked by the presentation of faces are compared to those evoked by non-faces stimuli, the former show a larger negative peak between 130 to 200 ms post-stimulus presentations (Bentin et al., 1996; Botzel et al., 1995). This component is termed the N170 and it is larger on lateral occipital and occipito-temporal sites (Bentin et al., 1996). The N170 is associated with face processing stages (face encoding) prior to the individual face identification (Eimer, 2000a). Studies of the N170 in face inverted stimuli compared to upright faces showed latency modulations of the N170 (Bentin et al., 1996; Eimer, 2000b; Rossion et al., 2000; Sagiv and Bentin, 2001), while studies of scrambled faces (George et al., 1996), misalignment face halves (Letourneau and Mitchell, 2008) and Mooney faces (George et al., 2005) showed amplitude modulations of this component. The amplitude and latency modulation of the N170 suggest that this component is sensitive to facial configuration. Perceptual expertise has also been reported to modulate the N170 (Gauthier et al., 2003; McKone et al., 2007; Rossion et al., 2002; Tanaka and Curran, 2001). In these studies the N170 in response to pictures of objects within the individual field of expertise were compared to the responses to objects outside of this field. For instance, Tanaka and Curran found a larger N170 in response to the pictures of dogs and birds when they were presented to group of dog and bird experts respectively (Tanaka and Curran, 2001). The modulation of the N170 by perceptual expertise would suggest that these nonface stimuli may also processed configurally as with the face selective N170 responses.

Along with numerous studies reporting the type of stimuli that elicit and modulate the N170, several studies reported the correlation of the N170 component with conscious face perception (Fisch et al., 2009; Genetti et al., 2009; Rodríguez et al., 2012). In these studies the recognition performance was examined by the so-called "backward masking" paradigm (Breitmeyer, 1984). In each trial, after a short presentation of a target stimulus (a face or an object) a meaningless image (a mask) was presented to disrupt the recognition process. The subject was then asked to report whether he/she saw the face or not (see Figure 4.1 for a specific implementation).

Previous studies have aimed to manipulate human visual awareness by changing the physical properties of the stimuli, such as presenting the stimulus with varying time duration (Genetti et al., 2009) or adding different amounts of noise to the stimulus (Jemel et al., 2003). But changing the physical properties of the stimuli mixes up the effect of conscious face perception with the one elicited by the different physical properties of the stimuli. In this study we presented a backward masking paradigm using faces (cars) with varying degrees of Gaussian noise. The Gaussian noise was added during the experiment using a double-staircase procedure, thus obtaining different levels of noise in which subjects failed to recognise the stimuli. This experiment enabled us to study the effect of conscious face perception using identical stimuli at a fixed noise level as well as studying the effect of stimulus uncertainty by comparing the N170 responses in the different noise levels.

Moreover, we studied the single-trial N170 to reveal the mechanism underlying the changes in the average N170 responses due to the conscious face perception and stimulus uncertainty.

My main contribution to this study was to perform the single-trial analysis of the evoked responses, allowing extracting information about the mechanisms underlying conscious face perception and stimulus uncertainty that was otherwise impossible to extract using classical ERP analysis.

4.2 Materials and methods

4.2.1 EEG recordings

Recordings were performed in the sound proof chamber at the Neuro-Engineering lab. Twenty-two participants (mean age 27.9, range 21-37, 2 lefthanded, 12 females) were seated comfortably in a chair 50 cm from the viewing point and were asked to remain still and relaxed while performing a backward masking experiment. The subjects had normal or corrected-to-normal vision with no report of neurological impairments. The EEG data was recorded continuously using 64 electrodes placed according to the international 10-20 system, band pass filtered between 0.1 Hz and 100 Hz and sampled at 256 Hz, using a common average reference.

4.2.2 Stimuli

Two sets of pictures: twenty pictures of faces and twenty pictures of cars, both in frontal view, were selected. Faces were selected from the Stirling Psychological Image Collection (<u>http://pics.psych.stir.ac.uk/</u>) while cars were downloaded from different websites. A backward mask was generated using
randomly shuffled pieces of different images (Quian Quiroga et al., 2008b). Each picture was converted to grayscale, cropped to a resolution of 411 x 527 pixels and its mean brightness was normalised across all the images. Zero mean Gaussian noise, was added to each picture of cars and faces. The added noise had 10 different variances increasing linearly form 0 to 1, relative to the mean brightness of the picture. Images were presented in the center of a CRT Monitor with a grey background, a resolution of 1024 x 768 pixels and a refresh rate of 70 Hz.

4.2.3 Paradigm

Trials started with a fixation cross, appearing in the middle of the screen for a varying time between 500 to 700 ms, followed by a picture of a face or a car with a certain degree of noise shown for 57 ms, and a mask shown for 443 ms. The subject was instructed to report if he/she saw a face or not by clicking the left or right mouse respectively. Figure 4.1 shows the timing and the order of the stimulus presentations in one trial.

A double-staircase procedure for the face images was implemented by changing the variance of the added Gaussian noise to obtain the threshold of perception (a 50% performance at detecting faces). The descending staircase started with the highest level of variance, 1, and went to the lowest variance, 0 (no noise) with a step size of 0.1, while the ascending staircase started with variance of 0 and went to variance of 1. Along with the threshold of perception, 50%, for each subject a lower and a higher noise level in which the detection performance was around 70% and 30% were also selected. In the following we

refer to these noise levels as the supra-threshold and sub-threshold respectively.

The experiment consisted of 1200 trials divided in 5 blocks of 240 trials each. Each block consisted of 40 randomly interleaved of trials of faces without noise, 40 trials of cars without noise, 70 trials of ascending and 70 trials of descending staircases and 20 trials of cars with the threshold condition as determined by the staircase procedure for the current block. The last 20 trials, the catch trials, were added to assess the performance of the subject in terms of the number of false positives (trials in which the subject reported the appearance of a face while a car was presented). After each block the subject had a chance to take a short break. The whole experiment lasted approximately 1 h and 15 min.



Figure 4.1 Structure of a trial. Trial started with a fixation cross (500-700 ms) followed by a face or a car image (57 ms) and followed by a backward mask (443 ms). Finally the subject was asked to report if the presented image was face or not (adapted from (Navajas et al., 2013)).

4.2.4 ERP analysis

After recordings, the EEG signals were re-referenced to the average electrodes and trials that were contaminated with eye movements, eye blinks and other artefacts were removed by visual inspection. For each trial, 500 ms pre- and 500 ms post-stimulation were extracted and filtered between 1 to 70 Hz using a second order Butterworth filter. The PO7 and PO8 electrode sites were selected for further analysis given that a visual inspection of the evoked topographies and average ERPs showed the best ERP responses of the P1, N170 and P2 in these two sites.

Trials were classified according to the subject's report (seen and unseen) and according to the level of noise (sub-threshold, threshold and suprathreshold), thus having six different conditions (i.e. sub-threshold seen, threshold seen, supra-threshold seen, sub-threshold unseen, threshold unseen and supra-threshold unseen). For each noise level the average ERP of the seen and unseen trials were obtained.

Evoked responses to non-face stimuli were obtained from the correct rejections of catch trials (i.e., trials in which the presented stimulus was a car and the subject reported correctly not seeing a face). The average evoked responses of the non-face stimuli were compared with the seen and unseen evoked responses in the threshold condition.

For the statistical analysis the average N170 was identified as the local minima between 150 and 190 ms and the average P1 and P2 components were identified as the local maxima between 80 and 120 ms and between 200 and 240 ms respectively.

4.2.5 Single-trial ERP analysis

The single-trial ERPs were obtained using the proposed NZT denoising algorithm. We used the NZT to denoise an average evoked response in the threshold seen condition and then we kept the same set of wavelet coefficients to denoise all the channels for all the subjects in the six conditions. For each channel the single-trial N170 responses were identified as the local minima between 120 and 200 ms. The single-trial P1 responses were identified as the local maxima between the 80 ms and the latency of the N170 peak and the P2 responses were identified as the local maxima between the 80 ms and the latency of the N170 peak and the N170 peak and 240 ms. This information was used to study the mechanism underlying differences in the average responses in different conditions. More precisely it was used to figure out if any increase (decrease) in the average ERP was due to the increase (decrease) of the single-trial amplitudes or to a better (poorer) time locking to the stimulus onset; i.e. a lower (higher) latency jitter. The latency jitters were estimated as the standard deviation (SD) of single-trial latencies of each component.

A linear discriminant analysis (Fisher, 1936) was implemented to assess the correlation between the subjects' report and the single-trial responses. Moreover, we used a leave-one-out cross-validation procedure to decode the subjects' behavioral responses using the single-trial peak amplitudes of the P1, N170 and P2 recorded in channels PO7 and PO8. Furthermore the statistical significance (the p-value) of the decoding performance was estimated using:

$$p - value = \sum_{j=k}^{n} P_j \tag{4.1}$$

where

$$P(k) = \binom{n}{k} P^{k} (1-P)^{n-k}$$
(4.2)

is the probability of getting k hits in n trials (Quian Quiroga and Panzeri, 2009).

4.3 Results

4.3.1 Average ERP analysis

Firstly we assessed the existence of the N170 response by comparing the average ERPs responses to faces and cars without noise. An ANOVA analysis showed a significant difference for the N170 face-sensitive response (p<0.001) compared to the cars but not for the P1 and P2 components. Secondly we studied the dependency of the N170 with conscious face perception and with the uncertainty introduced by adding noise, by analysing the seen and unseen evoked responses in the three threshold conditions. Note that the double-staircase procedure introduced a mean noise variance of 0.20 ± 0.12 for supra-threshold condition, 0.32 ± 0.17 for threshold, and 4.5 ± 0.21 for the sub-threshold condition.

Grand averages of the evoked potentials for all the six conditions and the scalp topographies of seen and unseen evoked responses in the threshold condition at the time of N170 are shown in Figure 4.2. The scalp topographies show a larger activity at the time of N170 with the seen trials compare to the unseen trials. Comparing the three noise levels, we found that the only component significantly modulated by the noise level (p<0.001) and conscious face perception (p<0.001) was the N170. Moreover, at the threshold condition, the average ERP responses elicited by seen trials showed a significantly larger



Figure 4.2 Neural correlates of conscious versus unconscious face perception. a) Grand average ERPs for the sub-threshold, threshold and supra-threshold conditions recorded from PO8 electrode. b) Scalp topographies for the seen, unseen and seen-unseen faces at the time of N170 response at the threshold condition. The unit of the colour bar in b is microvolt (adapted from (Navajas et al., 2013)).

N170 compared to the average signal elicited by cars and by unseen trials (p<0.001).

4.3.2 Single-trial analysis

We used the NZT denoising method to denoise the single-trial ERPs and from there we extracted the peak amplitudes of the P1, N170 and P2 as the local maxima (minima) of the denoisied trials in different windows (time windows as defined in section 4.2.5). Figure 4.3(a) illustrates an average ERP, 15 singletrial ERPs and the extracted P1, N170 and P2 peaks for a typical subject. Analysis of the extracted single-trial peaks showed that the N170 amplitudes were significantly (p<0.001) larger for the seen trials compared to the unseen trials. However no significant differences were observed with the single-trials P1 and P2 components.



Figure 4.3 Decoding the subjects' report with single-trial ERPs. a) Denoised average and single-trial ERPs recorded at PO8 in a typical subject. The ERP components are indicated with the marks. b) Distribution of single-trial N170 used for decoding. Blue (red) dots represent the single-trial N170 for seen (unseen) trials recorded at PO7 and PO8 electrodes. The black line indicates the linear discriminant. The blue and red lines represent the projection of the normalised single-trial N170 to the axis perpendicular to the linear discriminant. c) The p-values of the decoding performance in a logarithmic scale. Red lines show the median of the distribution of the p-values for each component (adapted from (Navajas et al., 2013)).

Knowing the significant differences in the single-trial N170 responses, we applied a linear discriminant analysis to use this feature to decode the subjects' report (have seen a face or not). We used the amplitudes of N170 responses in the seen and unseen trials at PO7 and PO8 electrodes as two sets of features for decoding. Figure 4.3(b) shows the single-trial N170 at electrode PO7 and PO8 in seen (blue) and unseen (red) trials. The black line indicates the linear discriminant. The decoding performances were significantly (p<0.05) above chance for most of the subjects (18 out of 22 subjects) with mean decoding performance of 60.1% and SD of 4.2%. We also examined if we could decode

the subject's report using the P1 and P2 components, but with these two components the decoding performance was at the chance level for most subjects (16 out of 22 subjects). The mean decoding performance for the P1 component was 50.04% with a SD of 11.0% and for the P2 component, 54.8% with a SD of 6.3%. The p-values of the decoding performance are shown in Figure 4.3(c) in a logarithmic scale. Red lines show the median of the distribution of the p-values for P1 (0.26), N170 (0.01) and P2 (0.11).

Next, we studied the single-trial amplitude and latency changes of the ERPs with the different noise levels. No significant differences in the amplitude of the P1, N170 and P2 components were observed comparing the three threshold conditions. With the N170 the amplitude differences observed in the average signal, but not in the single-trials, suggested different latency variability for the different noise levels. To assess these differences in latency variations, we calculated the latency-corrected average ERPs for the three threshold conditions, by aligning the single-trial N170 responses to the average N170 peak. Figure 4.4 (top) depicts the grand average ERPs for seen trials in the three noise levels and their latency-corrected grand averages.

As shown in this figure, the N170 differences in the three threshold conditions vanished after the latency alignment and the differences between these three noise levels became non-significant. However, the differences between the seen and unseen trials remained significant (p<0.05) even after the latency alignment, Figure 4.4 (bottom). An ANOVA test reveled a significant modulation of the N170 latency jitter by noise level but not by conscious report. No significant differences were observed with the P1 and P2 latency jitter in either case.



Figure 4.4 Single-trial analysis of ERPs. Grand average ERPs and their latency-corrected in the three threshold conditions (up) and in threshold condition for seen and unseen trials (bottom). Note with the noise effect vanished after the latency alignment while it was remained for the conscious face perception. Bands around mean values denote SEM (adapted from (Navajas et al., 2013)).

4.4 Discussion

Neural correlates of face perception have been widely studied in visual perception and object categorisations. Studies with functional brain imaging (fMRI) have shown that the inferotemporal cortex around the fusiform gyrus responds more to the flashes of faces rather than the other object categories (Kanwisher et al., 1997). Evidence for face selective responses has been also obtained from intracranial (Allison et al., 1999) and the single-cell recordings (Quian Quiroga et al., 2008b; Tsao et al., 2006) in humans and monkeys.

Several studies have reported the correlation of the N170 component with conscious face perception (Fisch et al., 2009; Genetti et al., 2009; Jemel et al., 2003; Pegna et al., 2011). However in most of these studies, conscious face perception effects were assessed by changing the physical properties of the

stimuli. In this work, using identical stimuli, we studied the effects of conscious face perception and stimulus uncertainty, by adding different degrees of Gaussian noise.

Analysing the average ERPs, we showed larger N170 responses with the recognised trials compared to the unrecognised trials in all the threshold conditions. Moreover, we showed that the amplitude of the average N170 diminished with increasing the noise level. However these two effects were only observed with the N170 component and not with the average P1 and P2 components.

In addition we investigated the mechanism underlying the modulation of the average ERP components by studying the single-trial amplitudes and latencies of these components. We showed that the amplitude modulation introduced by the conscious face perception was due to the attenuation of the single-trial amplitudes of the unseen trials. However the amplitude modulation introduced by stimulus uncertainty (adding more noise) was due to the larger latency variations across trials.

Chapter 5

5 A method to evaluate the presence of phase-resetting and additive components in the generation of ERPs

5.1 Introduction

In spite of the wide usage of ERPs in clinical and cognitive neuroscience, there is still a large debate about the mechanisms underlying their generation. There are two main antagonist theories: the first one, known as the additive model, states that ERPs arise as relatively fixed-latency and polarity neural responses adding to the background EEG (Hillyard, 1985; Jervis et al., 1983; Schroeder et al., 1995; Makinen et al., 2004). More specifically, it is assumed that an ERP waveform arises from a burst of firing of multiple single neurons in response to stimulation. The second theory, known as phase-resetting model, claims that ERPs are due to a phase locking of ongoing EEG rhythms in response to the stimulus. (Sayers et al., 1974; Brandt, 1997; Başar, 1999; Makeig et al., 2002; Jansen et al., 2003). Alternatively, ERP generation may be due to a mix of both mechanisms (Min et al., 2007).

For nearly 40 years, a large number of papers have been published discussing these two opposing theories, and proposing evidence in support of either ERP generation mechanism. In support of the phase-resetting model some works reported that, from a uniform distribution of phases, the presentation of the stimuli triggered a phase concentration across trials, i.e. phases are reset to a similar value after stimulation (Makeig et al., 2002; Rizzuto et al., 2003; Klimesch et al., 2004; Hamada, 2006).

However the finding of a phase concentration doesn't assure a phaseresetting mechanism because, given that oscillations are usually not clear in the on-going EEG, it is necessary to apply band-pass filtering (or more

sophisticated techniques such as wavelets) to have a reliable estimation of the phases (Hamada, 2006; Rizzuto et al., 2003). The problem is that filtering introduces ringing artefacts that may make a single pulse look like an oscillation (Freeman and Quian Quiroga, 2013). To illustrate this, in Figure 5.1(a) we filtered a delta function (upper plot) with a broad and narrow band elliptic filter (middle and lower plots, respectively). Note that the original delta function turned into an oscillation after filtering, especially with the narrow band filter. Thus, oscillations observed after ERP filtering may be artificial, that means arising from ringing effects produced by the filters used Figure 5.1(b)). Due to the use of band-pass filtering it is then difficult form the analysis of phase concentration or the observation of evoked oscillations to dissociate between the phase-resetting and additive models.



Figure 5.1 Ringing effect introduced by digital filtering. a) A delta function (upper plot) with a broad and narrow band elliptic filter (middle and lower plot respectively). Note that the original delta function turns into an oscillation after filtering, especially with the narrow band filter. b) An ERP waveform before and after filtering. Note that filtering introduces ringing effects and the presence of spurious oscillations.

Further studies combined the phase concentration analysing with the information of post-stimulus power changes in the single-trials (Klimesch et al., 2004; Fell et al., 2004; Fuentemilla et al., 2006; Hanslmayr et al., 2007). These studies proposed that the pure phase-resetting model would be supported by the finding of a phase concentration but without any changes in the signal power, while the additive model would give a power increase after stimulus onset (Fell et al., 2004; Fuentemilla et al., 2006). However, this test is based on the lack of statistical significance, which could be due to a real lack of a power increase, or to a low number of trials, signal to noise ratio, etc. Moreover, the statistics to obtain power and phase-resetting values involve different measures with different sensitivities and specificities, which are difficult to compare. In other words, a not significant change in power (with a significant phaseresetting) may also turn significant if more trials are analysed. Moreover, it is possible that the actual mechanism is not one or the other, but a mix of both models. Therefore, it is problematic to take no changes in post-stimulus power as evidence for phase-resetting model. Conversely, changes in post-stimulus power do not falsify the existence of phase-resetting.

In this chapter, with the help of the NZT denoising algorithm, we proposed a novel discrimination technique to observe whether ERPs can be explained by the presence of phase-resetting or by additive components. The key aspect is that we avoid the use of filtering and therefore, artefacts due to ringing effects. Our main assumption is that if two components of an ERP are part of an oscillation, their latencies should in principle co-vary. We remark that this does not necessarily needs to be the case as: i) the two components could be generated by the resetting of two independents oscillations, and ii) it is also

possible that two additive components may co-vary, e.g. given by a first tonic excitation of neurons followed by hyperpolarization. In any case, we argue that the first of these alternative hypotheses would already challenge the standard model of phase-resetting (as ERPs would be generated by a more complex mechanism than the resetting of single oscillations) and second, the finding of no co-variation between the main ERPs would give a good indication of the presence of additive components.

The method we propose relies on aligning the latencies of the ERPs, analysing the peak amplitude increases or decreases before and after the alignment. We hypothesize that for ERPs generated purely by phase resetting aligning one component should also align the other one (due to latency co-variation), thus obtaining an increase in the value of both ERP peaks. On the contrary, if the two components are independent, aligning one of them should have no effect or even decrease the peak value of the other one (as it would disrupt the alignment to stimulus onset). This method has also two underlying assumptions: i) we assume some latency variability between trials, so that latency alignment is meaningful and ii) we assume we start from a well-defined ERP – i.e. with a sufficient SNR – or otherwise, if no clear ERP is present, we would be aligning ongoing oscillations. We then quantify the contribution of additive evoked components and phase-resetting to the generation of the ERPs and show the use of the method with real visual and auditory ERPs.

5.2 Materials and methods

5.2.1 Simulation of the additive model

For different signal to noise ratios (SNRs), 100 trials of visual event-related potentials (VEPs), sampled at 512 Hz and going from -1 s to 1 s, were simulated by adding two phasic peaks onto background EEG noise (Yeung et al., 2004; Yeung et al., 2007). The positive peak corresponded to a half-cycle of 9 Hz sinusoid with varying latency across trials (mean latency =109 ms; latency jitter=21 ms). This component simulated the P1, while the N2 was simulated with the negative half-cycle of a 9 Hz sinusoid with varying latency across single-trials (mean latency=157 ms and latency jitter= 25 ms). Figure 5.2(a) shows five simulated trials with those two components, in red. To simulate the background EEG recordings, we used the surrogates of a short segment of a real EEG activity of one subject recorded from occipital site (O1 electrode) with eyes open fixating on a red circle in the centre of screen. The surrogates were constructed by applying the Fourier Transform, shuffling the phases and then applying the Inverse Fourier Transform (Schreiber and Schmitz, 2000). The algorithm preserves the power spectrum of the original signal. The simulated ERPs were obtained by adding the simulated P1 and N2 peaks to the surrogate EEGs (with different amplitudes, to model different SNRs) as shown Figure 5.2(a), in black. The average VEPs of the hundred simulated single-trial VEPs is also shown in the same figure in blue.

5.2.2 Simulation of the phase-resetting model

As with the additive model, for different SNRs, hundred epochs of VEPs, elicited by phase-resetting (sampled at 512 Hz and running from -1 s to 1 s) were simulated. Phase-resetting VEPs were generated using sinusoidal signals with a randomly varying frequency (Yeung et al., 2004; Yeung et al., 2007) between 5 Hz to 12 Hz over different trials. The random phase prior to the stimulus onset turned to a fixed phase after the stimulus onset. The resetting time was varied randomly across the single-trials (mean resetting time=75 ms; SD=4 ms). As a result we obtained simulated P1 and N2 peaks with varying latency across single-trials (P1: mean latency=107.5 ms; latency jitter=20 ms and N2: mean latency=161 ms; latency jitter=23 ms). As before (see Sec. 5.2.1), surrogate signals of an EEG recording were used to simulate the on-going EEG.

Figure 5.2(b) illustrates five trials of the simulated ERP oscillations in red, the simulated single-trial ERPs (the simulated oscillations + the simulated background EEG) in black and the average VEPs of 100 ERP trials in blue. The simulated ERPs were generated in a way that the latency variability of the components did not differ significantly from each model, as the measure we will describe for assessing additive contribution or phase-resetting relies on a latency alignment.



Figure 5.2 Simulated VEPs based on the additive and oscillation models. The additive model (black traces) simulated by adding two phasic peaks (red traces) to the background EEG. The phase-resetting model (black traces) synthesised by adding different oscillations (traces in red), with random phases prior to the stimulus onset which turned to a fix phase after the onset, to the background EEG. Averages (blue) were obtained by adding 100 trials of the simulated ERPs.

5.3 Experimental set up and empirical data

For this study, we used the same real VEP and AEP signals from 25 voluntary healthy subjects (18-30 years old) described in Chapter 3 of this thesis. Similar to Chapter 3 for the VEPs we studied the response in the occipital (O1) electrode and for the AEPs the central (Cz) electrode, but here we used non-target responses (mean number of trials=100) to investigate the basis of visual and auditory evoked potentials generation.

5.4 Description of the method

As mentioned above, filtering introduces spurious oscillations, thus confounding the dissociation between the phase-resetting model and the additive models. The key issue is to assess whether ERPs are due to a phase resetting of on-going oscillations or due to additive components avoiding filtering. Here, our main assumption is that if two ERP components, such as P1 and N2, are part of an oscillation, their latency should co-vary. This means that if we identify the latency of the single-trial responses, doing a latency-corrected average for one peak (P1) will not only increase the amplitude of the same peak but also the following one (N2). In contrast, if the P1 and N2 are two independent additive components, then aligning one peak should have no effect or even decrease the amplitude of the second one (as both can be independently locked to the stimulus).

To clarify this idea Figure 5.3 shows an average VEP simulated based on the additive model (black, see Sec. 5.2.1) and an average VEP given by pure phase-resetting model (black, see Sec. 5.2.2). In both cases the latencycorrected averages (red) were obtained by first denoising the single-trial ERPs (using the method described in Chapter 3, see below) then aligning the P1 latencies across single-trials, and finally averaging the aligned trials. With the additive VEPs, aligning the latencies of the first peak (P1) gives a larger P1 (P1 < latency-corrected P1 (P1_lc)), but reduces the amplitude of the N2 (latencycorrected N2 (N2_lc) < N2). In contrast, with the VEPs generated by phaseresetting, aligning the latencies of the first peak (P1) gives a larger value not only of the P1 (P1 < P1_lc) but also of the N2 (N2_lc > N2). In the next section, we propose a measure to quantify this observation.



Figure 5.3 Average simulated ERPs before and after correcting the latency jitter. (a) An average VEP generated based on the additive model before (black) and after (red) latency correction. (b) An average VEP generated based on the phase-resetting model before (black) and after (red) latency correction.

5.4.1 Estimation of the single-trial ERP latencies

We used the NZT denoising method to estimate the latencies of the singletrial ERP responses. First we obtained the denoised single-trial responses of the real VEPs (AEPs) and the simulated VEPs using the NZT algorithm and then we estimated the ERP components in each trial. For both the real and simulated VEPs the single-trial P1 responses were identified as the local maxima between 70 and 160 ms and the single-trial N2 responses were identified as the local minima between the latency of the P1 and 70 ms after the latency of the P1.

Analogously, for the real AEPs the single trial N1 responses were identified as the local minima between 60 and 150 ms and the single-trial P2 were identified as the local maxima between the latency of the N1 and 90 ms after the latency of the N1.

5.4.2 Aligning of the single-trial latencies

Having estimated the latencies of the single-trial ERPs, the raw single-trial responses (i.e. without any filtering) were aligned to the P1 latency of the average signal, thus obtaining latency-corrected averages.

5.4.3 Quantification of phase-resetting

Here our main goal was to quantify the peak amplitude changes of the ERP components after latency correction. Based on our hypothesis, if two ERP components, such as P1 and N2, are part of an oscillation, their changes in amplitude should co-vary. In other words, if the amplitude of one increases after alignment, we should expect an increase of the amplitude in the second one. We measured the original amplitudes of the P1 and N2 and then we aligned the latencies of the P1 (similar results were obtained aligning to N2) and calculated the differences as:

$$\Delta P1 = |P1_lc| - |P1| \tag{5.1}$$

$$\Delta N2 = |N2_lc| - |N2| \tag{5.2}$$

and their ratio as:

$$PR = \frac{\Delta N2}{\Delta P1} \tag{5.3}$$

In the phase-resetting case, we expect to have a positive value for PR since an increase in P1 after alignment gives an increase in N2, which is close to 1 for a pure oscillation. For the additive model we expect to have a value

close to zero (no increase in N2 when aligning P1) or negative (a decrease in N2 when aligning P1).

5.5 Results

5.5.1 Simulated data

To evaluate the performance of the proposed method we applied it to simulated VEPs. Figure 5.4 shows an average simulated VEP based on the additive model (a) and its five levels of decomposition (b), in grey. The average ERPs were obtained by averaging 100 simulated trials. The average signal was decomposed in to five scales using wavelet decomposition. The coefficients in each scale were denoised using the NZT method (coefficients in red) and the denoised signal (top, red) was obtained by wavelet reconstruction using the denoised coefficients. Subsequently, the denoised single-trial ERPs were reconstructed by using the same set of coefficients in each trial. The same set of denoised coefficients was also kept constant to denoise all the simulated VEPs with different SNRs. Figure 5.4(d) illustrates 15 single-trial responses of the simulated VEP (in grey) and the denoised signals (in red).

Moreover, the average and single-trial P1 and N2 responses were extracted by identifying the local maxima and minima of the denoised signals in different time windows (Figure 5.4 blue and green asterisks respectively) and the original single-trials were aligned to the P1 latency of the average denoised signals. Then the latency-corrected averages were obtained by averaging the aligned single-trials.



Figure 5.4 Automatic wavelet denoising of an average VEP simulated based on the additive model. (a & c) Original (grey) and denoised (red) average VEP. (b) Full wavelet decomposition (grey) and wavelet coefficients automatically chosen by the NZT denoising algorithm (red). (d) Original (grey) and denoised (red) single-trials. Blue and green asterisks indicate the estimated P1 and N2 responses respectively.



Figure 5.5 Automatic wavelet denoising of an average VEP simulated based on the phase-resetting model. (a & c) Original (grey) and denoised (red) average VEP. (b) Full wavelet decomposition (grey) and wavelet coefficients automatically chosen by the NZT denoising algorithm (red). (d) Original (grey) and denoised (red) single-trials. Blue and green asterisks indicate the estimated P1 and N2 responses respectively.

Figure 5.3(a) illustrates the average VEP of Figure 5.4 in black, and its latency-corrected in red. As it is shown, aligning the single-trial P1 latencies increased the P1_lc amplitude but decreased the N2_lc amplitude.

The same analysis was done with the simulated VEP signals created using the phase-resetting model. Figure 5.5 illustrates the average (a) and its 5 level decomposition coefficients (b) before and after the denoising, as well as the original (d) and the denoisied single-trials, in grey and red respectively. The P1 and N2 peaks were estimated as before, and the latency-corrected average was obtained (Figure 5.3(b)).Unlike the case of additive model, here aligning the P1 latencies not only increased the P1_lc but also increased the N2_lc.

Finally, the *PR* values were obtained using equation 5.3. Figure 5.6 illustrates the *PR* values for the simulated ERPs based on the additive model (107 simulations, blue dots) and based on the phase-resetting model (120 simulations, red dots) for different signal to noise ratios. Low SNRs (SNRs < 13) indicate small evoked potentials compared to the baseline EEG, while high SNRs indicate high evoked potentials. As expected, for all SNRs (except one), the *PR* values of ERPs simulated by phase-resetting were positive. In contrast, for the additive ERPs smaller values were obtained. For the lower SNRs, the additive components were very small compared to the background noise and the average signals mainly contained the on-going EEG, so we should expect similar *PR* values as the ones obtained by the VEPs simulated by phase-resetting (as we are just aligning ongoing oscillations). Next we implemented a linear discriminant analysis (Fisher, 1936) to separate the *PR* values of the additive VEPs from those of the phase-resetting VEPs (the cyan line in Figure 5.6). We used the *PR* values obtained with the additive and phase-resetting

model as two sets of features for decoding. Furthermore, to assess the decoding performance we used a leave-one-out cross-validation procedure (performance 90%, 216 hits out of 240 PR values). We estimated the statistical significance (the p-value) of the decoding performance using equation (4.1) and we found that it was highly significant (p<0.001).



Figure 5.6 The *PR* **values for the simulated ERPs.** Blue dots represent the *PR* values for the simulated VEPs based on additive model and the red ones the *PR* values of the phase-resetting model at different signal to noise ratios. The cyan line indicates the linear discriminant which separates the *PR* values of the additive model from the ones of the phase-resetting model. Note that compare to the phase-resetting model, smaller *PR* values are obtained with the additive model and for SNRs > 13 we have a clear separation of two models.

5.5.2 Real data

5.5.2.1 Real VEPs

For the real VEPs we studied the responses in the occipital (O1) electrode. Figure 5.7 shows an average VEP (a) and its five levels of decomposition (b), in grey. The average ERPs were obtained by averaging several single-trial responses. In each trial the stimulus was presented at time zero and the corresponding visual ERP components were triggered within the first 300 ms after the onset time. The averages were decomposed in to five scales using wavelet decomposition and the denoised average signals (top, red) were reconstructed using the denoised coefficients obtained with the NZT method (coefficients in red). Subsequently, the denoised single-trial ERPs were reconstructed by using the same set of coefficients in each trial. Figure 5.7(d) illustrates 15 single-trial responses of the average VEP (in grey) and the denoised single-trials (in red). Note that the same set of denoised coefficients was kept constant to denoise all the VEPs.

Next, for each subject, the average and single-trial P1 and N2 responses were extracted by identifying the local maxima and minima of the denoised signals in certain time windows (Figure 5.7 blue and green asterisks respectively) and the original single-trials were aligned to the P1 latency of the average denoised signals. Then the latency-corrected averages were obtained by averaging the aligned single-trials. Figure 5.9(a) illustrates the average VEP of Figure 5.7 in black, and its latency-corrected in red. As it is shown, aligning the single-trial P1 latencies increased the P1_lc amplitude while decreasing the N2_lc amplitude.



Figure 5.7 Automatic wavelet denoising of an average VEP recorded from O1 electrode. (a & c) Original (grey) and denoised (red) average VEP. (b) Full wavelet decomposition (grey) and wavelet coefficients automatically chosen by the NZT denoising algorithm (red). (d) Original (grey) and denoised (red) single-trials. Blue and green asterisks indicate the estimated P1 and the N2 responses respectively.



Figure 5.8 Automatic wavelet denoising of an average AEP recorded from Cz electrode. (a & c) Original (grey) and denoised (red) average AEP. (b) Full wavelet decomposition (grey) and wavelet coefficients automatically chosen by the NZT denoising algorithm (red). (d) Original (grey) and denoised (red) singletrials. Blue and green asterisks indicate the estimated N1 and the P2 responses respectively.

5.5.2.2 Real AEPs

For the real AEPs we used the responses in the central (Cz) electrode. Figure 5.8 shows an average AEP (a) and its five decomposition levels (b), in grey. As with the real VEPs, the stimulus was presented at time zero and the corresponding auditory ERP components were triggered within the first 300 ms after the onset time at each trial. The denoising was performed in each scale of decomposition ((b) coefficients in red) and the denoised average AEPs were obtained by reconstructing the signal using the denoised coefficients ((a) and (c) in red). Subsequently, the denoised single-trials were reconstructed by using the same set of coefficients in each trial. Note that, the same set of denoised coefficients was kept constant to denoise all the AEPs.

Figure 5.8(d) illustrated 15 single-trial responses of the average AEP (in grey) and the denoised single-trials (in red). For each subject, the average and single-trial N1 and P2 responses were estimated by identifying the local minima and maxima of the denoised signals in different time window (Figure 5.8(d) blue and green asterisks respectively). Then the original single-trials were aligned to the N1 latency of the average denoised signals and the latency-corrected averages were obtained by averaging the aligned single-trials. Figure 5.9 illustrate the average AEP of Figure 5.8 in black, and its latency-corrected average in red. As we expected, aligning the single-trial N1 latencies increased the N1_lc amplitude while decreasing the P2_lc amplitude.



Figure 5.9 Latency-corrected averages of real VEP and AEP. (a) Original average VEP (black) and its latency-corrected average (red). (b) Original average AEP (black) and its latency-corrected average (red). Note that aligning single-trial P1 (N1) latencies increases the P1_lc (N1_lc) while decreases the N2_lc (P2_lc).

Furthermore, for both modalities, the PR values were calculated for each subject using equation 5.3. Figure 5.10 illustrates the PR values for the real VEPs (black asterisks) and AEPs (pink asterisks). As shown in this figure, for most subjects the PR values are mainly negative or close to zero, under the separatrix line, thus favouring the additive model.



Figure 5.10 The *PR* values for the real and simulated ERPs. Asterisks indicate the *PR* values for the real VEPs (black) and AEPs (pink). Blue dots represent the *PR* values for the simulated VEPs based on the additive model and the red dots represent the *PR* values of the phase-resetting model at different signal to noise ratios. The cyan line indicates the linear discriminant which separates the *PR* values of the additive model from those of the phase-resetting model. Note that the *PR* values for the real ERPs are mostly under the separatix line in the additive part. ERPs with significant *PR* values in the additive part are highlighted with the red circles.

5.5.2.3 Baseline controls

It is widely known that the background EEG consists of oscillations with random phases. Therefore, analysing the EEG signals, prior to the stimulus onset (the baseline EEG), we expected to have similar PR values to the ones obtained with the phase-resetting model (positive PR values).

For both simulated modalities (VEPs and AEPs), we further assessed our results by generating hundreds of surrogate background EEGs, finding the PR values for the surrogate data and comparing them with the PR values obtained

from the real ERPs. This simple procedure allows statistically testing whether the ERPs are generated by a phase-resetting of ongoing oscillations or whether there was an additive component present.

For each subject, hundreds of surrogate background EEGs were calculated from the background EEG signals in each single-trial. Then we obtained 100 sets of surrogates, each of which having 100 single-trials. For each set the average and the latency-corrected averages were obtained, thus obtaining 100 averages with their corresponding latency-corrected averages for each subject.

Then for each subject we measured the PR values for the surrogates and we used a nonparametric test to check if the PR value of their corresponding ERP was placed significantly out of the distribution of the surrogates. We estimated the P value as the ratio of the number of the surrogates PR values placed lower than the PR value of the ERP. Subjects with PR values significantly out of the distribution of the background oscillations are highlighted with the red circles in Figure 5.10.

With the real VEPs, we assessed our findings by identifying a window between 640 to 540 ms prior to the stimulus onset and we obtained the most positive value in this window. Analogous to the post-stimulus ERPs we obtained the most negative peak between the latency of the positive peak and 70ms after this latency. Then we formed the latency-corrected averages for each subject as shown in Figure 5.11(a). We did the same analysis for the real AEPs, but finding the negative peak first and then obtaining the latency-corrected average based on the negative peak, (Figure 5.11(b)).



Figure 5.11 Latency-corrected averages in the baseline of real VEP and AEP. (a) Original average VEP (black) and its latency-corrected average (red). (b) Original average AEP (black) and its latency-corrected average (red). Note that in the baseline aligning single-trial P1 (N1) latencies not only increases the P1_lc (N1_lc) but also the N2_lc (P2_lc).

Compared to the latency-corrected averages of the post-stimulus ERPs with the baseline analysis, (for both modalities) aligning one peak increased not only the peak itself but also the following peak, as expected.

Furthermore, for both modalities we measured the PR values (Figure 5.12 green asterisks) and compared them with the one obtained from the poststimulus ERPs. Unlike the PRs of the post-stimulus ERPs, the baseline PRs were positive and placed above the separatrix line, indicating oscillatory nature of the background EEGs. Notice that, since there is no evoked component in the baselines, these PR values are placed close by and have small SNRs.



Figure 5.12 The PR values for the real ERPs, baselines and simulated ERPs. Asterisks indicates the PR values for the real VEPs (black), AEPs (pink) and baselines (green). Dots represents the PR values for the simulated VEPs generated based on additive model (blue) and the phase-resetting model (red) with different signal to noise ratios. The cyan line indicates the linear discriminant which separates the PR values of the additive model from the ones of the phase-resetting model. Note that the baseline PR values are positive and placed above the separatrix line.

5.6 Discussion

Since at least the mid 1970's there has been a large debate regarding the neural basis of ERP generation (Sayers et al., 1974; Jervis et al., 1983; Hillyard, 1985; Başar, 1999; Makeig et al., 2002; Lopes da Silva, 2006; Yeung et al., 2007; Turi et al., 2012). The so-called additive model considers ERPs as phasic bursts of neural activities added to the background EEG due to stimulation. According to this hypothesis, ERP components are generated by activation of different brain areas upon stimulus presentation (Mangun, 1992) which results

in post-stimulus power increase and amplitude enhancement (Shah et al., 2004).

Many studies have challenged the "pure additive model" (i.e. ERPs being generated only by additive components) by presenting evidence of synchronized oscillations in response to a stimulus (Makeig et al., 2002; Rizzuto et al., 2003; Fuentemilla et al., 2006; Duzel et al., 2005; Gruber et al., 2005; Luu and Tucker, 2001; Mazaheri and Picton, 2005). Moreover, the finding of a phase concentration across the single-trials has been accounted as evidence supporting the phase-resetting model (Makeig et al., 2002; Hamada, 2006; Klimesch et al., 2004; Rizzuto et al., 2003). The caveat of these studies is that ERP responses are typically band-pass filtered in order to visualize evoked oscillations or to estimate the phase of the signal to assess a phase concentration. Filtering, however, introduces ringing effects that can make a single phasic component look like an oscillation, thus compromising the interpretation of the results.

Yeung and colleagues evaluated the most common analysis methods supporting the phase-resetting hypothesis by applying them to the analysis of simulated ERP data based on the additive model (Yeung et al., 2004; Yeung et al., 2007). In line with our arguments above, they concluded that conventional evidence for phase-resetting presented in previous works should be taken with caution. In particular, Luu and Tucker proposed that the appearance of synchronised oscillations in the single-trial traces proves the phase-resetting hypothesis (Luu and Tucker, 2001). They used narrow band filters to show synchronised oscillation in the EEG and ERPs. However, Yeung and colleagues showed that narrow band pass filtering produces artificial oscillations in the

filtered data and one might see a similar type of oscillation by filtering a simulated additive ERP (Yeung et al., 2004). Analogously, they showed that the phase synchronization measured by the phase-locking factor (Tallon Baudry et al., 1996) can be also seen with phasic bursts of neural activity. Likewise, they argued that the shared scalp distribution of spectral power in the EEG and ERPs and the correlation between spectral power in the EEG and ERP amplitude cannot be taken as evidence of phase-resetting hypothesis.

In this thesis we presented a novel technique to assess the degree of phase-resetting and additive components in the generation of ERPs. Based on our proposed hypothesis if two components of an average ERP are part of an oscillation, their latency should co-vary and increasing (decreasing) the amplitude of one component should increase (decrease) the amplitude of the second one. We quantified these amplitude changes after latency alignment and introduced a quantification factor, the PR, which we applied to simulated data and to real VEPs and AEPs. According to our quantification factor, if the ERP components are generated based on the phase-resetting model, the PR value will have a positive value, while if the ERPs are generated based on the additive hypothesis, the PR value will be zero or a negative value greater than or equal to minus one.

In order to evaluate our results we simulated ERP with different SNRs based on the phase-resetting model and the additive model and we measured their PR values. For SNRs greater than about 13, which was the case for most of the real VEPs and AEPs, the PR values of the ERPs simulated by phase-resetting model were above zero, while those simulated by the additive model were smaller and placed below zero. The method holds for SNRs > 13 since for

the lower SNRs the additive components were small and we mainly aligned the background oscillations.

We also measured the PR values for the post-stimulus ERP components and for the pre-stimulus baselines of the real VEPs and AEPs. Similar to the additive model, the post-stimulus ERPs had negative or close to zero PRvalues. In contrast, all the pre-stimulus EEG signals had positive PR values, in accordance with phase-resetting model.

The main objective of this chapter was to offer a quantitative method which avoids filtering the signal, and the consequent filtering artefacts. We tried the method with the real VEPs and AEPs, and we showed that at least these particular evoked responses are more in line with the additive than the phaseresetting model. However, these results shouldn't be generalized to ERPs evoked using different tasks, in different conditions and in different brain areas. As it is shown by Shah and colleagues (Shah et al., 2004), different mechanisms may underlie the generation of brain responses at different processing levels. In particular they studied local field potentials and current source density (CSD) at both low and high levels of visual processing - at primary visual cortex V1 and inferotemporal (IT) cortex, respectively. They showed that in area V1 an obvious evoked response (net local excitation) appeared following the stimulus onset, with a very small pre-stimulus oscillation, thus supporting the additive model. However in IT the ratio of pre to poststimulus oscillatory activity was shown to be larger compared to V1, indicating IT to be more in line with phase-resetting model.

Closer to our work, Mazaheri and Jensen (Mazaheri and Jensen, 2006) introduced a quantitative tool, termed as the phase-preservation index (PPI), to
evaluate phase-resetting by quantifying the phase relationship between pre and post-stimulus oscillatory activity in the alpha frequency band of event-related fields (ERFs), measured using magnetoencephalography (MEG). They examined whether the phase of the background alpha oscillations is affected by the visual stimuli and they showed a phase consistency up to 300 ms poststimulus. However, they found a power increase accompanied with a phasealignment in the theta frequency band after the stimulus onset, while no significant theta activity was found prior to the stimulus presentation. Considering that the power increase they found suggested the presence of an additive model, they argued that the relationship between neural generations of the ongoing alpha activities and the ERFs can be explained by the so-called dual-generator hypothesis. This hypothesis indicates that two different neural events generate the ERFs and the alpha oscillations. Based on dual-generator model the ERF generators are quiescent prior to stimulus onset and become active after the presentation of the stimulus (Mazaheri and Jensen, 2006).

Chapter 6

6 General discussion and conclusion

6.1 General discussion

6.1.1 Automatic denoising of single-trial event-related potentials

Event-related potentials are hardly recognisable in the single-trial traces due to their low amplitude compared to the on-going EEG. Conventional analysis of ERPs was mainly based on averaging several single-trial responses to identical stimuli and studying the average signal without considering variations in the single-trials. However, different studies have shown the links between changes in the single-trials responses and cognitive processes, such as learning, sensitization and habituation (Quian Quiroga et al., 2007; Jongsma et al., 2006). The use of the wavelet transform to extract the single-trial ERPs has been reported in different studies (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000; Bartnik et al., 1992; Effern et al., 2000b; Effern et al., 2000a). Previously, an ad-hoc wavelet denoising scheme was proposed to enhance the visualisation of ERPs in the single-trials (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000). This method was based on denoising the average ERPs considering the time and frequency ranges in which the single-trial ERPs are expected to occur. Although this method has proven very useful for different applications of single-trial analyses, its main disadvantage is that one needs prior knowledge about the time and frequency ranges of the ERPs and the input of an expert user to select the wavelet coefficients manually (Quian Quiroga et al., 2007). This adds subjectivity to the denoising process and it is not practical for large number of channels, where different channels may require different selection of coefficients. In this thesis we improved this approach and presented an automatic denoising method (NZT method) for the extraction of the singletrial ERPs from the noisy background EEG. We evaluated the performance of the proposed method with simulated ERPs as well as real visual and auditory ERPs.

With the synthetic ERPs, the denoising performance was better than the one obtained with Donoho's level dependent thresholding and with the nondenoised data. The NZT method provided the lowest RMS error (P<0.001) in the extraction of the single-trial ERPs. The errors of the amplitudes and latencies of the extracted ERP components were also compared with the ones in the original data and the ones extracted by Donoho's technique and in general, the NZT denoising method gave the lowest estimation error.

For the real data, besides the very different characteristics of the ERPs in the visual and auditory modalities and at different electrodes, NZT denoising removed most of the baseline and background EEG activity; the single-trial ERPs were more clearly traceable with the denoised data. Most importantly, the selection of coefficients was very similar to the one done manually in the previous studies (Quian Quiroga and Garcia, 2003; Quian Quiroga, 2000), but in this case the selection was fully automatic.

The possibility of single-trial analyses opens the opportunity of a paradigm shift and the development of new experiments to study the identification of evoked responses in trial-by-trial bases. One such example has been the development of the learning oddball paradigm, where the predictability of a target stimuli is changed half-way through a series of stimuli and a single-trial analyses allowed tracking changes in the P3 response and how it correlated with the implicit learning of the sequence (Jongsma et al., 2006). A similar paradigm has been also used to study how bold and ERP responses correlate

on trial by trial bases, thus enabling combining the optimal time resolution of the ERP with the spatial resolution of fMRI (Eichele et al., 2005).

In this thesis, we used the proposed denoising algorithm to investigate the neural correlates of conscious face perception and the neural basis of ERPs generation by studying evoked responses in the single-trial level. Analysing trial-by-trial changes of latencies and amplitudes of evoked responses can provide crucial information about the mechanism underlying the modulation of average responses (Quian Quiroga et al., 2007). An example of such analysis is the study of modulation of an average mismatch negativity (MMN), a negative component in response to an odd stimulus in a series of regular stimuli, in sleep-deprived subjects after performing an auditory discriminating task (Quian Quiroga et al., 2007; Atienza et al., 2004). In this study with the analysis of the average ERPs it was first assumed that the reduced MMN in sleep-deprived subjects was due to a recruitment of a larger number of neurons involved in the task during sleep (Atienza et al., 2004) however single-trial analysis showed that this reduction was due to a larger latency jitter of the MMN responses (Atienza et al., 2005) in sleep-deprived subjects. Another example is the singletrial analysis of omission evoked potentials (OEPs), evoked responses to stimulus omission within a regular sequence of stimuli, in musicians versus nonmusicians which revealed a lower latency jitter in the OEPs of the musicians compared to the non-musicians (Quian Quiroga et al., 2007; Jongsma et al., 2004).

6.1.2 Single-trial analysis of conscious face perception

Several studies have reported the correlation of the N170 component with conscious face perception (Fisch et al., 2009; Genetti et al., 2009; Jemel et al., 2003; Pegna et al., 2011). In line with these works, the study described in Chapter 4 investigated the effect of conscious face perception and stimulus uncertainty (introduced by adding Gaussian noise) with the average ERPs. Moreover, we studied the underlying mechanisms of the amplitude and latency variations in the average N170 by analysing the single-trial responses.

Single-trial analyses have been used previously to study the N170 response to face and non-face stimuli (Gaspar et al., 2011; Philiastides and Sajda, 2006; Rousselet et al., 2007). For example Rousselet and his colleagues showed an amplitude increase in the single-trial responses to faces compared to non-faces stimuli (noise, textures and houses), which was maximum at frequency range of 5 to 15 Hz (Rousselet et al., 2007). While these works mainly focused on the study of the modulation of the N170 responses to face versus non-face stimuli, in this thesis we investigated the mechanism underlying amplitude modulation introduced by conscious face perception and stimulus uncertainty.

The analysis of the average N170 responses showed that the amplitude of the N170 was larger for the recognised compared to the non-recognised faces. Moreover, the average signals decreased as the noise level increased. The analysis of the single-trial amplitudes and latencies of the N170 showed that while the amplitude modulation introduced by the conscious face perception was due to the attenuation of the single-trial amplitudes of the unseen trials, the

amplitude modulation introduced by stimulus uncertainty (adding more noise) was due to a larger latency jitter.

6.1.3 Neural basis of ERP generation

Although ERPs are one of the most popular techniques in the analysis of human brain responses to sensory and cognitive tasks, the neural basis underlying the ERP generation, and its relation to the spontaneous EEG, is still under debate. In this thesis, we proposed a novel technique to dissociate the phase-resetting model from the additive model without the use of filtering. Based on our hypothesis, if two components of an average ERP are part of an oscillation, their latency should co-vary, i.e. increasing (decreasing) the amplitude of one should result in increasing (decreasing) the amplitude of the second one.

We obtained latency-corrected average ERPs and quantified the amplitude differences between the ERP components of the original signal and those of the latency-corrected signal. We used the NZT denoising algorithm in order to estimate the single-trial ERP latencies to generate the latency-corrected averages. We introduced a quantification factor to estimate the contribution of the evoked and/or phase-resetting activities underlying ERPs generations, the so called phase resetting value (*PR* value). Finally, in order to evaluate our hypothesis we applied the proposed method to the simulated VEPs based on the additive model and the phase-resetting model.

According to our quantification factor if the ERP components are generated based on the phase-resetting model, the *PR* value will be positive and typically less or equal to one $(0 < PR \le 1)$ while if the ERPs are generated based on the

additive hypothesis, the *PR* value will be zero or negative, typically not below minus one $(-1 \le PR \le 0)$.

We quantified the PR values for the simulated ERPs generated with the additive and phase-resetting model. The results revealed positive PR values for the ERPs generated by phase-resetting and negative (or close to zero) PR values for the ERPs simulated with the additive model, thus indicating the ability of our measure to distinguish the two models.

We further analysed the real ERPs (15 VEPs and 10 AEPs) both the prestimulus background EEG and the post-stimulus ERP components. For all the real data, as a control, we calculated the PR values obtained from the baseline EEG, which, as expected, were positive, thus indicating an alignment of ongoing oscillations. However, the post-stimulus PR values were negative or close to zero suggesting the additive model as the mechanism underlying ERPs generations. Overall, the proposed method supports the contribution of additive evoked components and also presents a measure to quantify the contribution of the two models in ERP generation.

In line with our results, Turi et al. (Turi et al., 2012) evaluated the presence of additive evoked components in local field potential (LFP) recordings from awake behaving macaques performing a visuo-motor integration task, and in human magnetoencephalography (MEG) recordings of steady-state visual evoked fields (SSVEFs). SSVEF is a sinusoidal oscillatory response of brain to a repetitive visual stimulus such as a flickering light that follows the repetition frequency of the stimulus. In this study the SSVEF obtained by flickering LEDs at different rates between 10 to 84.2 Hz. They used constrained ICA to remove the spontaneous, induced and phase-resetting components to isolate the additive evoked components and they verified the contribution of additive evoked components in the visual areas V2/4 in the LFP recordings and in MEG-SSVEFs.

6.2 General conclusion

In this thesis we developed a fully automatic denoising algorithm in order to visualise event-related potentials (ERPs) in single-trial traces. Moreover, we used this method to extract information about the mechanisms underlying conscious face perception, and to investigate the neural basis underlying ERP generations.

The description of the implementation of our automatic denoising method, the so called NZT denoising technique, was presented in Chapter 3. The NZT is based on the wavelet transform and it introduces an automatic selection of wavelet coefficients based on the inter- and intra-scale correlation of neighbouring wavelet coefficients and how their values deviated from baseline. We tested the performance of the NZT with the simulated ERPs and with real visual and auditory ERPs. With the simulated ERPs we showed that, compared to the data without denoising and compared to Donoho's denoising technique, the NZT significantly improved the observation of the single-trial ERPs and also the estimation of the amplitudes and latencies of the single-trial responses. With the real data we showed that the NZT removed most of the baseline and background EEG activity and improved visualisation of the ERPs in single-trials.

In Chapter 4 we used the NZT denoising algorithm to study conscious face perception and we showed the advantage of single-trial analysis over the study of the average ERPs. In this chapter we showed that, with the average signal, a larger N170 was observed for the recognised trials compared to the not recognised trials for all the threshold conditions (different noise levels). We also showed that the amplitude of the average N170 diminished when increasing the noise level. However, by studying the N170 responses in the single-trials we found that different neural mechanisms were responsible for these two amplitude modulations. More specifically, we showed that the amplitude modulation introduced by the conscious face perception was due to the attenuation of the single-trial amplitudes of the unseen trials, whereas the amplitude modulation introduced by stimulus uncertainty (adding more noise) was due to the generation of the higher latency variations across single-trials.

In Chapter 5, we proposed a novel technique to study whether ERPs are due to phase-resetting of ongoing EEG, or due to additive neural responses adding to the background EEG in response to the stimulus presentation. To test the method we used ERPs simulated based on the phase-resetting model and based on the additive model. This analysis also applied to real data and it revealed that the sensory components of VEPs and AEPs are mainly generated based on the additive model rather than the phase-resetting model.

After more than half a century of using average evoked potentials and designing paradigms to avoid single-trial fluctuations for getting better averages, the implementation of fully automatic single-trial analyses, and in particular, the identification of the evoked responses in the single-trials, opens the opportunity of a paradigm shift and the development of new experiments, where single-trial variations and the study of their correlation with behaviour is not avoided, but seeked. This will be of particular interest to neuroscientists who are studying cognitive processes, for example, those studying the dynamics underlying learning processes. Furthermore, this can have clinical relevance to study patients with different types of learning problems such as attention deficit hyperactivity disorder (ADHD), dementia, mild cognitive impairment, etc.

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