# Effects of Chiropractic Spinal Manipulation on Brain Activity

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# EFFECTS OF CHIROPRACTIC SPINAL MANIPULATION ON BRAIN ACTIVITY

**BY**
**MUHAMMAD SAMRAN NAVID**

DISSERTATION SUBMITTED 2020

AALBORG UNIVERSITY
DENMARK

# EFFECTS OF CHIROPRACTIC SPINAL MANIPULATION ON BRAIN ACTIVITY

by

Muhammad Samran Navid

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2020

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| Dissertation submitted: | June 2020 |
| PhD supervisor: | Professor Asbjørn Mohr Drewes, MD, DMSc, PhD<br>Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark |
| Co-supervisors: | Heidi Haavik, BSc (Chiropractic), PhD<br>New Zealand College of Chiropractic, New Zealand |
| | Imran Khan Niazi, MSc, PhD<br>New Zealand College of Chiropractic, New Zealand |
| | Dina Lelic, MSc, PhD<br>Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark |
| PhD committee: | Salome Kristensen, Clinical Associate Professor (chair)<br>Aalborg University |
| | Dean L. Smith, Clinical Associate Professor<br>Miami University |
| | Amit N.Pujari, Senior Lecturer<br>University of Hertfortshire |
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# CV

**Education:**

| | |
|---|---|
| 2015 | MS – Biomedical Engineering<br>Department of Biomedical Engineering and Sciences<br>National University of Sciences and Technology (NUST)<br>Islamabad, Pakistan |
| 2012 | BS – Computer Engineering<br>Department of Electrical Engineering<br>National University of Computer and Emerging Sciences (NUCES)<br>Lahore, Pakistan |

**Publications:**

- **Navid MS**, Niazi IK, Lelic D, Nedergaard RB, Holt K, Amjad I, et al. Investigating the Effects of Chiropractic Spinal Manipulation on EEG in Stroke Patients. Brain Sciences 2020;10:253. doi:10.3390/brainsci10050253.

- Jochumsen M, **Navid MS**, Rashid U, Haavik H, Niazi IK. EMG- Versus EEG-Triggered Electrical Stimulation for Inducing Corticospinal Plasticity. IEEE Transactions on Neural Systems and Rehabilitation Engineering : A Publication of the IEEE Engineering in Medicine and Biology Society 2019;27:1901–8. doi:10.1109/TNSRE.2019.2932104.

- **Navid MS**, Niazi IK, Lelic D, Drewes AM, Haavik H. The Effects of Filter's Class, Cutoff Frequencies, and Independent Component Analysis on the Amplitude of Somatosensory Evoked Potentials Recorded from Healthy Volunteers. Sensors (Basel, Switzerland) 2019;19:2610. doi:10.3390/s19112610.

- Jochumsen M, **Navid MS**, Nedergaard RW, Signal N, Rashid U, Hassan A, et al. Self-Paced Online vs. Cue-Based Offline Brain–Computer Interfaces for

Inducing Neural Plasticity. Brain Sciences 2019;9:127. doi:10.3390/brainsci9060127.

- **Navid MS**, Lelic D, Niazi IK, Holt K, Mark EB, Drewes AM, et al. The effects of chiropractic spinal manipulation on central processing of tonic pain - a pilot study using standardized low-resolution brain electromagnetic tomography (sLORETA). Scientific Reports 2019;9:6925. doi:10.1038/s41598-019-42984-3.

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# LIST OF PAPERS

This thesis is based on the following papers:

I. **Navid MS**, Niazi IK, Lelic D, Drewes AM, Haavik H. The Effects of Filter's Class, Cutoff Frequencies, and Independent Component Analysis on the Amplitude of Somatosensory Evoked Potentials Recorded from Healthy Volunteers. Sensors (Basel, Switzerland) 2019;19:2610. doi:10.3390/s19112610.

II. **Navid MS**, Lelic D, Niazi IK, Holt K, Mark EB, Drewes AM, et al. The effects of chiropractic spinal manipulation on central processing of tonic pain - a pilot study using standardized low-resolution brain electromagnetic tomography (sLORETA). Scientific Reports 2019;9:6925. doi:10.1038/s41598-019-42984-3.

III. **Navid MS**, Niazi IK, Lelic D, Nedergaard RB, Holt K, Amjad I, et al. Investigating the Effects of Chiropractic Spinal Manipulation on EEG in Stroke Patients. Brain Sciences 2020;10:253. doi:10.3390/brainsci10050253.

IV. Niazi IK., **Navid MS**, Lelic D, Shafique M, Holt K, Amjad I, et al. (in preparation). Impact of spinal manipulation on the cortical drive of lower limb muscle of chronic stroke patients.

# ABBREVIATIONS

| | |
|---|---|
| BSI | Brain symmetry index |
| CI | Confidence interval |
| CP | Cold-pressor |
| CSP | Cortical silent periods |
| DAR | Delta-Alpha ratio |
| EEG | Electroencephalography |
| EMG | Electromyography |
| EP | Evoked potentials |
| EPSP | Excitatory postsynaptic potential |
| ERP | Event-related potentials |
| FIR | Finite impulse response |
| FMA | Fugl-Meyer Assessment |
| HVLA | High velocity, low amplitude |
| IC | Independent component |
| ICA | Independent component analysis |
| IIR | Infinite impulse response |
| IPSP | Inhibitory postsynaptic potential |
| LORETA | Low-resolution electromagnetic tomography |
| MEP | Motor evoked potentials |
| SEP | Somatosensory evoked potential |

| | |
|---|---|
| sLORETA | Standardized low-resolution electromagnetic tomography |
| SNR | Signal-to-noise ratio |
| TA | Tibialis anterior |
| TMS | Transcranial magnetic stimulation |

# ENGLISH SUMMARY

Over the past decade, a lot of research has evaluated the neurophysiological effects of spinal manipulation. It has been proposed that spinal manipulation alters cortical excitability or neural plasticity. However, most of the studies have been performed in subclinical pain patients. Therefore, it would be beneficial to extend the research in different patient populations for a better understanding of the neural mechanisms altered by spinal manipulation.

The objective of this PhD thesis was to investigate the effects of spinal manipulation on the neural processing of pain, and cortical excitability of the damaged brain after stroke.

The PhD thesis is based on four studies. Study I was conducted on healthy persons, whereas Study II was based on subclinical pain patients. Studies III and IV were carried on chronic stroke survivors. In study I, each person participated in two experimental sessions. In contrast, studies II, III, and IV had a placebo-controlled, single-blinded, randomized, crossover design in which each participant received a control intervention and a chiropractic intervention in random order on separate days. Stimulations and recordings were performed before and after each intervention.

Study I assessed the effects of preprocessing on somatosensory evoked potentials (SEPs), where the electroencephalography (EEG) was recorded during median nerve stimulation. The main findings of this study were that the N30 SEP amplitude is reduced when preprocessed by (i) a filter with a higher high-pass cutoff frequency, and (ii) the use of independent component analysis, irrespective of the class and cutoff frequency of the filter. These results indicate that preprocessing SEPs with different parameters does not produce the same output. The findings of this study are important for comparison, reproducibility, and replicability of SEP based studies

Study II focused on evaluating the neurophysiological effects and corresponding brain sources to pain following the spinal manipulation. In this study, EEG was recorded during rest and tonic pain. The results showed that the change in spectral power of EEG due to pain was nullified by the spinal manipulation, which may suggest that spinal manipulation affects the development of pain habituation by affecting the cortical processing of pain.

Studies III and IV evaluated the effects of spinal manipulation on the neurophysiology of chronic stroke survivors. In study III, EEG was recorded during rest and median nerve stimulation. The results showed that the N30 SEP amplitude was increased after the spinal manipulation, which may reflect an improvement in the early sensorimotor function. In study IV, motor-evoked potentials (MEPs) were elicited using transcranial magnetic stimulation. The results showed that spinal manipulation

increased the MEP amplitudes, which implies that spinal manipulation increased the cortical excitability in patients with stroke.

In conclusion, the findings of the thesis suggest that care should be taken for reporting and using the SEP preprocessing parameters and that spinal manipulation extends beyond a local effect in muscles, joints, and ligaments. The manipulation has a significant impact on cortical processing of pain, and also seems to have an apparent neuroplastic effect in patients surviving a stroke. Therefore, it can be hypothesized that spinal manipulation reduces maladaptive neural plasticity. However, further research is required in these populations, with advanced neurophysiological, imaging, and statistical methods to improve our understanding of the effects of spinal manipulation and the clinical implications of the neuroplastic changes.

# DANSK RESUME

I det sidste årti har der været en del forskning somr har undersøgt de neurofysiologiske virkninger af kiropraktik. Den gængse hypotese er at kiropraktik ændrer på den kortikale eksitabilitet og neurale plasticitet, men det meste forskning er udført på patienter med subklinisk smerte. Derfor vil det være gavnligt at inkludere forskellige patient populationer for at opnå en bedre forståelse af de neurale mekanismer som ændres som følge af kiropraktik.

Formålet med denne ph.d. afhandling var at undersøge effekten af kiropraktik på neurofysiologien bag smerte og den skadede hjerne efter apopleksi.

Afhandlingen er baseret på fire studier. Studie I blev udført på raske forsøgspersoner, mens studie II blev udført på personer med subklinisk smerte. Studie III og IV blev udført på patienter med apopleksi. I studie I deltog forsøgspersonen i to eksperimentelle sessioner, mens der i studie II, III og IV blev udført forsøg som var placebo-kontrolleret, enkeltblindet og randomiseret med overkrydsningsdesign, hvor hver forsøgsperson modtog en kontrolintervention og en kiropraktiske intervention i randomiseret rækkefølge på forskellige dage. Stimulation og optagelse af signaler blev udført før og efter hver intervention.

I studie I blev effekten af valget af præ-processeringsteknikker målt på somatosensoriske evokerede potentialer (SEPs) ud fra elektroencefalografiske (EEG) optagelser under stimulation af nervus medianus. Hovedresultaterne af studie I var at N30 SEP-amplituden reduceres ved brug af (i) et filter med en højere knækfrekvens og (ii) brug af "independent component analysis" uafhængigt af filtertypen og knækfrekvensen. Disse resultater indikerer at præ-processeringsteknikker med forskellige parametre giver forskellige resultater. Resultaterne af dette studie er vigtige i forhold til sammenligninger og reproducerbarhed af fremtidige SEP-baserede studier.

Studie II fokuserede på evalueringen af den neurofysiologiske effekt og de tilhørende hjerneområder på smerte efter kiropraktik. I studie II blev der målt EEG under hvile og tonisk smerte. Resultaterne viste at en reduktion i den spektrale "power" i EEG'et pga. smerte blev "nulstillet" af kiropraktik, hvilket tyder på at kiropraktik påvirker udviklingen af habituering af smerte via normalisering af den kortikale processering.

I studie III og IV blev effekten af kiropraktik på neurofysiologiske mål evalueret hos patienter med apopleksi. I studie III blev der målt EEG under hvile og under stimulering af nervus medianus. Resultaterne viste en større N30 SEP-amplitude efter kiropraktik, hvilket kan indikere en forbedring i den tidlige sensoriske-motoriske funktion. I studie IV blev der målt motor-evokerede potentialer (MEP) ved brug af transkranial magnetisk stimulation. Resultaterne viste at kiropraktik øgede MEP-

amplituderne, hvilket betyder, at kiropraktik ændrer den neurale plasticitet efter apopleksi i gunstig retning.

Konklusionen af resultaterne i denne ph.d. afhandling er at man skal være omhyggelig med rapporteringen og brugen af parametre i SEP præ-processeringsteknikker, samt at kiropraktik har mere udbredte effekter i centralnervesystemet end de lokale virkninger på muskler, led og ligamenter. Kiropraktik har en signifikant effekt på den kortikale processering af smerte, og påvirker den centrale processering af sensoriske og motoriske funktionerhos patienter med apopleksi. En hypotese er derfor at kiropraktik reducerer den maladaptive neuroplasticitet ved disse patienter. Der er dog stadig brug for yderligere forskning i disse patientgrupper med avanceret neurofysiologiske, billeddannende og statistiske metoder for at forbedre vores forståelse af effekten af kiropraktik på centralnervesystemet.

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# CHAPTER 1. ELECTROENCEPHALOGRAPHY

*Electroencephalography* (EEG) is a method to study the electrical activity of the brain using electrodes placed on the scalp (M. X. Cohen, 2017; Nunez & Srinivasan, 2006; VandenBos, 2016). It is one of the most powerful non-invasive brain imaging techniques to study the electrophysiological activity of the brain (M. X. Cohen, 2017). The main advantage of EEG is its high temporal resolution, whereas the most likely disadvantage is that it cannot measure the small-scale and asynchronous activities of the neurons (M. X. Cohen, 2017).

This chapter briefly answers the questions: what are the generators of EEG, what are its types, and how is it processed.

## 1.1. GENERATION OF EEG

The movement of ions across cell membranes generate action potentials (Choi & Kim, 2018). When the action potential propagates to a synapse, a postsynaptic potential is generated (Choi & Kim, 2018). The excitatory postsynaptic potential (EPSP) increases the chance of the target neuron to fire, whereas the inhibitory postsynaptic potential (IPSP) tries to stop the target neuron from firing (Nunez & Srinivasan, 2006). These potentials produce electric fields around the neuron (Choi & Kim, 2018; Nunez & Srinivasan, 2006).

The electrical field generated by a single neuron is very weak and cannot be measured by EEG (Britton et al., 2016; Choi & Kim, 2018; X. M. Cohen, 2014). However, the electrical activity generated by the postsynaptic potentials fired synchronously by the cerebral cortex neurons, particularly pyramidal neurons, have a magnitude large enough to be detected by EEG (Britton et al., 2016; Choi & Kim, 2018; X. M. Cohen, 2014; Nunez & Srinivasan, 2006). Approximately 10,000-50,000 of these neurons are required to fire synchronously to produce a signal strong enough to be measured by scalp EEG (X. M. Cohen, 2014).

## 1.2. TYPES OF EEG

The EEG can be broadly classified into spontaneous EEG and evoked or event-related potentials.

### 1.2.1. SPONTANEOUS EEG

The brain generates spontaneous or continuous EEG in the absence of any sensory stimuli (Nunez & Srinivasan, 2006). In a living brain, the EEG is neither flat nor random but contains rhythms (M. X. Cohen, 2017). These rhythms, also known as neural oscillations, are grouped based on the frequencies of the oscillations. The typical frequencies with commonly used bandwidths are:

- delta: 1-4 Hz
- theta: 4-8 Hz
- alpha: 8-12 Hz
- beta: 12-30 Hz
- gamma: 30-80 Hz

These oscillations have been observed on multiple temporal and spectral scales (Varela et al., 2001). Many studies have shown that different processes, such as perception, cognition, motor, and emotion, are linked with specific neural oscillations (Buzsaki, 2006; Engel et al., 2001; Herrmann et al., 2010; Kistler et al., 2000; Klimesch et al., 2008; Siegel et al., 2012).

The two types of spontaneous EEG used in the PhD studies were resting-state EEG (studies II and III) and tonic pain EEG (study II).

#### 1.2.1.1 Resting-state EEG

Resting-state EEG is a kind of spontaneous EEG that can be defined as the brain activity generated by a person involuntarily or without any external stimulus during rest or relaxed wakefulness (Laufs, 2008; Musso et al., 2010; Raichle & Snyder, 2007). This kind of EEG was seen as early as 1929 when brain oscillations (8-12 Hz) in the posterior region were found during the state of wakefulness and closed eyes (Berger, 1929). These oscillations were called ‘alpha rhythm’.

Usually, there is considerable variability in resting-state EEG data, and it is suggested to have at least 2 minute long recordings to obtain a better estimate of the power of different frequency bands (Brismar, 2007). Additionally, resting-state EEG drifts over time, likely due to changes in the level of attentiveness (Gram et al., 2015). Different methods, such as focusing on a spot (on-screen) or a simple mathematical task, are recommended to maintain attention (Dowman et al., 2008; Jobert et al., 2012).

#### 1.2.1.2 Tonic pain EEG

Tonic pain EEG is a continuous EEG recorded during painful tonic stimulation (Gram et al., 2015; Nir et al., 2012). Tonic pain is used to study neural mechanisms of consistent pain. A brief painful stimulus (in milliseconds) may only cause the onset of pain perception, and it may not be able to simulate the experience of clinical pain (Nir et al., 2010, 2012), where autonomic and cognitive processing also takes place. On the other hand, tonic pain can produce a more comparable sensory experience to that of clinical pain (Huber et al., 2006), and that is why it was employed in study II.

### 1.2.2. EVOKED POTENTIALS

The evoked potentials (EPs) are neural responses to specific sensory stimuli, such as a flash of light, touch, or (small) electric shocks (Nunez & Srinivasan, 2006; VandenBos, 2016). Multiple stimuli are provided, and to reduce noise, the EPs are obtained by averaging the EEG segments corresponding to the stimuli. Event-related potentials (ERPs), on the other hand, are recorded in a similar fashion as EPs but usually have higher latencies (such as cognitive events) (Luck, 2014; Nunez & Srinivasan, 2006). Compared to ERPs, EPs are related to elementary sensory stimuli; however, the terms EP and ERP are often used interchangeably (VandenBos, 2016).

In studies I and III, EPs known as somatosensory evoked potentials (SEPs) were used. Figure 1–1 shows an example of individual and averaged EPs (SEPs).

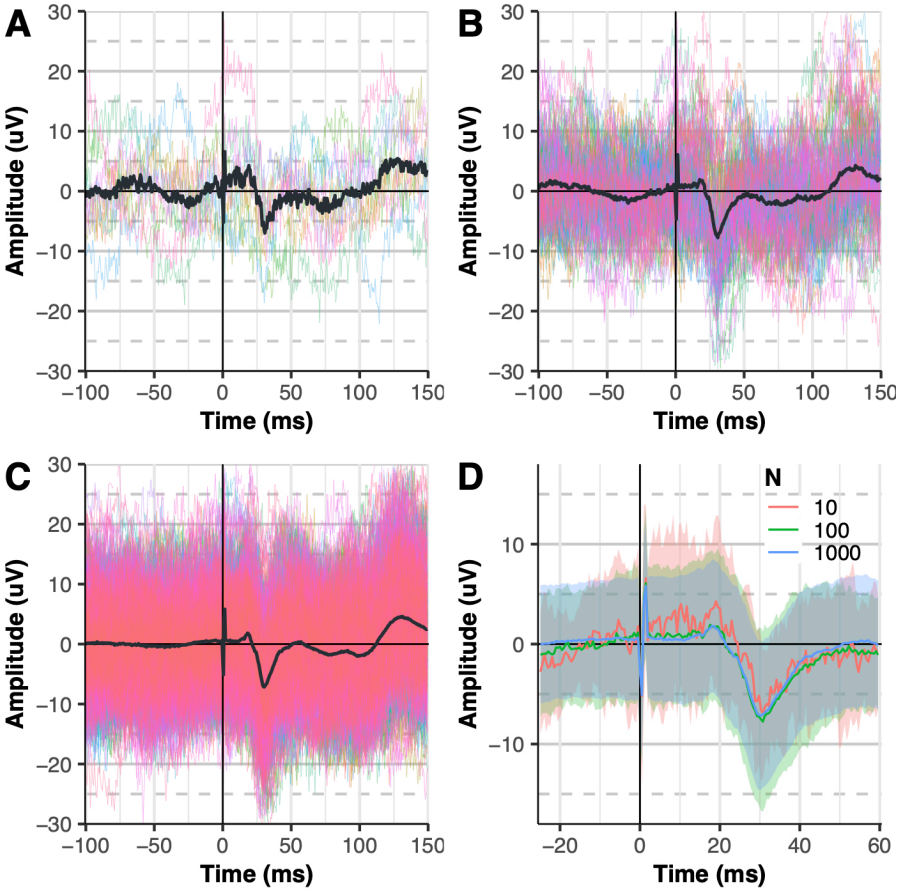


*Figure 1–1. Somatosensory evoked potentials (SEPs) and the influence of noise. Individual epochs as well as their averages (in black) are shown for (A) n = 10, (B) n =100, and (C) n =1000 epochs. The stimulus time is at 0 ms. The averaging process reduces the variability in the signal by (i) removing brain activity which is not related to the event/stimulus, and (ii) removing random noise or processes arising from other environmental factors. (D) shows the mean ± SD of SEPs based on a different number of epochs. Although it appears that n = 100 gives a reasonable averaged SEP as n =1000, however, the variability is quite high. Furthermore, after baseline correction, the baseline (pre-stimulus period) of n =1000 averaged SEP is better centered around 0 μV compared to n = 100 averaged SEP, which shows the assumption that the pre-stimulus activity is clean and does not contain any activity related to the event. Therefore, it makes the calculations on post-stimulus activity more reliable.*

### 1.2.2.1 Somatosensory evoked potentials

The somatosensory evoked potential (SEP) is an electrical potential recorded at the surface of the skin (or scalp), which is elicited in response to peripheral nerve

stimulation (Passmore et al., 2014; H H Taylor, 2007; Toleikis, 2005). The median, ulnar, radial, peroneal, and tibial nerves are most commonly stimulated using transcutaneous electrical stimulation (H H Taylor, 2007).

Like other EPs, multiple stimuli are required to obtain clean averaged SEP waveforms. The amplitudes and latencies of peaks in the SEPs are used for analysis (Passmore et al., 2014). The time window of the peaks of interest is up to 100 ms with respect to the stimulus (H H Taylor, 2007); however, so-called 'early peaks' which are within 35 ms of the stimulus, have been found useful clinically (Giblin, 1964; H H Taylor, 2007). The early SEP peaks used in the PhD studies are N20 (III) and N30 (I and III).

In healthy subjects, the N20 peak corresponds to the earliest cortical processing related to the stimulation in the primary somatosensory cortex (SI) (Passmore et al., 2014; H H Taylor, 2007). It is found in the parietal region, contralateral to the side of stimulation (Passmore et al., 2014). The N30 peak, on the contrary, is considered to be associated with complex cortical processing and generated at the motor, premotor, and prefrontal cortices (Balzamo et al., 2004; Cebolla et al., 2011; Waberski et al., 1999). The frontal N30 is considered to reflect sensorimotor integration (Rossi et al., 2003). Figure 1–2 shows the N20 and N30 peak complexes.

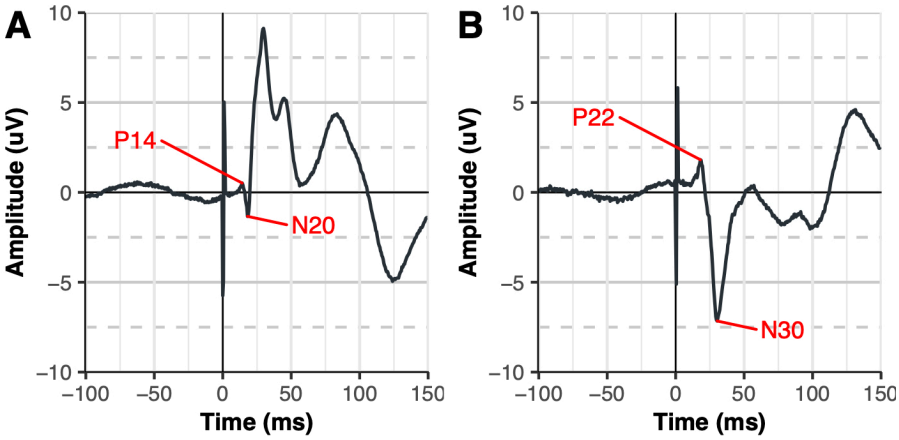


*Figure 1–2. N20 and N30 SEP peaks. (A) The N20 SEP peak complex from contralateral to stimulation central-parietal channel, and (B) the N30 SEP peak complex from contralateral to stimulation frontal channel. The absolute difference of the marked peaks gives the (A) N20 and (B) N30 amplitudes. The latencies of the peaks are measured with respect to the stimulus onset (0 ms).*

## 1.3. EEG PREPROCESSING

EEG signals recorded from the scalp contain activity from the brain as well as from non-neural sources such as from eyes, muscles, heart, skin, and power lines (Luck, 2014). This reduces the signal-to-noise ratio (SNR) because the non-neural activity or artifacts are 5-10 times bigger than the signal of interest (Jochumsen, 2015). There are multiple ways to increase the SNR, but the most basic and often used are filtering and artifact rejection and correction.

### 1.3.1. FILTERING

The ubiquitous step in the EEG preprocessing is filtering (Widmann et al., 2015). Filters can be classified based on their class, type, cutoff frequencies, and order.

Digital filters have two classes; finite impulse response (FIR) and infinite impulse response (IIR). The main difference between the two is that FIR applies some weights to the input to produce the output, whereas the IIR is recursive in nature, i.e., it takes some of its output back as input (i.e., feedback) (S. Smith, 2003). FIR filters usually have better performance than IIR filters; however, the execution of the FIR filter is slower than the IIR filter (S. Smith, 2003; Widmann et al., 2015).

Type of the filter depends on the frequencies of the signal which are being allowed to pass and which are being attenuated. High-pass filters allow high frequencies to pass and attenuates low frequencies. Low-pass filters work in the opposite manner, i.e., they allow low frequencies to pass while attenuating high frequencies. Band-pass filters allow a particular range of frequencies to pass, whereas band-stop or notch filters stop a particular range of frequencies. Each filter in a frequency-domain has an equivalent filter in time-domain, and vice versa (Luck, 2014; S. Smith, 2003). However, the precision of a filter in one domain is inversely proportional to the precision in the other domain (Luck, 2014). Figure 1–3 shows frequency-domain filters.

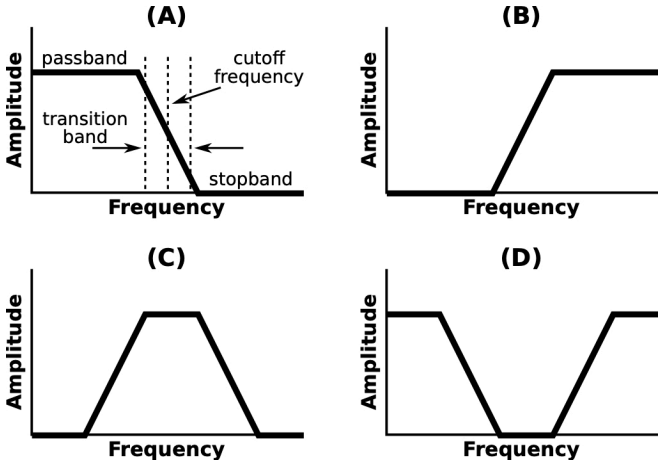


*Figure 1–3. Frequency domain filter responses. (A) Low-pass, (B) high-pass, (C) band-pass, and (D) band-stop filters.*

The frequency where the amplitude of the signal is reduced by some factor, usually by 50%, 70.7%, 90%, or 99%, is defined as the cutoff frequency of the filter (S. Smith, 2003; Widmann et al., 2015). This cutoff frequency is in the middle of a transition band, which is between the frequencies allowed to pass (passband) and frequencies being attenuated (stopband). The width of the transition band is defined by the order of the filter. Higher-order means narrow transition bandwidth, which is better at separating the frequency bands. However, since the precision in one domain is inversely proportional to the precision in the other domain (Luck, 2014), precision in the frequency domain with high order produces distortions and ringing artifacts in the signal in the temporal domain. Figure 1–3A shows passband, stopband, and transition band in a low-pass filter.

The freely available book 'The Scientist and Engineer's Guide to Digital Signal Processing' (S. Smith, 2003) at http://www.dspguide.com/ and guidance for designing filters for electrophysiological data (Widmann et al., 2015) are recommended for further reading.

Study I evaluated the effects of filtering parameters on the N30 amplitude.

### 1.3.2. ARTIFACT REJECTION

EEG is usually stored in a continuous form. Before further processing, segments of EEG, also known as epochs, are extracted, which are time-locked to the stimulus.

Each epoch (usually) has the same length and contains a period of EEG prior to the stimulus and a period of EEG after the stimulus. The period before the stimulus is known as the pre-stimulus or baseline period. Before averaging the epochs, the average of the baseline period is subtracted from the whole epoch. This process is known as baseline correction and minimizes voltage offsets and drifts in the EEG data (Luck, 2014). Baseline correction is also required to avoid issues with artifact rejection.

The epochs, or trials with artifacts, are discarded to increase the statistical power of the analysis as well as to reach a valid conclusion from the results (Luck, 2014). The epochs can be marked by manual inspection, automatic methods, or a mixture of both. The epochs can be removed if they contain blinks, saccades, electromyography (EMG), amplifier saturation, or sporadic activity (X. M. Cohen, 2014; Luck, 2014), among other artifacts.

Blink artifacts are usually present in the frontal channels, and they do not destroy the neural EEG but linearly add to it (X. M. Cohen, 2014). Similarly, the voltage deflection due to eye movements at a channel is a linear function of the magnitude of the eye movement (Luck, 2014). The epochs with blinks and saccades can be kept and corrected by using independent component analysis (ICA) (Luck, 2014). However, this strategy may not work for experiments that require focusing on tasks and blinking, or eye movements might indicate that the participant did not see the stimulus (X. M. Cohen, 2014). The step-function can be used to detect eye blinks and movements (Luck, 2014).

EMG bursts are added in the EEG if the participant moves, sneezes, coughs, or speaks. This artifact is present mostly in the electrodes located near the face, neck, and ears (X. M. Cohen, 2014).

Amplifier saturation, on the other hand, is caused by slow voltage drifts, and EEG may become flat for some period. A moving window of some length, such as 100-150 ms long, can detect this flat-line EEG by comparing the absolute voltage in that window to a threshold, e.g., 2 μV (Luck, 2014).

### 1.3.3. INDEPENDENT COMPONENT ANALYSIS

Independent component analysis (ICA) can be used to correct the artifacts, especially those which are related to eye blinks and movements (Luck, 2014). ICA uses the statistical properties of the EEG, unlike other methods for source localization (section 1.4), which are based on the biophysics of the voltage conduction (Luck, 2014).

ICA calculates the time courses of the underlying components by finding the unmixing matrix $W$, such that when it is multiplied with the data matrix $X$, produces the time course matrix $U$ of the independent components (ICs) (Luck, 2014; Onton et al., 2006; Onton & Makeig, 2006).

$$\boldsymbol{U = WX} \tag{1}$$

If there are $n$ channels and $t$ time points, the dimensions of $X$ and $U$ are $n * t$, and $W$ is $n * n$. Such an unmixing matrix $W$ is required which produces ICs that are maximally independent, meaning that there is no relationship between the time courses of any two ICs while keeping the cortical source locations spatially fixed (Luck, 2014; Onton et al., 2006; Onton & Makeig, 2006).

Equation (1) implies that

$$\boldsymbol{X = W^{-1}U} \tag{2}$$

where $W^{-1}$ is the inverse of $W$, and is called the mixing matrix. The mixing matrix $W^{-1}$ (dimensions $n * n$) have the weights with which the component activity is projected at the scalp (i.e., IC scalp map/topography). The portion of the original data $X$ that is contributed by the $i$th IC ($X_i$) is calculated by

$$\boldsymbol{X_i = W_i^{-1}U_i} \tag{3}$$

The whole data $X$ are, therefore, obtained by summing the ICs ($X_i$)

$$\boldsymbol{X = \sum_{i=1}^{n} X_i} \tag{4}$$

Guidelines to use ICA for identifying brain and non-brain components are discussed in Appendix A.

In study I, the effects of ICA application on the N30 amplitude were evaluated.

## 1.4. SOURCE LOCALIZATION

The electrical activity from cortical neurons can be represented by a dipole (Britton et al., 2016; Choi & Kim, 2018; Nunez & Srinivasan, 2006). The direction of a dipole is parallel to the orientation of the pyramidal neurons responsible for generating it (Britton et al., 2016). The modeling of the electrical activity generated by a dipole, which *will be* recorded by the scalp electrodes, is known as a forward problem. It is

relatively easy to solve since information about the source is known (Choi & Kim, 2018; Luck, 2014; Michel et al., 2004; Michel & Brunet, 2019). The reverse of forward problem is an inverse problem, in which the location and strength of the source are to be calculated based on the information or signal recorded at the scalp (Choi & Kim, 2018; Luck, 2014; Michel et al., 2004; Michel & Brunet, 2019). The inverse problem has no unique solution, and there will be an infinite number of solutions that can produce the same scalp distribution (Helmholtz, 1853; Michel et al., 2004; Plonsey, 1963). Therefore, a priori assumptions are required about the generation of EEG, and better assumptions lead to more reliable source localization (Michel et al., 2004; Michel & Brunet, 2019).

Source localization can be performed by using equivalent current dipole models or distributed source models.

### 1.4.1. DIPOLAR SOURCE MODEL

Dipolar models assume that a small number of dipoles or sources can model the potentials recorded at the scalp (Choi & Kim, 2018; Luck, 2014; Michel et al., 2004). The number of dipoles that can be estimated, however, is limited to the number of electrodes (Michel & Brunet, 2019). The least-squares method for dipolar modeling involves fixing, adjusting, and adding dipoles in an iterative manner (Choi & Kim, 2018). Each model is then used to calculate the potentials generated by the dipole(s), which will be recorded at the scalp (i.e., forward problem) and compared with the observed potentials. The difference is assessed by the least-squares error, and the model with the minimum least-square error is accepted as the best model that explains the measurements (Choi & Kim, 2018; Michel et al., 2004). However, there are limitations to this approach, as (i) the actual number of dipoles is unknown and it is required to estimate the number of dipoles (which is usually done based on physiological knowledge (Michel et al., 2004)), but that estimated number cannot represent the actual big number of dipoles (Choi & Kim, 2018), and (ii) the minimum least-squares source estimate is not necessarily close to the real sources (Choi & Kim, 2018; Michel et al., 2004).

The dipolar source model was used in study III to estimate the location and strength of the sources of the N30 peak.

### 1.4.2. DISTRIBUTED SOURCE MODEL

Distributed source model assumes that sources are present in the cortical pyramidal neurons (Choi & Kim, 2018; Luck, 2014). Instead of a small number of dipoles, the

model assumes that the brain is a 3D grid with many points where each point is considered a possible location of a source (Luck, 2014; Michel et al., 2004). The number of points in the grid is generally a lot more than the number of recording electrodes, and no a priori assumption about the number of dipoles is required (Choi & Kim, 2018; Michel et al., 2004).

There are multiple algorithms for distributed source localization, but most of them are modifications of the Minimum-Norm Estimate. The Minimum-Norm Estimate selects the model, which has the minimum overall source activity and produces the observed scalp distribution (Hämäläinen & Ilmoniemi, 1994). This algorithm does not estimate the deeper sources very well (Choi & Kim, 2018; Luck, 2014; Michel et al., 2004; Michel & Brunet, 2019). Weighted Minimum-Norm Estimates are, therefore, used to compensate this depth-bias (Choi & Kim, 2018; Michel et al., 2004; Michel & Brunet, 2019). One of the Weighted Minimum-Norm Estimates is the low-resolution electromagnetic tomography (LORETA) method (Pascual-Marqui et al., 1994). LORETA uses the solution with smooth spatial distribution using a Laplacian operator (Choi & Kim, 2018; Luck, 2014; Michel et al., 2004; Michel & Brunet, 2019). The smoothness of the distribution is based on the physiological reason that the activity of neighboring neurons is correlated (i.e., it is synchronous and simultaneous with gradual changes) (Choi & Kim, 2018; Luck, 2014; Michel et al., 2004; Michel & Brunet, 2019). Due to the smoothness constraint, LORETA is appropriate for estimating the center of the activity but not for the extent of activated areas (Luck, 2014). The standardized low-resolution electromagnetic tomography (sLORETA) is a similar method but normalizes the estimates by taking into account the variances of the data and sources (Pascual-Marqui, 2002). It is claimed that sLORETA has zero-localization error in noise-free conditions, and the least localization error in noisy environments compared to other methods (Pascual-Marqui, 2002).

The distributed source model, sLORETA, was used for localization of the brain activity during tonic pain in study II, and rest in studies II and III.

# CHAPTER 2. CHIROPRACTIC MANIPULATION

Chiropractic is a manual therapy that aims to improve the function of the nervous system by adjusting the spine (Haavik, 2014; Haavik & Murphy, 2012; New Zealand Chiropractic Board, 2004). It is also used as a safe and effective treatment for improving musculoskeletal issues, such as low-back pain, neck pain, shoulder pain, and osteoarthritis, among others (Bronfort et al., 2010, 2012). Chiropractic manipulation is also known as chiropractic care, chiropractic intervention, chiropractic spinal adjustment, spinal adjustment, chiropractic spinal manipulation, and spinal manipulation (Haavik, 2014).

This chapter discusses the basics of spinal manipulation and its effects on neurophysiology and neural plasticity.

## 2.1. BASICS OF MANIPULATION

A chiropractor assesses the spine for abnormal movement, tenderness, and tightness associated with vertebral motion segments (Cooperstein et al., 2010, 2013; Degenhardt et al., 2005; Schneider et al., 2008). These vertebral motion segment abnormalities are called vertebral subluxations by chiropractors and are thought to affect the physiological function and general health by inducing maladaptive neural plastic changes (Haavik, 2014; Haavik & Murphy, 2012; New Zealand Chiropractic Board, 2004). After the assessment, the chiropractor adjusts the spinal joints considered to have abnormal movement or function by using his/her hands or a mechanical adjusting device to apply a quick but controlled thrust to the spinal joint (high velocity, low amplitude (HVLA)) (Haavik, 2014). This procedure is known as a chiropractic adjustment or spinal manipulation.

In studies II and III, the spinal manipulations provided to the subclinical pain patients and stroke survivors were HVLA adjustments, which have also been used in earlier studies that have assessed the neurophysiological effects of the treatment (Haavik & Murphy, 2012; Lelic et al., 2016; Niazi et al., 2015). In these studies, an experienced chiropractor performed HVLA adjustments to the spine or pelvic joints (Cooperstein & Gleberzon, 2004). If required, multiple levels of the spine were adjusted. The locations selected for the spinal adjustments were based on the biomechanical features normally used by chiropractors as clinical indicators for chiropractic adjustments (Triano et al., 2013). These included tenderness to palpation of the relevant joints, manual palpation for the restricted intersegmental range of movement, palpable

asymmetric intervertebral muscle tension, and any unusual or blocked joint play and end-feel of the joints (Triano et al., 2013).

## 2.2. SAFETY OF MANIPULATION

Concerns arose about the safety of chiropractic manipulation because several studies found a statistical relationship between chiropractic manipulation and vertebral artery dissections (Rothwell et al., 2001; W. S. Smith et al., 2003). However, large population-based studies have shown that there is no increased risk of having a vertebral artery dissection after seeing a chiropractor compared with seeing a medical doctor (Cassidy et al., 2009, 2017; Kosloff et al., 2015). A recent independent review by Church et al. (Church et al., 2016) on this topic has concluded that there is no causal relationship between cervical manipulations and cervical artery dissections. The authors of this review suggested that the statistical relationship between chiropractic and stroke was due to people who had a stroke in progress ended up with a head or neck pain, and that some sought chiropractic care for this; hence there is an association, but that the stroke was likely in progress and not caused by the manipulations. This review suggested that if neck manipulations actually caused vertebral artery dissections, there would be an increased risk identified in large population-based studies such as those of Cassidy et al. (Cassidy et al., 2009, 2017) and Kosloff et al. (Kosloff et al., 2015).

## 2.3. NEURAL PLASTICITY MODEL OF MANIPULATION

Neural plasticity, or brain plasticity, refers to the ability of the nervous system to change (in form and function) and adapt to the environment (Cech & Martin, 2012; Kaas, 2001). These plastic changes occur throughout life and are a mechanism for learning new skills as well as recovering from injuries (Kaas, 2001). Positive changes for an individual are termed adaptive neural plasticity (De Ridder et al., 2017). However, negative changes can also occur, and this is known as maladaptive neural plasticity (De Ridder et al., 2017; Kaas, 2001). Studies have shown that pain, musculoskeletal disorders, motor disorders, and injury promote maladaptive neural plasticity (Falla, 2004; Kaas, 2001; Seifert & Maihöfner, 2011; van Vliet & Heneghan, 2006; Wall et al., 2002). It is thus hypothesized, that maladaptive neural plasticity, due to long-term pain, is one of the reasons for affected person's symptoms and functional disturbances instead of the actual initial physical injury or functional issue itself (Brumagne et al., 2000; Haavik & Murphy, 2012; Michaelson et al., 2003; Paulus & Brumagne, 2008).

Based on more than a decade of research, Haavik et al. (Haavik & Murphy, 2012) have hypothesized a model to explain how vertebral subluxation leads to altered sensorimotor integration and maladaptive neural plasticity, which over time causes pain and dysfunction. The model additionally explains how spinal manipulation may promote adaptive neural plastic changes by enhancing afferent input to the central nervous system. The model is shown in Figure 2–1.

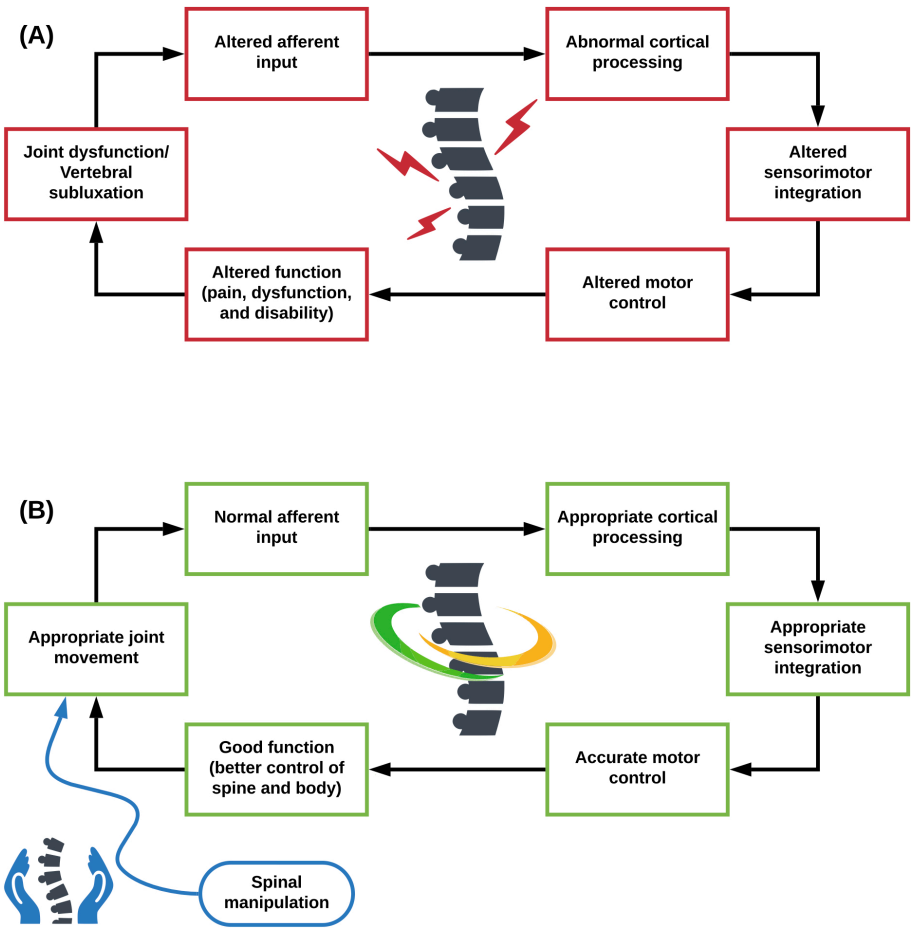


*Figure 2–1. Hypothesized neural plasticity model. (A) Spinal dysfunction leading to altered sensorimotor integration, which in turn causes bodily dysfunction. (B) Spinal manipulation normalizing the spinal segments to restore cortical processing and body functions. (The figure is inspired by figure 1 of Haavik et al. (Haavik & Murphy, 2012)).*

## 2.4. NEUROPHYSIOLOGICAL EFFECTS OF MANIPULATION

Over the past decade, there has been a lot of research to evaluate the neurophysiological effects of spinal manipulation (a few of them are discussed below). Most of the studies have been performed in subclinical pain patients. Subclinical pain refers to recurring low-intensity neck or back pain, for which medical treatment has not yet been sought (Haavik & Murphy, 2012). The neurophysiological effects of the treatment can be evaluated better in such a group of individuals since they do not have prevailing pain or receive analgesics, which can be a confounding factor in the interpretation of results of neurophysiological testing as pain and analgesics can affect sensory processing and motor control (Haavik & Murphy, 2011; Lelic et al., 2017; Rossi et al., 2003).

Using SEPs recorded from subclinical pain patients, it has been suggested that spinal manipulation affects the cortical activity associated with early sensory processing and sensorimotor integration (Haavik-Taylor & Murphy, 2007; Haavik Taylor et al., 2010; Haavik Taylor & Murphy, 2010). In these studies, the N20 and N30 SEP amplitudes were reduced after the manipulation session, and the changes persisted for at least 20-30 minutes (Haavik-Taylor & Murphy, 2007). The mechanism responsible for this change in early sensorimotor integration following spinal manipulation is thought to be due to the barrage of mechanoreceptive input that occurs during the manipulation, in particular from the deep muscle afferents (Haavik-Taylor & Murphy, 2007; Haavik Taylor et al., 2010; Haavik Taylor & Murphy, 2010; J. G. Pickar & Bolton, 2012; J G Pickar & Wheeler, 2001; Joel G. Pickar, 1999; Joel G. Pickar & Kang, 2006; Joel G Pickar, 2002; Joel G Pickar et al., 2007). These early sensorimotor integrative changes are most likely the reason for improved function following spinal manipulation, such as improved elbow joint position sense (Haavik & Murphy, 2011), increased multimodal integration of sound and visual information, and the ability to take a faster step (K. R. Holt et al., 2016). A decrease in N30 SEP peak following spinal manipulation was also found in a more recent study (Lelic et al., 2016), where the source localization of this peak demonstrated that the changes primarily occur in the prefrontal cortex. The prefrontal cortex is associated with cognitive thinking and decision-making using somatosensory input and information from other internal and external sources (Passmore et al., 2014). Therefore, the changes in the prefrontal activity following spinal manipulation may also explain the improved sensorimotor integration, as well as the functional improvements found, following chiropractic care in other studies (Haavik-Taylor & Murphy, 2007; K. R. Holt et al., 2016; Heidi Haavik Taylor & Murphy, 2008, 2010).

Proprioceptive processing appears to be impacted by vertebral function (Haavik & Murphy, 2012). For example, people with subclinical neck pain have reduced elbow joint position sense and reduced shoulder joint position sense and kinesthesia (Haavik & Murphy, 2011; Paulus & Brumagne, 2008). This is considered to be due to the altered central interpretation of neck proprioceptive signals in subjects with recurrent

neck pain and dysfunction (even on pain-free days), which probably reflects an offset in the egocentric reference frame or a decreased capacity to switch between reference frames (Paulus & Brumagne, 2008). Furthermore, studies have shown that spinal manipulation can improve the accuracy of elbow position sense, even after a single session of spinal manipulation (Haavik & Murphy, 2011). Other studies have also demonstrated that spinal manipulation can influence proprioception (Haavik & Murphy, 2011; K. R. Holt et al., 2016; Palmgren et al., 2006). It was reported that after 3-5 sessions of manipulation over five weeks, patients with cervical pain showed higher accuracy of head reposition, indicating improved spinal proprioception (Palmgren et al., 2006). Similarly, 12-weeks of chiropractic care (that consisted of spinal manipulation only) showed improved ankle joint position sense and sensorimotor function in older people (K. R. Holt et al., 2016).

Several additional studies have shown further changes in sensorimotor integration after spinal manipulation by assessing motor control. Using transcranial magnetic stimulation (TMS), shorter cortical silent periods (CSP) were observed following spinal manipulation (Heidi Haavik Taylor & Murphy, 2008). Originally, these were considered to reflect altered processing in spinal and cortical inhibitory pathways (Heidi Haavik Taylor & Murphy, 2008). However, follow up work has demonstrated that these changes in the TMS-induced CSP are associated with an increase in low threshold motoneuron excitability in a lower limb muscle (Haavik, Niazi, et al., 2018). The study utilized EMG recorded from the surface and intramuscular fine-wire electrodes using a combination of probability and frequency-based analysis techniques to characterize the TMS-induced CSP observed following spinal manipulation (Haavik, Niazi, et al., 2018). Another study, measuring the H-reflex, has also shown that chiropractic spinal manipulation can increase low threshold motoneuron excitability (Niazi et al., 2015). Yet, another study using TMS- induced input-output curves, in both upper and lower limb muscles, has shown that spinal manipulation can increase corticospinal excitability (Haavik, Niazi, Jochumsen, et al., 2017). The results from this TMS study indicated that the corticospinal excitability increases following spinal manipulation and the changes occur at the cortical level instead of at the level of the spinal cord (Haavik, Niazi, Jochumsen, et al., 2017).

H-reflex and V-wave studies performed in subclinical pain patients (Niazi et al., 2015) and Taekwondo athletes (Christiansen 2018) corroborated this notion, as they both found that spinal manipulation resulted in improved motoneuron excitability, increased strength, and a large increase in V-waves, with minimal or no change in the H-reflex. Similarly, a recent study by Holt et al. (K. Holt et al., 2019), showed that a single session of spinal manipulation increases the strength of plantar flexor muscles in chronic stroke patients by approximately 65%, which was again accompanied by increased V-wave amplitudes and no changes in the H-reflex, suggesting that these changes in strength are due to supra-spinal neural plastic changes, rather than changes in spinal excitability.

# CHAPTER 3. THESIS OBJECTIVES AND FINDINGS

This chapter discusses the aims of the PhD thesis and summarizes the methods and results of the four studies, which are the basis of the thesis.

## 3.1. AIMS OF THE THESIS

Previous studies evaluating the effects of chiropractic spinal manipulation on neurophysiological changes have been done mostly in subclinical pain patients; on days they were not experiencing any pain, as discussed in Chapter 2. Very few studies have looked at what happens in the brains of this population when they are experiencing pain. Nor have there been many studies that have looked at the effects of spinal manipulation on brain function of other populations, such as pain populations (Didehdar et al., 2020), or populations that have experienced brain damage, such as chronic stroke victims (K. Holt et al., 2019). Therefore, this thesis sought to expand on previous findings by exploring what happens in subclinical pain participants following chiropractic manipulations when they were experiencing experimental tonic pain. Furthermore, this thesis sought to expand on previous work by further exploring what happens following spinal manipulation in the brains of people who have suffered from a stroke. Thus, the thesis aimed to assess the effects of spinal manipulation on the brain activity of (i) subclinical pain patients in response to tonic pain, and (ii) stroke survivors. Four studies were conducted to achieve these aims.

While preparing for this thesis, and discovering the differences found in the literature regarding the processing of SEPs, study I was conducted first with a focus to evaluate whether preprocessing affects SEPs, as SEPs were to be used as a major parameter for assessment in the subsequent studies. Study II focused on the effects of spinal manipulation in the subclinical population undergoing experimental tonic pain, whereas studies III and IV evaluated the effects of the treatment in stroke survivors.

## 3.2. STUDY I

The objective of the study was to assess how different EEG preprocessing parameters affect the amplitude of the N30 SEP peak.

There were two sessions, separated by at least a week, of whole-scalp EEG recordings from 17 healthy subjects while their right median nerve was stimulated 1000 times. The EEG was preprocessed using, at a time, one of the twelve possible combinations of the class of filters (two types: FIR and IIR), the cutoff frequency of filters (three passbands: 0.5-1000 Hz, 3-1000 Hz, and 30-1000 Hz), and the usage of ICA (used: yes or no). After preprocessing and rejection of bad epochs, the amplitude of N30 SEPs was calculated from the contralateral to the stimulation frontal electrode by taking the absolute peak-to-peak amplitude of the P22 and N30 peaks.

The linear mixed effect model showed that (i) the class of filters, FIR and IIR, did not affect the N30 amplitude, (ii) the cutoff frequency 30-1000 Hz significantly reduced the N30 amplitude compared to the other two frequency bands (both $p < 0.0001$), whereas the N30 amplitude was similar between cutoff frequencies 0.5-1000 Hz and 3-1000 Hz, and (iii) the use of ICA significantly reduced the N30 amplitude. Figure 3–1 shows these results arranged in two ways for easy understanding.

The results of the study implied that the choice of EEG preprocessing parameters for N30 SEPs analysis is important as this may impact the interpretations of results, replicability, and comparison of studies.

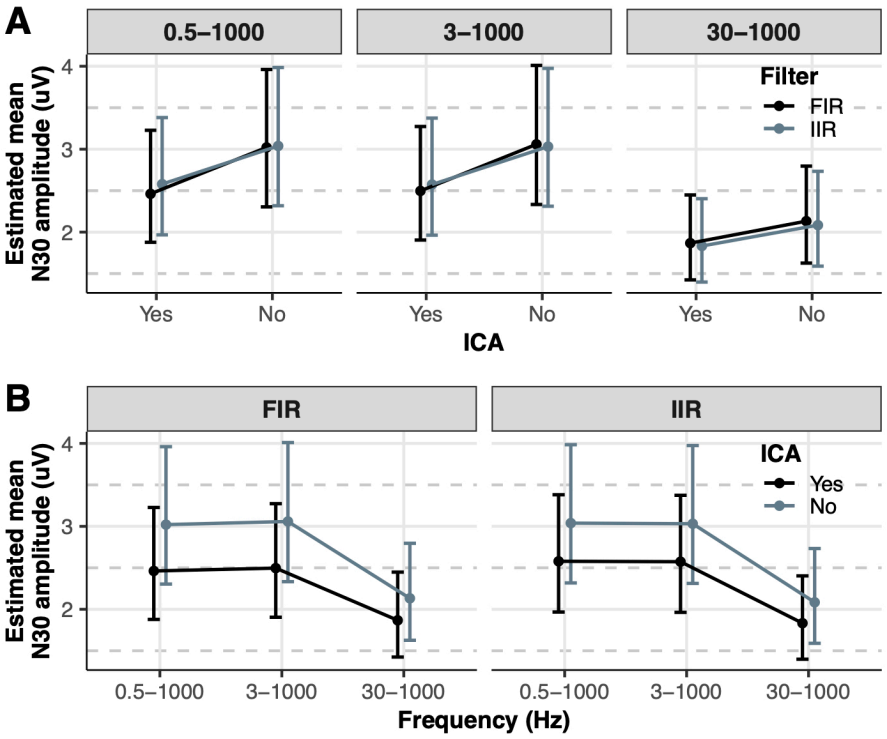


*Figure 3–1. Effect of preprocessing on N30 SEP amplitude. The error bars show the estimated mean N30 amplitude ± 95% CI. (A) The class of filter (FIR or IIR) did not affect the N30 amplitude. (B) Filtering with the 30-1000 Hz band significantly reduced the N30 amplitude compared to the 0.5-1000 Hz and 3-1000 Hz filtered data. The use of ICA reduced the N30 amplitude irrespective of the (A) class and (B) cutoff frequency of the filters.*

## 3.3. STUDY II

The objective of the study was to assess the effects of a single session of chiropractic spinal manipulation on the perception of pain and neural activity during pain.

In this crossover study, fifteen subclinical pain participants received an active intervention and a control intervention in random order on separate days. Before and after each intervention, whole scalp EEG was recorded during rest and tonic pain stimulation. The tonic pain was given by the cold-pressor (CP) test in which the participants immersed their left hands in cold water at 2 °C for 80 seconds. The pain and unpleasantness scores were also recorded. Source localization and power spectral analysis were performed on the resting-state and tonic pain EEGs in the delta, theta, alpha, and beta bands.

The sLORETA based source localization showed that the power decreased in all bands after the control intervention, where the significant decreases were seen in the delta and alpha bands (both $p < 0.05$) (Figure 3–2A). The neural activity stayed the same after the chiropractic spinal manipulation (Figure 3–2B). The power spectral analysis showed similar results. The pain score decreased by 9% after the control intervention ($p < 0.05$), whereas the unpleasantness scores were decreased by 7% after both interventions (both $p < 0.05$).

The results implied that there was habituation to pain following control intervention as the pain score and neural activity were decreased, which is a typical response to continuous or repetitive pain. In contrast, the pain score and neural activity were similar before and after the active intervention, which implied that chiropractic spinal manipulation might affect the development of pain habituation by altering the processes in which the central nervous system responds to the pain.

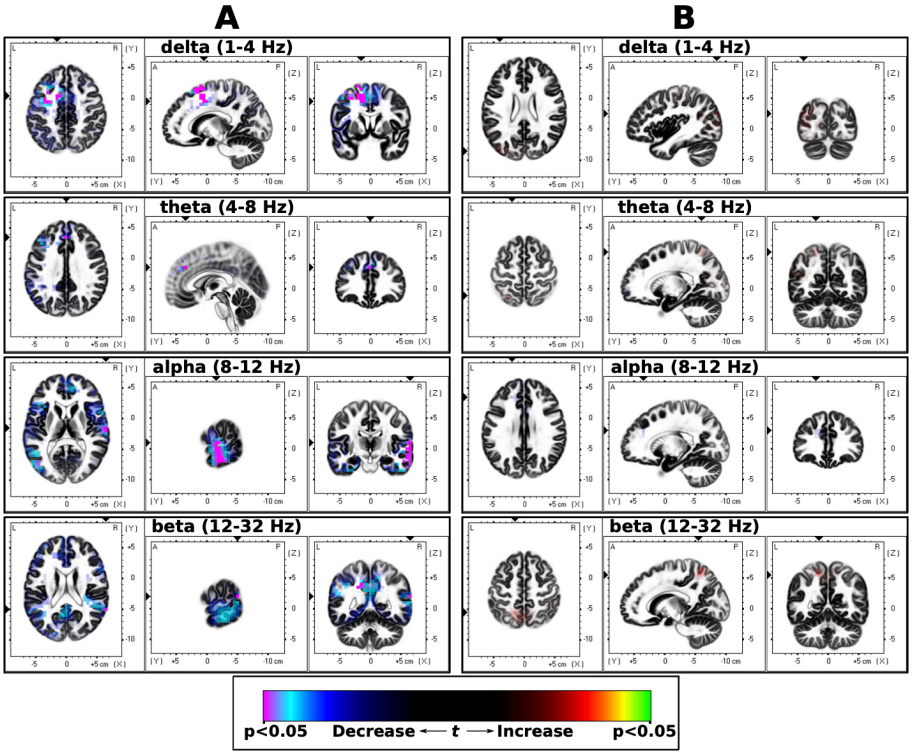


*Figure 3–2. sLORETA plots. Slice views of source locations with changes in the brain activity where the two-tailed t-values are maximum for each frequency band during the cold-pressor test after (A) control and (B) chiropractic interventions (i.e., post- vs. pre-intervention). (A) There was a decrease in brain activity in all frequency bands after control intervention with a significant reduction in activity in the delta and alpha bands ($p < 0.05$ = magenta colored), and a marginally significant decrease in the theta and beta bands ($p = 0.05$). (B) The brain activity did not change, or it was 'reset' after the spinal manipulation. The color scale indicates critical t-values.*

## 3.4. STUDY III

The objective of the study was to assess the effects of a single session of chiropractic spinal manipulation on the early SEPs, and resting-state EEG recorded from chronic stroke patients.

In this crossover study, seventeen male patients received an active intervention and a control intervention in random order on separate days. Before and after each intervention, whole scalp EEG was recorded during rest and non-paretic median nerve stimulation. For resting-state EEG analysis, power spectra, delta-alpha ratio (DAR), brain-symmetry index (BSI) were calculated. For SEPs analysis, the early N20 and

N30 peaks were examined. Additionally, source localizations of the resting-state EEG power spectra and the N30 SEP peak were performed.

The SEPs analysis showed a 39% increase in the amplitude of the N30 SEP peak after the active intervention ($p < 0.01$). However, the latency and the strength of brain sources underlying the N30 peak were not modified after either intervention. The other parameters, N20 peak, and the resting-state EEG's power spectra, DAR, BSI, and source localization, were not affected by the intervention. Figure 3–3 shows the amplitudes of the N20 and N30 SEP peaks.

The results implied that chiropractic spinal manipulation increased the N30 peak amplitude in patients suggesting that the intervention evokes changes in the early sensorimotor interaction after stroke.

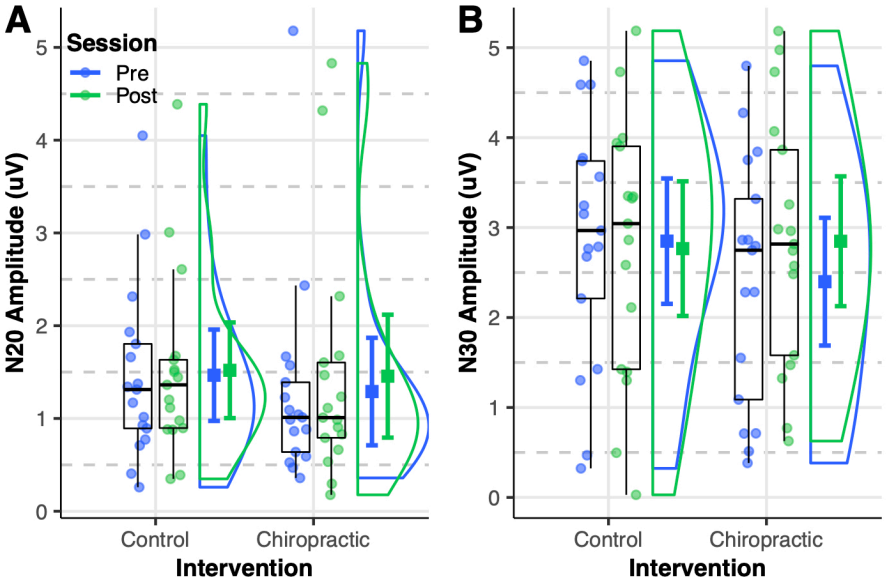


*Figure 3–3. SEPs amplitude. Dots represent (A) N20 and (B) N30 SEP amplitudes of analyzed subjects. Boxplots show the median, 25$^{th}$ and 75$^{th}$ percentiles. The error bars show mean ± 95% CI. The distribution plots show the density distribution estimated by a Gaussian kernel with SD of 1.5. (A) The N20 amplitude was not altered by either intervention. (B) The N30 amplitude was significantly increased after the spinal manipulation. The figure was made using the scripts provided by Allen et al. (Allen et al., 2019).*

## 3.5. STUDY IV

The objective of the study was to assess the effects of a single session of chiropractic spinal manipulation on the motor control of chronic stroke patients.

In this crossover study, twenty-nine patients received an active intervention and a control intervention in random order on separate days. Before and after each intervention, TMS was used to evaluate the central excitability of the paretic lower limb (tibialis anterior (TA) muscle).

The preliminary analysis performed on motor evoked potentials (MEPs) showed that peak-to-peak MEP amplitude was increased by approximately 0.15 mV after the active intervention ($p < 0.01$) (Figure 3–4A). The percentage change in the MEP amplitude was very high (~126%) after the active intervention ($p < 0.0001$) (Figure 3–4B). The amplitude and percentage change of MEPs were not affected by the control intervention.

The results implied that chiropractic spinal manipulation increased the cortical excitability to TA muscle, which may be beneficial for stroke recovery.

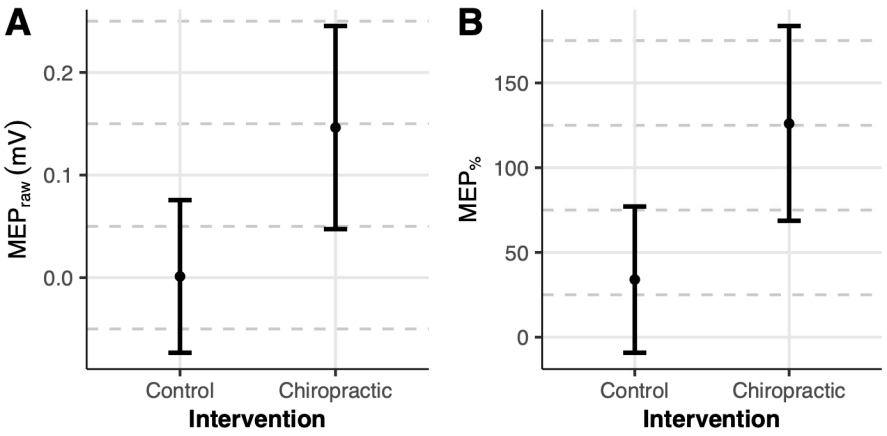


*Figure 3–4. MEPs. The error bars show mean ± 95% CI. (A) Absolute peak-to-peak MEP amplitude with respect to pre-intervention MEPs set to 0 mV. (B) Percentage change in MEP amplitude with respect to pre-intervention MEPs set to 0 mV. Spinal manipulation significantly increased the MEPs in (A) absolute units and (B) relative units.*

# CHAPTER 4. GENERAL DISCUSSION

The series of studies in this thesis evaluated the effects of spinal manipulation on the neural activity during experimental pain and the neurophysiology of stroke survivors. Additionally, the impacts of preprocessing parameters on somatosensory evoked potentials were assessed.

This chapter discusses the main findings and limitations of the studies as well as the future directions for this research.

## 4.1. PREPROCESSING OF SEPS

Filtering is a ubiquitous step in EEG processing, which improves the SNR of the EEG signals (Widmann et al., 2015). However, filtering can modify the signals in an undesired way (Widmann et al., 2015), such as by introducing artificial components (Acunzo et al., 2012), alternating the onset latencies (VanRullen, 2011) and amplitude of the neural activity peaks (Widmann et al., 2015). For processing SEPs, there are multiple guidelines available (ACNS, 2009; American Clinical Neurophysiology Society, 2006; American Electroencephalographic Society, 1994; Passmore et al., 2014; Toleikis, 2005). Additionally, there are general guidelines for processing EEG and ERP (Acunzo et al., 2012; Luck, 2014; Widmann et al., 2015; Widmann & Schröger, 2012). Yet, a literature review (Navid et al., 2019) showed that these guidelines for preprocessing SEPs were rarely followed adequately. In addition, the reporting of the preprocessing parameters was also incomplete and not sufficient to be replicated. Therefore, study I assessed the effects of filtering and the use of ICA on the amplitude of the N30 SEP peak.

We found that the class of filters (FIR and IIR) did not affect the N30 SEP amplitude. One of the possible reasons could be that the order of these filters was very different (7420 for FIR and 2 for IIR), which could have compensated for the differences in the filters. However, we found that it was easier to design the FIR filter compared to the IIR filter. The N30 amplitude obtained after filtering with cutoff frequencies 0.5-1000 Hz and 3-1000 Hz was similar; however, it was low when filtered with 30-1000 Hz. The possible reason is that since EEG activity follows 1/f function (i.e., more power in the lower frequencies and vice versa for the higher frequencies) (X. M. Cohen, 2014), and the neural activity up to 30Hz was removed, there was less power and less amplitude left. Similarly, the use of ICA reduced the N30 amplitude, as the power from non-brain components, such as activities of the eye, muscle, and power lines, was removed.

Study I suggested that preprocessing the same data with different parameters (selected from the guidelines mentioned earlier) had a major effect on the amplitude of the N30 SEP peak. Since this can influence the interpretation of results, replicability, and comparison of studies, study I suggested that preprocessing should be done carefully and reported appropriately.

## 4.2. SPINAL MANIPULATION AND PROCESSING OF PAIN

Chiropractic is often used as a safe and effective treatment for improving musculoskeletal issues (Bronfort et al., 2010, 2012). The changes in neural plasticity following spinal manipulation have been assessed by multiple studies (Baarbé et al., 2014; Haavik Taylor et al., 2010; Haavik Taylor & Murphy, 2007; Lelic et al., 2016; Murphy et al., 2010; Niazi et al., 2015), and it has been shown that spinal manipulation reduces pain (Gay et al., 2014; Haavik, Niazi, Holt, et al., 2017; Teodorczyk-Injeyan et al., 2006). However, the underlying neural mechanisms are not well understood (Goertz et al., 2012; Millan et al., 2012; Joel G Pickar, 2002; Ruddock et al., 2016; Srbely, 2010). Therefore, study II focused on evaluating the effects of spinal manipulation on the neural processing of pain.

In this study, the tonic pain model was used, since experimental tonic pain produces sensory experience comparable to clinical pain (Huber et al., 2006; Nir et al., 2010, 2012). The CP test was used to evoke tonic pain, as it resembles clinical pain and is a validated method to estimate neural processing of tonic pain (Gram et al., 2015).

First, we evaluated the neural processing of tonic pain and compared it with other studies. The sLORETA results showed higher activity during pain compared to resting-state in all frequency bands. Similarly, high neural activity has been found in other studies based on EEG (Backonja et al., 1991; Chang et al., 2002; Ferracuti et al., 1994; Le Pera et al., 2000; Shao et al., 2012), PET (Casey, 1999) and fMRI (Frankenstein et al., 2001; Wager et al., 2013). We found that activity changed in the insula (all bands) and anterior cingulate cortex (delta, alpha, and beta bands), which are the most common reported regions activated due to pain (Peyron et al., 2000; Zhuo, 2008). Some studies, on the other hand, have not shown a similar trend in the change in power of alpha-band due to tonic pain, such that the alpha activity was reduced following tonic pain (Babiloni et al., 2006; Nir et al., 2012; Shao et al., 2012). The possible reasons could be differences in the strengths and type of stimulations used for inducing tonic pain. For example, Shao et al. (Shao et al., 2012) used a CP test with a higher temperature (10 °C) than used in this study (2 °C), Babiloni et al. (Babiloni et al., 2006) utilized CO2-laser stimulation, and Nir et al. (Nir et al., 2012) used heat stimulation. However, based on the changes in neural activity and regions where these changes occurred, the results implied the possibility of negative emotions

(Craig et al., 1996; Tracey & Mantyh, 2007; Wager et al., 2013; Zhuo, 2008) and attention to pain (Babiloni et al., 2006; Klimesch, 1999).

Second, the neural activities after the control and spinal manipulation interventions were compared. After the control intervention, the pain score and neural activity related to tonic pain were decreased. This was an anticipated result since habituation to constant or repetitive painful stimuli is a normal reaction in humans and animals (LeBlanc & Potvin, 1966; Strempel, 1976, 1978). The brain regions (limbic lobe, temporal lobe, and frontal lobe) where the decrease in activity was mostly seen were a subset of regions that were activated during the tonic pain itself. This implied that a decrease in activity in these regions reflects pain habituation. On the contrary, the results showed that spinal manipulation nullified or reversed the change in the spectral power of EEG due to pain. One plausible reason can be that spinal adjustments impacted the afferent input from the spine. These altered inputs likely affected the process of habituation and sensitization to pain. Previously, it has been reported that spinal manipulation reduces sensitization to pain (Bishop et al., 2011; Ruddock et al., 2016). However, it is expected that a reduction in sensitization will increase the habituation, instead of decreasing it (Thompson, 2009). Therefore, the possible reason for this is that spinal manipulation not just decreases sensitization, but also 'resets' the facilitatory and inhibitory processes involved in habituation.

Thus, study II suggested that chiropractic spinal manipulation 'resets' the habituation to pain. Habituation to pain can increase the extent of maladaptive neural plasticity caused by pain. Prolonged maladaptive neural plasticity is thought to be the reason for the symptoms and functional disturbances in chronic pain sufferers, instead of the actual initial physical injury or functional issue itself (Brumagne et al., 2000; Haavik & Murphy, 2012; Michaelson et al., 2003; Paulus & Brumagne, 2008). The results of study II, while preliminary, have potential implications for an explanation as to why spinal manipulation may alter or reduce maladaptive neural plasticity, which may be one of the reasons for the improvement of symptomatology and functionality in chronic pain sufferers after this intervention.

## 4.3. SPINAL MANIPULATION AND STROKE NEUROPHYSIOLOGY

Stroke is the second-most common cause of death globally (Benjamin et al., 2018). The possible mechanisms involved in post-stroke motor recovery include the facilitation and modulation of neural plastic changes in the brain (Li, 2017). Many studies have suggested that there are neural plastic changes after spinal manipulation (Baarbé et al., 2014; Haavik Taylor et al., 2010; Haavik Taylor & Murphy, 2007; Lelic et al., 2016; Murphy et al., 2010; Niazi et al., 2015). Therefore, it was considered

worthwhile to evaluate the effects of spinal manipulation on the neurophysiology of stroke survivors. Hence, studies III and IV focused on this.

In study III, median nerve SEPs were utilized because SEPs are often used to measure the somatosensory processing after stroke, and abnormalities in median nerve SEPs usually predict functional outcomes for stroke survivors (Al-Rawi et al., 2009; Haupt et al., 2016; Keren et al., 1993; Lee et al., 2010; Tedesco Triccas et al., 2019; Yoon et al., 2018; Zeman & Yiannikas, 1989). In stroke survivors, the abnormalities in SEPs are mostly long interpeak periods, missing or reduced peak amplitudes, and prolonged latencies of the peaks (Al-Rawi et al., 2009; Feys et al., 2000; Gott et al., 1990; Tedesco Triccas et al., 2019; Zeman & Yiannikas, 1989).

We found a 39% increase in amplitude of the N30 SEP peak after the spinal manipulation intervention. Previous studies in healthy and subclinical populations have shown that N30 SEP amplitude decreased after spinal manipulation (Haavik-Taylor & Murphy, 2007; Haavik Taylor & Murphy, 2010; Lelic et al., 2016; Heidi Haavik Taylor & Murphy, 2010), and this decrease was found to take place mainly in the prefrontal cortex (Lelic et al., 2016). The N30 SEP peak is thought to be generated at the motor, premotor and prefrontal cortices (Balzamo et al., 2004; Cebolla et al., 2011; Waberski et al., 1999), and is associated with early sensorimotor integration (Rossi et al., 2003). Therefore, it is likely that the increase in the N30 amplitude in the chronic stroke survivors after manipulation reflects altered sensorimotor integration. This change in sensorimotor integration may explain the 65% increase in plantarflexion muscle strength found after spinal manipulation in a chronic stroke population in a previous study (K. Holt et al., 2019). None of the other SEP parameters, such as the N30 latency, N20 peak, and brain source strengths underlying the N30 peak, were significantly changed in this study.

Resting-state EEG was also recorded in this chronic stroke study, since electrophysiological changes in the brain networks, such as functional connectivity (Urbin et al., 2014), and the power spectrum (Saes et al., 2019), has been associated with motor impairment (Carter et al., 2012) in stroke survivors. Increased power in delta and theta bands has been linked to brain damage (Andraus & Alves-Leon, 2011; Britton et al., 2016; S. Finnigan & van Putten, 2013; van Putten & Tavy, 2004). Furthermore, it has been proposed that the DAR and pairwise-derived BSI can be valuable markers of neurological function in stroke survivors (S. Finnigan et al., 2016). However, in study III, the power spectral analysis revealed that the power across the delta, theta, alpha, beta, and gamma bands was not significantly affected by a single session of spinal manipulation. The DAR, BSI, and sLORETA based source localization were also not significantly affected.

In study IV, MEPs were used in this chronic stroke population as several previous research studies have shown changes in corticospinal excitability after spinal manipulation (Haavik-Taylor & Murphy, 2007; Haavik, Niazi, et al., 2018; Haavik,

Niazi, Jochumsen, et al., 2017; Haavik & Murphy, 2007). Therefore, TMS was used to estimate the changes in the corticospinal excitability in a group of chronic stroke survivors pre and post chiropractic spinal manipulation and a control session. TMS has been shown to be a reliable method to record corticospinal excitability (Carroll et al., 2001; Kamen, 2004; Malcolm et al., 2006). In study IV, we found increased MEPs after the spinal manipulation intervention. Similar results were found in a previous study that was conducted in subclinical pain patients (Haavik, Niazi, Jochumsen, et al., 2017). Therefore, it is likely that the increase in MEPs shows an altered balance between excitatory and inhibitory elements of the corticospinal volley. Similar to the previous study (Haavik, Niazi, Jochumsen, et al., 2017), the results in study IV indicate that the changes after spinal manipulation are at the cortical level and not at the level of the spinal cord. The increased cortical excitability can be the reason for increased plantarflexion muscle strength found in a chronic stroke population after spinal manipulation (K. Holt et al., 2019).

## 4.4. LIMITATIONS

The main limitation of studies II and III is that the length of the washout period between the spinal manipulation and control interventions may be too short. Previous work has shown that the changes in neural plasticity after spinal manipulation can persist up to at least a week (Haavik, Özyurt, et al., 2018). This can be a reason that there were no changes seen in the resting-state EEG parameters in study II and III and SEP parameters in study III. Future studies should consider having more than a week between interventions to have a reasonable washout period or use a parallel-group design.

This thesis is based on basic science and exploratory research. Therefore, the sample sizes used may not have been large enough. In some cases, we had no previous data to make power calculations. Other studies exploring pain (Haavik, Niazi, Holt, et al., 2017; Lelic et al., 2012) and those conducted in stroke populations (Agius Anastasi et al., 2017; S. P. Finnigan et al., 2007; Saes et al., 2019; van Putten & Tavy, 2004; Wang et al., 2010) have used similar sample sizes to what we chose for the studies in this thesis. However, future studies that explore and extend the work of this thesis should consider a larger sample size.

Another limitation to keep in mind for studies III and IV of this thesis is the heterogeneity of the chronic stroke participants. One of the inclusion criteria for the stroke survivors to participate in these studies was that they had to have suffered from a stroke at least 12 weeks before enrollment. There was no restriction on the type of stroke and the affected brain regions. Therefore, there were differences in the brain morphology of the participants due to non-uniformity in the type and location of the lesion(s). Thus, it is possible that the procedure of source modeling used in study III

was inappropriate for this chronic stroke population. It has been shown in simulation-based studies that a realistic head model for each subject can improve the efficiency of source modeling (Cuffin, 1996; Leahy et al., 1998; Waberski et al., 1998). The source analyses in study III were performed on a healthy brain model, which did not take into account the number, location, and size of the lesion(s) present in the brains of the participants. Therefore, this represents a significant limitation and may explain why no significant changes were detected in the source localization of the N30 SEP peak and resting-state EEG after spinal manipulation and control interventions in the study, despite the apparent significant increase in the N30 SEP amplitudes. Future studies may wish to have more stringent enrollment criteria to avoid this issue; however, this will likely make the recruitment of patients more challenging, and the results of such studies may not be much generalizable to the majority of the stroke population. Another means to avoid this problem is to base brain source localization calculations on brain images (such as MRI scans) of each participant.

In study II and III, the spectral power and sLORETA based source localization of the resting-state EEG were not affected by the spinal manipulation. It is possible that the spinal manipulation does not affect the parameters of the resting-state EEG, and that is why no changes were seen in them after the intervention in these studies. Additionally, it is also possible that the analyzed parameters were not predictive of changes after spinal manipulation in the populations used in these studies. For example, increased DAR has previously been found in (sub-) acute stroke patients (S. Finnigan et al., 2016). However, another study performed in chronic stroke survivors did not show changes in this measure (Saes et al., 2019). Study III was carried out in chronic stroke survivors; therefore, it is possible that this parameter is not predictive of recovery in chronic stroke where any neuroplastic changes are permanent, and consequently, it was not affected by the interventions in our study.

Finally, since this thesis is based on basic science studies, the reader is cautioned from extrapolating the results to clinical implications for pain and chronic stroke populations. Future work will need to explore what potential clinical implications chiropractic care may have for preventing the development of chronic pain and for improving the functional ability for chronic stroke survivors.

## 4.5. CONCLUSION

Taken together, the findings of this thesis suggest that spinal manipulation has a significant impact on cortical processing during pain and for chronic stroke survivors. Since spinal manipulation is relatively accessible, economical, and safe, it may be better to consider it as a conservative treatment option before other expensive, and more invasive options are considered. This concerns not only for pain syndromes but also for a variety of neurological dysfunctions such as stroke survivors. However,

further research is required, with advanced methods, larger sample sizes, and improved designs to improve our understanding of the effects of spinal manipulation as well as its clinical effects in patient populations such as chronic stroke survivors. There is now a significant body of basic science evidence showing clear beneficial neuroplastic effects of chiropractic manipulation; however, the clinical implications of these effects still need to be adequately elucidated.

## 4.6. FUTURE PERSPECTIVES

It has been shown that the preprocessing parameters affect the amplitude of the N30 SEP peak. However, the study did not evaluate which of the parameters are efficient, i.e., which combination of parameters improves the SNR and statistical power of a study by amplifying the experimental effects. Modeling of SEPs and statistical techniques can be used in future studies to identify the parameters which are better able to detect the effects of the treatments and increase the power of the studies.

Almost all of the studies based on SEPs discussed in this thesis have used peak-to-peak amplitude calculation of the early somatosensory peaks. After this, ANOVA was used to find the effects of the treatment. This technique possibly reduces the power and capability of the EEG as usually one channel, or sometimes a few channels, are used in the analysis. Additionally, the assumptions required for ANOVA are almost always violated in an ERP based study (Luck, 2014). SEPs have been used for more than 30 years (Nash et al., 1977); therefore, this can be the reason that the same methodology is still being used (e.g., for comparison purposes or continuation of previous lab projects) even after advancements in both EEG and statistical methods. Future studies, therefore, should test other statistical methods on SEPs, such as those based on permutation statistics and cluster-based approaches (Luck, 2014; Maris, 2012; Maris & Oostenveld, 2007). These methods can use whole scalp EEG, or all channels of EEG at the same time to do statistical analyses without increasing the type 1 error while keeping the type 2 error low. Additionally, no prior assumptions about the data distribution are required, which makes these methods more robust.

Similarly, most of the studies have utilized only the amplitude and latency of the SEP peaks to evaluate the effects of the treatment. Future studies can use other properties of the SEP data, such as time-frequency information, as this has been used in a few previous studies (Cebolla et al., 2011, 2014).

The resting-state EEG was not changed after spinal manipulation in studies II and III. It is possible that spinal manipulation does not affect resting-state spectral power. However, the resting-state analyses performed in the studies were based on power measurements only. More sophisticated methods to analyze resting-state EEG, such as phase synchronization (within-frequency and cross-frequency) (Klimesch et al.,

2008) and functional connectivity (Bastos & Schoffelen, 2015; Tedesco Triccas et al., 2019), may be able to give insights into the mechanisms behind neural processing after the interventions. Future studies can also verify the effects of spinal manipulation on resting-state EEG using multiple methods and larger sample sizes.

### 4.6.1. ONGOING STUDY

A pilot clinical trial was conducted in fifty-five chronic stroke patients to evaluate the changes in their motor function due to longitudinal (4-weeks) spinal manipulation intervention along with physical therapy compared to physical therapy alone. The participants were randomly divided into two groups (active and control) and received either 4-weeks of (i) spinal manipulation + conventional physiotherapy or (ii) sham spinal manipulation + conventional physiotherapy. The Fugl-Meyer Assessment (FMA) of Motor Recovery was performed at baseline, 4-weeks, and 8-weeks (i.e., at 4-weeks post-intervention). Preliminary results (Figure 4–1) showed that based on FMA scores, both groups showed improvement at 4-week and 8-week assessments. However, after 4-weeks, the group with combined interventions had more improvement than the group which received only physiotherapy ($p < 0.05$). The same trend was observed at the 8$^{th}$-week assessment, but the difference between the groups was not significant. More detailed data analysis is in process.

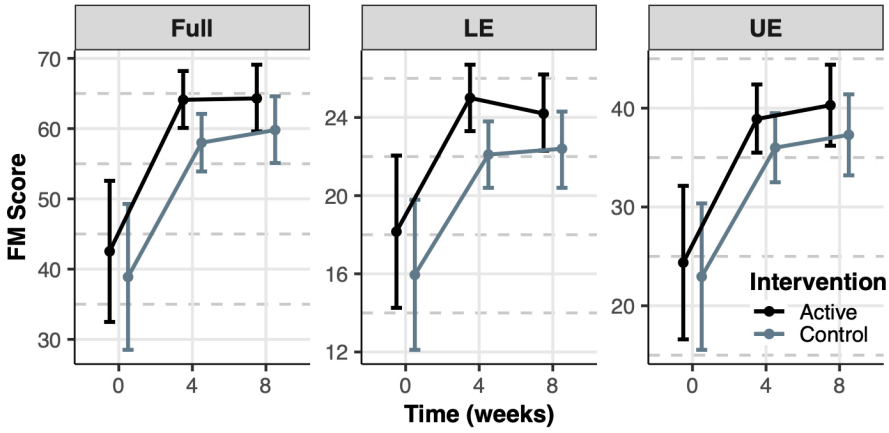


*Figure 4–1. Fugl-Meyer (FM) Score. The error bars show mean ± 95% CI. After 4-weeks of intervention, the active group which received both spinal manipulation and physical therapy showed more improvement in FM score compared to the control group which received physical therapy with sham spinal manipulation. Significant differences between the groups at the 4$^{th}$ week were found in full FM and FM-LE scores (both $p < 0.05$). Abbreviations: LE = Lower Extremity; UE = Upper Extremity.*

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# APPENDICES

**Appendix A. Guidelines ICA ..... APP 1**

Preprocessing steps ..... APP 1

Evaluation of ICs ..... APP 2

Literature list ..... APP 9

# Appendix A. Guidelines ICA

In this appendix, guidelines are provided on how to run ICA and how to interpret the results to separate neural ICs from non-neural ICs. The guidelines are based on the papers (Chaumon et al., 2015; Jung et al., 2000), websites (Miyakoshi, n.d.; *SCCN: Independent Component Labeling*, n.d.), discussion forum (*EEGLAB mailing lists*, n.d.) and personal experience.

## Preprocessing steps

In my opinion, based on the EEGLAB forum (*EEGLAB mailing lists*, n.d.), the primary concern of analysts regarding ICA is the order of steps for EEG preprocessing. There is no hard and fast rule for this; however, the following order of steps is recommended by some experts (including (Miyakoshi, n.d.)):

1. Import data and keep it in double precision. EEGLAB (Delorme & Makeig, 2004) by default keeps data in single precision. This can be changed in the 'Memory and other options' menu.
2. Downsample the data to approximately 250 Hz to decrease computational cost. Also, ICA will be able to perform better by not processing high-frequency data. Although, this has not been empirically tested.
3. High-pass filter the data with a cutoff frequency of 1-2 Hz (Winkler et al., 2015).
4. Remove bad channels.
5. Interpolate bad channels.
6. Re-reference the EEG data to common average reference.
7. Epoch data. The resting-state EEG can be segmented as well to make epoch cleaning more systematic.
8. Reject bad epochs such as those associated with EMG bursts or sporadic events.
9. Run ICA. It is important to have full-ranked data for the process. The data gets rank-deficient by average referencing and by channel interpolation. Therefore, use the PCA option or remove channels from the data to address this problem.
10. Plot ICA components and their properties to guide in the removal of bad ICs.

There can be, however, deviations from this order, such as for making the preprocessing pipeline more objective. For example, after step 2, the PREP pipeline (Bigdely-Shamlo et al., 2015) can be used to identify the bad channels and obtain the average referenced data, followed by step 3 on the PREPed data. This flow removes the steps 4-6.

ICA requires full-ranked data. For this purpose, in studies I and III bad channels were removed to reduce the data dimension instead of using PCA, since it was found that PCA reduces the quality of ICA analysis (Artoni et al., 2018). However, channels ca also be removed in a way to have a uniform channel distribution across the scalp (Miyakoshi, n.d.).

It is possible to apply ICA results from thoroughly cleaned data to moderately clean data to keep more data for analysis. This was done in studies I and III, where ICA matrices were computed on downsampled data, and bad ICs were marked. Afterward, the ICA matrices were applied to the broader bandpass filtered data, which had a higher-sampling rate. This was followed by the removal of the marked bad ICs.

The amount of data required for a reasonable quality of ICA decomposition should be equal or greater than the number of electrodes squared times a factor, $k$ (Onton & Makeig, 2006). Onton et al. (Onton & Makeig, 2006) have suggested that the minimum value of $k$ should be 25. Therefore, for a 62-channel EEG, a minimum of $62^2 * 25 = 96{,}100$ samples are required. At a sampling rate of 256 Hz, this criterion is met with an approximately 7 minutes of EEG.

## Evaluation of ICs

The figures below show different types of ICs with guidance on how to identify brain and artifact components. The figures are based on the graphical user interface developed during the PhD, which was inspired by (*SCCN: Independent Component Labeling*, n.d.).

The template is shown in Figure A–1, where the numbers show the placement of the following IC properties:

1. Scalp topography
2. Average of all epochs
3. Averages of the first and the last halves of the epochs
4. ERP image
5. Power spectrum (with different range of x-axes)
6. Time series of the component
7. Number of the IC and percentage data variance it accounts for (pvaf) (sorted in descending order of pvaf)
8. Dipole fits of the component
9. Residual variance (RV) (preferably < 15%)

The average epochs and the ERP image were calculated from the component's temporal data. For EPs, these show the data aligned with respect to the stimulus. For

resting-state data, which was also segmented into continuous epochs, the time progressed from left-to-right in each epoch and bottom-to-top among epochs.

The dipole fit and the RV were not always accurate to guide in classifying ICs.

The components are divided into the brain (Figure A–2, Figure A–3, and Figure A–4), eye (Figure A–5 and Figure A–6), muscle (Figure A–7), line noise (Figure A–8), bad channel (Figure A–9), and ambiguous (Figure A–10) components.

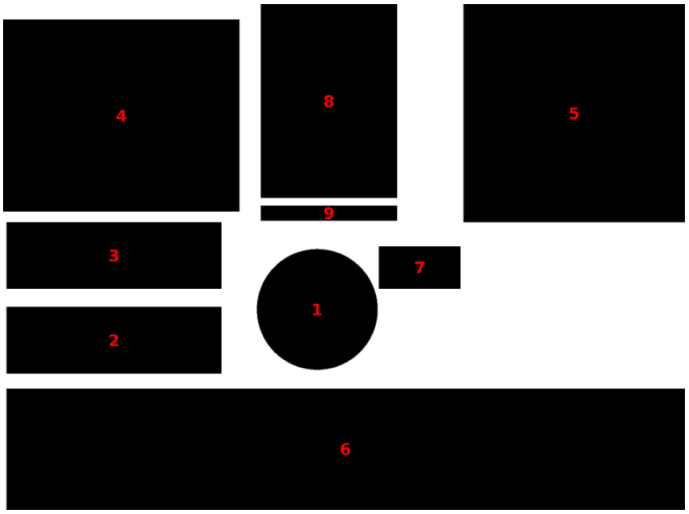


*Figure A–1. Template for IC labeling. (1) Scalp topography, (2) average of all epochs, (3) averages of the first and the last halves of the epochs, (4) ERP image, (5) power spectrum, (6) time series of the component, (7) number of the IC and percentage data variance it accounts for (pvaf), (8) dipole fits of the component, and (9) residual variance (RV).*

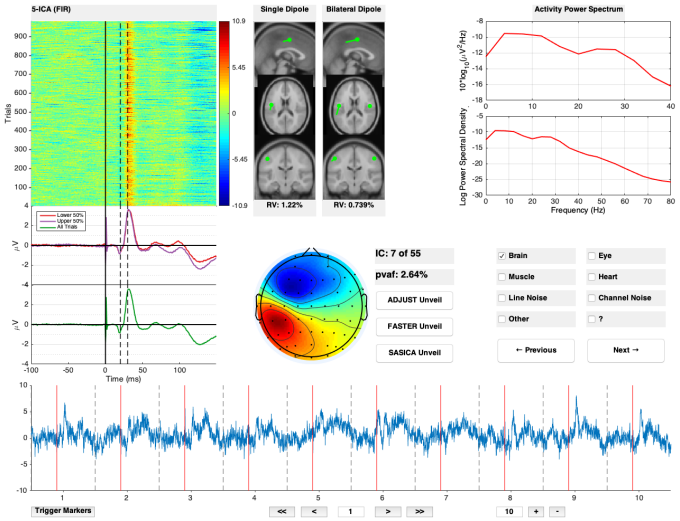


*Figure A–2. Brain component. The scalp topography shows a dipolar activity. All trials in the ERP image and the average evoked activities of the first half trials, the second half trials, and all trials show peaks that are time-locked to the stimulus. The power spectrum gives a hint of a peak in the alpha band. The pvaf ranks the component high. The RVs of the dipole fits are very low, and the locations of single and bilateral dipoles fit very well with the SEP physiology.*

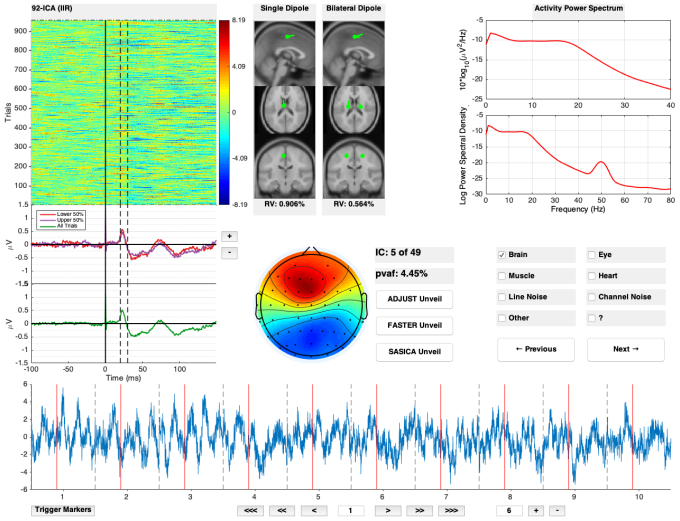


*Figure A–3. Brain component. The scalp topography shows a dipolar activity. The trials in the ERP image does not show a time-locked activity; however, this is captured by the average evoked activities of the first half trials, the second half trials, and all trials. The power spectrum shows 1/f pattern (i.e., decrease in power as frequency increases) with a small peak in the beta band. The pvaf ranks the component high. The RVs of the dipole fits are very low, and the locations of single and bilateral dipoles fit very well with the SEP physiology.*

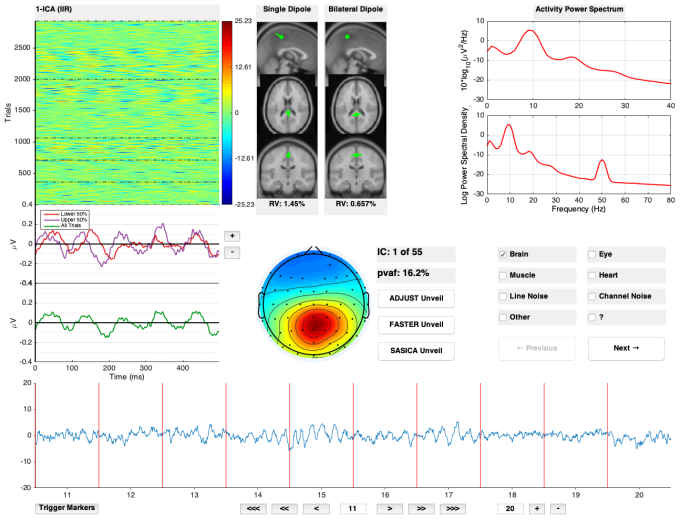


*Figure A–4. Brain component. The scalp topography shows a dipolar activity. This is a continuous data segmented in 0.5 s long epochs. The data is not time-locked and does not show any pattern in the ERP image and the average evoked activities. The power spectrum shows a 1/f pattern, with peaks at physiological frequencies (10 Hz alpha and 18 Hz beta). The pvaf ranks the component first. The RVs of the dipole fits are very low, and locations of single and bilateral dipoles fit well within the scalp.*

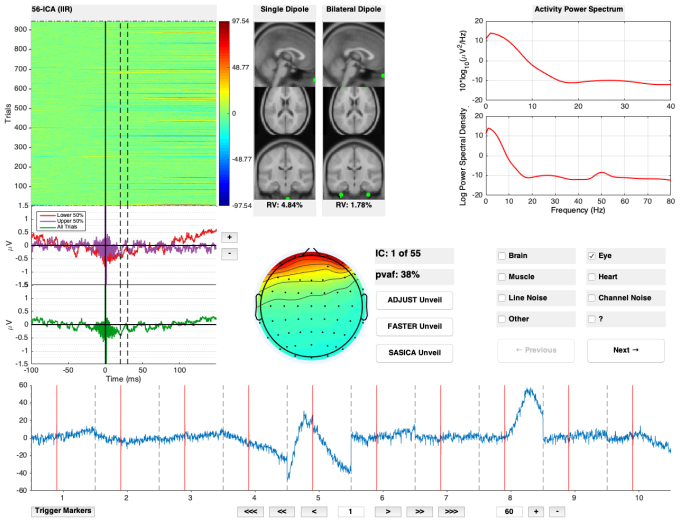


*Figure A–5. Eyeblink component. The scalp topography shows a flat activity except in the frontal region. The time series shows high amplitude variations in a gaussian shaped form e.g., in trials 5 and 8. There is no pattern in the ERP image and the average evoked activities; however, high variation in amplitudes can be seen in the ERP image. The power spectrum shows most of the power is in the low-frequency band. The pvaf ranks the component first. The RVs of the dipole fits are low, and the location of bilateral dipoles is near the eyes.*

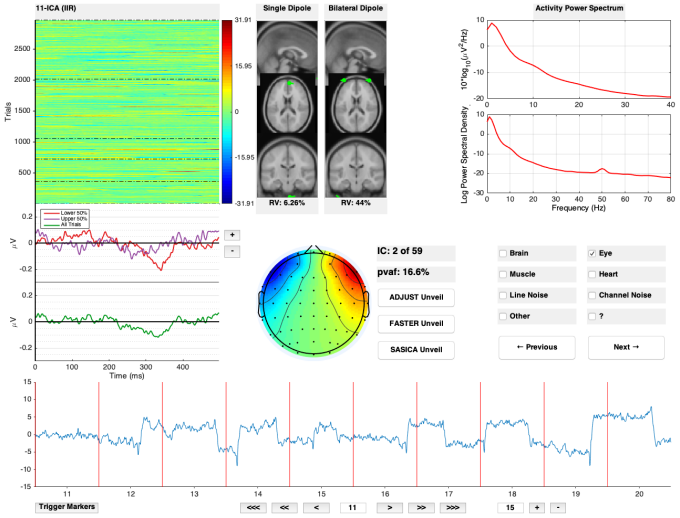


*Figure A–6. Eye movement component. The scalp topography shows frontal activity, with the sides having opposite polarities. The time series shows a step-like function. The power spectrum shows most of the power is in the low-frequency band with no peaks at physiological frequencies. The pvaf ranks the component second. The RV of the bilateral dipole is high (although a lower RV is preferred); however, the location of dipoles is near the eyes.*

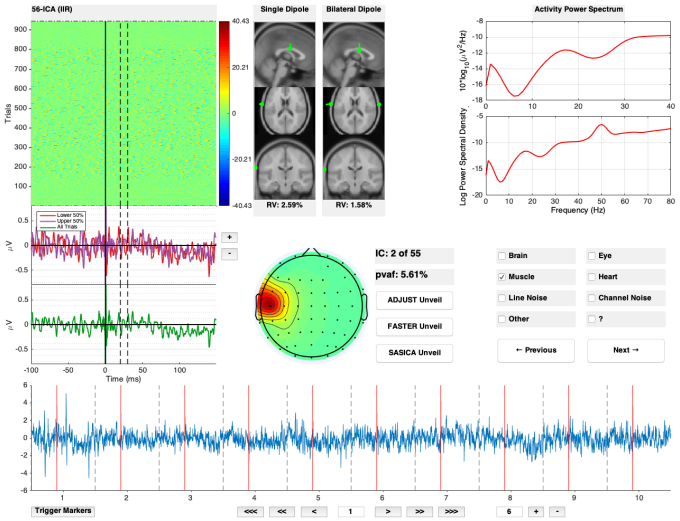


*Figure A–7. Muscle component. The scalp topography shows a temporally concentrated activity. There is no time-locked activity in the ERP image and the average evoked activities; however, high variation in amplitudes randomly scattered can be seen in the ERP image. The power spectrum shows most of the power is in the higher frequency bands in a square-root (√) shape. The pvaf ranks the component high. The time series show quickly varying spiky activity. The RVs of the dipole fits are low, and the locations of the single and bilateral dipoles are outside the scalp.*

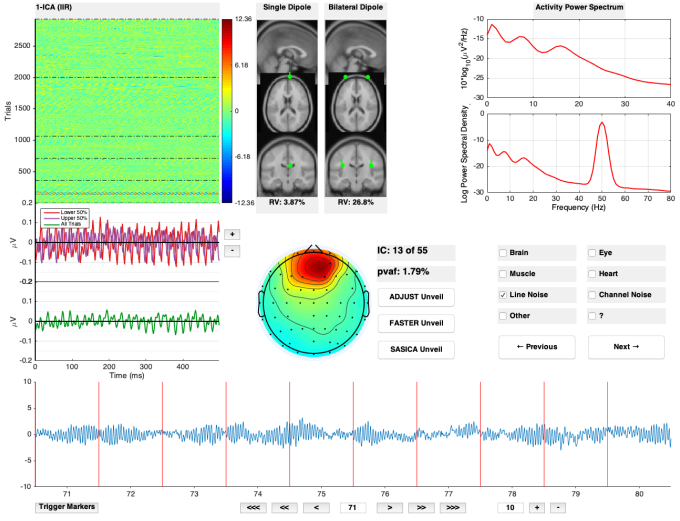


*Figure A–8. Line noise component. The power spectrum shows a huge peak at 50 Hz. The time series, ERP image, and the averages show oscillations. The ERP image also shows oscillations as alternating red and blue colors. The scalp topography and dipole fits are sometimes not informative and may indicate a dipolar activity like in this example.*

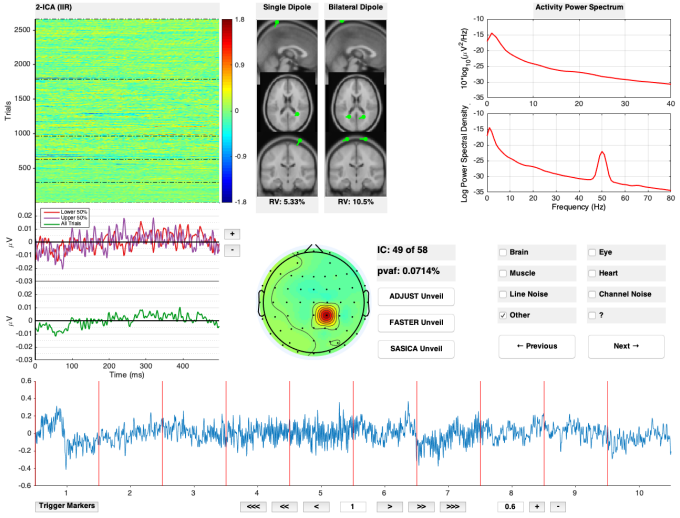


*Figure A–9. Bad channel component. The scalp topography shows focal activity at only one channel. The time series, ERP image, and the averages show abruptly changing activity. The power spectrum shows a 1/f activity; however, this should not be confused with the brain component's power spectrum because the scalp topography does not show dipolar activity.*

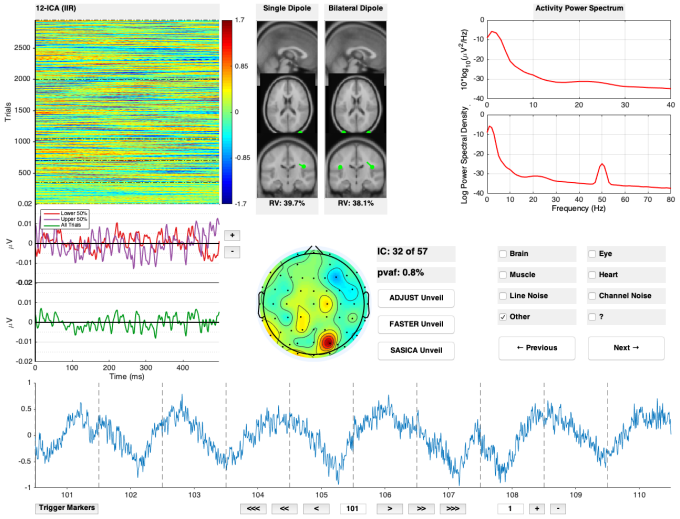


*Figure A–10. Ambiguous component. The scalp topography is non-dipolar. The power spectrum shows a low-frequency activity. The time series shows that there is some kind of slow oscillations; however, this is not visible in the ERP image and the averages. The dipole fit RVs are high, and the locations of dipoles are outside the scalp. This component has a mixture of attributes of components described above, but combined, they cannot explain any physiological activity or environmental noise.*

# LITERATURE LIST


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# NOTES

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