ANALYSIS OF THE EFFICACY OF EPIONE

THERAPIES TO TREAT PHANTOM LIMB PAIN

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To my Lord and Savior, Jesus Christ, for the grace by which I am saved through
faith.

To my wife, Alli, for all of your endless love.

To my parents, Greg and Becky, for feeding my curiosity.

To my siblings, Shaphan, Rachel, and Elizabeth, for not killing me when I was an
annoying little brother. I am better now ... I think.

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d Cohen's difference of means

N_p Number of pre-therapy scores

N_t Number of in-week therapy scores

μ_p Mean of pre-therapy scores

$\mu_{p_{neg}}$ Mean of pre-therapy scores for negative facing subscales

μ_t Mean of in-week therapy scores

$\mu_{t_{neg}}$ Mean of in-week therapy scores for negative facing subscales

LIST OF ABBREVIATIONS

AAU	Aalborg Universitet
AUH	Aalborg Hospital
BOLD	Blood Oxygen Level Dependent
BPA	Brachial Plexus Avulsion
BPI	Brief Pain Inventory
BPI-IS	Brief Pain Inventory - Interference Scale
BPI-SF	Brief Pain Inventory - Short Form
CCP	Common Clinical Protocol
CES-D	Center for Epidemiological Studies - Depression Questionnaire
CHUV	Centre Hospitalier Universitaire Vaudois
CNS	Central Nervous System
CPG	Chronic Pain Grade
CRPS	Complex Regional Pain Syndrome
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
EEP	EPIONE Extraction Program
EMG	Electromyogram
EPFL	Ecole Polytechnique Federale de Lausanne
EPIONE	FP7 EU Health program project studying PLP therapies
Excel	Microsoft® Excel for Mac Version 15.32
FES	Functional Electrical Stimulation
FIG	MATLAB Figure File
fMRI	Functional Magnetic Resonance Imaging
GAM	Group Analysis Module

GMI	Graded Motor Imagery
GQPAA	Groningen Questionnaire Problems After Arm Amputation
HRF	Hemodynamic Response Function
iE	invasive Electrical stimulation
iEH	invasive Electrical stimulation with prosthesis
IUPUI	Indiana University - Purdue University Indianapolis
LEP	Laser Evoked Potential
LTD	Long-term Depression (of a nerve)
M1	Primary Motor Cortex
MATLAB	MATLAB$^\circledR$ and Application Compiler Toolbox Release 2016a
MPI	Multidimensional Pain Inventory
MPQ	McGill Pain Questionnaire
NAP	Nonoverlap of All Pairs
niE	non-invasive Electrical stimulation
niEH	non-invasive Electrical stimulation with prosthesis
niM	non-invasive Mechanical stimulation
niMH	non-invasive Mechanical stimulation with prosthesis
NMDA	N-Methyl-D-aspartate
NP	Neuropathic Pain
NRS	Numeric Rating Scale
PAP	Post-amputation Pain
PEQ	Prosthesis Evaluation Questionnaire
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire
PLP	Phantom Limb Pain
PLS	Phantom Limb Sensation
PNS	Peripheral Nervous System
PPC	Posterior Parietal Cortex
PsyP	EPIONE Psychophysical Platform

PsyP-Map	Psychophysical Map of sensation
p-score	Pre-therapy Score
PVCN	Posteroventral Cochlear Nucleus
RCT	Randomized Controlled Trial
RID	Requirement Identifier
RLP	Residual Limb Pain (also Stump Pain)
RS	Referred Sensation
S1	Primary Somatosensory Cortex
S2	Secondary Somatosensory Cortex
SCR	Single Case Research
SD	Standard Deviation
SEP	Somatosensory Evoked Potential
SES	Surface Electrical Stimulation
SF-MPQ	Short Form - McGill Pain Questionnaire
SIDNE	Stimulation-induced Depression of Neuronal Excitability
SNR	Signal-to-Noise Ratio
SR	System Requirements
SVG	Scalable Vector Graphics
TENS	Transcutaneous Electrical Nerve Stimulation
TEP	Tactile Evoked Potential
t-score	Therapy Score
TMR	Targeted Muscle Reinnervation
UCSC	Universita Cattolica Del Sacro Cuore
UI	User Interface
UR	User Requirement

ABSTRACT

Comoglio, Caleb C. M.S.B.M.E., Purdue University, May 2017. Analysis Of The
Efficacy Of Epione Therapies To Treat Phantom Limb Pain. Major Professor: Ken
Yoshida.

The primary objectives of this thesis are (1) to discuss the current understanding
of phenomena associated with, proposed mechanisms of, and suggested treatments
for amputation related pain, (2) to describe the software developed for analyzing
results of a clinical study for the treatment of phantom limb pain (PLP), (3) to
discuss the methods for a multi-center trial by the EPIONE consortium along with
presenting preliminary results, and (4) to discuss the methods and results of a case
study involving a new therapy modality for alleviating PLP. Each objective has been
expanded into a chapter as described below.

Chapter 1 serves as a literature review introducing the topic of amputation, associ-
ated phenomena, and proposed mechanisms. The chapter also discusses the currently
available treatments and the instruments used to measure PLP. Key topics include
the definition of PLP, the prevalence of PLP, current treatment options for PLP, and
experimental measurement of PLP. The final objective of this chapter is to introduce
topics related to the investigation paradigm utilized for the studies following in Chap-
ter 4 and Chapter 5. Therefore, a minor emphasis has been put on surface electrical
stimulation (SES) and operant conditioning.

As with any multi-center clinical study, coordination is key. Chapter 2 introduces
the common clinical protocol (CCP) and methods of analysis for the clinical trials
conducted by the EPIONE consortium. In order to analyze results in an automated
fashion, a software tool was developed. This tool, the EPIONE Extraction Program
(EEP) along with its extension the Group Analysis Module (GAM), is the focus of

Chapter 3. A high-level overview of the requirements, process flow, and software testing are described. This chapter also discusses the methods of analysis for several self-report instruments used to determine effect size in Chapter 4 and Chapter 5. The outputs of the software tools make up the results presented and described in these chapters. In addition to the details included in Chapter 3, supplemental information is available in Appendix A and Appendix B, which are the detailed User Guides for the EEP and GAM.

Chapter 4 reviews the pilot study data conducted by the EPIONE consortium. The primary and two secondary instruments used for analysis are discussed. This chapter provides a brief overview of results from the group. Each clinical site used slightly different variations of a common clinical protocol to better understand what effectively drives alleviation of PLP and to allow comparison of results.

The work done at Indiana University - Purdue University Indianapolis (IUPUI) represents a small part of several other universities involved in the EPIONE consortium. Chapter 5 focuses on a case study at IUPUI with a more in-depth review of data collected throughout the study period. Using SES, we seek to reverse cortical reorganization by giving meaningful stimuli through existing circuitry. In this chapter the present work is discussed by introducing a case study in detail with an analysis of psychophysical data.

1. AN INTRODUCTION TO PHANTOM LIMB PAIN

With amputation comes many new experiences and sensations. Most credit the discovery and early characterization of phenomena associated with amputation to Ambroise Paré (16th century) and, nearly 250 years later, Silas Weir Mitchell in 1866 [1, 2]. Since then, substantial research has been conducted to further understand the consequences, mechanisms, and phenomena associated with amputation through the investigation of physical and psychological changes after amputation. This chapter has several goals. The first is to introduce the topic of amputation and the associated sequelae. Second, discuss the epidemiology and several proposed etiologies of the sequelae, focusing on phantom limb pain (PLP). Third, review methods for measuring the manifestation of PLP, specifically with respect to psychophysical aspects and cortical representation. Fourth, explore the proposed treatments of PLP and consider a potential new therapy paradigm.

Multiple studies have estimated the prevalence of limb loss and the subsequent effects of amputation. As many as 185,000 amputations occur every year in the United States [3, 4]. It was estimated that 1.6 million Americans were living with the loss of a limb in 2005, which translates to a ratio of 1:190 Americans; 65% of these individuals have lower extremity amputations [4]. Fifty-four percent of amputation cases occur after diagnosis of dysvascular disease, and 70% of amputees with dysvascular disease (or 38% of the amputee population) were noted to have a comorbidity of diabetes [4]. An unfortunate reality for many amputees is a relatively high rate of reamputation (26% among those with dysvascular amputation [4, 5]). Reamputation refers to those who underwent an additional procedure or additional procedures to the previously amputated limb or the contralateral limb within 12 months of the original procedure. In 1996 U.S. medical care costs exceeded $4 billion yearly for dysvascular amputations alone [5], which is only about half (54%) of the amputee community [4]. Ziegler-

Graham et al. predict the number of amputees in the U.S. will reach beyond 3 million by the year 2050 [4]. This, coupled with the high prevalence of post-amputation pain (PAP) and the high degree of pain experienced, easily makes the case that phantom pain is a relevant problem. To further complicate the issue, the amputee community is ill-informed in regards to PLP; 41.6% of amputees have never heard of the phenomenon [6].

1.1 Epidemiology and Etiology of Phenomena and Sequelae Associated with Amputation

Individuals commonly notice the presence of a phantom limb shortly after amputation. This phenomenon, known as phantom limb sensation (PLS), is the mental construction of the limb that is no longer present post-amputation. The phantom limb, or phantom, can be represented in a number of forms, from normal orientations to those that are not easily described or even physically possible. The phantom can also present pain to the amputee in many varieties, such as tingling, burning, stabbing, etc. This phenomenon is known as PLP or phantom pain. PLP is a subset of PLS where the sensations specifically cause discomfort. Amputees also experience other common painful phenomena, such as neuropathic pain (NP) and residual limb pain (RLP; also known as stump pain). NP is pain due to the damage or dysfunction of the somatosensory nervous system and RLP is pain in the remaining portion of the amputated limb. All of these painful phenomena fall under the umbrella of PAP.

1.1.1 Phantom Limb Sensation (PLS)

While the mechanism of the PLS phenomenon is not clear, it is common among amputees; as many as 80-90% of amputees experience PLS [7–9]. In general PLSs are localized to the distal region of the phantom, i.e. the hand, foot, fingers, or toes, and are typically not constant [10]. Rather, the sensations peak intermittently, sometimes on a monthly basis and sometimes several times a week [9,11]. Sensations

can be provoked in various ways, such as stump movement, touching the stump, and urination [8]. In a study involving 255 amputees, 79% reported nonpainful PLS, and of those individuals 27% (most common) described the sensations as tingling, 26% as itching, 13% as feeling asleep, among others [9]. Another related phenomenon is perceived movement of the phantom, where the amputee is able to consciously move the orientation or sense movement of the phantom. Eight days after amputation 36% of amputees felt movement of the phantom with 19% feeling spontaneous movements (i.e. movements that were not consciously driven) [8]. Similarly, another study by Kooijman et al. found 38% to experience movement [11]. For some amputees, electromyogram (EMG) patterns in the stump during imagined movements of the phantom limb are distinguishable and non-random, indicating hand motor commands are preserved after amputation and there exists an inherent understanding of how to manipulate/move the phantom [12]. The modulation of signal seen in the stump did not appear in experiments with the intact limb, which supports current theories post-amputation reorganization at some level. The efforts to move the phantom were not only observed through muscle movements, but also through peripheral nerve activity, i.e. Dhillon et al. recognized nerve activity in the residual limb during attempted movements [13]. Furthermore, they recognized activity in the central nervous system (CNS), specifically in the motor cortex, during phantom movements. These findings emphasize the current understanding of phenomena associated with amputation; the sensorimotor cortices and related peripheral innervation are actively involved in the perception of the phantom limb [13].

An altered kinesthesia is also common. For example, as many as 30% of amputees experience telescoping, which is the gradual shortening or retraction of the phantom limb, as depicted in Figure 1.1 [8,14]. In some amputees the phantom limb no longer reflects the original anatomy. In this example the phantom limb shortens and is drawn into the stump. In these situations the residual limb and phantom hand or foot are no longer in an orientation that matches the original volume or limb, which

causes confusion and concern to many amputees. Telescoping has also been linked to increased levels of phantom pain [15].
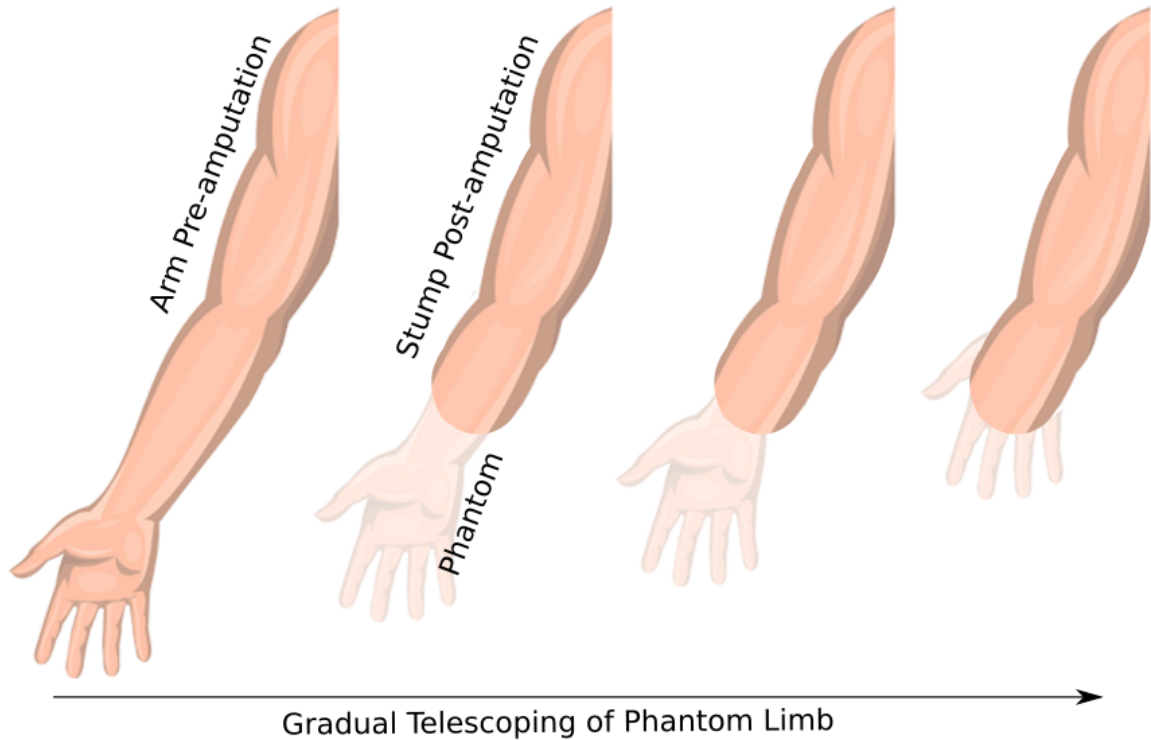
Fig. 1.1. The Phantom limb retracts into the stump over time in some amputees.

In some circumstances PLSs can be helpful in adjusting to the use of a prosthetic device, where the phantom limb embodies the prosthesis [16]. Murray describes the embodiment phenomenon as a transition of a prosthesis from an extracorporeal structure to a corporeal one, meaning the prosthesis becomes part of the identity of self. This fits into the field of psychoprosthetics, which uses a psychological framework to analyze and explain the phenomena associated with prostheses and the amputation rehabilitation process. Corporeal embodiment does not occur in all amputees, which is not well understood. Murray attributes this embodiment transformation to practice, i.e. increased use of the prosthesis [16]. Despite the possible utility of PLSs, in many

cases the phantom sensation evolves into the form of PLP, which can be not only a hindrance, but a phenomenon that has a strong negative effect on the amputee's quality of life [17]. The phantom limb can also be debilitating when the sensations are painful; 54% of amputees who experience painful phantom sensations, or PLP, regarded the pain as somewhat bothersome (27% said extremely bothersome) [18].

Phantom sensations are not pathognomonic to amputation of a limb [19]. In fact studies have recognized phantom sensations in other sensory systems. Phantom eye syndrome has been found to affect as many as 51% of patients with orbital exenteration with 26% feeling pain [20]. Phantom eye sensations most commonly came in the form of elementary visual hallucinations such as white light or colored light and were triggered by darkness, stress, and fatigue, among others [20]. Another argued case of phantom sensation is tinnitus, where individuals experiences phantom auditory sensations, most commonly described as ringing in the ears, steady tones, or hissing [21]. Tinnitus has been linked to hearing loss, i.e. up to 90% of cases are linked to hearing loss [21]. Like PLS, tinnitus describes false perceptions; however, tinnitus is unique because it also occurs in individuals who are otherwise healthy. Sectioning of relevant cranial nerves has not proven successful for the treatment of tinnitus, lending to support the current proposed mechanism of maladaptive neural plasticity [21, 22].

1.1.2 Phantom Limb Pain (PLP)

The prevalence of PLP, or phantom pain, widely varies in literature. A survey by Ephraim et al. (with 914 respondents), phantom pain was reported in 79.9% of amputees with 38.9% reporting the pain as severe (≥ 7 on a 0-10 analog scale) [18]. Ephriam et al. recognized no significant difference of the rates of phantom pain based on etiology, age, or level of amputation; they also noted that the rate of PLP for upper limb amputees was 83%, consistent with the rest of the study population [18]. Eleven percent of the amputees in this study were upper limb (10% unilateral), leaving 89%

as lower limb (79% unilateral). The mean pain intensity for phantom pain of all study participants was 5.5 ± 2.6 [18]. Others have found prevalence rates ranging between 40% and 85% [6, 9, 11, 23, 24]. Various explanations have been offered for discrepancies in the prevalence, such as response rates and bias from choice of study population. However, the clear cause of the differences is not known. The range for PLP prevalence in amputees generally referenced in literature is 50-80%.

The quantification and description of PLP is important in understanding the effectiveness of treatment. From the standpoint of self-reporting scales, pain can be defined in terms of intensity, affect, quality and location [25]. Most research studies have opted to primarily measure intensity and bothersomeness using the visual analog scale (VAS) or the discrete version called the numeric rating scale (NRS). Average ratings of pain, in terms of the VAS, fall in the range of 5.1 to 5.5 out of 10 [9, 18]. Ehde et al. found that when asked how bothersome the pain is (scale of 0-10, 0 being not at all bothersome, 10 being as bothersome as could be) 32% of respondents reported pain as being severely bothersome (≥ 7) and only 10% rated the PLP as not bothersome at all [9]. Likewise, Ephraim et al. found only 19% of respondents not to be bothered by the PLP they experienced [18]. Amputees tend to describe PLP as knife-like (stabbing), sticking, burning, squeezing, etc. [8, 10, 26].

A final metric or description of PLP is needed to quantify frequency and length-of-time of the pain. Efforts have been taken to define how often amputees felt PLP, and how long the pain was present. Amputees suffering from PLP experience the pain at different intervals; 31% report a frequency less than 1 episode per month, 14% a few times a day, and 7% have constant pain [24]. Another study found 14%, 24% and 24% for the same time frames, respectively [11]. Kooijman et al. found a fairly uniform distribution among frequencies of phantom pain attacks from feeling PLP a few times per year, month, week, day and constant pain, ranging from 14-24% [11]. Kern et al. found of those experiencing PLP, 56.1% have pain lasting less than 5 hours daily and many (27%) felt pain constantly [6]. Ephraim et al. reported frequency in terms of never, sometimes, always (20.1%, 58.7%, 21.2%, respectively) [18]. Ehde et al. found

81% of amputees to experience intermittent PLP, between once a week or less and 4-6 times per week [9]. Among these studies the rates are different for frequency of pain, as shown in Figure 1.2.
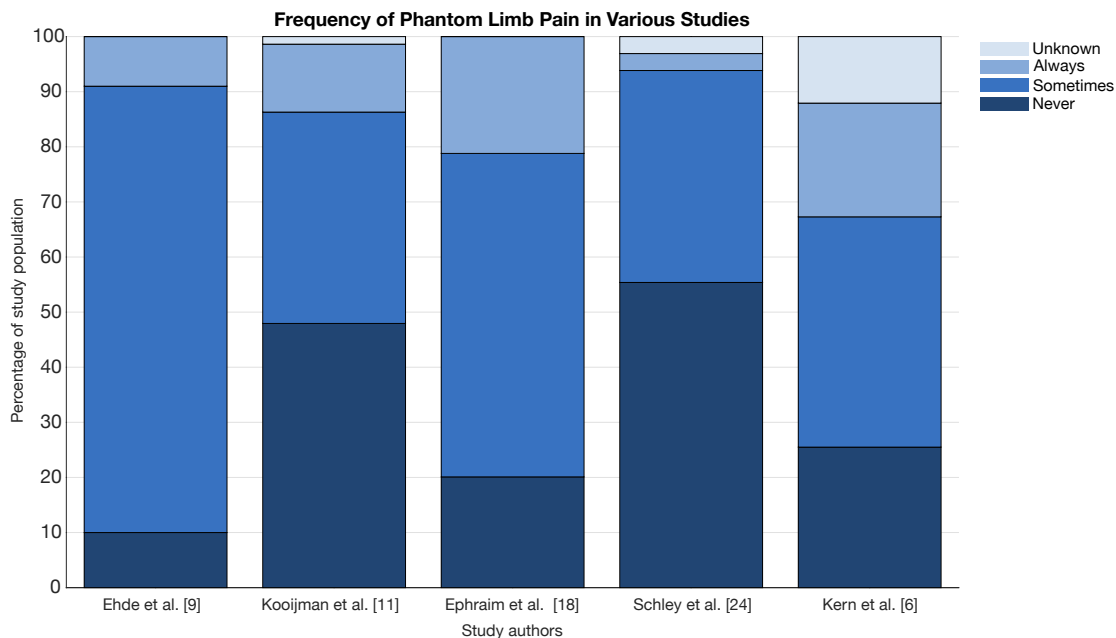
Fig. 1.2. Various rates have been reported in literature for the frequency of PLP episodes. Most respondents reported PLP as occurring at a frequency somewhere between never and always. Several variables could explain discrepancies among studies, including epidemiology and etiology of amputation, years since amputation, size of sample population, etc. The effect of these factors on PLP presentation is not well understood

The median follow up period for the study by Schley et al. was 3.2 years while the median follow up period for the study by Kooijman et al. was 19.1 years. Also, the events leading to amputation (i.e. the study population) were slightly different among studies, where 98% of the Schley et al. data came from traumatic cases [24], 78% from traumatic cases in the study by Kooijman et al. [11], and 50% for the study by Kern et al. [6]. Conversely, frequency and duration of PLP have also been found to decrease within 6 months after amputation [10]; this contradicts the discrepancy in the constant pain rate between Schley et al. (7% at 3.2 years after amputation) [24]

and Kooijman et al. (24% at 19.1 years after amputation) [11]. It is not clear which findings are more representative of the general amputee population. Ephraim et al. found of amputees 10+ years post-amputation; 74% were experiencing phantom pain [18]. The measure of length-of-time of pain has been reported in several ways, which makes it difficult to compare among reports in literature. PLP tends to flare episodically for seconds to minutes, but some have reported pain lasting several hours to a day or even longer [9, 10, 26].

Triggers of PLP

Some have sought to understand the common comorbidities and triggers associated with phantom pain. Those who indicate a depressed mood are more likely to report severe pain and pain that is extremely bothersome [18]. Phantom pain comes in many forms with many triggers. Often times PLP can flare during emotional distress, stump pressure, urination, cold temperature, or while coughing [8]. Pre-amputation pain has been recognized in several studies to be associated with phantom pain after the amputation [8, 10, 24]. Many have suggested a correlation of PLP and RLP; however, Kooijman et al. suggested that RLP acts as a trigger of PLP [11]. This claim has not been substantiated by subsequent research. Giummarra et al. suggest several categories of triggers, the most frequent of which is "Movement and 'behavioral schema' triggers"; these include activities such as scratching an itch, gesturing with the phantom, etc. [27].

1.1.3 Residual Limb (Stump) Pain (RLP)

A substantial number of amputees experience pain in their residual limb. As with other descriptors of pain, the rates vary widely in literature. Rates of stump pain span from 22% - 76% [8,9,11,18,24,28,29]. More recent surveys support rates on the higher side (61% - 67.7%) [18,24,28]. Ehde et al. reported that, in response to asking which pain is the worst, the highest rated site (33%) was the residual limb, over phantom

limb, back, and others [9]. RLP was also found in another study to be more impairing than PLP or back pain [30]. Only 4% - 13% of amputees experiencing RLP think of it as not bothersome at all [9, 18]. On average, the intensity of the RLP falls in the moderate pain range at 5.4 on a 0-10 scale and is commonly described as aching or burning [9]. This is supported by Ephraim et al., who found that for the individuals experiencing RLP, the pain was almost uniformly spread among mild, moderate, and severe (41.8%, 28.3%, and 29.9%, respectively), with mild being slightly more prevalent [18]. Similar to PLP, RLP tends to present itself in episodes and can last seconds, minutes, hours, or longer [9]. RLP does not tend to diminish with time after amputation [18]. Looking for the cause behind the pain is an elusive question. O'Reilly et al. propose the pain is a result of neuromata [31, 32], which are sensitive bundles of nerve endings that result from inability to reconnect with the target tissue [33]. Taken together, the high rate of prevalence and the impact on the quality of life highlight the degree to which RLP is a debilitating problem that needs to be addressed. A clear path to treating the issue of RLP is to look at treatment methods for NP. Neuromata are often associated with this type of pain, since inherently neuromata are a result of damage to the Peripheral Nervous System (PNS).

Amputees, often times, cannot distinguish between PLP and RLP [14, 34]. Generally this confusion arises when pain is felt in the vicinity of the amputation site, where the phantom and residual limbs meet. RLP and PLP tend to correlate, especially in intensity [26]. Schley et al. found that 86% of amputees experiencing phantom pain also experienced stump pain [24].

1.1.4 Neuropathic Pain (NP)

NP plays a role in phantom phenomena [19]. Casale et al. suggest that there is a significant link between neuromata and PLP [7]. Neuromata make the surrounding area more sensitive to stimuli (mechanical, chemical, electrical), which explains

correlations of pain and various triggers (e.g. touch, mood, stress, etc.) [7]. Many of the descriptors of PLP and RLP reflect what would be expected of NP, i.e. burning, stabbing, etc., which leads one to conclude that PLP and RLP are forms of NP, and may link to the development of neuromata in the stump. Neuromata are the most common cause of pain in one study [31]. However, not all neuromata result in pain. For example, the same study found 159 neuromata in the sample population, but only 91 (57%) were painful in response to transducer pressure [31]. Another study supports this finding with similar rate of pain occurrence at 67% [32]. Furthermore, when neuroma excision is not always successful. In a small case study neuroma excision relieved pain in only two of the six patients [35]. On the other hand, retrospective studies of neuromata removal found surgery to be a very successful method for relinquishing pain [36,37]. Nevertheless, even though the links among neuromata, PLP and RLP are uncertain, it does not rule out that PLP and RLP arise from NP origins. Nikolajsen et al. found a link of PLP to N-methyl D-aspartate (NMDA) receptors through treatment with ketamine and concluded that PLP and RLP have mechanisms linked to both peripheral and central systems [38]. NMDA is an excitatory neurotransmitter which interacts with NMDA receptors. NMDA receptors are known to be associated with neural plasticity, having a role in long term potentiation and long term synaptic depression. They are also involved in sensory transmission; A-delta and C fibers use NMDA receptors among others in transmitting painful stimuli up nociceptive pathways at synapses in the Rexed laminae of the dorsal horn [39]. Furthermore, having these roles gives way to one of the current, proposed mechanisms for NP, which points to NMDA receptors as a culprit for injury-induced central sensitization leading to secondary pain presentations such as allodynia and hyperalgesia [39, 40]. For this reason, as discussed later, NMDA receptors are a popular target for medicinal treatment approaches to alleviate NP [40].

Whereas, PLP is pain in the phantom and RLP is pain in the stump, linking the two to NP offers an explanation that neither form of pain would exist without injury to the PNS. This also assumes that RLP and PLP are not generated through

traditional means of activating nociceptor pathways. Although, this theory does not explain all observed conditions of phantom pain, e.g. people who are congenitally limb-deficient. As many as 20% of these individuals experience phantom limbs at some level (either sensation or pain), even though there is no injury, per se [41].

1.1.5 Secondary Effects of PAP

It is not just the rate of amputations and the severity of the pain that makes this problem relevant, but also the impact of PAP on an individual's every day life. The multifaceted attack of PAP through various mediums, such as PLP, RLP, and other forms, interferes with daily activities [30]. Amputation and PAP negatively affect the self-perceived quality of life through fatigue and diminished mood [42]. This leads to high rates of depression among amputees (as high as 41%) presenting a vicious cycle, as there are substantial links among depression, level of pain, and bothersomeness of pain for PLP and RLP [18, 43]. Depression secondary to amputation could be remediated by educating the population on the risks of amputation and providing mental health services [44].

1.2 The Proposed Loci and Mechanisms of PLP

1.2.1 Neurologic Locus of PLP

The root cause of PLP is not clear as effects of amputation appear in each level of the nervous system, indicating multiple compounding sources of pain. Evidence suggests that PLP is the result of a multi-faceted, combined system response from cortical, peripheral, segmental, and even psychological origins [15]. Most propositions of mechanisms discuss cause and effect on the level of the CNS or PNS. Because of the many proposed mechanisms, further partitioning is necessary. Therefore, mechanisms are discussed below according to the relevant neurologic locus: peripheral, spinal, supra-spinal, and cortical [15, 45].

Predominant Mechanisms of the Peripheral Neurologic Locus

The Tinel sign (also "tingling" sign) was originally proposed to identify regions of peripheral nerve regeneration, specifically regarding cases of nerve injury [46]. Similarly, one can use the Tinel sign on an amputee to locate nerve injuries that cause sensations or pain in the stump or phantom (referred sensation or RS). Commonly, the location that causes sensation or pain is at the site of a severed nerve, which has morphed into a neuroma. These neuromata (known as terminal neuromata) are typically formed within 1 - 12 months after nerve transection [47], but start to form within hours [33]. A study in rats found that ectopic discharges from injured peripheral nerves have a role in initiating NP, but do not have a significant role in the maintenance of NP [48]. The onset of ectopic discharges is correlated with the onset of allodynia (pain from a stimulus that would normally be nonpainful) shortly after nerve transection, indicating these are responses to or results of injury [48]. However, in animal studies ectopic discharges diminished over time, while tactile allodynia was maintained [15, 48]. These circumstances in the periphery seem to demonstrate two effects of nerve transection, but do not identify the source or mechanism of pain. For example, neuromata have been found to be sensitive to mechanical and chemical stimuli [15, 33], so much so that PLP can be heightened from tapping [49]. However, a study on two amputees found that PLP persisted even after blocking PLP associated neuromata with lidocaine [49]. This causes further suspicion that PLP and other phantom phenomena are not caused by peripheral mechanisms; rather, they are merely accentuated by peripheral factors.

Predominant Mechanisms of the Spinal Neurologic Locus

Deafferentation of the dorsal horn is thought to be linked to PAP, specifically through central sensitization, which is the increased activity of the dorsal horn afferent targets due to decreased suppression from the brainstem [45, 50]. Deafferentation could be a result of amputation, or it could be another type of injury such as brachial

plexus injury. Jensen et al. proposed that pain may be induced from atrophy of deafferented dorsal horn neurons and changes to receptive fields in the spinal cord [8]. Spinal reorganization has also been recognized in functionally inactive regions and is reversible if the relevant nerves regenerate [45, 51]. It has also been manipulated through operant conditioning of spinal reflexes (a well known mechanism for learning). Thompson and Wolpaw reviewed several studies that took advantage of the operant conditioning paradigm to alter reflexes [52]. Because of the integration of sensory information in the spinal cord (especially connections involved in gating through suppressive inhibitory interneurons), spinal mechanisms are important to consider [53].

Predominant Mechanisms of the Supra-spinal Neurologic Locus

Florence and Kaas found in animal studies that cortical reorganization was linked to reinnervation and sprouting afferents subcortically in the brainstem and thalamus [54]. Some have linked amputation to significant changes to the cuneate nucleus in the brainstem, which typically projects to the thalamus and transmits afferent sensory information, especially from the hand [54, 55]. Xu and Wall found changes in the cuneate nucleus to occur within minutes to hours after injury in primates [56]. Further evidence of supra-spinal reorganization was demonstrated in adult squirrel monkeys [57]. Churchill et al. found that somatotopic reorganization of the thalamus and brainstem was of a similar extent to what is reported for the cortex [57].

Predominant Mechanisms of the Cortical Neurologic Locus

A traditional theory, as proposed by Ramachandran et al., is that cortical reorganization is the primary mechanism of PLP, which is typically discussed in terms of plasticity of the primary somatosensory cortex (S1) [58, 59]. Directly following amputation, the mapping of S1, i.e. Penfield's Homunculus, no longer matches the anatomical structure. Changes occur in the sensory and motor cortices adapting to

both the altered anatomy and the loss of sensory input [59]. Specifically, the plasticity of the cortex allows neighboring regions of the somatosensory homunculus to take over the region that previously mapped to the, now deafferented, limb [58]. However, this mechanism also has missing links when looking at clinical experiences. A case study of two amputees found that some experience RS in the phantom hand while touching the ipsi- or contra-lateral foot [60]. Another study found RSs in the upper leg and genitals that mapped to the phantom in upper limb amputees [27]. Flor et al. found significant differences in activity among amputees experiencing phantom pain compared to those not experiencing PLP in regions such as SI, the secondary somatosensory cortex (S2), and the posterior parietal cortex (PPC) [59]. Other cortical changes have also been evaluated, such as unmasking of pre-existing synapses of neighboring cortical regions, e.g. of SI, and of pre-existing trans-commissural connections, e.g. for coordinated movements of multiple limbs [61]. The latter is of particular interest because it may explain cortical reorganization ipsi-lateral to the amputation as seen by Schwenkreis et al. [62, 63].

Referred Sensation and Related Mechanisms. While all phantom sensations are in a sense "referred", the definitions of PLS and RS are slightly different. PLSs are generally understood to be any sensation felt in the phantom limb, whereas RSs are perceived feelings in a body part when another body part is being stimulated (such as the residual limb or the face). RS is a common occurrence in amputees [58, 59]. While it is possible to feel RSs without nerve injury by stimulating proximal regions of a peripheral nerve as demonstrated by Forst et al. [64], RSs typically are amplified in amputees (i.e. more regions of the body such as the face and ear map to the phantom limb). Similar to amputation, substantial RSs have been noted in individuals with type I complex regional pain syndrome (CRPS) [65], spinal cord injury [66, 67] and other nerve related ailments. As with other aspects of phantom phenomena there is debate on the mechanism of RSs. This phenomenon is thought to originate from mechanisms that are separate from other phantom phenomena, as they are non-neuropathic in nature [19]. Flor et al. found correlation of RSs to increased

activity of the PPC [59], while Ramachandran et al. supported reorganization of S1 to be the primary mechanism [58]. Stimulation of the remaining nerve in the residual limb has also elicited RSs; Dhillon et al. achieved this through stimulation with implanted electrodes [13]. Similarly, Forst et al. were able to evoke RSs through surface electrical stimulation in healthy subjects by placing surface electrodes over the ulnar and median nerves [64].

The mapping of RSs requires the analysis of three primary locations: (1) the area being stimulated, (2) the area being referred, (3) the cortical location of somatosensory processing. Several questionnaires call for a subject to locate the areas of pain [68], but because non-painful sensation are generally not bothersome [29], the location and mapping of RSs has not been addressed except cortically. This is a useful measure to determine changes in the presentation of pain. RSs can be evoked by touch; the Tinel sign is a simple method for identifying these regions [46, 69].

Several interesting phenomena, which likely have different mechanisms, are considered RSs. For example, the RSs evoked by touching the face of an amputee (as done by Ramachandran et al.) likely has a mechanism primarily in the cortex [58, 59]. However, an RS evoked from stimulation of the proximal region of a peripheral nerve (as done by Dhillon et al.) likely can be explained by peripheral and/or spinal mechanisms [13, 64].

Psychological Aspects of Pain

Emotional and psychological states have a large role in interfering with amputees' lives [43, 70, 71]. The initiative on methods, measurement and pain assessment in clinical trails (IMMPACT) recommends testing effects on emotional functioning when conducting pain-related clinical trials [72]. Since amputees have exhibited differences from the general population in this respect, it is reasonable to assume that it also plays a role in the experience of PLP and other post-amputation phenomena. In general PLP is not a symptom of psychological distress [73]. Katz and Melzack reported that

depression and anxiety were not predictors of PLP [74]. This is further supported by Darnall et al. who found extremely bothersome RLP or PLP lead to increased odds of depressed symptoms, but depressed symptoms do not necessarily indicate bothersome RLP or PLP [44]. Darnall et al. concluded that one of the highest risk factors for depressive symptoms is PAP [44]. Both Hill and Katz cautioned researchers on the assumptions related to depression and PLP saying claims of psychological explanations of pain are unsubstantiated and study populations may be inherently biased [14, 73]. Along the same lines, some have suggested that the causal relationship between pain and mood is only uni-directional, i.e. negative mood states are a result of pain, but pain is not a result of negative mood [75]. Even though the relationship of PAP and depression is still under investigation, the relationship of depression and amputation seems to be quite clear. In addition to depressive symptoms, evidence of anxiety, insomnia, and other psychological ailments are prevalent [70]. This demonstrates a need for mental health services among the amputee population.

1.2.2 "Phantom" Pain in Non-Amputees - a Complicated Issue

The traditional definition of PLP refers to pain in a limb that is not present. However, there are also instances of sensation and pain in a limb that has lost connection to the CNS (deafferentation), from brachial plexus avulsion (BPA) or intraspinal injury for example. These scenarios have been dubbed as "phantom" because the individual does not experience pain or even sensation through typical nociceptive and sensory pathways, because they are no longer connected. In this regard "phantom" sensations have been found in individuals who have brachial plexus injuries [76–78]. In addition to the similar descriptions of pain, after BPA individuals experience RSs in the deafferented limb from touching the ipsi-lateral face [77]. Brachial plexus injuries also lead to cortical reorganization [79]. Most often pain is described as tingling, pins and needles, burning, sharp, or paroxysmal [80], which is reason to believe BPA causes NP [53]. The underlying mechanisms of pain as a result of BPA are not well

defined. In comparing symptoms one must consider that brachial plexus injuries are often incomplete, meaning the limb remains partially sensate because it is still partially neurologically intact. If individuals with BPA or intraspinal injury experience PLP, the phantom pain and phantom sensations convolute with trace sensations from the limb. Furthermore, the presence of the limb further complicates discriminating phenomena as phantom or not. While the pain presents in a similar fashion to that of pain as a result of amputation, the presence of the limb makes it difficult to know if the mechanisms are the same.

1.2.3 Theories of Why PLP Presents

In the study of phenomena associated with amputation, an important thought to consider is that a single mechanism will likely not explain all phenomena. This idea was proposed by Sherman et al. in their evaluation of the mechanism of PLP, which concludes that different presentations of pain should be treated differently clinically, but does not suggest how [81]. Several theories have been proposed over the years to explain PAP and phantom phenomena. Ronald Melzack and Patrick Wall have had many contributions to this list and evolution of theories including the Gate Theory of Pain, the Neuromatrix theory, and others, which are discussed below.

Gate Theory

Gate Theory is a prominent pain theory developed in the 1960s [82]. The concept in its most basic form can be summarized as a complex multi-input, multi-layered system, where inputs at various layers can relay "off" or "on" signals, which cascade to determine whether or not pain is perceived [82,83]. More specifically, Gate Theory suggests that portions of the dorsal horns, such as the substantia gelatinosa, and the brain are active contributors to the system, which excite, suppress, and modulate signals to downstream targets [84]. Wall reinforced the theory after a few years discussing new findings in the field and how they relate to the previously proposed

theory [85]. In development of the theory there were many unknowns as to how the theory was implemented physiologically. In returning to the topic Wall proposed that descending control involves the periaqueductal grey matter and nucleus raphe magnus [85]. The theory was proposed ahead of its time, pushing the field forward to better understand mechanisms of pain [83]. Since its introduction, Gate Theory has evolved over several decades to account for new findings [83, 85]. It provided the framework for future theories of mechanisms that incorporate the CNS and an individual's unique life experiences [14, 84]. Melzack proposed a new theory as a derivative from Gate Theory called the Neuromatrix Theory, which emphasizes a sense of self in the perception of pain [84].

Neuromatrix Theory

The Neuromatrix Theory relies on the concept of a network of neurons that defines a genetically determined feeling of self [86, 87]. The neuromatrix is thought to extend beyond the somatosensory areas of the cortex to the limbic and thalamocortical systems [61]. Melzack proposed the neuromatrix could be molded by sensory input and is comprised of "thalamocortical and limbic loops", which cyclically process and synthesize input and output patterns. These patterns are what Melzack deemed the neurosignature, an individual's pattern of synaptic connections impressed on the neuromatrix [87]. An altered neurosignature, due to amputation for example, would result in the experience of a phantom limb through sensations and possibly pain [34]. The Neuromatrix Theory considers sensory input and transmission on a "level of equal importance" as hormonal mechanisms of stress, meaning pain does not exist solely in a space of neural mechanisms, but also has psychological factors [87]. The diffuse nature of the theory, i.e. pain (or even phantom sensation) being the output of a large, complex psychophysical system, makes it difficult to isolate and test clinically [14,34,61]. Furthermore and even more perplexing, the theory does not offer an explanation for why some amputees experience phantom pain or phantom sensation

and others do not [34]. Giummarra et al. offer examples of seven phantom limb related experiences that are not explained by the Neuromatrix Theory and concludes that Neuromatrix Theory may provide explanations of PLP, but not PLS [61]. While Neuromatrix Theory is intriguing and will likely spark discovery in the current age of pain research (like Gate Theory did in the 1960s), it lacks some explanation for phantom phenomena.

Mal-adaptive Cortical Plasticity

The idea of mal-adaptive cortical plasticity is that the sensorimotor cortex reorganizes in a way that causes pain post-deafferentation. Whereas it is clear that the cortex reorganizes post-amputation, the extent of the relationship between reorganization and pain is unclear [15]. Evidence supporting this theory compared hand and lip movements among upper limb amputees and healthy controls, where amputees experiencing PLP showed reorganization of the mouth and hand region of S1 and the primary motor cortex (M1) [88]. In a study of brain-machine interfaces with patients experiencing phantom pain, Yanagisawa et al. found that attempting to merge and amplify neural signaling to cortical representation of the phantom actually increased pain [89].

Pain Memory

The pain memory hypothesis supposes that phantom pain mimics pre-amputation pain because of implicit pain "memories" established in the somatosensory system [15, 34]. The hypothesis relies on plasticity of the somatosensory cortex due to nociception [15]. In a small study involving capsaicin injection, sensitivity of SI to nociception has been measured, improving validity of the hypothesis [90]. Further support for the hypothesis is that phantom pain commonly embodies pain that was experienced pre-amputation [74], and several studies have found correlations between pre-amputation pain and phantom pain [8,91]. However, this theory does not account for the amputees

who experience PLP but do not experience pain pre-amputation. Furthermore, some amputees feel pain due to the phantom limb being in an unnatural or biologically impossible orientation, which does not support this hypothesis.

Sensory Confusion

The hypothesis of sensory confusion assumes that pain is a result of ramping due to broken feedback mechanisms. While feedback loops exists sub-cortically, evidence also points to involvement of frontal and parietal brain areas in the "incongruence of motor intention and sensory feedback" [15, 92]. Similar to Gate Theory, this hypothesis relies on closed-loop control of peripheral and central mechanisms, which modulate sensorimotor information during movement. Harris compares this effect to the feeling of nausea when senses do not agree on body position or balance [92].

1.3   Measuring PLP

Pain has both behavioral and physical properties and can be largely subjective. Intensity, affect, quality and location are the primary experiential dimensions of pain [25]. Pain intensity refers to the extent of the pain and can be subjective based on historical experience of the individual reporting the pain. Pain affect refers to the "emotional arousal or changes in action readiness caused by the sensory experience of pain," as so eloquently put by Jensen and Karoly [25]. In essence pain intensity refers to the extent of pain while pain affect refers to the emotional experience related to pain or the extent to which the individual is bothered by the pain. Pain quality refers to the descriptors of pain with respect to sensation, such as tingling, burning, sharpness, etc. and also includes the time-related aspects of pain, such as frequency, length-of-time of pain, etc. Pain location defines the area pain is perceived. Each of these four dimensions of pain are important to measure when studying the effectiveness of treatments and therapies for PLP. However, the measurement of PLP is a complicated issue. When measuring pain in a research setting (clinical or animal), there are

additional considerations, such as the effects of habituation and sensitization [93]. Because of these barriers, pain-researchers utilize multiple measures and consider behavioral presentations of discomfort in analysis [94]. Across studies of proposed therapy methods, various pain measures and scales have been utilized; in regards to PLP, studies tend to describe the degree of pain and the extent the pain interferes with the individual's life through various psychophysical measurement modalities [14]. This variety of methods makes comparisons of results difficult.

1.3.1 Psychophysical Measures of Pain

In order to understand the effects of a given therapy modality, one must measure the various aspects of pain. Several validated measures are available to do this. The instruments used in the present study for effect determination are the visual analog scale (VAS), neuropathic pain symptom inventory (NPSI), profile of mood states - short form (POMS-SF) and are discussed below. These were chosen because of the sensitivity they have shown in previous studies, but also because they are validated in the languages being used by the EPIONE consortium, i.e. Danish, English, French, Italian, and Swedish. The primary measure of effect and two secondary measures are introduced below and are utilized for analysis in Chapter 4 and Chapter 5. In addition, an exploratory measure, the brief pain inventory-interference scale (BPI-IS), is discussed below, which is shown in Chapter 5. These four self-report questionnaires are the focus of the EPIONE Extraction Program (EEP) and Group Analysis Module (GAM), which is introduced in Chapter 3. More details for these instruments are included in Chapter 2.

Self-report Questionnaire

While self-report questionnaires are an obvious way to gather information and understand the pain being perceived, the subject to subject (inter-subject) variation cannot be predicted. For example, Dar et al. found, in a small study of injured vet-

erans, that severely injured individuals have a higher pain tolerance and higher pain threshold than lightly injured individuals [95]. In a study of thermal pain thresholds, Wasner et al. explored preconditioning as a means of testing sources of inter-subject variations; however, in terms of pain thresholds, the study found no difference in subjects who were preconditioned and subjects who were not preconditioned [96]. This is a relevant finding because of the concern for scale recalibration presenting a potential source of variability in self-report data. The proposition of scale recalibration is an issue that is not addressed in the realm of PLP. However, in other research areas, this has not been validated as a source of variation. Lacey et al. found no evidence of scale recalibration in individuals suffering from chronic illness (specifically with regards to quality of life ratings) [97]. Nevertheless, studies typically rely on validated instruments and assessments to characterize pain and understand the effects of a given treatment for a population.

The Visual Analog Scale (VAS)

Psychophysical measures involve those that describe an individual's perception. A commonly used instrument is the VAS. With respect to pain intensity, an individual experiencing pain ranks the pain somewhere between "no pain" and the "pain as bad as it could be" by marking a line spanning between the two extremes (commonly separated by 10-cm). The individual's severity of pain can be enumerated by measuring the length from 0 (no pain) to the marking [94]. The primary measure of most studies describing the prevalence of PLP is typically some version of pain intensity; most often this is done with the VAS [14]. The VAS and the discrete version, NRS, can be used for any measure in which there are two extremes. The VAS has been used to understand other aspects of phantom phenomena, such as intensity of PLS [23], and it can be useful in describing the effect of a treatment or therapy. In fact it is used frequently outside of the realm of PLP [94]. When describing the intensity of phantom pain, the VAS is often used along with the interpretation or adaptation

into mild, moderate, and severe pain. Jensen et al. attempted to standardize these descriptors to pain ranges, 1-4, 5-6, 7-10, respectively, by considering factors such as pain interference and impact on quality of life [98].

The Neuropathic Pain Symptom Inventory (NPSI)

The idea of using a VAS or NRS has been adopted and adapted to quantify other unmeasureables because of its dependability [94]. The NPSI utilizes several NRSs to quantify the qualities of NP [99]. Ultimately, the responses are combined to form subscores, which represent different aspects of NP, i.e. burning, pressing, paroxysmal, evoked, and paresthesia (or dysesthesia), and overall NP. In the case of NPSI, paresthesia/dysesthesia are defined by the same subscore, which is related to feeling pins and needles and feeling tingling [99]. The usefulness of the NPSI is that it not only demonstrates the presence of NP, but also the presentation of the pain. Having this capability offers the opportunity to study the effects of treatment on subtypes of NP as well as the effects on overall NP. Mackey et al. proposed extracting information on NP from the short-form McGill pain questionnaire (SF-MPQ; discussed further in subsection 1.3.2); this method takes advantage of an existing questionnaire, but it is not as specific as other measures, such as NPSI [100]. Other measures specifically related to NP exist, such as the neuropathic pain scale (NPS) [101], the neuropathic pain questionnaire (NPQ) [102], the "neuropathic pain four questions" (DN4) [103], the Leeds assessment of neuropathic symptoms and signs (LANSS) [104], among others; however, these alternative instruments are either not strongly validated, not detailed enough, or are designed to differentiate non-NP from NP and not to assess NP [99]. The NPSI has been validated in several languages among various populations [99, 105, 106]. A German study found NPSI test-retest reliability to be suboptimal [105], compared to the original study [99]. Although, in the German study the time lag was 24 hours (compared to 3 hours in the original study [99]). While this is a notable finding, it does not change the validation of the instrument as it is reasonable

to expect changes in the presentation of pain in a 24 hour period; temporal variation is a known characteristic of NP [107].

The Profile of Mood States-Short Form (POMS-SF)

In traumatic lower limb amputees, the prevalence of depression was 41.6% [43]. In a broader population base of various etiologies, significant depressive symptoms were seen in 28.7% [44] (compared to 4.9% point prevalence and 17.1% life-time prevalence in the general population [108]). Ephraim et al. aptly noted the correlation of depression and the presence of PLP, where increased pain intensity corresponded to heightened depressive symptoms [18]. The finding suggests that there is a need to continuously monitor and swiftly treat depression in amputees [18]. In a more general sense, mood correlates to the intensity and perception of pain greatly [75]. Some attempts have been made to treat pain using the class of drugs called antidepressants and through psychological treatments of pain [107, 109]; however, these have been ineffective [110]. Mood does not act as an effective target for treatment. However, it may act as an indicator of positive or negative effect because of its correlation to pain.

The POMS-SF is comprised of 37 descriptors of mood. Each descriptor is ranked by the study subject on a 5-point scale (1="Not at all", 5="Extremely") and is incorporated into a subscale, which can be used to characterize the individual's mood. The subscales are depression, vigor, confusion, tension, anger, and fatigue. Whereas depression has been shown to positively correlate with pain, other mood descriptors could provide more insight on the relationship of PLP and psychological state.

The Brief Pain Inventory - Interference Scale (BPI-IS)

The brief pain inventory (BPI) has been adapted into a more succinct questionnaire as the BPI short form (BPI-SF), which is a validated instrument for pain interference [111–113] The final series of questions is known as the BPI-IS. Questions are

non-specific to phantom pain and describe how pain has interfered with daily living over the past 24 hours. The 7-question interference scale utilizes 11-item NRSs to describe pain's interference with general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life. The NRSs span from 0 ("Does not interfere") to 10 ("Completely interferes").

Problems with Measuring PLP and Other Phantom Phenomena

One factor not addressed by Jensen et al. when describing the standardization of the VAS with respect to PLP is the associated anchors of the VAS [98]. Anchors are defined as the descriptions of the minimum and maximum scores. Jensen et al. used a scale of $0 - 10$ with anchors of "0 = no pain" and "10 = pain as bad as it could be" [98]. A prime example of this inconsistency in research related to PLP can be found in reports of the intensity of pain. In Table 1.1 several examples demonstrate how intensities are reported among various authors. The outcome of not utilizing a standard instrument for measuring pain intensity is data that is not directly comparable. While it may be possible to normalize the various scales back to the standard scale proposed by Jensen et al., correlations have not been proposed among the various scales.

Table 1.1. Different anchors for the VAS make pain intensities difficult to compare across studies.

Article Authors	Pain Scale	Anchors
Sherman and Sherman [23]	$0 - 100$	Anchors not described
Montoya et al. [26]	$0 - 10$	No pain / Unbearable pain
Smith et al. [29]	$0 - 100$	Extremely mild / Extremely intense
Ehde et al. [9]	$0 - 10$	No pain / Pain as bad as it could be
Marshall et al. [30]	$0 - 10$	No pain / Pain as bad as it could be
Ephraim et al. [18]	$1 - 10$	Mild pain / Extremely intense pain
Schley et al. [24]	$0 - 100$	Anchors not described

Furthermore, interpretation of changing VAS scores is non-trivial. Jensen et al. suggest that a change in pain intensity from "7 to a 4 might be considered more beneficial and more clinically relevant than a reduction from a 4 to a 1, at least in terms of the impact of the treatment on function and quality of life [98]." This conclusion suggests that both the change in pain intensity as well as the baseline or reference pain intensity are important factors to keep track of in establishing effective treatments and therapies. In the present study multiple modalities are explored using a common clinical protocol, discussed further in Chapter 2. The format of psychophysical measures, including details such as anchors, is consistent allowing direct comparability of effectiveness.

1.3.2 Other Proposed Self-Report Measures of PLP

Because of the lack of standardization, several questionnaires and instruments have been developed or adapted for measuring PLP. Hill notes in a literature review of PLP, the McGill pain questionnaire (MPQ) and SF-MPQ have been used in several studies [14]. The McGill pain questionnaire and its variants have significantly contributed to the understanding of pain (in general) and PLP, and it acts as a primary instrument in many pain studies [114]. Alternate measures of depression include the Center for Epidemiological Studies - depression questionnaire (CES-D) [18]. The chronic pain grade (CPG) [9, 30, 115] distributes an individual's pain into one of four grades based on intensity and disability associated with pain. Grade I is the least intense and least disabling, while Grade IV is the most intense and most disabling [115]. Flor et al. and Montoya et al. used a 122-item phantom-and-stump phenomena interview as a primary instrument [26, 116]. The interview is a compilation of several standard instruments to separately analyze stump and phantom sensations and pain, including a modified version of the MPQ, several VASs to describe average pain severity and intensity of non-painful sensations, descriptors of sensations, along with several open-ended questions [26]. Montoya et al. also utilized

the West Haven-Yale multidimensional pain inventory (MPI) to evaluate the severity and interference of stump and phantom pain [26]. Smith et al. [29] used the prosthesis evaluation questionnaire (PEQ; developed by Legro et al. [117]). The PEQ highlights intensity, frequency, and bothersomeness of phantom, stump, and back pain as well as phantom sensations [29]. Further evidence of lack of standardization is that study designs have opted to utilize self-designed questionnaires such as the Groningen questionnaire problems after arm amputation (GQPAA) by Kooijman et al. [11]. Ultimately the choices of questionnaires in the present work came down to a criterion of language. In order to accommodate all of study sites, the partners of the EPIONE consortium opted to use the VAS, NPSI, and POMS-SF as the primary and secondary instruments.

1.3.3   Measuring Cortical Reorganization

Cortical plasticity or cortical reorganization is a popular topic in the study of post-amputation phenomena. This is mainly because of the desire to understand the underlying mechanisms. While plasticity is not unique to the cortex [54], it gets particular attention because of the relationship of the somatosensory mapping and observations of RSs in the facial region [58]. From the perspective of characterization, studies have investigated the differences in cortical activity among amputees and healthy controls. Lotze et al. studied the locus of activation for hand and lip movements using functional magnetic resonance imaging (fMRI), comparing amputees with PLP (n=7), amputees without PLP (n=7), and healthy controls (n=7) [88]. Reorganization of the hand and lip areas in M1 and S1 was recognized in patients with PLP but not others. Many studies have also investigated the cortical differences between the activities utilizing the affected limb versus the individual's healthy limbs. This paradigm attempts to have an individual serve as his or her own control. Measurement of changes to the cortex can be done through several modalities. Blood oxygen level dependent (BOLD) fMRI is used most often because of the ability to relate ac-

tivation to particular cortical structures. Most studies that use event-related BOLD fMRI to look at cortical reorganization focus on S1 and M1 [88, 116]. Other instruments include electroencephalogram (EEG) coupled with some type of somatosensory evoked potential (SEP) in the periphery, such as tactile evoked potential (TEP) or laser evoked potential (LEP) [59, 118]. Coupling both EEG and MRI, Flor et al. used EEG to record cortical activation during RSs elicited by TEP, and used the activation map to overlay an anatomical image captured via magnetic resonance imaging [59].

Some disadvantages should be considered when using BOLD fMRI to study cortical differences. The main disadvantage is the length of time required for measurement. BOLD fMRI contrast relies on the hemodynamic response function (HRF), which is an increase in oxygenated blood (specifically oxyhemoglobin) compared to a resting state. The underlying assumption is that the increase in blood in a particular region is a causal, time-delayed effect of increased neuronal activity. These details reveal a reason behind the intensive time requirements of fMRI, as stimuli do not elicit instantaneous responses. Beyond the time dynamics of the biological system, the larger contributor to lengthy experimentation paradigms are issues of signal-to-noise ratio (SNR). To alleviate the poor SNR, fMRI paradigms typically utilize signal averaging, thus longer measurement times. Analysis of fMRI results involves an understanding of both estimation efficiency (ability to estimate the HRF) and detection power (ability to detect activation) as described by Liu and Frank [119, 120]. Furthermore, a recent study attempting to validate fMRI statistical analysis methods found high rates of false positives [121].

1.3.4 Pros and Cons of Different Measurement Approaches

If relating back to the four primary dimensions of pain (intensity, affect, quality, and location), various instruments have positive aspects and points of weakness. For this reason several research studies have implemented multiple instruments. Depending on the study design this could have different effects on self-report data. Thorough

questionnaires and interviews (such as the MPQ or the phantom-and-stump phenomena interview) allow for detailed description of the pain, but take substantial time and concentration for the study participant. This could cause frustration and bias if the participant is enrolled in a study of temporal effects of treatment and having to complete a questionnaire multiple times, for example. Substantial effort should be taken to consider the length of time a study participant spends responding to questionnaires and the number of times a study participant responds to a particular questionnaire. On the other hand there are disadvantages of being too brief [25]. Brevity is just one consideration in the list of primary trade-offs, where targets should be set to reduce the required contact time between the health care provider (HCP) and patient, while maximizing the collection of relevant pain characterization data.

1.4   Current Treatment/Pain Management Methods

The proposition of treating PLP has been under study for decades. In 1980 Sherman et al. reported on 68 different possible methods [122, 123]. To this day a concise method for treatment has not been identified. Flor suggested more than 30 commonly used treatments for PLP in 2002, only a small fraction of which have shown any success in randomized controlled trials (RCTs) [34]. Ideally, treatment methods of PAP and phantom limb phenomena would be developed from a mechanistic approach, i.e. the mechanism of pain would be utilized to address and reverse the pain. Since the mechanisms are not well understood, therapies tend to treat the symptoms, leading to a high number of available treatments, low rates of success, and high rates of dissatisfaction among patients [122, 124]. Current treatments of PAP can be broken down into medicinal and non-medicinal methods. Medicinal treatments of pain utilize various methods of application: topical, oral, and local injection. A wide variety of non-medicinal treatments have been explored, taking advantage of mechanical and electrical sensitivity of PAP. Other methods have used traditional pain management

techniques, while some have ventured into the psychological treatment of pain. All-in-all treatment of any form of PAP has been largely unsuccessful.

1.4.1   Current Standard of Care

In 1983 a study found that only 17% of amputees were offered treatment for PLP even though 61% reported experiencing PLP [23]. Potentially, this was because treatments and therapy were largely ineffective at the time or because the medical community was not convinced the phantom pain existed or was treatable. Over the years medical care providers have come to accept the reality of phantom sensation and pain. Several authors have noted a variety of responses from physicians to those suffering from PLP such as, "it is in your head" or PLP is "psychogenic [34,125–127]." Conversely, while the limb may no longer be present, the pain and sensations seem real. Another study in 1997 found nearly one-third of amputees who discussed PLP with their doctor were told no treatment was available [128]. Kern et al. attempted to study the success rates of relevant treatment methods by surveying amputees. Seventy-one percent (N=537) of the amputees suffering from PLP had never received or sought after treatment; 19% felt their doctors were incompetent on the topic [6]. Of those who did receive treatment for phantom pain, the treatment with the highest success rate was opioids via oral or IV administration at 67%. The second highest treatment method was opioid injection via intrathecal pump at 58%. Neither of these treat the root problem but only temporarily mask the pain [6]. Whereas the medical and scientific communities are more accepting of the reality of PLP, the current standard of care is still up for debate. A focus group of health professionals found that information given to patients experiencing PLS and PLP is grossly inconsistent, indicating a necessity for a standard of care to be developed [126].

1.4.2 Medicinal Treatments

Medicinal treatments are among the most successful at alleviating PLP. Opioids/Opiates have shown a success rate as high as 67.4% [6], in particular morphine via injection and oral administration has shown successful reduction of but not elimination of PLP and RLP in a randomized controlled trial [109, 129, 130]. However, long-term analgesic efficacy has not been verified [6, 109]. Anticonvulsants have also shown moderate success (52%) [6]. Gabapentin is a commonly used anticonvulsant, which has had controversial results in RCTs. Bone, et al. showed reduction of PLP in comparison to a placebo but no significant change in secondary measures, such as depression, mood or sleep interference [131]. Conversely, a separate RCT showed no significant difference between gabapentin and placebo groups [132]. Some side effects were noted; however, these were not significantly different from the control groups [131, 132].

Alviar et al. reviewed three NMDA receptor antagonists as possibilities: memantine, dextromethorphan, and ketamine [109]. The review identified only ketamine [133] and dextromethorphan [134] to provide pain relief from this class of pharmacologic interventions [109]; however, both studies were underpowered [109] and treatment with ketamine had substantial side effects, including dizziness, light hallucinations, and hearing impairment [133]. NMDA receptor antagonists have shown moderate success at relieving pain. The unsuccessful cases may be related to the mode of administration; each memantine trial reviewed utilized oral administration while other studies of this intervention method were successful with injection [109].

Various other options have been explored and proposed for treatment including antidepressants, calcitonins, and local anesthetics [109]. In patient surveys, antidepressants have shown to be ineffective. Only 36.4% noted this method as effective [6]. This ineffectiveness was supported in a RCT of amitriptyline that failed to show positive results [109, 135]. Furthermore, amitriptyline had a significant adverse effect of dry mouth over the placebo [135]. Local anesthesia was largely ineffective according

to patient surveys (21.6% success) [6]; RCTs of intravenous infusion with Lidocaine have shown successful treatment of RLP but not of PLP [129].

1.4.3   Non-medicinal Treatments

Several non-pharmacological approaches have been proposed and tested as possible treatments for PLP, such as proper stump management, electrical stimulation, and mental imagery. Treatments vary significantly in regards to stimulus modality, psychological demand, and efficacy. Many therapies are proposed in case studies and uncontrolled trials, but either do not reach the stage of conducting a RCT or are not successful in a RCT, which makes identifying potential effective treatments in literature difficult [136]. Some of the more prominent methods are discussed below.

Nerve and Stump Management

Several methods have been proposed to thwart PAP related to neuromata; a universal method has not been accepted [37, 124]. Proper care of the stump and preventative measures in surgery are crucial to mediate pain. Painful neuromata are common among amputees; nearly 30% undergo surgery after amputation with the hopes of relieving neuroma related pain [6]. Often they form from improper surgical technique during the original amputation [124]. Studies have shown that simply excising the neuroma and applying traction to the nerve (encouraging the nerve to retreat into the stump) is not a successful procedure, only demonstrating successful results 33% of the time [137]. Over the years several techniques have emerged to ameliorate this painful phenomenon [124]. A recent review of neuromata treatment and prevention found nearly 200 techniques, supporting the perfect solution has not yet been found [124]. Some techniques have proven successful and appear notable; excision with silicone capping (83% success [138]) or centro-central anastomosis (94%-95% success [139,140]) are prime examples [124]. On the other hand, techniques such as these also present unnecessary risks to the patient. Silicone capping involves the

introduction of a foreign body, which risks immunological response and inflammation in the stump [37]. Centro-central anastomosis lengthens the time of surgery due to the meticulous nature of microsurgery, which means more opportunities for infection [37].

One of the most notable techniques is nerve transposition [124]. Mackinnon et al. demonstrated the capability of minimizing neuroma formation in an animal model [141]. Rerouting the transected nerve into adjacent muscle without tension, resulted in significantly smaller neuromata compared to control groups in primate models [141]. Mackinnon and Dellon revisited the technique emphasizing the importance of separating the nerve ending from the scar tissue [142]. This study found different success rate depending on a patient's previous experience ranging from 56% - 100% for good or excellent results [142]. The nerve transposition technique had good or excellent results in 81% of cases (42 patients) [142].

Another method that has had some success is targeted muscle reinnervation (TMR) [143]. This is the act of intentionally ligating the original innervation of a nearby muscle to direct alternative peripheral nerves to the muscle. Generally TMR utilizes a muscle that is no longer providing functional advantages to the patient with the hopes of the muscle acting as a target for the nerve. The long term goal for these patients is that they could intuitively move their phantom, which would cause muscle activity in the targeted muscle; then, this muscle activation could be recorded, e.g. via EMG, to manipulate an active prosthetic. Conveniently, this method serves a dual purpose by also preventing the formation of neuromata. In a retrospective study six months after surgery, the method appears to be successful [143]. All patients reporting pain reported reduced or eliminated pain, and just under 90% were able to operate a TMR-controlled prosthesis [143].

Peripheral nerve surgery, such as TMR, is a treatment option for managing pain related to neuromata that has shown success in several studies, and is an excellent example of advancement in the field [124]; however, the degree of functionality provided by this method is often not necessary for lower extremity amputees. Rather than transferring the transected afferent nerve fibers to an alternative muscle or re-

gion, some have suggested merely tying the sensory nerves to nearby muscle away from areas forming scar tissue. If done during the amputation surgery, it could prevent formation and excision of the neuroma post-amputation, thus lowering overall patient risk through reduction of procedures and procedural time [37]. This procedure, proposed by Ducic et al. as an outpatient operation has had great success in a retrospective study of 21 neuroma excisions; patients reported an the average preoperative pain of 8.04 that decreased to 1.07 on the visual analog scale (ranging 0-10) [37]. Furthermore, 85% reported improved quality of life [37]. The key to this technique involved suturing the nerve-ending (after neuroma excision) to the nearby muscle. Some have proposed applying light traction to the nerve is sufficient, but an important detail to many of the techniques is to keep the nerve tension free [124].

Electrical Stimulation

Electrical stimulation of the residual limb, especially transcutaneous electrical nerve stimulation (TENS) or functional electrical stimulation (FES), has had success in case studies and small trials. However, as is the case with other therapy methods, the effectiveness of TENS has not been shown with a RCT [144]. Other forms of electrical stimulation have shown promise as well. Peripheral Nerve Stimulation showed significant improvement in regards to pain and quality of life, but the study lacked a placebo and had a small number of participants [145]. Others have attempted applying TENS to areas other than the residual limb, such as the contralateral limb [146] and the ears [147]. Both of these methods showed a positive effect in small, short-term trials, but neither were compared to placebo groups. Sensory discrimination training using TENS has shown positive results (reduction in PLP and effect in cortical reorganization) in a small comparative study of 10 amputees [148]. This method involved the application of random, non-meaningful stimulation patterns of varying frequency, intensity, and location. Trial subjects were instructed to identify different patterns with the hypothesis that distraction from the pain actually reduces the pain [148].

Success indicates there is a positive relationship among discrimination ability, cortical reorganization, and decreased PLP; although, the long term effects of this method were not reported [148].

Considerations for FES of Peripheral Nerves. Studying the effect in cats, Agnew et al. found that 8 hours of high-rate, high-amplitude electrical stimulation resulted in irreversible damage of sciatic nerve axons [149]. In an earlier paper [150], this effect was referred to as stimulation-induced depression of neuronal excitability (SIDNE). SIDNE, which according to the authors differs from long-term depression (LTD) because it does not involve a change in efficacy of the synapses and does not worsen day-to-day, can occur in the CNS if axons are subjected to "prolonged, high frequency microstimulation [150]." McCreery et al. stimulated the posteroventral cochlear nucleus (PVCN) for 7 hours per day to find that with high enough intensity SIDNE could be induced, but was still reversible. The speculated mechanism attributed the effect to the entry of calcium into the neurons activating second-messengers and several downstream pathways.

Lu et al. studied the effects of electrical stimulation on peripheral nerve regeneration in Sprague-Dawley rats [151]. Methods involved transecting the right sciatic nerve, separating the nerve endings by 10-mm, and surrounding the nerve endings by a silicone rubber chamber. Stimulation was applied for 15 minutes every other day at 1 mA (1, 2, 20, 200 Hz depending on group). Results included histological samples as well as tests of nerve conductivity that showed the 2-Hz stimulation group to have the most mature structure. Lu et al. concluded that in regards to peripheral nerve regeneration, stimulation (depending on frequency) can have a positive or negative effects. Note, control group had 100% success in regenerating a nerve cable spanning the 10-mm gap; however, the conclusion was that the nerves generated under 2-Hz stimulation were healthiest [151]. Cogan et al. suggest many culprits when it comes to the cause of tissue damage and that macroelectrodes and microelectrodes have different challenges when it comes to preventing tissue damage (especially charge density and charge per phase), but they did not address continuous

stimulation [152]. Patel and Butera used stimulation frequency of up to 70 kHz to block nerves, but did not report on the possible effects of continuously stimulating at these high frequencies [153]. Prodanov et al. [154] reviewed FES in 2003 and pointed to two other articles by McCreery et al., which also discussed the negative effects of continuous electrical stimulation [155, 156]. The 1995 McCreery paper indicates that low frequency stimulation does not lead to early axonal degeneration, independent of stimulus amplitude [156].

Imagery

Mental imagery coupled with various techniques, such as muscle relaxation [157] or virtual visual feedback [158, 159], present enlightening results that may reveal psychological aspects of PLP. Ipsi-lateral cortical reorganization could be a target for mental imagery, especially when utilizing coordinated bimanual movements through visual feedback [62, 63]. Mental imagery and muscle relaxation showed a significant reduction in PLP, PLS, and pain interference compared to a positive control group [157]. The positive control group maintained the same physical therapy schedule as the test group, while the test group exercised mental imagery, in addition to the physical therapy. The success of this trial demonstrates an advantage of coupling physical stimulus with psychological exercise. Graded motor imagery (GMI) utilizes gradual training in three strategies: (1) implicit motor imagery, (2) explicit motor imagery, (3) mirror visual feedback [160]. Implicit motor imagery training involves laterality recognition, or identification of images representing left limbs versus right limbs; explicit motor imagery practices movement of the phantom limb, or focusing on consciously manipulating the phantom; and, mirror visual feedback exercises the movement of the phantom while the patient utilizes visual feedback. Typically, the visual feedback involves placing the contralateral limb in front of the mirror, the amputated limb behind the mirror, and simultaneously moving both the contralateral and phantom limbs. Bowering et al. reviewed studies, including work on PLP by

Moseley [161], using this multi-pronged approach and found it to successfully treat chronic pain [162]. While the method has been proposed to treat PLP and PAP, the effects have not been thoroughly evaluated in this context [163]. Some have compared the effects of mental imagery through virtual visual feedback (also known as mirror therapy) to that of TENS when applied to the non-amputated limb [146]. Both groups showed reduction in pain over a 4-day treatment phase, but neither group performed significantly better than the other.

This type of mental imagery could be considered a form of conditioning, where participants actively and consciously reinforce imagined movement with feedback (e.g. visual or tactile). Imagery is supported by Macuga and Frey [164], who found that imagery, i.e. actively simulating movements, stimulates more brain regions than passive observation. Studies on operant conditioning have shown to alter CNS organization in the spinal cord, specifically through retraining of spinal cord mediated reflexes [52]. Thus, in these circumstances psychological treatment has physiological implications. Psychological treatments have had positive results for the treatment of NP in a few, small studies; however, treatment recommendations for NP have moved toward a multimodal approach incorporating psychological treatment with pharmacological or nonpharmacological methods [165]. This serves as a possible opportunity that has not yet been thoroughly explored in the realm of PAP, through the combination of psychological and nonpharmacological treatment.

No single treatment method seems to be a superior method for alleviating PLP. This may be due to the nature of non-mechanism based therapy development, treating symptoms rather than the root cause. In order to develop successful therapies, we should first seek to understand the primary mechanisms driving PLP in the background [45]. We should also seek to understand the effects of various methods by reporting results in a consistent way. Several studies and the measured effects have been reported and reviewed; the unfortunate reality is that many of the therapy methods are difficult to compare in terms of effect because there is not a standard metric for PLP.

1.5 A New, Proposed Paradigm for Treatment of PLP

Evidence suggests that therapies should include a level of cognitive involvement along with physiological stimulation [165]. Through a multi-facet approach the EPI-ONE consortium seeks to challenge the status-quo of PLP therapy. The multi-center clinical trial design, as described by Yoshida et al., evaluates several distinct methods of sensory feedback and reinforces the subject's RSs with meaningful stimuli during therapy [166]. Treatment modalities span invasive and non-invasive techniques to activate the peripheral circuitry, some of which also incorporate the operation of a hand or leg prosthesis, providing a level of visual feedback, as well. Methods for evaluation involve an intensive regimen of psychophysical questionnaires including the VAS for measurement of pain, along with the POMS-SF, and NPSI, as well as other exploratory measures. Participants also undergo two fMRI sessions, before and after the 4-week therapy phase to measure the level of cortical reorganization.

2. METHODS FOR INVESTIGATING THE EFFECTS OF COGNITIVELY REINFORCED STIMULATION ON PHANTOM LIMB PAIN

2.1 Introduction

The methods described in this chapter address the design and implementation of a multi-center clinical trial for cognitively reinforced stimulation as a treatment for phantom limb pain (PLP). Crucial details to ensure comparability among treatment groups, such as inclusion/exclusion criteria and data collection methods, are discussed. Additionally, the methods of assessment to establish the degree of effectiveness are described. The visual analog scale (VAS), the primary measure, neuropathic pain symptom inventory (NPSI) and profile of mood states-short form (POMS-SF), secondary psychophysical instruments, reflect various aspects of pain. The methods described here were used for collecting and analyzing the data presented in Chapter 4 and Chapter 5.

2.2 Study Organization

Several facets of a clinical trial must be considered to successfully implement the study. In addition to the treatment modalities, this section outlines the common clinical protocol (CCP), which ensures the data collected at each site is comparable.

2.2.1 Treatment Modalities

The factors of the experimental design lie within the type of sensory feedback, which has two primary categories: invasive and non-invasive. The invasive category utilizes implanted transverse intrafascicular multichannel electrodes (TIMEs) to elicit

sensation, whereas the non-invasive methods include electrical or mechanical (tactile) surface stimulation/feedback. An additional factor that evokes visual feedback and proprioception is the operation of a prosthesis. Utilizing electrical or mechanical stimulation through six different intervention modalities, demonstrated in Figure 2.1, diversifies the proposed treatment to better understand the positive and negative effects of each treatment strategy. Figure 2.1, adapted from Figure 1.3 of the EPIONE project 18-month report, shows the intervention methods and planned assessments for determining effect.

Because of the variety of clinical implementations, the methods for sensory augmentation are split among seven clinical sites. The clinical site(s) for each modality is/are shown in Table 2.1. In order to coordinate efforts and to ensure data are comparable among test sites, the consortium developed a CCP, which is discussed in subsection 2.2.2. Note, the preliminary results of the EPIONE consortium are discussed in Chapter 4, and the Indiana University - Purdue University Indianapolis (IUPUI) clinical site case study are discussed in Chapter 5. Each of the clinical sites achieved proper ethical approval from local authority and is registered on clinicaltrials.gov, as shown in Table 2.2.

2.2.2 Common Clinical Protocol (CCP)

While there are slight variations among clinical sites, such as with inclusion/exclusion criteria, the consortium developed a CCP for all sites to follow. These guidelines are mainly written with respect to experimental timeline and data collection methods in order to avoid the problem of incomparable data, such as differing anchors in the VAS, discussed in subsection 1.3.1. The experimental timeline in the CCP requires 7-9 weeks of intensive subject participation with an optional 8 week follow-up period. During the baseline phase the subject is exposed to a battery of stimuli for threshold determination, sensation characterization, and therapy parameter development. Threshold determination is the process of ramping the intensity, pulse width,
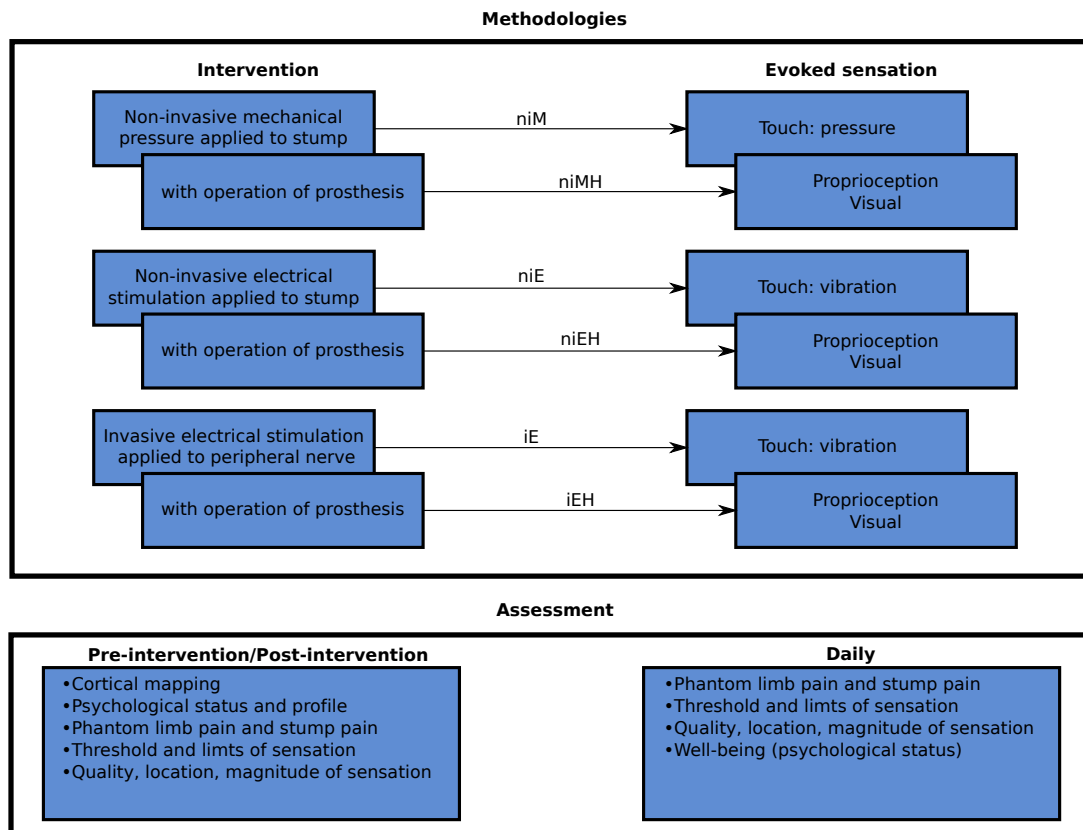
Fig. 2.1. The basic design of experiment is demonstrated here. Six methodologies elicit various evoked sensations and are analyzed for effectiveness in several capacities. Pre-intervention and post-intervention measures (as well as daily measures) are utilized to focus on pain intensity, pain quality, psychological profile, and cortical mapping. The objective of the study is to develop a strategy for PLP intervention by narrowing the focus of sensory feedback modalities and delivery systems. niM = non-invasive mechanical, niMH = non-invasive mechanical with prosthesis, niE = non-invasive electrical, niEH = non-invasive electrical with prosthesis, iE = invasive electrical, iEH = invasive electrical with prosthesis.

and frequency parameters to find the sensation and discomfort thresholds for each parameter. Doing so gives a target range for the therapist during sensation characterization and therapy. Sensation characterization involves the matching of referred sensations (RSs) to stimuli. The subject is given a stimulus, focuses on the stimulus, and records the location and quality of the RS. Once the subject reports an RS and

Table 2.1. Treatment delivery strategies proposed by the EPIONE consortium. The EPIONE consortium consists of 7 clinical sites: Aalborg Hospital (AUH), Aalborg Universitet (AAU), Centre hospitalier universitaire vaudois (CHUV), Ecole Polytechnique Federale de Lausanne (EPFL), Lunds Universitet (ULUND), and Universita Cattolica Del Sacro Cuore (UCSC) and IUPUI.

Invasive/ Non-invasive	Clinical Test Site	Intervention Method
	AAU, IUPUI	Electrical Stimulation (niE)
Non-invasive	EPFL	Electrical Sensory Feedback with Hand Prosthesis Operation (niEH)
	ULUND	Mechanical Stimulation (niM)
	ULUND	Mechanical Sensory Feedback with Hand Prosthesis Operation (niMH)
Invasive	AUH	Electrical Stimulation (iE)
	CHUV+EPFL, UCSC	Electrical Sensory Feedback with Hand Prosthesis Operation (iEH)

characterizes it, the description is paired with the stimulus parameters and stored for therapy sessions.

2.2.3   Inclusion/Exclusion Criteria and Study Population

The inclusion/exclusion criteria are designed to limit the variability in data due to external noise-factors. Various alterations to these criteria were made to accommodate the local requirements. For example, the upper age limit may be lowered or the lower age limit raised if another limit is imposed by the local authority. The inclusion/exclusion criteria according to the CCP appear in Table 2.3.

Table 2.2. The clinical sites for the EPIONE consortium are all registered on clinicaltrials.gov.

Clinical Site	ClinicalTrials.gov Identifier	Study Name
AAU	NCT02488668	Surface Electrical Stimulation for Treatment of Phantom Limb Pain (EPIONE)
AUH	NCT02493842	Direct Nerve Stimulation for Treatment of Phantom Limb Pain (EPIONE)
CHUV+EPFL	NCT02569918	Use of Hand Prosthesis With Surface Electrical Stimulation for Treatment of Phantom Limb Pain (EPIONE)
CHUV+EPFL	NCT02796495	Use of Hand Prosthesis With Direct Nerve Stimulation for Treatment of Phantom Limb Pain (EPIONE)
IUPUI	NCT02519907	Surface Electrical Stimulation for Treatment of Phantom Limb Pain (EPIONE)
UCSC	NCT02506608	Use of Hand Prosthesis With Direct Nerve Stimulation for Treatment of Phantom Limb Pain (EPIONE)
ULUND	NCT02589080	Phantom Limb Pain: Efficacy of Non-invasive Sensory Feedback Through the Prosthesis (EPIONE)

2.2.4 Experimental Timeline

The experimental timeline spans 17 weeks and is divided into 6 phases, which are pre-screen (1 week), baseline (2 weeks), entry (1 week), intervention/therapy (4 weeks), outcome (1 week) and follow-up (8 weeks, optional). The first week, pre-screen, of the trial timeline is used to determine whether or not the potential subject meets the site-specific inclusion and exclusion criteria (described in subsection 2.2.3). The pre-screen, baseline, and entry visits make up the pre-therapy period, where data is collected to serve as points of reference for data collected throughout the therapy phase and during the outcome phase. After the pre-screen phase, the study subjects establish baseline measures for self-report questionnaires and attend sessions

Table 2.3. Inclusion/Exclusion criteria

Inclusion/ Exclusion	Criteria
Inclusion	- Adult man or woman > 18 years and < 70 years. - Unilateral transradial amputation or unilateral lower extremity amputation. - Other treatments for PLP tried with poor results. Patient accepts the study protocol as explained by the physician. - The subject must experience intractable PLP more than 6 on Numeric Rating Scale (NRS) or VAS (0-10 scale). The frequency of PLP attacks must present itself more than once a week. - Amputation should be in the chronic, stable phase, such that the stump has healed and the person apart from phantom pain, is healthy and able to carry out the experiment.
Exclusion	- Cognitive impairment - Current or prior psychological impairments: Major personality disturbance (i.e. borderline, antisocial), Major depression, Bipolar I - Pregnancy - History of or active substance abuse disorder - Acquired brain injury with residual impairment - Intellectual Disability (IQ < 70) - Prior neurological or musculoskeletal disease - Current or prior dermatological conditions - Excessive sensitivity to electrical stimulation with surface electrode. People afraid of electrical stimulation or pain. - Persons with other diseases that may affect the function of the nervous system (Diabetes, HIV, Renal Failure) - Persons with pacemakers

to identify and locate areas of RS on the residual limb. Prior to initiating the therapy phase, the subject undergoes a functional magnetic resonance imaging (fMRI) session to establish baseline functional maps for given tasks. The therapy phase lasts 4 weeks and requires the subject to attend 3-5 sessions per week, in which he/she completes

psychophysical questionnaires according to Table 2.4. Following the therapy phase, a second fMRI along with a barrage of self-report questionnaires are completed in the outcome phase to compare to the pre-therapy data. Some of the instruments are clinical site specific.

Table 2.4. Outline of experimental instruments and their use in the experimental timeline (P=Pre-Screen, B=Baseline, E=Entry, TX=Therapy, O=Outcome, F=Follow-up) [166]. X indicates administration of the instrument. D indicates administration of the instrument (at each scheduled session) in the given phase. *indicates the primary instrument for assessment of efficacy. **indicates the secondary instruments for assessment of efficacy.

Type	Abbr	Test Name	Clinical Assessment (CCA)					
			P	B	E	TX	O	F
Mental Status	PHQ-9	Patient Health Questionnaire	X		X		X	X
	POMS-SF**	Profile of Mood States			X	X	X	X
	WASI	Weschler Abbreviated Scale of Intelligence	X					
Phantom Pain	NPSI**	Neuropathic Pain Symptom Inventory	X		X	X		X
	VAS*	Visual Analog Scale	X	D	D	D	X	D
	BPI	Brief Pain Inventory			X		X	X
	PsyP-Map	Psychophysical Map of Sensation			X	D	X	D
	PGIC	Patient Global Impression of Change					X	
Cortical Map	SEP	Somatosensory Evoked Potential			X		X	
	fMRI	functional Magnetic Resonance Imaging			X		X	
	TMS	Transcranial Magnetic Stimulation			X		X	

2.3 Data Collection

As demonstrated in Table 2.4, the VAS serves as the primary instrument for measuring effect, while the NPSI, and POMS-SF serve as secondary measures. The VAS, NPSI, and POMS-SF fall under the umbrella of self-report questionnaires. These self-report questionnaires are chosen to represent the preliminary data shown in Chapter 4 because they span the primary experiential dimensions of pain [25]. The VAS serves as a measure of pain intensity, the POMS-SF reflects pain affect, and the NPSI measures pain quality. Several other instruments are incorporated in the clinical study, as shown in Table 2.4; however, all besides the VAS, NPSI, and POMS-SF are out

of scope for this review of preliminary, pilot data and will be covered in subsequent reports on a center-by-center basis. Chapter 5 discusses these exploratory data in more depth for the case study at IUPUI.

2.3.1   Pain Intensity

The VAS is utilized in several capacities to characterize the effects of therapy. First, it is utilized to determine the immediate effects of therapy, inquiring about present pain intensity and average pain over the last hour. Secondly, the VAS informs of changes to pain intensity on a daily basis by asking about average pain over the last 24 hours. These measures are collected before and after pre-therapy visit, as well as before and after each therapy session, allowing comparison of therapy scores to those collected in the pre-therapy period. The VAS is presented as an integer-enumerated, continuous line spanning 0-10 with the 0-anchor being "No pain" and the 10-anchor being "Worst pain imaginable".

2.3.2   Pain Affect

The POMS-SF, as described by Baker et al., reflects a subject's present state of mood [167]. The POMS-SF uses 37 questions on 5-point NRSs (from 1="Not at all" to 5="Extremely") to describe the subject's mood, which gets summarized 6 categories. In the pilot study the POMS-SF was utilized weekly, but the frequency was increased to every visit to better understand effects of therapy after the preliminary results were collected.

2.3.3   Pain Quality

The NPSI, presented by Bouhassira et al., measures the qualities of neuropathic pain (NP), in terms of six subscores [99]. The individual completing the questionnaire answers 12 questions, 10 of which are utilized in the pain quality assessment. The

other two questions refer to the timing and frequency of pain. The NPSI uses NRSs spanning $0 - 10$ with the 0-anchor being "None" and the 10-anchor being "worst imaginable" in the context of each question. In the preliminary pilot study, Chapter 4, the NPSI was seldom used (once per week during therapy). However, the frequency was increased to every visit in later rounds of testing.

2.4 Methods for Assessment

Methods for analyzing data in single case research (SCR) vary widely in literature. While it is important to conduct randomized controlled trials (RCTs) to determine an effect with confidence, pilot studies often rely on small sample sets to determine whether or not to continue to conduct a larger trial. There are several methods to analyze single case data [168]. Rather than relying on a diverse sample set, the methods for SCR require a higher sample size per subject to establish reasonable power. Unlike Cohen's d, which assumes normal distributions [169], the nonoverlap of all pairs (NAP) method proposed by Parker and Vannest does not assume a distribution shape [170]. In justifying the necessity of a new method for analyzing effect in SCR, Parker and Vannest specify two advantages of NAP over parametric methods: (a) SCR commonly fail to meet the parametric assumptions of independence, normality, homoscedasticity and (b) NAP does not rely on equal variance and normality. While NAP allows interpretation of results for which typical parametric methods cannot, one should not discount the value of properly powered experiments. Like other methods for SCR the NAP is a crude metric that can be used in determining treatment validity at a pilot study level.

The following subsections discuss the methods used to analyze data from each of the instruments included in the EEP. These are categorized according to the aspect of pain to which they relate, e.g. the VAS relates to pain intensity. There are two basic methods for establishing effect for these data. The NAP method is used for the

VAS scores, while the BPI interference scale (BPI-IS), NPSI, and POMS short form (POMS-SF) subscores all rely on variations of Cohen's d for effect size.

2.4.1   Pain Intensity

The scores from the VAS are analyzed using the NAP method [170]. This is possible because of the brevity of the questionnaire. In order to use the NAP method, data is separated into bins, one pre-therapy bin, combining the scores from pre-screen, baseline, and entry, and one bin for each week of therapy. Note, these terms are further defined in Chapter 2, where the common clinical protocol is discussed. The scores from each therapy bin (t-scores) are then compared individually to each pre-therapy score (p-scores), creating an $N_p \times N_t$ comparison matrix. If a t-score is lower than a p-score (i.e. pain intensity drops during therapy) the comparison receives a value of 1, if the t-score and p-score are equal the comparison receives a value of 0.5 and if the t-score is greater than the p-score, the comparison receives a value of 0. To calculate the NAP score, these comparisons are averaged together. As an example if the scores improve, the expected NAP is between 0.5 and 1.0. Typically, this measure spans $0.5 - 1.0$, where 0.5 represents a chance-level result [170]. Some have reported the measure spanning $0 - 1$ using a linear transformation, where 0 is the chance-level result [168]. However, because of the possibility of negative results (especially in immediate measures of pain after surface stimulation), in the present work the measure is expanded from the typical range of $0.5 - 1$ to $0 - 1$ where 0.5 still represents a chance-level result. As suggested by Parker and Vannest scores from $0 - 0.49$ represent deteriorating performance [170]. Using the limits for positive effect established by Parker and Vannest [170] and reflecting the limits over the midline to create limits for negative effect, the following guidelines in Table 2.5 for effect were created. The NAP analysis method and the limits in Table 2.5 are used for all three of the VAS measures described above.

In addition to the NAP, it is beneficial to look at general trends of the VAS, especially referring to the pre-therapy pain intensity. Thresholds for mild, moderate, and severe pain are adapted from recommendations by Jensen et al., who suggested 0= no pain, 1-4= mild pain, 5-6= moderate pain, and 7-10= severe pain [98].

Table 2.5. Using the NAP method (ranging $0 - 1$ and centered at 0.5 as chance-level) for analyzing VAS scores allows interpretation of positive and negative results. NAP limits can be calculated from Cohen's d using the equation provided by Parker and Vannest [170]; however, they suggest broadening the limits for effect for SCR.

NAP Limits from Cohen's d	Adjusted NAP Limits	Effect
$0 \quad - 0.30$	$0 \quad - 0.07$	Large/Strong Negative
$0.31 - 0.37$	$0.08 - 0.33$	Medium/Moderate Negative
$0.38 - 0.62$	$0.34 - 0.66$	None
$0.63 - 0.69$	$0.67 - 0.92$	Medium/Moderate Positive
$0.70 - 1$	$0.93 - 1$	Large/Strong Positive

As described later, depending on the distribution of the pain in the NAP analysis, two datasets with the same averages for p-scores and t-scores could give very different results. While this is normally an expectation, i.e. tighter distributions have more power, only analyzing the NAP scores without referring back to the VAS scores and trends does not paint the full picture. This is especially true for PLP since pain often comes in flares.

2.4.2 Pain Affect

POMS-SF

The POMS-SF subscales are analyzed by comparing differences in average p-scores and average t-scores from each therapy week. Effect size is determined using the standard deviation (SD) of a larger population [167]. According to Cohen's conventional

framework, a large effect is reflected by a difference in mean scores that is 80% of the SD, and a medium effect requires a difference in mean scores that is 50% of the SD [169]. Ideally, the SD used for calculating Cohen's d would come from a large population of individuals in a similar stage of life, demographic, and etiology to the sample population of interest. In this case the non-depressed population is used from Baker et al. as a reference sample [167]. This is appropriate for the pilot study; however, when expanding to a larger RCT, a better representative reference sample could improve the impact of the results. The Cohen's d for each week is calculated according to the following equation,

$$d = \frac{\mu_t - \mu_p}{\sigma} \tag{2.1}$$

where μ_t represents the mean score in a therapy week, μ_p represents the mean score in the pre-therapy period, and σ represents the SD of the reference population. In order to generate thresholds for effect, Equation 2.1 was algebraically solved for the required change in average score to achieve a strong or medium effect, as in Equation 2.2.

$$\mu_t - \mu_p = \Delta\mu = d \cdot \sigma \tag{2.2}$$

The POMS-SF vigor score is positive facing, i.e. an increase in the mean score from pre-therapy to therapy (positive d) indicates a positive result, following Equation 2.2. Conversely, the other five POMS-SF subscales are negative facing, i.e. an increase in the mean score from pre-therapy to therapy is a negative effect. For negative facing scores a positive d is a negative change (or drop) in the score. These subscales have the opposite conditions of that in Equation 2.2 and require changing the direction of the calculation in Equation 2.2 by simply multiplying by -1, as in Equation 2.3,

$$-(\mu_{t_{neg}} - \mu_{p_{neg}}) = -\Delta\mu_{neg} = d \cdot \sigma \tag{2.3}$$

where μ_{neg} represents the mean of a negative facing subscale, as defined above. Table 2.6 shows the limits for effect interpreted from Baker et al. [167] using Equation 2.2. These values represent changes in the subscale, or $\Delta\mu$ in Equation 2.2.

Table 2.6. The limits for effect are adapted from the SDs in the sample population of a study by Baker et al. [167]. Cohen's d is considered to be bidirectional, allowing the interpretation of both positive and negative effects.

POMS-SF Subscale	Subscale Range	Strong Negative Effect ($d = -0.8$)	Medium Negative Effect ($d = -0.5$)	Medium Positive Effect ($d = 0.5$)	Strong Positive Effect ($d = 0.8$)
Anger	$7 - 35$				
Confusion	$5 - 25$				
Depression	$8 - 40$	3	2	-2	-3
Fatigue	$5 - 25$				
Tension	$6 - 30$				
Vigor	$6 - 30$	-4	-2	2	4

Even though the effect-thresholds are the same for each of the negative facing scores, the possible range for a given score varies because of the method of subscale calculation described by Baker et al. [167].

BPI-IS

While the BPI-IS is not one of the primary or secondary instruments, it is discussed in detail in Chapter 2 using the following methods. After collection of the BPI-IS, a final score is calculated from the responses by averaging the responses to the seven interference questions, arriving at a "total interference"; as with the others this ranges from 0 ("Does not interfere") to 10 ("Completely interferes"). Using SDs from a reference population, the effect-thresholds for the difference of p-scores and t-scores are demonstrated in Table 2.7. Analysis involves the comparison of all individual subscales for this exploratory measure. Note, in this instrument the thresholds include 2 significant figures. This is different from the other instruments. The purpose is that if the subscales were rounded to the nearest integer, some subscales (e.g. Mood) would have the same thresholds for both moderate and strong effect.

Table 2.7. The limits for effect in the BPI-IS are adapted from the SDs in the reference population [112]. Cohen's d is considered to be bidirectional, allowing the interpretation of both positive and negative effects. All subscales range $0-10$.

BPI-IS Subscale	Large Negative Effect $(d = -0.8)$	Medium Negative Effect $(d = -0.5)$	Medium Positive Effect $(d = 0.5)$	Large Positive Effect $(d = 0.8)$
General Activity	2.4	1.5	-1.5	-2.4
Mood	2.4	1.5	-1.5	-2.4
Mobility	2.5	1.5	-1.5	-2.5
Normal Work	2.5	1.5	-1.5	-2.5
Relationships	2.4	1.5	-1.5	-2.4
Sleep	2.7	1.7	-1.7	-2.7
Enjoyment of life	2.8	1.8	-1.8	-2.8
Total	2.1	1.3	-1.3	-2.1

2.4.3 Pain Quality

Pain quality, measured with the NPSI, is analyzed in a similar fashion to the POMS-SF and BPI-IS. SDs taken from a reference population [171] are utilized to compare the means for t-scores and p-scores as in Equation 2.1. The NPSI subscales are all negative-facing requiring the transformation in Equation 2.3. In this case SDs from the reference population were broken up into four subgroups according to the reference study protocol [171]. Because the SDs for the four subgroups were reported separately and varied slightly, the maximum baseline SD of the four subgroups was used as the reference SD for each subscale. Table 2.8 demonstrates the effect-threshold or the required delta for each NPSI subscale.

2.4.4 Group Analysis

In order to analyze the group data, the same thresholds are used as described in the previous subsections. Equation 2.4 demonstrates how the weekly average scores are calculated for each subscore,

$$\bar{y}_{i\cdot} = \frac{1}{n} \sum_{j=1}^{n} y_{ij} \tag{2.4}$$

Table 2.8. SDs from *Table 1: NPSI scores at baseline*, provided by Bouhassira et al. [171], allow the interpretation of positive and negative effects with respect to pain quality. All subscales of the NPSI are negative facing, meaning that the desired (positive) effect is a drop in magnitude. Recall that all NPSI subscales range from 0-10 except the NPSI - Total subscale, which ranges 0-100.

NPSI Subscale	Subscale Range	Strong Negative Effect $(d = -0.8)$	Medium Negative Effect $(d = -0.5)$	Medium Positive Effect $(d = 0.5)$	Strong Positive Effect $(d = 0.8)$
Burning Pressing Paroxysmal Evoked Paresthesia/ dysesthesia	$0 - 10$	2	1	-1	-2
Total	$0 - 100$	16	10	-10	-16

where i denotes the therapy week, j denotes the subject index for the group, n is the total number of subjects, y_{ij} is the averaged subscore for a subject, and $\bar{y}_{i.}$ is the group average for a given subscore. An overall average calculated according to Equation 2.5,

$$\bar{y}_{..} = \frac{1}{an} \sum_{i=1}^{a} \sum_{j=1}^{n} y_{ij} \tag{2.5}$$

where a denotes total number of time periods for analysis and $\bar{y}_{..}$ represents the overall average across subjects and time periods for a subscore. Calculating the sample standard deviation across subjects utilizes the results of Equation 2.4 and Equation 2.5 as in Equation 2.6,

$$S_i = \sqrt{\frac{1}{n-1} \sum_{j=1}^{n} (\bar{y}_{.j} - \bar{y}_{..})^2} \tag{2.6}$$

where S_i represents the sample standard deviation across subjects for a subscore and is calculated for each time period. Calculating the group difference scores for comparison against thresholds in Table 2.8, for example, is done with Equation 2.7,

$$\bar{D}_i = \frac{1}{n} \sum_{i=1}^{n} (\bar{y}_{i.} - \bar{y}_{1.}) \tag{2.7}$$

where $\bar{D}_i$ is the average difference score for a psychophysical subscore and $\bar{y}_{1.}$ is the pre-therapy score.

Handling Problematic Data

In the current paradigm the difference scores are directly used to identify the effectiveness of therapy, and if data is collected according to the protocol, Equation 2.7 can be used. However, if data is missing Equation 2.7 breaks down and more sophisticated tools are needed. An important question to consider is how to handle missing data. Little et al. describe the likelihood of such occurrences as well as a few procedures for data handling [172]. A popular technique is imputation by the last observation carried forward, which simply means inserting the immediately previous data point into the empty position. Alternatively, data models can be created to estimate the missing data points, or a subject with missing data can be removed from the subject pool entirely. In any of these circumstances it is important to weigh alternatives and choose a method based off of sensitivity analyses [172].

2.5   Conclusions

In the midst of designing, the multi-center clinical trial, it became apparent that a substantial amount of data would be collected through the self-report question-naires. Each questionnaire has its own flavor of data collection. For example, the questionnaires use various NRSs and calculated subscales. The opportunity for data analysis errors is immense when converting to an effect size. The obvious solution

to this dilemma is automation. In order to automate the data consolidation, organization, and analysis, the EEP was conceived. For the EPIONE consortium, who identified the need to automate analysis of the self-report data coming from the EPIONE Psychophysical Platform (PsyP), the EEP is a software tool that consolidates and analyzes PsyP data. Unlike relying on each clinical site to review questionnaires individually and manually process results, the EEP automates analysis and reduces opportunities for analysis error and user error. Chapter 3 introduces the EEP and the EEP-Group Analysis Module, which takes output files from the EEP to establish group-wide effects. With the EEP software tools, researchers are able to accurately analyze SCR data and prepare group data for statistical analysis.

3. DEVELOPING A SOFTWARE FOR CONSOLIDATING SELF-REPORT DATA

3.1 Introduction

Prior to developing the software tool for data analysis, called the EPIONE Extraction Program (EEP), two business analysis models, the context diagram and process map, were created to understand the requirements. As with any software, important requirements were discovered and incorporated throughout development; however, going through the practice of predicting the structure, inputs, outputs, etc. before digging into the code, unveiled several requirements that could have severely delayed the date of delivery. After designing the software, the EEP was subjected to several tests to ensure the output consists of accurate, high quality results. Testing revolved around the requirements and primarily involved testing for data accuracy and software usability, assuring that the software meets expectations. In the end a software was developed to analyze data from the brief pain inventory (BPI), neuropathic pain symptom inventory (NPSI), profile of mood states (POMS) and visual analog scale (VAS).

3.2 Design Considerations

The two chief tools used to model the system interactions are the context diagram and process map. The context diagram is crucial to understanding who or what is expected to provide vital information to achieve the goal, which is in this case analyzing the data. This diagram, displayed in Figure 3.1, demonstrates the interactions of the EEP and user as well as the interactions of the EEP with the local system. Through depicting the software in this light, it became apparent that the user must

be familiar with the data being exported to some extent, i.e. the user must be able to point to the data of interest. Since this method is new to all of the consortium researchers, there is an expectation that some of the information required by the EEP could potentially be confusing to the user. For this reason another requirement is to provide "immediately available" help dialog to the user.
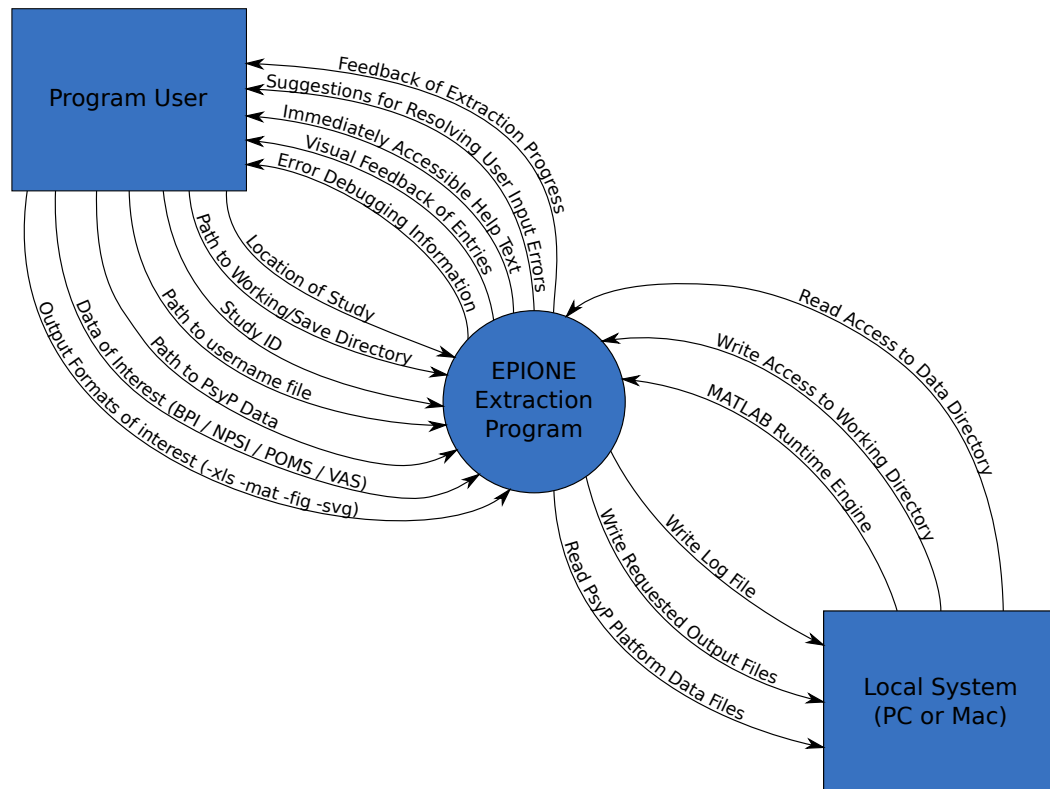
Fig. 3.1. Several interactions between the user and EEP and between the local system and EEP helps identify several requirements that need to be incorporated into the EEP.

Interacting with the host or local system is much simpler, but equally important. The main requirements that came out of analyzing this interaction deal with access permissions. Fortunately, the risk of not having permission to read or write to the various directories is low. Data from the EPIONE Psychophysical Platform (PsyP) are typically saved to a specific folder on the windows operating system, which does not

require special or administrator permissions to read or write. Furthermore, the users will typically navigate to a writable directory for saving output files. Nevertheless, these requirements are relevant to successfully generating an output. Installation of the MATLAB® Runtime Engine is a requirement for the EEP because of the expectation of using MATLAB® as the primary development tool. This developer platform was chosen because the format of the PsyP output data is native to MATLAB®.

The process map (Figure 3.2) reveals the underlying structure devised for the EEP. This is where the design of the software begins to take form. The top row of boxes represent the ways the user can interact with the EEP; notice how these buttons align very closely to the information provided by the user as displayed in the context diagram (Figure 3.1). The basic flow for the user to enter information into the EEP is: (a) the user clicks a button, informing the EEP what type of information the user would like to enter, (b) the EEP initiates the appropriate user interface (UI), if necessary, and (c) the user then points to or enters the information, which is saved.

Each button along the top row can operate independently and does not rely on any particular order. While this feature of the software is convenient and less restrictive, it opens up an opportunity for error if the user haphazardly tries to analyze results without entering all of the relevant information. Thus, a system requirement is necessary to prevent the software from attempting to analyze data if input information is missing. However, this alone is not enough. The system must also provide feedback to the user, requesting the missing information. This requirement was a suggestion from early beta-testing of the EEP with the partners at Aalborg; users suggested generating some form of feedback to the user on processing progress and upon completion of processing.
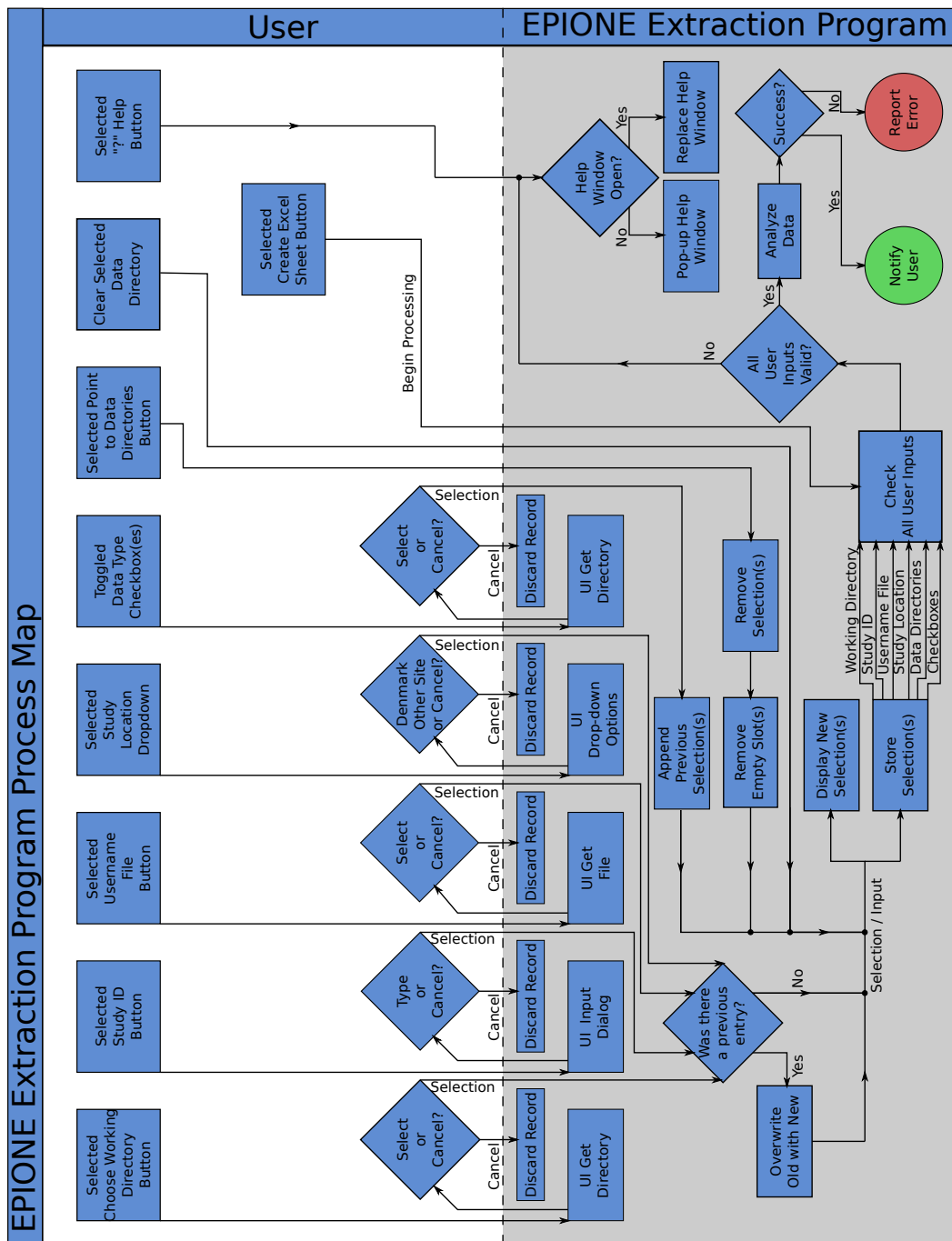
Fig. 3.2. The process map depicts the flow from user input to output of the EEP.

3.2.1 Designing Software to meet Specific Requirements

The information from the two models discussed above, along with several rounds of alpha and beta-testing of various features, led to the generation of the abbreviated list of requirements demonstrated in Table 3.1.

Table 3.1. The requirements are each given a unique requirement identifier (RID). The notation describes system requirements (SR) and user requirements (UR).

RID	Requirement
SR1	The system shall be available on Apple and PC platforms.
SR2	The system shall provide help buttons.
SR3	The system shall be capable of outputting data in Excel®, MATLAB®, and graphic formats.
SR4	The system shall have permission to read data from the user selected data directory.
SR5	The system shall have permission to write data to the user selected working directory.
SR6	The system shall create a log file for each run.
SR7	When an error occurs the system shall notify the user and write error information to the log file.
SR8	The system shall display a progress bar during processing.
UR1	The system shall allow the user to select a working directory.
UR2	The system shall allow the user to create an alphanumeric subject ID.
UR3	The system shall allow the user to select the username.xml file.
UR4	The system shall allow the user to select the directory containing PsyP data.
UR5	The system shall allow the user to specify the location of study as "Denmark" or "Other Site".
UR6	The system shall allow the user to request any combination of the four data types: BPI / NPSI / POMS / VAS.
UR7	If the user selects a data directory that does not contain one or more of the requested data types, the system shall process the requested data that does exist in the selected directory if any.

3.3 The EPIONE Extraction Program (EEP) Input Panel

The software was created with the requirements listed above (among others) as the principal reference for driving design decisions using MATLAB® R2016a with the application compiler toolbox. The requirements deal primarily with the UI of the software and not analysis of the resulting output. Comparing the EEP input panel (Figure 3.3) to the context diagram and process map, the layout of the input panel closely matches the models. Results analysis makes up an aspect that is both included and separated from the EEP. As discussed in the following section, the methods of analysis are slightly different for each instrument. For initial analysis of the self-report data, the first goal of the EEP is to consolidate and present the single case research (SCR) data in a format that is accessible to the researcher/user. For analysis of the self-report instruments, the user must compare the results to the thresholds of effect size, which are discussed in section 2.4.
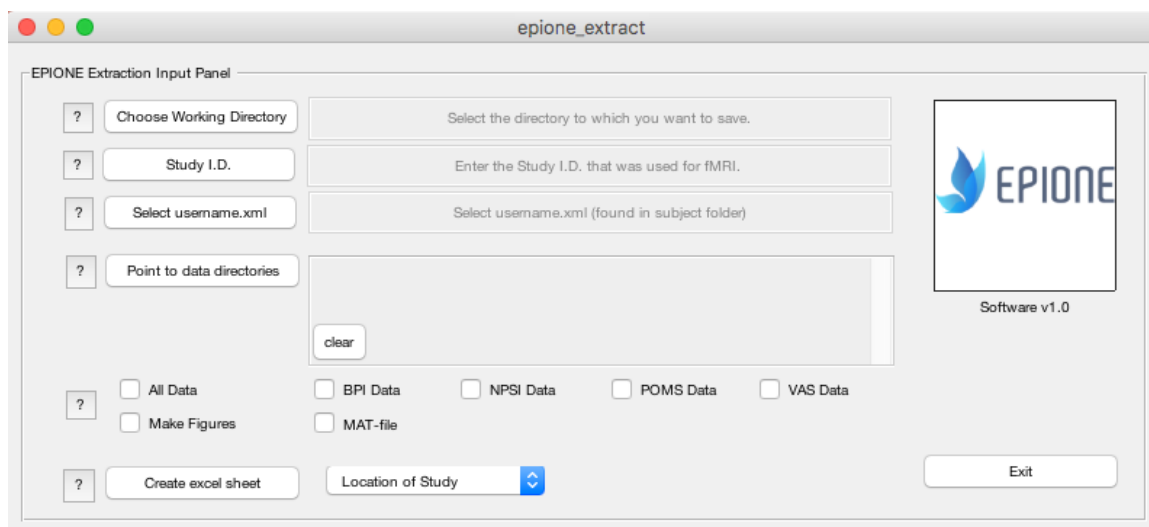
Fig. 3.3. The Layout of the of the EEP follows the basic flow of the process map. Many of the design considerations are a direct result of the preconceived requirements identified during modelling.

3.3.1 EEP Results File

Stakeholders requested the output of the EEP to be in a format for comparing results directly to the previously mentioned thresholds. In addition a researcher/user should be able to follow how the calculations of results were performed. Some final requirements of the software consider these details, where the effect size should not only be available after processing, but the details of the calculation should also be available to recreate the analysis if desired. As described in subsection B.2.3, the output file provides the raw data, intermediate calculations, and final results to fulfill these requirements.

3.4 Software Testing

Throughout the development of the EEP, individual processes were examined. Referring back to Figure 3.2 each process stream could operate independently, ensuring usability. However, testing the software as a system is a vital step to validation. In the end there were two vital considerations for testing: (a) is the information accurate and (b) is the software tool usable? The testing discussed in the remainder of this chapter focuses on usability, which relates to providing informative help messages, outputting results in a convenient format, and preventing foreseeable user errors. Testing of accuracy was completed by looking at randomly selected PsyP output files and comparing to the output of the EEP.

3.4.1 Providing Sufficient Help Documentation

An initial test of usability involved a use case where an EEP user, unfamiliar with the project is asked to open the software and complete analysis, with the immediately available help information. The following scenario was given to the user as background information:

"You have finished processing the data for your first subject in the psychophysical platform (subject z01cc); this study was conducted at Indiana University - Purdue University Indianapolis. His Study ID was ABC123. Data needed for preliminary analysis is VAS, NPSI, and POMS. In order to present the data to your principal investigator, you will need the figures in addition to the Excel® and mat-data."

The user was not given the user guide to check if the immediately available help messaging was sufficient for operation. A successful outcome for this test was determined to be if the user (a) selected the correct data types and (b) completed extraction. Analysis or interpretation of the EEP data was not included in this test.

In all three tests the users successfully navigated through each step of the EEP input panel and achieved the successful outcome criteria. Two users were able to achieve the successful criteria through the basic flow (i.e. following the process map as expected). The other user achieved the successful criteria through an alternative flow (i.e. the EEP prevented initial processing and requested the missing input information before proceeding). In this case the user did not select the location of study. The results of this test reveal that the software input panel is intuitive and easy to use, even in the absence of the user guide.

3.4.2 Varying Structures of PsyP Data

Two predictable, expected ways the analysis process could be impacted are by the data that are available to process and the data that are requested for processing. For example, it is possible for the user to request POMS-SF, NPSI, and VAS data when only POMS-SF and NPSI data are available in the data directory. This situation captures both scenarios, where (a) the BPI data were not requested (b) the VAS data were requested, but do not exist.

Because of the relevance and likelihood of this happening, a full factorial design was implemented to test these scenarios. Five data sets were created for this test

procedure. The first data set contains data for each of the instruments (BPI, NPSI, POMS-SF, and VAS). The other five data sets are comprised of the same files minus one instrument (i.e. the second data set has NPSI, POMS-SF, and VAS data, but no BPI data). Finally, a directory was created that did not contain any of the data in the first data set (i.e. the directory was empty). From the perspective of requesting data, there are 64 different scenarios. This is because there are four data types and two optional data formats (total of 6 binary user options). Therefore, with the full factorial design, 384 separate tests are required. For the test to be successful, each test must complete with the appropriate output files, or for the EEP to request the user to select data for processing (if no data types are selected on the input panel). If a data type is not present in the data directory selected by the user, the system, according to the previously defined requirements, must process the existing data that is selected by the user. This test ensures to the user requirements suggested previously are met. Specifically, it addresses whether or not the system allows the user to request any combination of the four data types (BPI / NPSI / POMS / VAS). The test also confirms whether or not the system can process the existing data even if data that do not exist are requested.

In each of the 384 tests, the program successfully met the requirements. This suggests that no matter what the input data structure looks like, the EEP should be capable of extracting any requested data that are available. This test generated 1,540 output files, so data accuracy and quality were verified by randomly selecting files from each group and comparing back to the true values, which showed an accuracy of 100%.

3.5 EEP-Group Analysis Module (EEP-GAM)

While the EEP provides a certain level of convenience to the user on its own, filling the need to evaluate SCR data, an additional module is required to complete the analysis. This is fulfilled by the EEP-Group Analysis Module (GAM). After

analyzing several subjects using the EEP, group analysis can be done by simply pointing to a particular output file from EEP analysis for each subject of the group. In this way the GAM acts as an extension of the EEP because it relies on data generated by the EEP during single subject analysis/extraction.

3.5.1 GAM Features

There are several useful, built-in features of the EEP-GAM, which is depicted in Figure 3.4. The input panel is organized into three sections, having a menu pane, workspace, and output pane. As demonstrated in Figure 3.4 a user can input subjects for multiple groups, which can be of any order or size. A user has the option to process BPI, NPSI, POMS, or VAS data and can generate outputs in three formats: Excel® files, mat-files, and figures. In addition, the workspace can be saved to add additional subjects to a group later or for future reference. Instructions for using the EEP-GAM can be found in Appendix B.

3.5.2 GAM Results Files

As with the EEP analysis, there are predictable situations to account for in regards to analysis. Since this module is an extension and not a stand-alone program, it relies on the consistent output format of the EEP. It is possible that a subject used in this module is missing data for a certain time period. This is acceptable; in these situations the GAM does not consider that particular subject in the affected measure and week, for example a group average is calculated using every available score. An additional scenario is if the user does not select all data types or formats to be processed. Each of these situations should be tested to ensure the program correctly accounts for the different situations. The data for each group can be consolidated into a single Excel® file and/or single mat-file if selected by the user. Each data type produces a single figure for every subscore, as well as a figure depicting the average of all subscores, e.g. if the "BPI" data type and the "Figures" output format are selected 18 figures
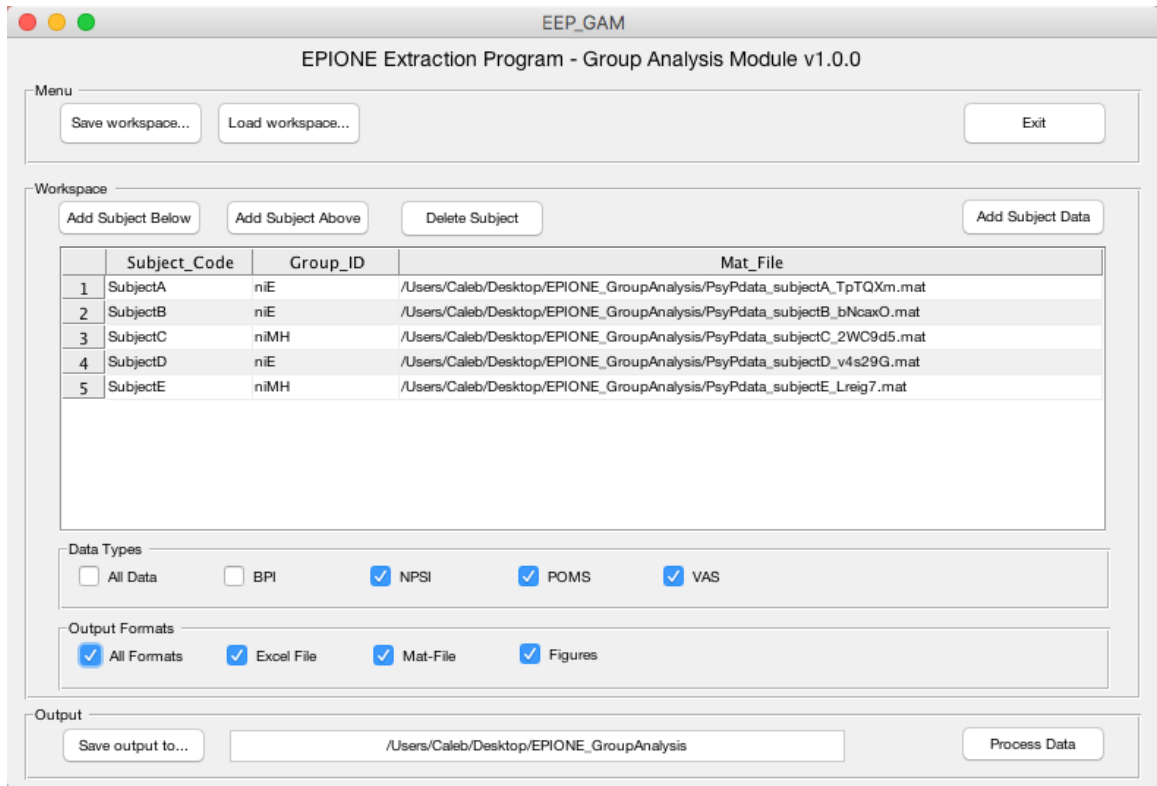
Fig. 3.4. The user interface of the EEP-GAM is intuitive and easy-to-use.

would be generated for each group, nine figures with the MATLAB® FIG extension and nine figures with the scalable vector graphics (SVG) extension. Both NPSI and POMS produce 14 figures and VAS produces 16 figures, addressing the VAS and NAP scores. If all data types and formats are selected, 33 FIG and 33 SVG files are created. The number of output files when analyzing two groups at one time totals up to 136 files if all data types and output formats are selected.

3.5.3 GAM Software Testing

Testing the software involves 128 cases for every combination of data type and output format selections. The subject table, demonstrated in Figure 3.4, has two groups and is an interesting use case for testing. In this situation there are two groups of unequal size and the subjects are assigned to the groups out of order. All

in all, the testing of 128 cases produced 7,184 output files. The randomly selected output files were compared to manually calculated results showing 100% accuracy. In the cases where no data types were selected or no data output formats were selected, the GAM prompted the user to make selections.

3.6   Conclusion

With the newly designed EEP and EEP-GAM, analysis of the self-report data should be exceptionally faster and more reliable than the alternative option of manual extraction and processing. Instead of hours to days, the EEP only takes up to 30 seconds to generate the output files and the EEP-GAM takes 2-3 minutes. Furthermore, the EEP and EEP-GAM reduce the opportunity for errors in manual processing. Developing requirements prior to beginning the development of the code likely prevented several project delaying road blocks. From the usability testing described above, the EEP seems to be a convenient, easy to use tool to add to the software developed during the EPIONE project. The self-report data shown in Chapter 4 and Chapter 5 were extracted using the EEP. This provided an opportunity to test the performance and robustness of the EEP with data of various structures and with data from several clinical sites.

4. A PILOT STUDY TO INVESTIGATE THE EFFECTS OF COGNITIVELY REINFORCED STIMULATION ON PHANTOM LIMB PAIN

4.1 Introduction

With the prevalence of amputation expected to double over the next few decades, mainly due to dysvascular conditions, the sequelae associated with amputation become more and more relevant [4]. Numerous treatment methodologies, including pharmacological, non-pharmacological and surgical, for phantom limb pain (PLP) have been proposed, but none have clearly demonstrated success in alleviating PLP [109, 122, 123]. This is further supported by lack of a standard of care for PLP [126]. The EPIONE consortium designed and implemented a multi-center clinical trial to test the effectiveness of a new therapy paradigm for PLP [166]. Using electrical stimulation coupled with operant conditioning, the consortium seeks to determine the feasibility of this mechanism-based approach for treating PLP. We are attempting to restore post-amputation central nervous system (CNS) changes through appropriate, meaningful sensations and natural sensory feedback to the phantom hand or transected nerves. Through this process we expect to control PLP and better understand the psychological, cognitive, and neuroplastic components in modulation of PLP. In trials with small sample sizes, paradigms involving electrical stimulation have demonstrated neuroplastic changes in the cortex [148]; similarly, elements of Graded Motor Imagery (GMI) [173], such as mental imagery and mirror therapy, have also shown success [146, 157]. Prior research in the field suggests a potential successful treatment may require the incorporation of sensory feedback with cognitive reinforcement [174]. Herein, several variants of this paradigm are proposed emphasizing the sensory feedback and operant conditioning guiding principles. In order to properly assess the

success of these modalities and to identify the effects of therapy, we utilize self-report questionnaires and functional imaging in the study design. Yoshida et al. provide a high-level overview of the EPIONE consortium's study design [166]; this chapter takes a deeper look at the methods involved in collecting data as well as some preliminary consortium-wide results of selected instruments.

4.2 Results

Results are organized according to the dimension of pain being measured. The VAS scores measure pain intensity. The POMS-SF measures pain affect and NPSI demonstrates changes to pain quality; both do so by observing changes from therapy to pre-therapy. Three niE subjects, one niEH subject, 1 niMH subject and 1 iE subject make up the group of preliminary data. The scores were averaged to create a seventh set of data, shown as "Group" in the figures below. These data represent the average effects of therapy for the preliminary dataset. Error bars on figures represent the maximum and minimum value reported for a particular subject. For the Group dataset, the maximum and minimum values reflect the absolute maximum and absolute minimum reported. The results of each subject in the following sections were extracted using the the EPIONE Extraction Program (EEP).

4.2.1 Pain Intensity: VAS Results

The primary measure of effect, average pain over 24 hours (Figure 4.1), shows an improving trend over four weeks of therapy. Five of the six subjects (83%) have pain trending downward from pre-therapy through the therapy phase. As depicted in Figure 4.1, one subject (who started the study experiencing only mild pain) stayed in the mild pain category. The third niE subject did not complete questionnaires in the third week of therapy, which is why no pain is reported. On average, pain decreased by 2 points on the VAS from pre-therapy to week-4 of therapy.
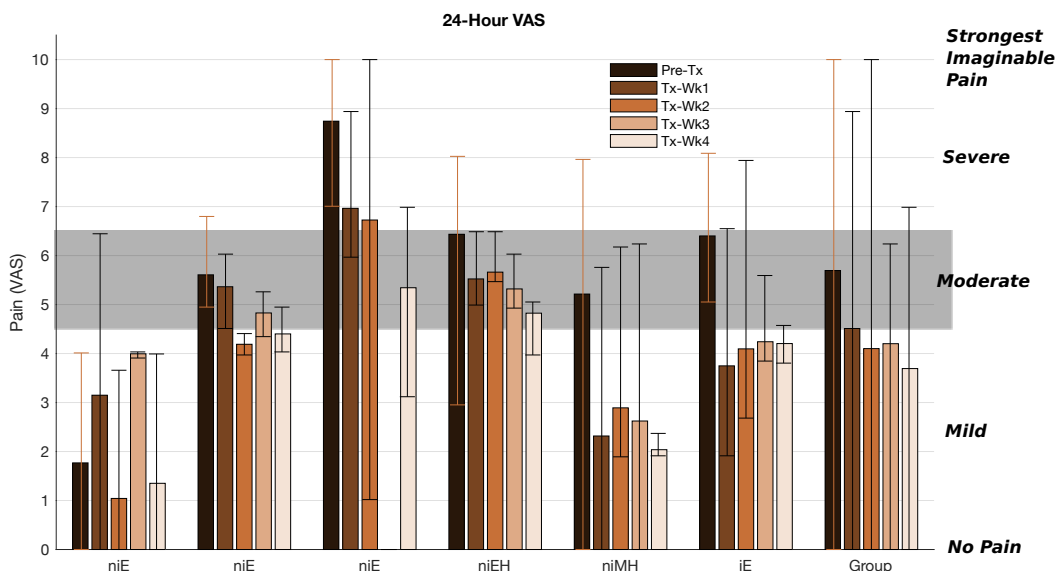
Fig. 4.1. VAS scores spanning pre-therapy through week-4 of therapy. Five of six show downward trend in pain intensity. On average pain intensity drops from moderate to mild. Error bars represent maximum and minimum.

Figure 4.2 demonstrates the level of effect of therapy for each subject. The low level of pain shown by the first subject in Figure 4.1 explains why the subject showed little to no effect on the nonoverlap of all pairs (NAP) results, as there was little room for improvement. In this case a positive outcome is that the therapy did not increase pain (which is supported by the NAP of 0.5-0.55 in Figure 4.2). Two subjects had strong improvements, three subjects had moderate improvements and two subjects had no improvement after 4 weeks of therapy according to the thresholds set forth by Parker and Vannest [170].

A result of particular interest is that of the subject receiving the niMH therapy. For this subject the average 24-Hour VAS dropped by 3.2 points comparing week-4 of therapy to the pre-therapy set (Figure 4.1). Comparing these data to that of the third niE subject (whose VAS scores dropped from pre-therapy to week-4 by 3.4 points), one might expect the level of effect to be similar. However, the NAP scores for this subject remained in the moderate, positive effect range with a score of 0.80 (Figure
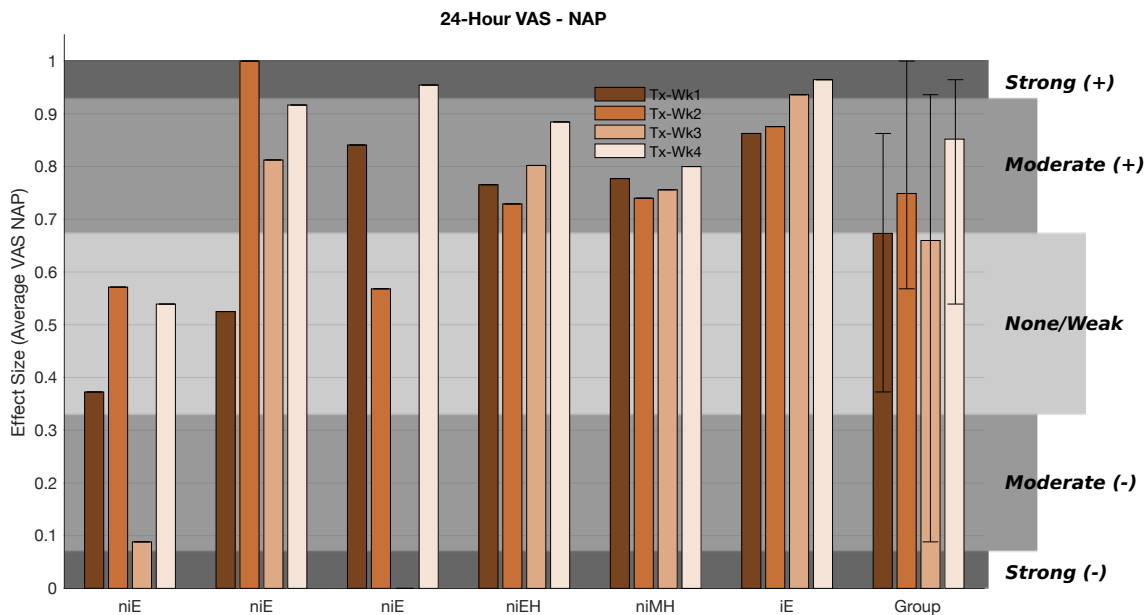
Fig. 4.2. The NAP method of analysis demonstrates therapy has moderate, positive effects on average for the operant coupled stimulation therapy paradigm. Error bars represent maximum and minimum.

4.2), while the third niE subject rose above the strong, positive effect threshold at 0.95. The explanation of these results lie in the distributions of the reported VAS scores. For example, if the pre-therapy scores fall only on both extremes, then the effect might not be as impactful as if the distribution were tight. If a subject had reported 5.2 for every pre-therapy score (the same average VAS as reported), the effect after completing the NAP method would be strong and positive at NAP = 1. Similarly, in the first niE subject, while the VAS scores stay in the mild range, the NAP scores approach the strong, negative threshold for effect. These circumstances bring to light the importance of observing both the VAS scores and the NAP scores when looking at effect.

In addition to the average pain over 24 hours, the alternative pain intensity measures of present pain and average pain over the last hour show no effect - moderate, positive effect for the group (shown in Figure 4.3). Both of these measures were

expected to stay near 0.5 on the NAP scale, and represent the immediate effects of stimulation. These measures act as indicators of whether or not the therapy sessions trigger or cause pain. If so, the NAP scores would dip into the negative effect regions, which occurred for some subjects. The spread of effects of therapy is quite broad, but remains fairly consistent week to week, within each set of scores.
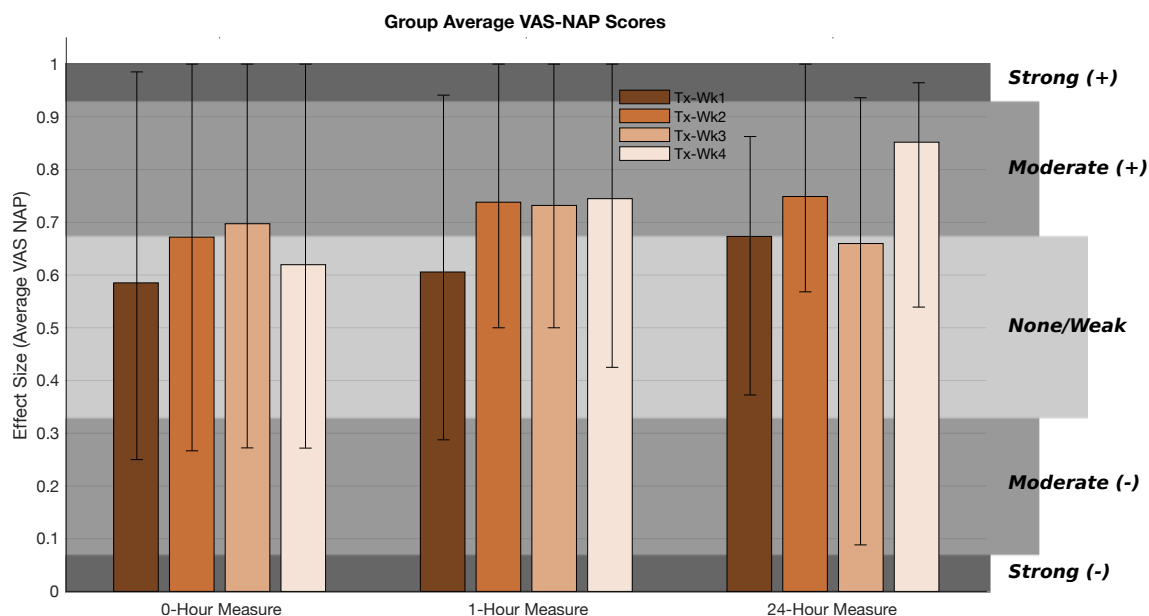
Fig. 4.3. Average pain over 24 hours and average pain over 1 hour show therapy has a moderate, positive effect. Present pain (0-Hour Measure) remains in the None/Weak region as expected. Error bars represent maximum and minimum.

The VAS results, shown in Figure 4.1, Figure 4.2, and Figure 4.3, show trends of improvement in 5 subjects (86%), both in average VAS score over 24 hours (Figure 4.1), and in NAP of the 24-Hour VAS (Figure 4.2). While the therapy negatively affected some subjects in the immediate pain scores, the general trend of the immediate effect of therapy is no effect - moderate, positive effect. The average 24-Hour VAS and VAS - NAP of the 24-Hour VAS appear to be sensitive to therapy and appropriate for measuring pain intensity. These moderate, positive of the pilot group results support the treatment modalities

4.2.2 Pain Affect: POMS-SF Results

Measuring pain affect can be done by reviewing the change in subscales over the therapy phase compared to the pre-therapy period. Figure 4.4 depicts the average POMS-SF scores reported from the pilot study group. Recall that each measure has a different spectrum, with different maximum and minimum possible scores. The minimum possible scores are shown within Figure 4.4; the ranges are also presented in Table 2.6. On average the group did not exhibit negative pain affect; scores remained at the bottom of the spectrum, which is a positive even though an improvement is not seen. Conversely, study participants began in the middle of the vigor spectrum, allowing observation of either positive or negative effects through the therapy phase. For the vigor subscale in week-2 and week-3 of therapy, the group shows strong and moderate, negative effects of therapy, respectively. In week-4 of therapy, the group average climbs back into the none-weak effect region. Despite the moderate correlation of vigor with both fatigue and depression seen by Baker et al. [167], the vigor score appears to be the only measure sensitive to therapy. This result calls for more investigation, leading to Figure 4.5.

The vigor score appears to be sensitive to therapy. Figure 4.5 depicts the average vigor scores for each subject along with the group average. Three subjects demonstrate negative effects of therapy, one subject shows no effect, one subject exhibits positive effects after four weeks of therapy, and one subject failed to complete the weekly questionnaires in the therapy phase (niMH). The subjects who exhibited positive effects in the VAS - NAP scores (depicted in Figure 4.2) are also the individuals showing effect (positive and negative) in the vigor subscale. For three of the four subjects showing effect in both instruments, the correlate is counter to expectation, reduction of pain (positive effect) corresponding with depreciating vigor (negative effect).

While some have suggested the inverse correlation of mood and pain [75], the POMS-SF does not appear to be sensitive to this correlation. Of the subjects sampled,
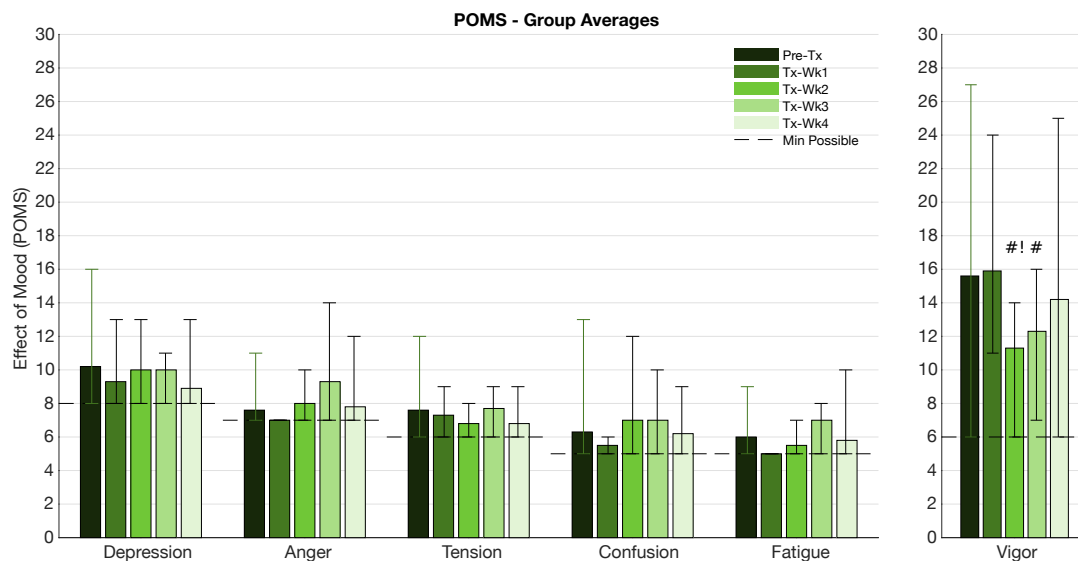
Fig. 4.4. The POMS-SF questionnaire, in general, is not sensitive to the pain affect associated with PLP. All of the negative facing scores were near the minimum possible score, on average, meaning it is not possible to observe a positive effect of therapy with this instrument (except in the vigor subscale). # indicates a moderate, negative effect and #! indicates a strong, negative effect.

all reported scores at the bottom of the possible range for the negative facing scores leaving no room for improvement. In order to better assess the effects of therapy, alternative instruments may be required. On the other hand, the vigor subscale demonstrated a negative effect of therapy on average. This result is of particular interest because it is counter to the expected result considering the effects seen in measuring pain intensity. There are several potential factors separate from PLP that could play into drop in vigor. For example, the rigor of the intensive therapy regimen could have taken a toll on the subjects' liveliness. The affective aspect of pain shows no change in a majority of the subscores. However, with respect to vigor, the pilot group show negative results in the second and third week of therapy.
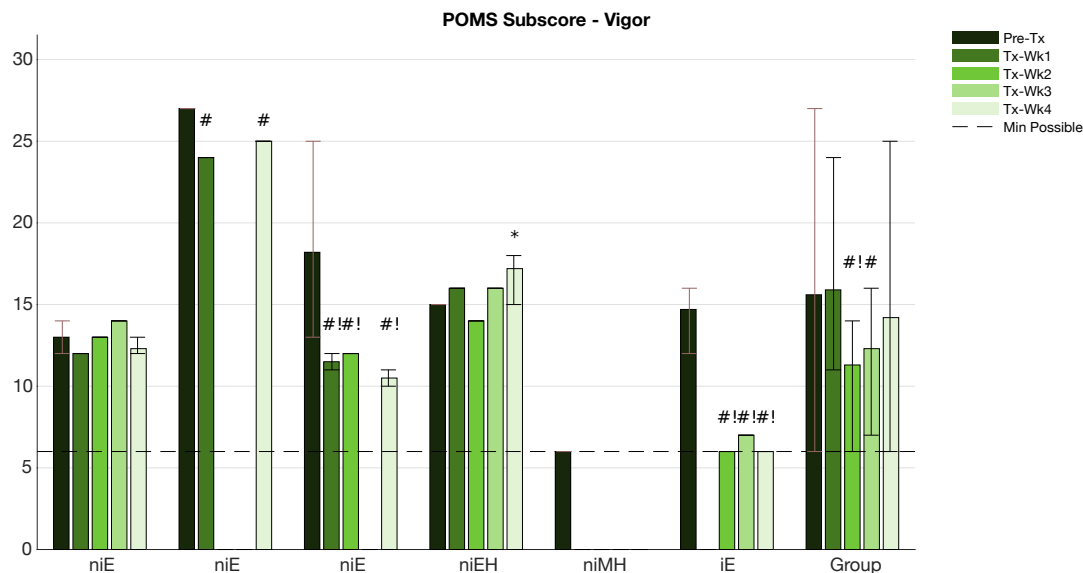
Fig. 4.5. The response to therapy in the POMS-SF vigor subscale are negative on average. On an individual subject-level results are mixed. One subject exhibits moderate, positive effects after four weeks of therapy, while two others exhibit strong, negative effects, and one shows moderate, negative results. * indicates a moderate, positive effect. # indicates a moderate, negative effect and #! indicates a strong, negative effect.

4.2.3 Pain Quality: NPSI Results

The measure of pain quality focuses on NP. While NPSI measures the intensity of a given descriptor, it also breaks out the pain into several categories allowing the observation of effect on several qualities of pain presentation. Five descriptors and one total score (all NPSI subscales) characterize the effect of therapy. On average effects are minimal with only moderate, positive results appearing in two subscales intermittently, depicted in Figure 4.6. Moderate, positive effect of therapy appeared in week-1 and week-3 of therapy for the paresthesia/dysesthesia subscale and week-3 of the paroxysmal subscale. Distributions of scores in each subscale are quite broad (ranging 0-10 in some cases). A deeper look at the total subscale provides an overview

of the effect of therapy on a per subject basis, since this score is itself a weighted average of the other subscales.
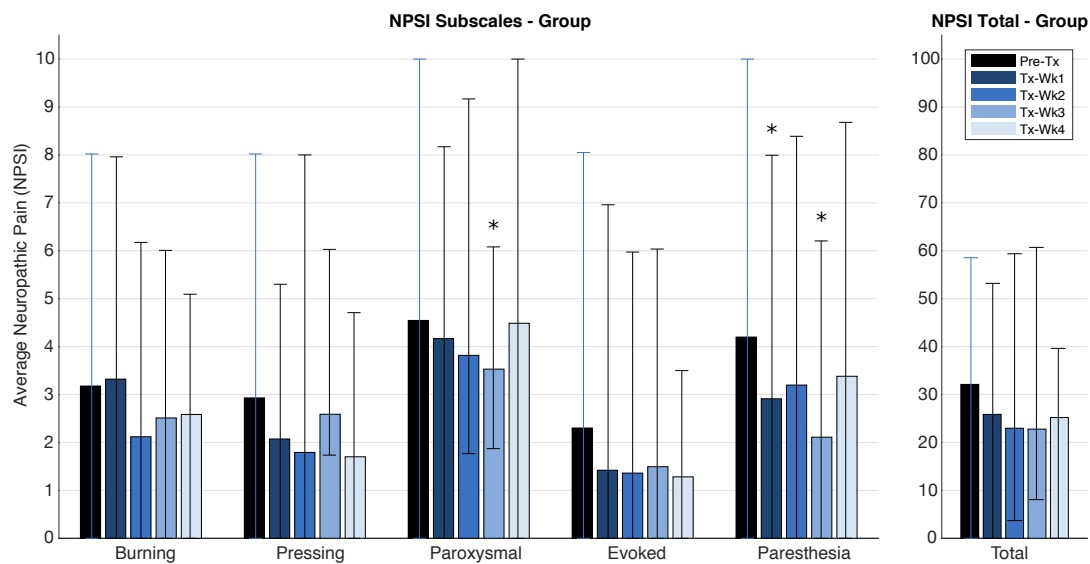
Fig. 4.6. NP symptoms throughout the therapy phase measured with the NPSI do not significantly change on average. Two subscales show moderate, positive effects intermittently. * indicates a moderate, positive effect.

Figure 4.7 illustrates the NPSI - Total subscale for each subject. While the group does not demonstrate an effect, the two subjects exhibiting the highest average total NP in the pre-therapy phase, show strong, positive effects. This data demonstrates a major limitation of the study, subject non-compliance. The third subject shows moderate and strong, positive effects in week-1 and week-2 of therapy, respectively. However, after not attending therapy sessions in the third week of the therapy phase, the total score rose in week-4. Unfortunately, it is impossible to say whether or not the change in effect is due to missing week-3 of therapy, but it is a notable potential factor.

One subject did not exhibit NP symptoms. As with the POMS-SF, when a subject reports scores at the bottom of the spectrum (as with subject 1), significant improvement is not possible, making the instrument negligible. In this case two possibilities
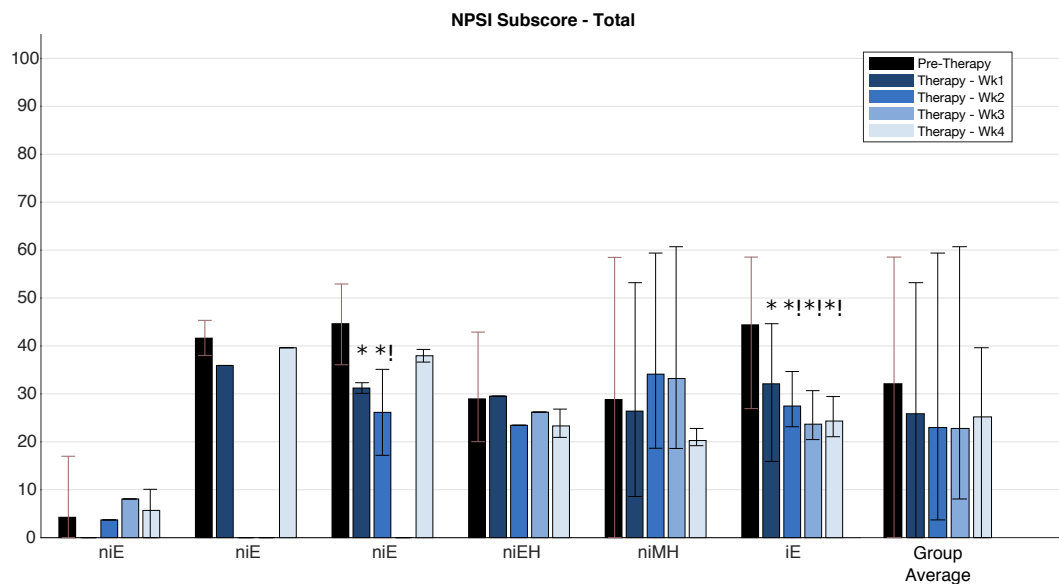
Fig. 4.7. The NPSI - Total subscale reflects the effect of therapy on NP as a whole. Two subjects reach levels of strong, positive effect. One subject does not have substantial NP and does not show up on this spectrum. * indicates a moderate positive effect and *! indicates a strong, positive effect.

are presented for analysis. First, the subset could be removed from the rest of the dataset. Second, the subset could be analyzed with alternative criteria, following that of non-inferiority. This is done by comparing the scores on the total subscale for subject 1 in each therapy week to the pre-therapy scores where positive results also include those which stay the same, i.e. the therapy is non-inferior to scores in the pre-therapy phase. Results for pain quality demonstrate moderate, positive results in a few NPSI subscores; however, the NPSI total score does not show changes over the therapy phase.

4.3   Discussion

The primary measures, VAS and NAP, show the therapy has promise. On average there is a moderate, positive effect of therapy in the first week that continues and increases through the therapy phase. A positive effect was found in three of the

four therapy methods presented (niE, niEH, and iE). In several subjects a moderate, positive effect is seen in the first week of therapy, which is unexpected. Without running a randomized controlled trial (RCT), placebo-effect cannot be ruled out. A major limitation in this analysis is number of comparisons used in the NAP analysis. Whereas, Parker and Vannest suggest a minimum of 169 comparisons of baseline to treatment scores, (13×13). Most data reported here were below 100 comparisons [170].

Most of the POMS-SF scores fall at the bottom of the spectrum, making it difficult to see any effects. The correlation of improved pain and improved depression is an expected result in the present data because of the association recognized in amputees [18]. As discussed in Chapter 5 (which includes results for the third niE subject), the improvement in depression was not indicated by the POMS-SF results, while it was by the patient health questionnaire (PHQ-9). Vigor (the positive-facing POMS-SF measure), requires analysis which is contrary to the other 5 POMS-SF subscores. Improvement in vigor would mean an increase from baseline. On average the vigor score had negative effects in therapy week-2 (strong) and week-3 (moderate), but improved back to baseline levels in week-4. Negative effects in the vigor spectrum without the similar results in depression and fatigue is unexpected. Baker et al. recognized a moderate inverse correlation of vigor scores with depression scores and fatigue scores (-0.40 and -0.45, respectively), which is a positive correlation of effect [167]. This could be due to a difference in study population, since Baker et al. reflects the psychometric analysis of cancer patients [167], but the cause for difference is unclear.

For NPSI the expectation is for different subjects to have different amounts of NP in each category or subscore; some subjects may be involved in the study and never report or have a certain type of NP. As evident from the first subject, some amputees experience little to no NP. Because the presentation of pain is different from subject to subject, the NPSI - Total subscale seems like a valid measure for analyzing the

effects of therapy on pain quality. While the average result is no effect, two subjects, subject-3 (niE) and subject-6 (iE), trend downward and exhibit strong improvement.

4.4 Conclusions

After reviewing the primary and two secondary instruments of preliminary datasets, the therapy method shows promise. Scores in each of the three reviewed trended toward improvement, some showing moderate, significant improvement. However, some also showed negative results and require close attention in future studies. An obvious limitation of this preliminary review of data for the pilot study is power. Limited sample size is cause for inconclusive results. In addition to the insufficient sample size of study participants, the amount of data collected from each subject is also limited. Questionnaires take substantial amounts of time and concentration; over-sampling can lead to frustration and biased results, so consideration of contact hours is quite important. Other limitations include subject non-compliance, e.g. not showing up to daily therapy sessions resulting in missing data, and reliance on self-report questionnaires without population norms of the sample demographic, e.g. using standard deviations from cancer studies to measure effects in a study of PLP. While the analysis is appropriate for a pilot study, improving the methods for measuring effect are advised.

Future directions involve specifying the therapy parameters and modalities. In the present pilot study, there are six possible modalities of applying treatment (four examined here) involving both non-invasive and invasive varieties. Additional pilot studies should first be conducted to rule out any modalities that appear to be obviously inferior. In order to narrow the treatment method, future research should focus on conducting randomized controlled trials comparing rates of success among the top performers with a sham group. A significant consideration of the present work focused on the cognitive aspects of treatment. While several have attempted surface electrical stimulation as a method of treating PLP [145–148] and others have attempted to train

to cognitively manipulate and take control of the phantom [146, 157], pairing stimulation with cognitive reinforcement is relatively novel. Doing so trains the subject to couple meaningful sensation (electrical or mechanical in this case) with the phantom, possibly improving mood, restoring reorganization of the CNS and alleviating pain.

5. A CASE STUDY OF COGNITIVELY REINFORCED ELECTRICAL STIMULATION FOR THE TREATMENT OF PHANTOM LIMB PAIN

5.1 Introduction

Chapter 4 discussed data from the entire pilot group. Here, a case study of two subjects at the Indiana University - Purdue University Indianapolis (IUPUI) clinical site is analyzed to demonstrate the methods, instruments, and analysis at a more specific level. Beyond the primary and two secondary measures sampled in Chapter 4, exploratory measures round out the analysis to form a complete dataset. The patient health questionnaire (PHQ-9), brief pain inventory (BPI), specifically the interference scale (BPI-IS), and psychophysical map of sensation (PsyP-Map) provide additional information to the affect and quality aspects of pain and phantom sensation. The patient global impression of change (PGIC) supplies the subject's perception. These data in addition to those collected through the profile of mood states - short form (POMS-SF), neuropathic pain symptom inventory (NPSI), and visual analog scale (VAS), introduced and discussed in Chapter 2, provide insight into the effectiveness of therapy. This study is approved through local authority under IRB number 1409138829, and is registered on clinicaltrials.gov (identifier: NCT02519907).

5.2 Methods

The methods involved in this case study follow the common clinical protocol (CCP; discussed in subsection 2.2.2), with three exceptions to the inclusion/exclusion criteria. First, the subject pool is widened to include unilateral upper and unilateral lower extremity amputees, including transradial, transhumoral, transtibial, and trans-

femoral amputations. Second, the age range is extended from $18 - 70$ out to $18 - 75$. Lastly, diabetes is removed from the list of exclusion criteria, i.e. a potential subject with diabetes is still eligible assuming the other inclusion/exclusion criteria are met. The reason for these changes is justified by population demographics and the etiology of amputation. Nearly 65% of all amputees are lower extremity, and 38% of all amputees are diabetic [4]; excluding these individuals severely limits the ability to recruit candidates.

Following the experimental timeline outlined in subsection 2.2.4, the frequency of measurement was slightly adjusted from the CCP. These adjustments follow Table 5.1, where the frequency of several instruments are heightened from once per week to every session/daily.

Table 5.1. Outline of experimental instruments and their utilization in the experimental timeline (P=Pre-Screen, B=Baseline, E=Entry, TX=Therapy, O=Outcome, F=Follow-up). This is adapted from Table 2.4. * indicates the primary instrument for assessment of efficacy. ** indicates the secondary instruments for assessment of efficacy. X indicates administration of the instrument. D indicates administration of the instrument (at each scheduled session) in the given phase

| Type | Abbr | Test Name | Clinical Assessment (CCA) | | | | | |
			P	B	E	TX	O	F
	PHQ-9	Patient Health Questionnaire	X		X		X	D
Mental Status	POMS-SF**	Profile of Mood States		D	D	D	X	D
	WAIS-IV	Weschler Abbreviated Scale of Intelligence	X					
	NPSI**	Neuropathic Pain Symptom Inventory	X	D	D	D	X	D
	VAS*	Visual Analog Scale	X	D	D	D	X	D
Phantom Pain	BPI	Brief Pain Inventory		D	D	D	D	D
	PsyP-Map	Psychophysical Map of Sensation			X	D	X	D
	PGIC	Patient Global Impression of Change					D	D
Cortical Map	fMRI	functional Magnetic Resonance Imaging			X		X	

With respect to the experiential dimensions of pain described by Jensen and Karoly [25], the PHQ-9 and POMS-SF demonstrate changes in pain affect, PsyP-Map and NPSI reflect changes to the pain quality and the VAS and nonoverlap of all pairs (NAP) represent pain intensity. An additional aspect of interest is the subject's

perception of therapy effectiveness (measured by the PGIC), which does not fall under the traditional dimensions of pain, but does provide an interesting perspective to study effectiveness.

5.2.1 Data Collection

Aside from measurement frequency, methods for data collection are the same as discussed in Chapter 4. Methods for several instruments (VAS, POMS-SF, NPSI) are discussed previously (see subsection 2.3 for data collection and section 2.4 for analysis methods). Methods involving BPI-IS are discussed in subsection 1.3.1 and in subsection 2.4.2, since it was included as data that can be extracted by the EPI-ONE Extraction Program (EEP). Below the remaining exploratory measures, PHQ-9, PsyP-Map, and PGIC, are described.

PHQ-9

The PHQ-9 measures depression utilizing 10 questions to understand the subject's level of depression over the last 2 weeks. Questions follow the 9 criteria for depression outlined in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [175]. Nine questions, each covering a particular symptom associated with depression and ranging from 0 ("Not at all") to 3 ("Nearly every day"), are used to describe the degree of depression. Summing the nine responses gives a total score, which indicates the degree of depression; it ranges from none/minimal (0-4) to severe (20-27). The tenth question describes how difficult different aspects of daily living have been, but does not contribute to the score of depression.

PsyP-Map

The psychophysical mapping questionnaire seeks to describe the quality and location of non-painful phantom sensations. While some of the questions are very similar

to those in other questionnaires, since the focus is on sensation, this instrument provides additional insight. Questions focus the frequency, quality, and impact to life of phantom sensation as well as the size of, (involuntary and voluntary) movement of, location of, and posture of the phantom. The question of frequency allows the subject to respond with one of the four following options: "A few times a week", "A few times a day", "A few times per hour", or "All the time". This is to better understand how often sensations occur, as described in previous studies [9, 11]. The quality of sensation can be described as itching, tingling, warmth, cold, electric sensations, movement, abnormal shape, abnormal position/posture, touching, and other. If "other" is selected the subject is asked to describe the sensation. In regards to size of the phantom (altered kinesthesia), the subject can respond by simply selecting, "bigger", "smaller", or "no difference in size". Subjects are asked to describe the voluntary and involuntary movements of the phantom; these are open ended since every subject experience could vary so greatly. Location of the phantom is an indicator of what areas are active. As stated in previous studies, amputees tend to lose sensation in the proximal regions of the phantom, while distal sensation remains [10]. The question of posture refers to fixed orientation of the phantom. Some predetermined options are available; however, an open-ended response can also be submitted. Finally, the impact to life describes how troubling the non-painful phantom sensations are in general (ranging from "not at all" to "very much"). In the PsyP-Map the subject draws the location of the phantom limb as shown in Figure 5.1, where the red area represents the subject's response. This mapping can be used along with the other PysP-Map responses to indicate changes in quality of sensation.

PGIC

The PGIC can is a useful instrument for understanding the perceived changes. The questionnaire is administered in the final week of therapy, in the outcome visit, and in the follow-up phase. The PGIC is a 7-point NRS ranging from 1 ("no change
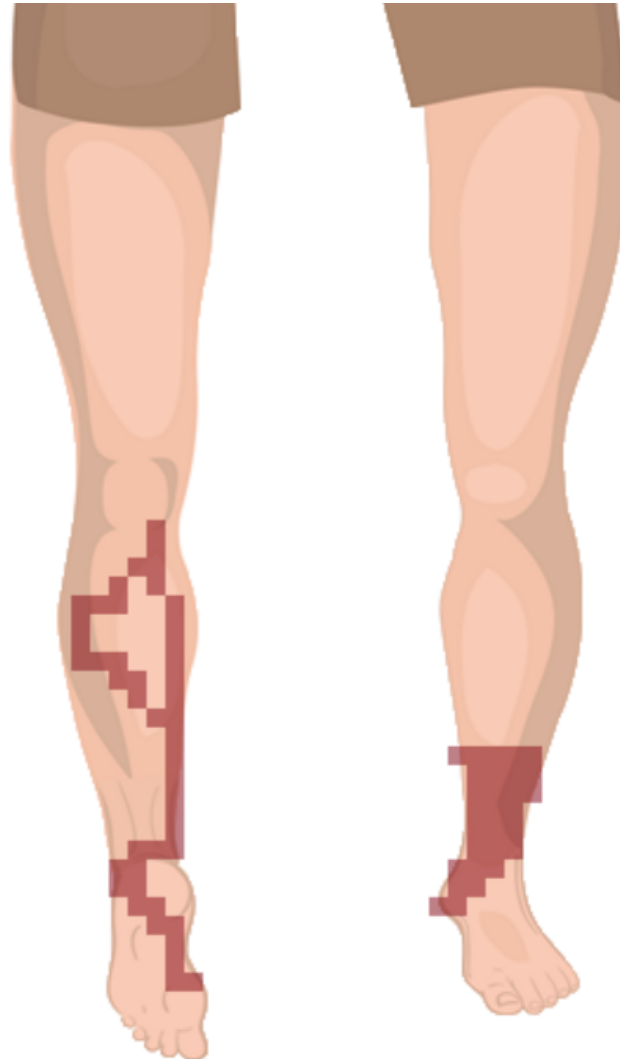
Fig. 5.1. The subject draws the location of the phantom in the PsyP-Map Questionnaire.

or worse") to 7 ("a great deal better"). In other studies the PGIC is asked a different way, allowing responses to range from positive to negative effect [72,99,176]. Here the PGIC is a one-sided measure, only able to capture improvement. For the subject-2 the traditional two sided PGIC was also administered along with the one sided PGIC.

5.2.2 Methods of Analysis

As discussed in section 2.4, Cohen's d for negative-facing scores is an important tool for measuring effect. The thresholds for effect are -0.8 and 0.8 for large/strong effects and -0.5 and 0.5 for medium/moderate effects. For each instrument that requires observing the change over time and does not have preset thresholds to observe, (i.e. BPI-IS, NPSI, and POMS-SF) the above thresholds for Cohen's d are utilized. Refer back to Equation 2.3 for more details. The PHQ-9 has preset threshold for determining degree of depression as discussed below. The exploratory instruments (PHQ-9, PsyP-Map, and PGIC) are merely observations and are not used to determine effect size.

PHQ-9

Analysis of the PHQ-9 refers to the thresholds determined by a large sample study. The general guidelines follow that of Table 5.2 generated from recommendations by Kroenke et al. [175]. While the difference from the pre-therapy period to the post-therapy period is noted, using the thresholds provides a more absolute measure of depression.

Table 5.2. PHQ-9 Thresholds from Kroenke et al. provide a measure of depression [175] before and after therapy.

Level of Depression	PHQ-9 Score Range
None	$0 - 4$
Mild	$5 - 9$
Moderate	$10 - 14$
Moderately Severe	$15 - 19$
Severe	$20 - 27$

PsyP-Map

The PsyP-Map is not a validated questionnaire, but a compilation of several prevalent phantom sensation qualities noted in previous studies [9–11]. For the sake of exploration and further understanding, analysis simply involves the comparison of results without demarcation of significance. Items of interest lie in how the phantom is perceived throughout the study and if it changes.

PGIC

The PGIC does not have a baseline measure to use for comparison. Rather, the goal is to understand how the subject perceived change and whether or not changes in other instruments are recognized by the subject's impression of change over the course of the therapy period.

5.2.3 Case Study Specific Details

Following the non-invasive electrical stimulation modality (niE), the IUPUI site completed the protocol with two subjects. Subject one was an adult male who had a left unilateral, transfemoral amputation as a result of diabetic neuropathy and microvascular disease. This subject was on a 300 mg maintenance dose of Gabapentin three times per day. Subject-2 was an adult male who had a right unilateral, transtibial amputation as a result of surgery. Enrollment in the study occurred > 2 years post-amputation, with the stump in a stable phase for both subjects. Subject-1 is also represented in Chapter 4 as one of the niE subjects.

5.3 Results and Discussion

Results are organized according to the dimensions of pain followed by the PGIC. For subject-1 the results of therapy week-3 are not present because the subject did not participate that week. Subject-1 attended two therapy visits in week-1, week-2,

and week-4. Subject-2 attended therapy sessions all four weeks, missing one session in the first week. In the following figures subject-1 results are reported in part A and subject-2

5.3.1   Pain Intensity

The VAS and NAP (represented in Figure 5.2A and Figure 5.3A, respectively) demonstrate a strong positive effect after the 4$^{\text{th}}$ week of therapy for subject-1. Average pain intensity over 24 hours dropped by more than 3 points from severe to moderate and the effect size in terms of NAP rose above the strong, positive threshold. The 0-hour and 1-hour control measures remain close to the moderate pain range stretching into all three regions in most weeks. Looking at the temporal sequence of results, the average 24-hour VAS drops week-to-week until the outcome visit, where the pain intensity stretches back into the severe range. For the NAP, this weekly improvement is not seen. The range of week-to-week VAS results from therapy week-2 give a clue to why there is a discrepancy. In week-2 of therapy the maximum and minimum score for average 24-hour VAS ranges over almost the entire VAS spectrum. While there is improvement if looking only at the average VAS, the NAP method tells a different story and the wider distributions of scores are accounted for. The 0-hour and 1-hour measures of intensity fell in the none/weak to moderate, negative effect range. This result is expected for the surface electrical stimulation method, as it can cause minor discomfort during the therapy sessions.
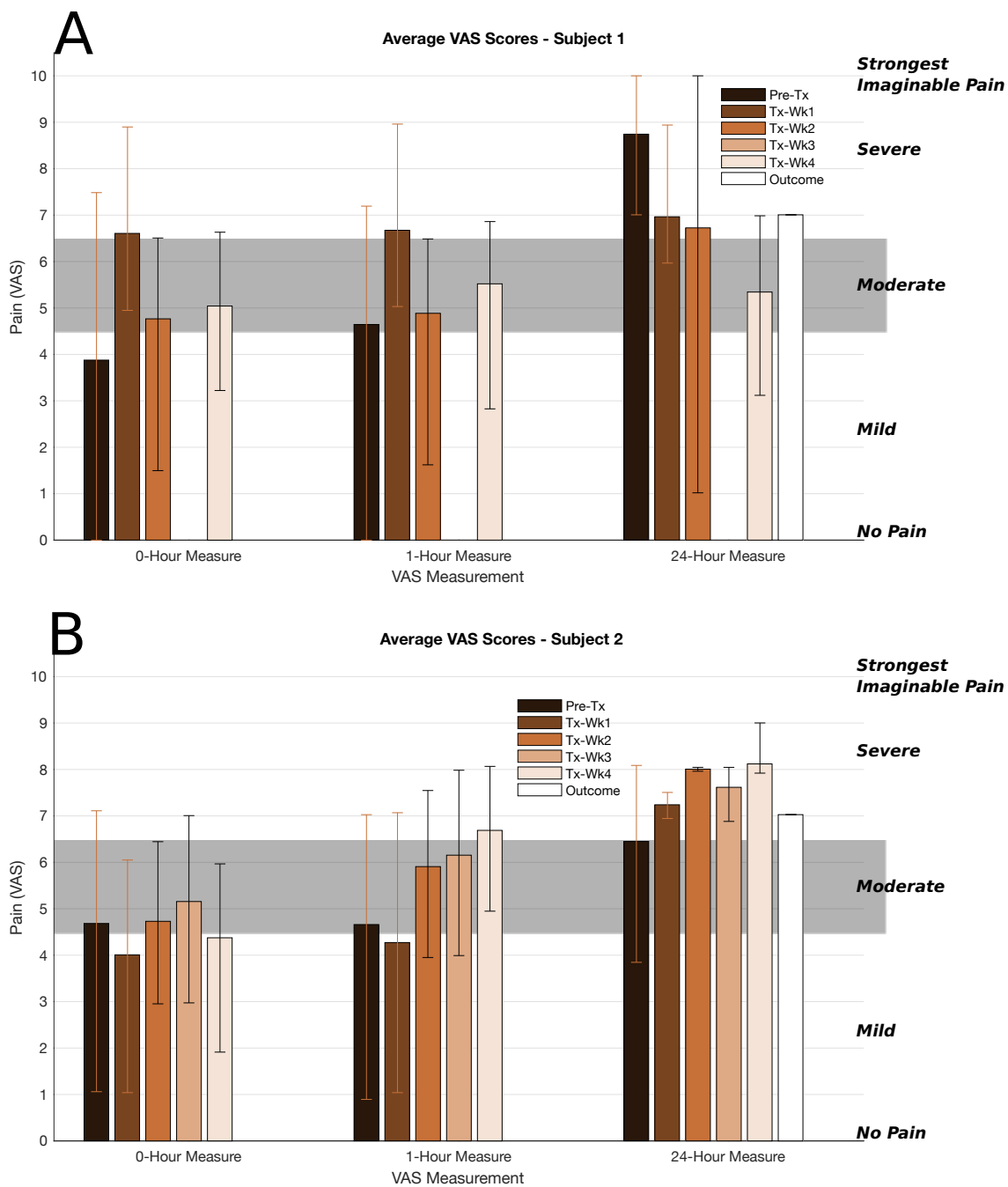
Fig. 5.2. In subject-1 (A) the primary outcome measure (average pain intensity over 24-hours) demonstrates a drop of average intensity from severe to moderate even after missing a week of therapy. Subject-2 (B) has the opposite trend with an increase in average pain intensity over 24-hours. Error bars represent the maximum and minimum.
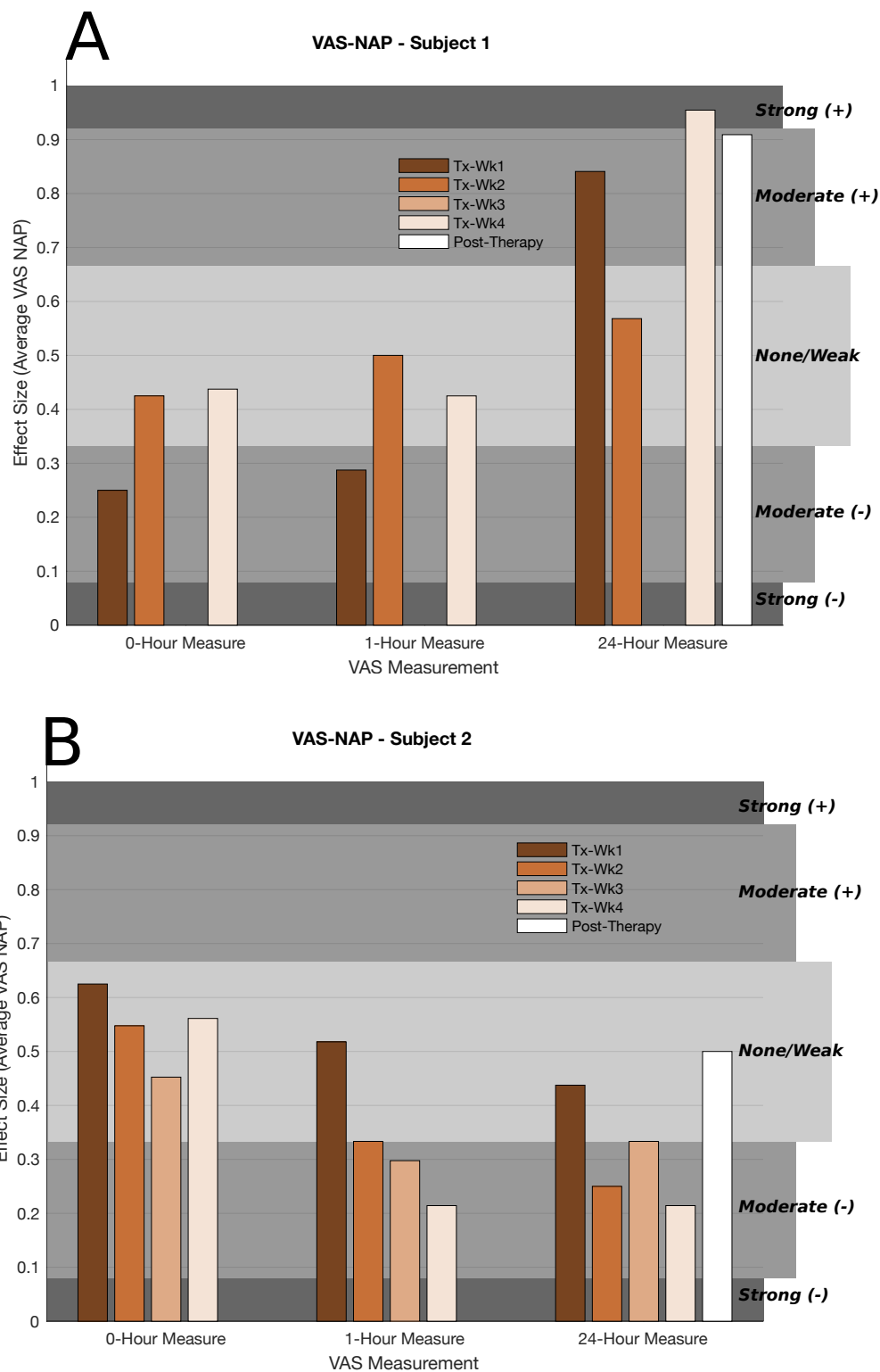
Fig. 5.3. The primary outcome measure (average pain intensity over 24 hours) demonstrates a strong, positive effect in subject-1 (A), even after missing a week of therapy. Subject-2 (B) experienced moderate, negative effects of therapy.

Subject-2 exhibits moderate negative effects of therapy. Figure 5.2B and Figure 5.3B show that the pain intensity increased throughout the therapy phase, and the NAP extends into the moderate negative effect range. After ending therapy the NAP returns to the no effect range. Compared to the results from subject-1, the ranges of the in-week pain intensity scores are much tighter for subject-2. The 0-hour pain intensity remains constant throughout the therapy phase; however, the 1-hour pain intensity rises week to week.

5.3.2 Pain Affect

Pain affect is measured by the POMS-SF, BPI-IS, and PHQ-9 instruments. In both subject-1 and subject-2, the POMS-SF shows limited response to therapy. This is because nearly all subscale fall on the low end of the spectrum. Using the threshold defined in subsection 2.6, two subscales show negative results and two subscales show positive results throughout the course of the study for subject-1. As for subject-2 moderate, positive effects are demonstrated in both depression and vigor. Figure 5.4 depicts the response of mood states over the therapy period. For subject-1 the depression subscale falls near the minimum possible value in the pre-therapy phase, which prevents observation of improvement. In this case a positive result is that all negative facing subscales are at the minimum possible score throughout the therapy phase. Of the negative facing subscales, only the confusion subscale reached a high enough value in pre-therapy period to show positive effect (which was a strong, positive effect in this case throughout the therapy period). Vigor presents a strong, negative result throughout the therapy phase, but reverses to a strong, positive effect in the outcome measure. These results are not particularly as expected, mainly because of the lack of correlation among subscales. Baker et al. propose evidence of inverse correlation between vigor and depression scores as well as an inverse correlation of vigor and fatigue scores [167]. However, the present data for subject-1 do not follow this expectation.
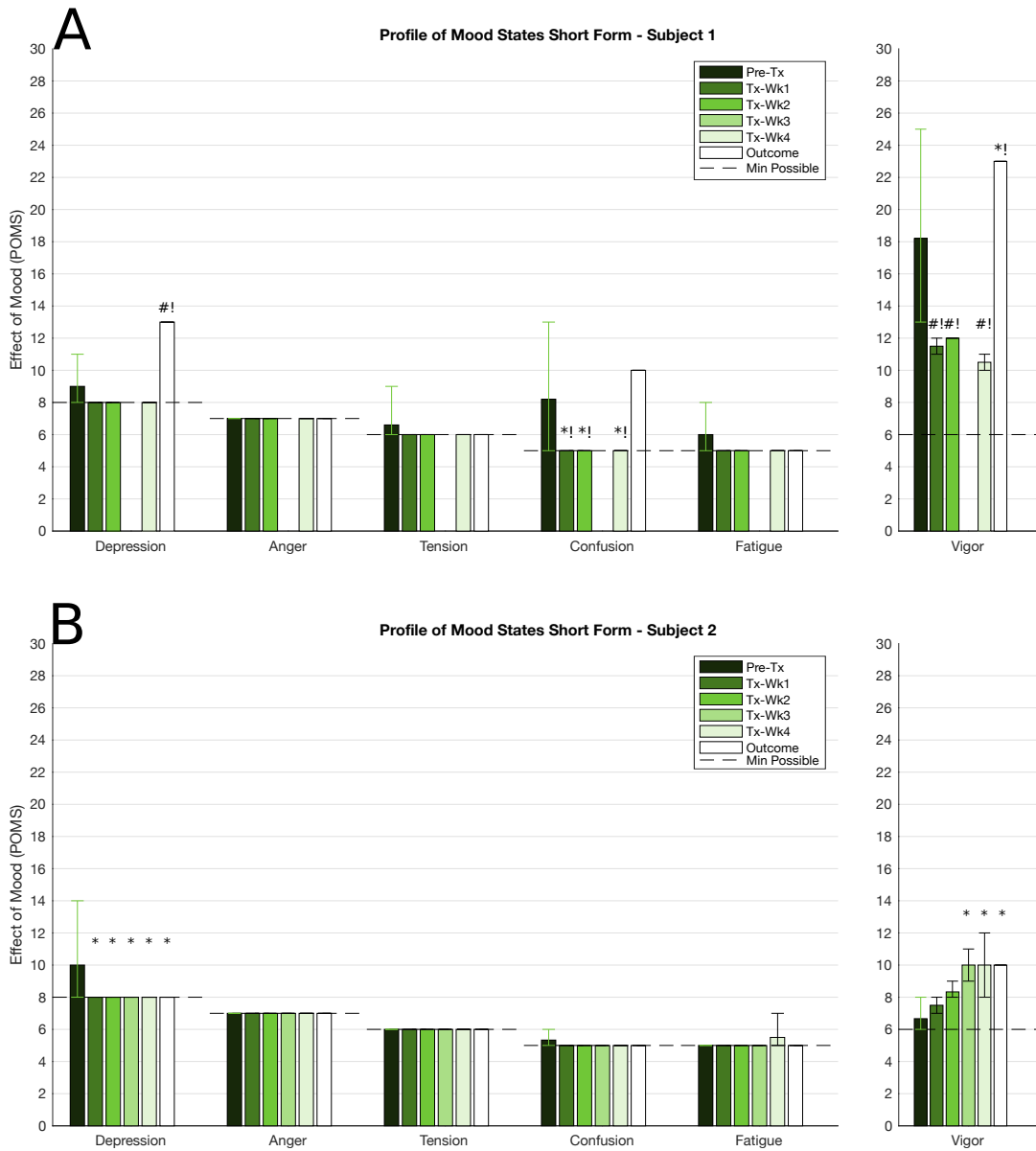
Fig. 5.4. The POMS-SF provides insight to a subject's mood state at each visit. Subject-1 (A) shows mixed effects. Subject-2 (B) demonstrates positive effects in depression and vigor. Error bars represent the maximum and minimum.* indicates a moderate, positive effect, *! indicates a strong, positive effect, # indicates a moderate, negative effect and #! indicates a strong, negative effect.

A strong, negative change in vigor is not reflected by a strong, negative change in depression or in fatigue. Furthermore, a strong, negative change in depression (in the outcome measure) is counter to the trend in Baker et al. because of the strong, positive change in vigor [167]. Subject-2 does demonstrate this correlation depression and vigor. However, just like with subject-1 the other scores do not have a high enough pre-therapy score to observe positive effects.

Two BPI-ISs (mood and sleep) demonstrate strong positive results in subject-1 (Figure 5.5A), when comparing the t-scores to p-scores according to the criteria in Table 2.7. Other interference scales also show a decrease from pre-therapy; however, the pre-therapy scores are not high enough to allow a sizable positive change. The total score (average of the interference scales) presents a moderate, positive effect, indicated by the drop of total pain interference. The total interference may be an appropriate measure for comparison across subjects since every subject will likely have a slightly different pain experience. Subject-2 (Figure 5.5B) experienced heightened mobility and worsened effects for sleep. It seems as though the benefits were canceled out in terms of over effect on the interference scale, as the total interference remained close to the pre-therapy average throughout the therapy phase.

The reduction of interference in regards to walking for subject-2 provides a clue to the possibility of external activities that could confound the results. During the study, subject-2 was testing out a new prosthetic limb and increased his daily exercise. In this regard his pain did not interfere as much as it had in the past; however, it begs the question of whether the effects are from the new prosthetic or from the therapy. This could also be said of the pain intensity measurements. It is reasonable to connect the increased pain intensity with increased use of a prosthetic.
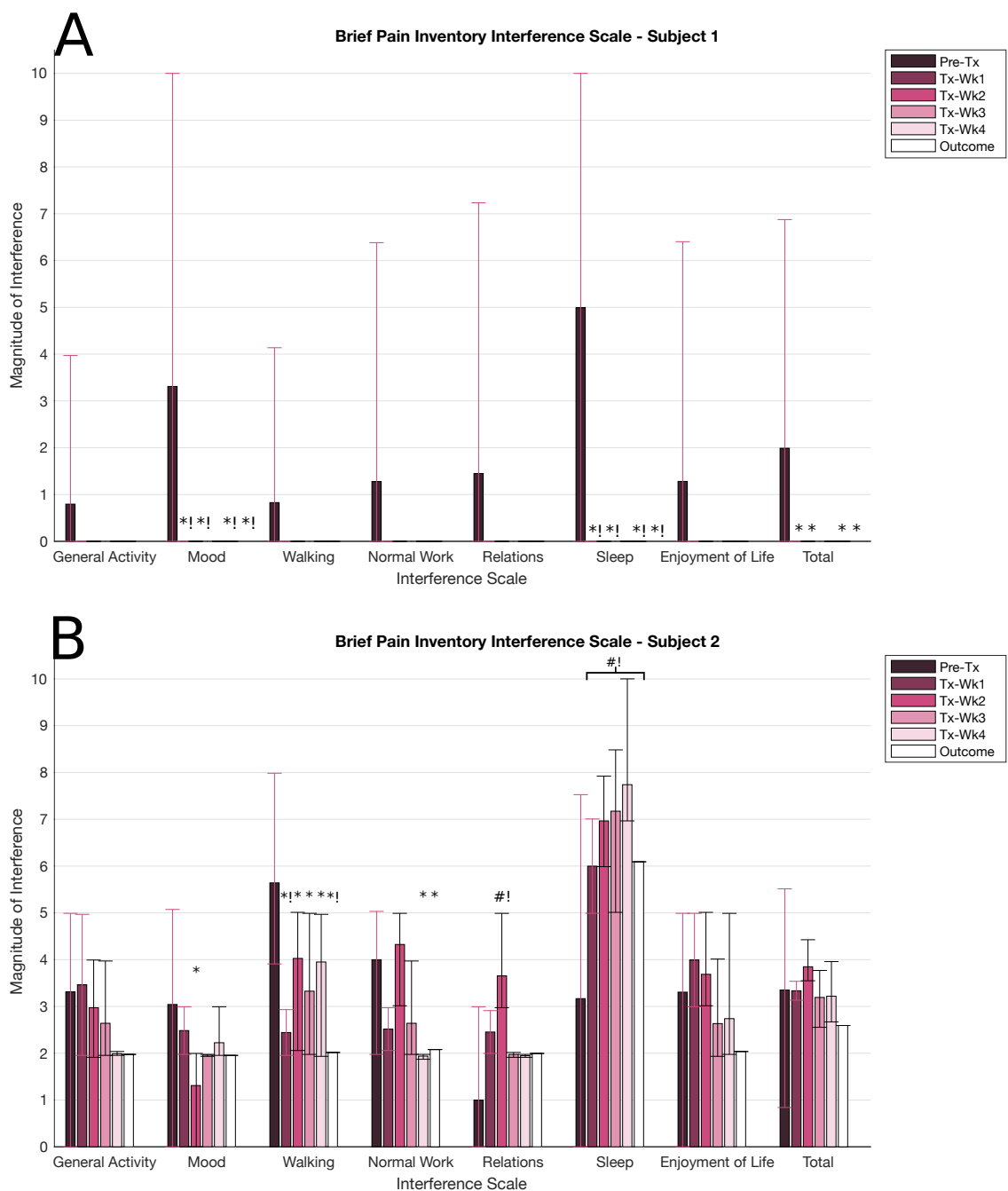
Fig. 5.5. The BPI-IS and total score appear to be sensitive to therapy for subject-1 (A) and especially for subject-2 (B). The BPI-IS may provide additional insight into the subject experience when looking at time-series correlations between BPI-IS and VAS. Error bars represent maximum and minimum. * indicates a moderate, positive effect, *! indicates a strong, positive effect, # indicates a moderate, negative effect and #! indicates a strong, negative effect.

The PHQ-9 provides insight to the longer term effects of therapy on mood, since it is not asked on a weekly basis. Within the pre-therapy period, it is prompted two times, in the pre-screen and entry phases. It is not reported again until the outcome phase. Table 5.3 demonstrates the change from pre-therapy to post-therapy for both subjects. In the Pre-Screen phase subject-1 exhibits moderately severe depression and moderate depression in the entry phase. Post-therapy the PHQ-9 score dropped below the threshold for mild depression, indicating a positive effect of therapy. This drastic change in depression level seems to reflect the results demonstrated in the pain intensity results. However, it is contrary to the POMS-SF results for depression. Depression reported by POMS-SF subscale shows a strong, negative effect in the outcome phase (with the score increasing from the pre-therapy). These results are inconsistent considering the questionnaires are administered in the same day. The likely explanation is that the POMS-SF reports on the subjects present state of mood, while the PHQ-9 is intended to describe depression over the last two weeks. These contrary results advocate for collecting additional data. As for subject-2 the PHQ-9 results are consistent with the POMS-SF results reported for depression. The moderate, positive results in the POMS-SF depression subscale correlate well with the reduction from moderate to mild depression in the PHQ-9. However, if averaging the pre-therapy measurements (to get a PHQ-9 score of 7.5 pre-therapy), subject-2 falls in the mild range for both pre-therapy and outcome.

5.3.3 Pain Quality

The NPSI demonstrates positive effects in several subscales for subject-1. Only one subscale (evoked) did not reach a high enough level in the pre-therapy period to be capable of demonstrating effect. The other five subscales demonstrate positive effects at some point throughout the therapy phase. The paroxysmal, paresthesia/dysesthesia, and total subscales exhibit strong, positive effects in week-2 of therapy. However, after missing a week of therapy, the pain symptoms revert back toward the pre-

Table 5.3. The PHQ-9 indicates the degree of depressive symptoms before and after therapy.

Subject	Clinical Assessment Phase	PHQ-9 Score	Level of Depression
	Pre-Screen	16	Moderately Severe
Subject-1	Entry	13	Moderate
	Outcome	3	None
	Pre-Screen	4	None
Subject-2	Entry	11	Moderate
	Outcome	6	Mild

therapy levels. To account for different perceptions and experiences of pain, the total subscale is used for comparison among participants, as described in subsection 4.2.3. Subject-2 experienced vast improvements for the burning symptom and moderate to strong improvements for paresthesia. Pressing and paroxysmal had mixed effects and the evoked symptom had moderate, negative effects toward the end of the therapy phase. Overall, however, the total NPSI subscale demonstrates no effect of therapy for subject-2.

The PsyP-Map provides a description of phantom sensation in general terms throughout the study. In the pre-therapy period phantom sensations are described by subject-1 as tingling, electric sensations, movement and abnormal position/posture descriptions with sensations occurring between a few times a week and all the time. The phantom limb is consistently described as smaller in size than the contralateral limb (indicating some degree of telescoping). Furthermore, the subject described both involuntary movement and the capability of moving the phantom at will. Involuntary movements involved "swinging the leg side-to-side" and the feeling of "hav[ing] a shoe on." The movements at will are described as moving toes up and down, moving the foot up and down at the ankle, and moving the limb side to side at the knee. An unsolicited comment is noted several times in the pre-therapy period of the subject not being able to "kick straight out". Finally, the orientation of the phantom limb in
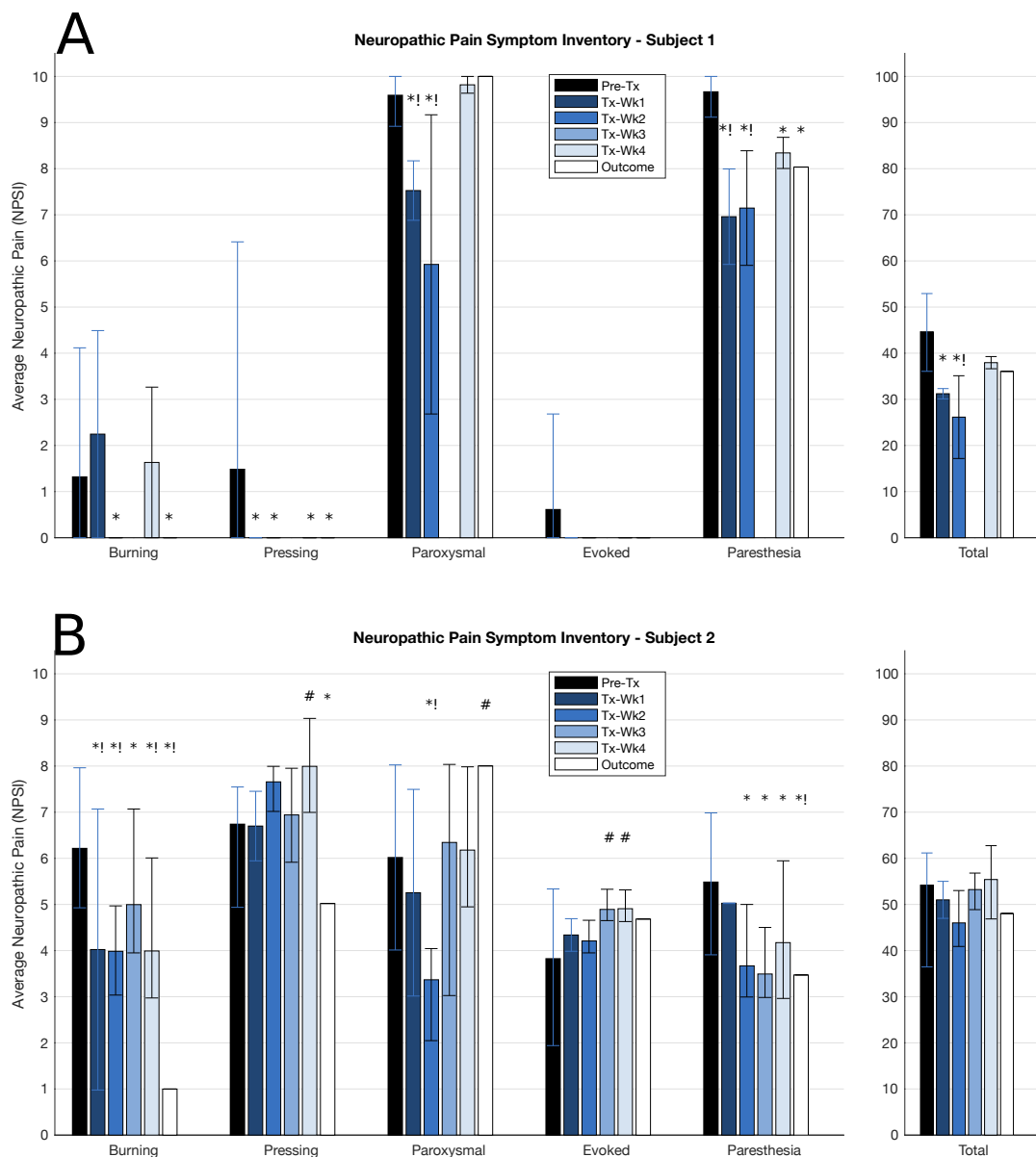
Fig. 5.6. Several NPSI subscales show sensitivity to therapy. If subject-1 (A) had not missed a week of therapy results may have been further improved. Subject-2 (B) reports positive effects in burning, but no effect overall. Error bars represent the maximum and minimum. * indicates a moderate, positive effect, *! indicates a strong, positive effect, # indicates a moderate, negative effect and #! indicates a strong, negative effect.

the pre-therapy period is described as both normal and unusual, but most commonly as knee bent.

Immediately in the first week of therapy the subject began stating phantom sensations occur all the time. This lasted through the first two weeks. After missing week-3 of therapy the the subject selected the "a few times a week" option. Sensation quality also changed when comparing therapy to pre-therapy. While the tingling sensation is always present, the electric sensations, movement, and abnormal position/posture are not selected as descriptors in the therapy phase. The size of the phantom remained smaller throughout therapy (as it does throughout pre-therapy). Involuntary movements changed after beginning therapy, where the leg no longer swings side-to-side. One unsolicited comment from week-1 of therapy reflects this change, "I used to feel [the phantom leg] swing back and forth by itself, but not now. Now, it just hangs there." Throughout the therapy phase movements at will also changed. Observing unsolicited comments, the movement capability appeared to gradually change. In the first week of therapy the subject describes the ability to "swing [the phantom] back and forth." He goes on to say, "I can move it up and down, like a kicking motion, slowly. It hurts in my quads a little when I do it." In week-2 of therapy the subject states "I do not feel my leg as much as I feel my foot - overall." At the outcome visit the subject was able to swing side-to-side, wiggle toes, and kick forward. The resting orientation of the phantom limb was with the knee-bent throughout the therapy phase.

Subject-2 described his phantom as tingling, feeling warmth, and electric sensations in the pre-therapy period and throughout the therapy period, and he noted that the phantom sensations were present all of the time, or constantly. The phantom would stay in a normal orientation, but was also uncomfortable for the subject. In the pre-therapy period the subject noted being moderately troubled by his phantom sensations. Once therapy began the subject selected "much" in response to how troubling are the phantom sensations. In the final week of therapy, the response was escalated to the highest possible response "very much troubled", indicating the phantom sensations became progressively more bothersome throughout the therapy phase.

5.3.4 Subject Perceptions

The PGIC indicates a lack of perceived change for subject-1. In both the final therapy visit and in the outcome visit the subject submitted a score of 1 for the PGIC, which in this study represents a result of no change or worse. While there appears to be a change in quality of phantom sensation, as well as a positive change in intensity, affect, and quality of pain, the subject's impression of change is not positive. Comparing this result to the unsolicited comments as described in subsection 5.3.3, the subject recognized a change in the presentation of phantom sensation; however, this evidently is not enough to elicit an overall positive impression of change.

Subject-2 received two versions of the PGIC; the first, as a one-sided questionnaire and the second as a two-sided questionnaire. In response to the one-sided questionnaire the subject scored the PGIC as *moderately better* at the end of therapy and as *almost the same* at the outcome visit. For the two-sided version of the PGIC the subject selected *much improved* at the end of therapy and *very much improved* at outcome. These results suggest that despite the mixture of positive and negative effects recognized in several subscales, the subject perceived an overall positive effect of therapy.

The results presented by the self-report data are compelling. Each subject had a different experience with therapy. Subject-1 experienced a drop in pain intensity (from severe to moderate) supported by the NAP analysis method, which shows a strong, positive effect of therapy. Furthermore, the NPSI secondary instrument demonstrates a reduction in several individual components of neuropathic pain symptoms. Exploratory measures such as the BPI-IS and PHQ-9 also demonstrate positive effects of therapy, reducing the interference of pain in daily living and improving depressive symptoms from moderately severe to none. On the other hand the vigor subscale of POMS-SF and the PGIC contradict the positive effects, where the subject experiences a strong, negative effect in the vigor category and had an impression of worse or no change from therapy. While subject-1 recognized a change in presen-

tation of the phantom (as made evident from the PsyP-Map), the change is either considered a negative change by the subject, or it is not strong enough to elicit a positive impression.

Subject-2 reported an increase in pain intensity (from moderate to severe) and moderate, negative effects in the NAP. The NPSI had several individual subscales that were sensitive to therapy, but the total score remained consistent throughout therapy. POMS-SF demonstrated an improvement in both depression and in vigor, leaving the overall effect of therapy as inconclusive. The exploratory instruments also had mixed results. BPI-IS showed an improvement in mobility (walking), but a decrement in sleep, and the PHQ-9 on average remained constant (at mild depression). The subject's report of how troublesome his phantom sensations were throughout the therapy phase got progressively worse, but the PGIC captured an overall positive impression of change.

5.4   Conclusions

This case study demonstrates the feasibility of cognitively reinforced SES as a therapy for PLP. Further research is needed to improve study power and to identify effects of therapy with more confidence. The major limitation of the study as noted in Chapter 4 is statistical power. Within each week of therapy subject-1 only attended two therapy sessions and subject-2 attended 2-3 sessions per week. With a small sample size of self-report data in each period, the effect of therapy is difficult to describe. Furthermore, analyzing the results on a single subject basis reduces power. We attempted to account for this in the VAS measurements by using the NAP analysis method for single case research (SCR); however, even this has limitations. Parker and Vannest suggest at least 13×13 comparisons, whereas the NAP analysis in the present study is under that threshold [170]. Future studies should improve analysis of study outcome measures through addressing both concerns. Ideally, a study would involve a take home system and the capability of participants to complete questionnaires

from home through an online system. As is evident from the present study, subject non-compliance is a notable hurdle. While the study criteria require attendance of $3 - 5$ therapy sessions per week, subjects of the present case attended on 2-3 sessions per week, and subject-1 skipped one week entirely. Had participation been more convenient, this non-compliance may have been avoided. It is inevitable that study participants will encounter stimuli and experience circumstances that can effect the study results. Whether it is dealing with a family crisis or experimenting with a new prosthetic, pain, mood, and daily life are inherently linked. Remarkably, several self-report questionnaires demonstrate some level of effect throughout therapy, despite these hurdles. However, the question that remains is whether or not the effects are a result of the therapy. In order to establish a more powerful argument either for or against the effectiveness of the therapy, the clinical team hopes to collect more data from additional subjects.

6. SUMMARY

6.1 Review of the Present Work

Chapter 1 discussed the recent trends in amputation and post-amputation pain (PAP). While amputation often extends life, preventing debilitating problems for individuals suffering from dysvascular disease for example, it can also present entirely new challenges to the patient. Amputation is on the rise according to Ziegler-Graham et al. [4], which means that post-amputation pain is becoming more and more relevant. The lack of a standard of care for various aspects of PAP is explained by the sheer lack of understanding of the underlying mechanisms [126]. Some aspects can be explained, such as neuromata related pain; however, more complicated aspects such as phantom limb pain (PLP) are far from being explained by a specific mechanism. Several mechanisms with origins at every level of the nervous system from cortical to peripheral are offered, but proving a mechanism is an entirely different matter. Relying on self-report questionnaires and intrinsically subjective data makes the study of pain and pain mechanisms complicated and turbid. For example an individual's milieu has significant effects on pain tolerance [95], and this factor cannot be easily accounted for when attempting to establish a standard therapeutic method.

Recent efforts by the EPIONE consortium have attempted to isolate a therapy that offers relief to PAP, with a focus on PLP. Utilizing sensory feedback via electrical or mechanical stimulation to reinforce imagined movement of the phantom is the focus of Chapter 2 and Chapter 4. A pilot study of several possible therapy methods offers insight into the expected feasibility of implementing each modality. Preliminary analysis of primary and secondary outcomes demonstrates an overall positive effect of therapy after just four weeks. However, additional effort is required to increase sample size for each modality to strengthen the statistical evidence.

In the midst of designing, initiating, and running the clinical trial, software was developed to reduce the opportunities for error and speed up the post-processing of the self-report data. This is the focus of Chapter 3. The software was designed with the primary and secondary instruments of the EPIONE consortium clinical trial in mind. In addition, several other design requirements were considered to ensure the softwares usability, accuracy, and precision. The software was validated using an example dataset, and subjected to a test of robustness with the pilot data presented in Chapter 4. Seeing that the software was capable of handling data of various shapes and sizes; it was considered ready-to-use.

The case study of surface electrical stimulation presented in Chapter 5 demonstrates mixed effects overall, and presents several challenges of translational research. According to the study's primary measure of pain intensity, pain reduced over the course of the therapy phase in one subject and increased in another subject. In addition, the subjects had differing overall impressions of change; one experienced no change from therapy, while the other reported a perceived improvement. These results give some insight into why translational research of pain is challenging. For example a single subject reported both a reduction of pain intensity and an overall impression of no change. It is impossible to isolate an individual from outside influences. The drop in depression seen in the patient health questionnaire (PHQ-9) of the case study could be from external experiences having nothing to do with the study. The same could be said of pain intensity. These issues illuminate why large sample sizes and randomized controlled trials are necessary for establishing the effectiveness of a therapy.

6.2   Limitations

The major limitation of the pilot study described in Chapter 4 and the case study described in Chapter 5 is sample size for both number of subjects and number of observations for each instrument. While these demonstrate the feasibility of the

suggested therapy methods, further study is required to prove the effectiveness. In addition, several instruments used in the present study utilize reference populations that are not necessarily representative of the study population for describing the degree of effect. Furthermore, some of the instruments used in the present study do not appear to be sensitive to the emotional and psychological aspects of pain experienced by an amputee. For example, the POMS-SF results largely fell on the bottom of the spectrum in most cases.

6.3   Future Work

In future work, studies should focus on improving the methods for collecting data and designing a study that minimizes the effects and opportunities of subject non-compliance. As discussed in Chapter 5, one subject of the case study skipped an entire week of therapy, making data interpretation difficult. Future studies should minimize time in the clinic for the subject by implementing a take home system. Self-report questionnaires should be administered through an easily accessible website or through a smartphone application. In both cases there are standards for protecting health data, such as Fast Healthcare Interoperability Resources. Secondly, the therapy should be updated to a take home system. According the code of federal regulations title 21 section 882.5890, transcutaneous electrical nerve stimulators for pain relief are class II devices [177]. Take home stimulators are available in the U.S. market. Adapting to a take home system and requiring only weekly visits instead of daily, coupled with online administration of self-report questionnaires would significantly reduce the amount of effort required to participate in the trial and likely increase participation. There is still much to do to understand the effectiveness of the proposed therapy method, but progress is made one step at a time, and this study serves as a small step toward alleviating PLP.

6.4   Support

This thesis work was supported by funding provided under the FP7 Health program (HEALTH-F2-2013-602547). In addition the Department of Biomedical Engineering at IUPUI provided a Research Assistantship, without which this thesis could not be possible.

6.5   Project Related Contributions and Activities

Shortly after collecting the pilot data discussed in Chapter 4, members of the EPIONE consortium submitted a conference proceeding on the clinical study design, to which I had the opportunity to contribute [166]. This conference paper highlighted the methods for implementing a clinical trial. Throughout the EPIONE project, I had the opportunity to contribute to project deliverables and other project related documentation. The two most significant deliverables to which I helped author were EPIONE Project Deliverable 1.3, "Collected results and experiences from first round of clinical trials," and EPIONE Project Deliverable 1.4, "Refined clinical protocol for delivering invasive / non-invasive nerve sensory feedback." In addition to the deliverables, I drafted a document which interpreted the manual for the psychophysical platform into clinical work instructions, which proved to be very useful at the IUPUI clinical site.

The EPIONE Extraction Program (EEP) and EEP - Group Analysis Module (GAM), are the major contributions to the EPIONE project. The development of these software tools, took a process that previously required days for each clinical subject and reduced it to minutes or even seconds. Furthermore, data accuracy was also strengthened by reducing the opportunity for human error in results handling. These programs are just a small piece of all the technology developed in the EPIONE project, but it serves an important purpose, saving time and money and improving data quality.

Participation in the EPIONE consortium took me across the globe. In the summer of 2015 and summer of 2016, I traveled to Aalborg, Denmark, and Lund, Sweden for the EPIONE General Assemblies. In Lund I introduced an early version of the EEP, and received critical feedback for the development of the software tool. These experiences not only improved my understanding of the project, but also improved on intangible, soft skills, by interacting with team members from other cultures and backgrounds.

LIST OF REFERENCES

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[1] S. Finger and M. P. Hustwit, "Five early accounts of phantom limb in context: Par, Descartes, Lemos, Bell, and Mitchell," *Neurosurgery*, vol. 52, no. 3, pp. 675–686; discussion 685–686, Mar. 2003.

[2] D. G. Kline, "Silas Weir Mitchell and "The Strange Case of George Dedlow"," *Neurosurgical Focus*, vol. 41, no. 1, p. E5, Jul. 2016.

[3] M. F. Owings and L. J. Kozak, "Ambulatory and inpatient procedures in the United States, 1996," *Vital and Health Statistics. Series 13, Data from the National Health Survey*, no. 139, pp. 1–119, Nov. 1998.

[4] K. Ziegler-Graham, E. J. MacKenzie, P. L. Ephraim, T. G. Travison, and R. Brookmeyer, "Estimating the prevalence of limb loss in the United States: 2005 to 2050," *Archives of Physical Medicine and Rehabilitation*, vol. 89, no. 3, pp. 422–429, Mar. 2008.

[5] T. R. Dillingham, L. E. Pezzin, and A. D. Shore, "Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 3, pp. 480–486, Mar. 2005.

[6] U. Kern, V. Busch, R. Mller, M. Kohl, and F. Birklein, "Phantom limb pain in daily practice–still a lot of work to do!" *Pain Medicine (Malden, Mass.)*, vol. 13, no. 12, pp. 1611–1626, Dec. 2012.

[7] R. Casale, L. Alaa, M. Mallick, and H. Ring, "Phantom limb related phenomena and their rehabilitation after lower limb amputation," *European Journal of Physical and Rehabilitation Medicine*, vol. 45, no. 4, pp. 559–566, Dec. 2009.

[8] T. S. Jensen, B. Krebs, J. Nielsen, and P. Rasmussen, "Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation," *Pain*, vol. 17, no. 3, pp. 243–256, Nov. 1983.

[9] D. M. Ehde, J. M. Czerniecki, D. G. Smith, K. M. Campbell, W. T. Edwards, M. P. Jensen, and L. R. Robinson, "Chronic phantom sensations, phantom pain, residual limb pain, and other regional pain after lower limb amputation," *Archives of Physical Medicine and Rehabilitation*, vol. 81, no. 8, pp. 1039–1044, Aug. 2000.

[10] T. S. Jensen, B. Krebs, J. Nielsen, and P. Rasmussen, "Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain," *Pain*, vol. 21, no. 3, pp. 267–278, Mar. 1985.

[11] C. M. Kooijman, P. U. Dijkstra, J. H. Geertzen, A. Elzinga, and C. P. van der Schans, "Phantom pain and phantom sensations in upper limb amputees: an epidemiological study," *Pain*, vol. 87, no. 1, pp. 33–41, Jul. 2000.

[12] K. T. Reilly, C. Mercier, M. H. Schieber, and A. Sirigu, "Persistent hand motor commands in the amputees' brain," *Brain: A Journal of Neurology*, vol. 129, no. Pt 8, pp. 2211–2223, Aug. 2006.

[13] G. S. Dhillon, S. M. Lawrence, D. T. Hutchinson, and K. W. Horch, "Residual function in peripheral nerve stumps of amputees: implications for neural control of artificial limbs," *The Journal of Hand Surgery*, vol. 29, no. 4, pp. 605–615; discussion 616–618, Jul. 2004.

[14] A. Hill, "Phantom Limb Pain: A Review of the Literature on Attributes and Potential Mechanisms," *Journal of Pain and Symptom Management*, vol. 17, no. 2, pp. 125–142, Feb. 1999. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0885392498001365

[15] H. Flor, L. Nikolajsen, and T. Staehelin Jensen, "Phantom limb pain: a case of maladaptive CNS plasticity?" *Nature Reviews. Neuroscience*, vol. 7, no. 11, pp. 873–881, Nov. 2006.

[16] P. Gallagher, D. Desmond, and M. MacLachlan, Eds., *Psychoprosthetics*. London :: Springer,, 2008. [Online]. Available: http://RX8KL6YF4X.search.serialssolutions.com/?V=1.0&L= RX8KL6YF4X&S=JCs&C=TC0000230281&T=marc

[17] A. Kneevi, T. Salamon, M. Milankov, S. Ninkovi, M. Jeremi Kneevi, and S. Tomaevi Todorovi, "Assessment of Quality of Life in Patients After Lower Limb Amputation," *Medicinski Pregled*, vol. 68, no. 3-4, pp. 103–108, Apr. 2015.

[18] P. L. Ephraim, S. T. Wegener, E. J. MacKenzie, T. R. Dillingham, and L. E. Pezzin, "Phantom pain, residual limb pain, and back pain in amputees: results of a national survey," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 10, pp. 1910–1919, Oct. 2005.

[19] M. Buonocore, "Where is hidden the ghost in phantom sensations?" *World Journal of Clinical Cases*, vol. 3, no. 7, pp. 542–544, Jul. 2015.

[20] M. L. Roed Rasmussen, J. U. Prause, M. Johnson, and P. B. Toft, "Phantom eye syndrome: types of visual hallucinations and related phenomena," *Ophthalmic Plastic and Reconstructive Surgery*, vol. 25, no. 5, pp. 390–393, Oct. 2009.

[21] S. E. Shore, L. E. Roberts, and B. Langguth, "Maladaptive plasticity in tinnitus–triggers, mechanisms and treatment," *Nature Reviews. Neurology*, vol. 12, no. 3, pp. 150–160, Mar. 2016.

[22] J. W. House and D. E. Brackmann, "Tinnitus: surgical treatment," *Ciba Foundation Symposium*, vol. 85, pp. 204–216, 1981.

[23] R. A. Sherman and C. J. Sherman, "Prevalence and characteristics of chronic phantom limb pain among American veterans. Results of a trial survey," *American Journal of Physical Medicine*, vol. 62, no. 5, pp. 227–238, Oct. 1983.

[24] M. T. Schley, P. Wilms, S. Toepfner, H.-P. Schaller, M. Schmelz, C. J. Konrad, and N. Birbaumer, "Painful and nonpainful phantom and stump sensations in acute traumatic amputees," *The Journal of Trauma*, vol. 65, no. 4, pp. 858–864, Oct. 2008.

[25] M. P. Jensen and P. Karoly, "Self-Report Scales and Procedures for Assessing Pain in Adults," in *Handbook of Pain Assessment*, 3rd ed., D. C. Turk and R. Melzack, Eds. New York, US: The Guilford Press, 2010, pp. 19–44. [Online]. Available: http://site.ebrary.com/lib/alltitles/docDetail. action?docID=10430943

[26] P. Montoya, W. Larbig, N. Grulke, H. Flor, E. Taub, and N. Birbaumer, "The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees," *Pain*, vol. 72, no. 1-2, pp. 87–93, Aug. 1997.

[27] M. J. Giummarra, N. Georgiou-Karistianis, M. E. R. Nicholls, S. J. Gibson, M. Chou, and J. L. Bradshaw, "The menacing phantom: what pulls the trigger?" *European Journal of Pain (London, England)*, vol. 15, no. 7, pp. 691.e1–8, Aug. 2011.

[28] R. Bekrater-Bodmann, M. Schredl, M. Diers, I. Reinhard, J. Foell, J. Trojan, X. Fuchs, and H. Flor, "Post-Amputation Pain Is Associated with the Recall of an Impaired Body Representation in DreamsResults from a Nation-Wide Survey on Limb Amputees," *PLoS ONE*, vol. 10, no. 3, Mar. 2015. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4350998/

[29] D. G. Smith, D. M. Ehde, M. W. Legro, G. E. Reiber, M. del Aguila, and D. A. Boone, "Phantom limb, residual limb, and back pain after lower extremity amputations," *Clinical Orthopaedics and Related Research*, no. 361, pp. 29–38, Apr. 1999.

[30] H. M. Marshall, M. P. Jensen, D. M. Ehde, and K. M. Campbell, "Pain site and impairment in individuals with amputation pain," *Archives of Physical Medicine and Rehabilitation*, vol. 83, no. 8, pp. 1116–1119, Aug. 2002. [Online]. Available: http://www.archives-pmr.org/article/S0003-9993(02)00035-7/abstract

[31] M. A. R. O'Reilly, P. M. R. O'Reilly, H. M. R. O'Reilly, J. Sullivan, and J. Sheahan, "High-resolution ultrasound findings in the symptomatic residual limbs of amputees," *Military Medicine*, vol. 178, no. 12, pp. 1291–1297, Dec. 2013.

[32] M. A. R. O'Reilly, P. M. R. O'Reilly, J. N. Sheahan, J. Sullivan, H. M. O'Reilly, and M. J. O'Reilly, "Neuromas as the cause of pain in the residual limbs of amputees. An ultrasound study," *Clinical Radiology*, vol. 71, no. 10, pp. 1068.e1–1068.e6, Oct. 2016. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0009926016302264

[33] K. Fried, R. Govrin-Lippmann, F. Rosenthal, M. H. Ellisman, and M. Devor, "Ultrastructure of afferent axon endings in a neuroma," *Journal of Neurocytology*, vol. 20, no. 8, pp. 682–701, Aug. 1991.

[34] H. Flor, "Phantom-limb pain: characteristics, causes, and treatment," *The Lancet Neurology*, vol. 1, no. 3, pp. 182–189, Jul. 2002. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S1474442202000741

[35] L. Nikolajsen, J. A. Black, K. Kroner, T. S. Jensen, and S. G. Waxman, "Neuroma removal for neuropathic pain: efficacy and predictive value of lidocaine infusion," *The Clinical Journal of Pain*, vol. 26, no. 9, pp. 788–793, Dec. 2010.

[36] A. Sehirlioglu, C. Ozturk, K. Yazicioglu, I. Tugcu, B. Yilmaz, and A. S. Goktepe, "Painful neuroma requiring surgical excision after lower limb amputation caused by landmine explosions," *International Orthopaedics*, vol. 33, no. 2, pp. 533–536, Apr. 2009. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2899049/

[37] I. Ducic, A. N. Mesbahi, C. E. Attinger, and K. Graw, "The role of peripheral nerve surgery in the treatment of chronic pain associated with amputation stumps," *Plastic and Reconstructive Surgery*, vol. 121, no. 3, pp. 908–914; discussion 915–917, Mar. 2008.

[38] L. Nikolajsen, C. L. Hansen, J. Nielsen, J. Keller, L. Arendt-Nielsen, and T. S. Jensen, "The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input," *Pain*, vol. 67, no. 1, pp. 69–77, Sep. 1996.

[39] D. Bleakman, A. Alt, and E. S. Nisenbaum, "Glutamate receptors and pain," *Seminars in Cell & Developmental Biology*, vol. 17, no. 5, pp. 592–604, Oct. 2006. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S1084952106001121

[40] S. Collins, M. J. Sigtermans, A. Dahan, W. W. A. Zuurmond, and R. S. G. M. Perez, "NMDA Receptor Antagonists for the Treatment of Neuropathic Pain," *Pain Medicine*, vol. 11, no. 11, pp. 1726–1742, Nov. 2010. [Online]. Available: https://academic.oup.com/painmedicine/article/11/11/1726/1934467/NMDA-Receptor-Antagonists-for-the-Treatment-of

[41] R. Melzack, R. Israel, R. Lacroix, and G. Schultz, "Phantom limbs in people with congenital limb deficiency or amputation in early childhood," *Brain: A Journal of Neurology*, vol. 120 (Pt 9), pp. 1603–1620, Sep. 1997.

[42] E. G. Trevelyan, W. A. Turner, and N. Robinson, "Perceptions of phantom limb pain in lower limb amputees and its effect on quality of life: a qualitative study," *British Journal of Pain*, vol. 10, no. 2, pp. 70–77, May 2016.

[43] A. Cansever, O. Uzun, C. Yildiz, A. Ates, and A. S. Atesalp, "Depression in men with traumatic lower part amputation: a comparison to men with surgical lower part amputation," *Military Medicine*, vol. 168, no. 2, pp. 106–109, Feb. 2003.

[44] B. D. Darnall, P. Ephraim, S. T. Wegener, T. Dillingham, L. Pezzin, P. Rossbach, and E. J. MacKenzie, "Depressive symptoms and mental health service utilization among persons with limb loss: results of a national survey," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 4, pp. 650–658, Apr. 2005.

[45] E. Hsu and S. P. Cohen, "Postamputation pain: epidemiology, mechanisms, and treatment," *Journal of Pain Research*, vol. 6, pp. 121–136, Feb. 2013. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3576040/

[46] E. N. Davis and K. C. Chung, "The Tinel sign: a historical perspective," *Plastic and Reconstructive Surgery*, vol. 114, no. 2, pp. 494–499, Aug. 2004.

[47] R. D. Boutin, M. N. Pathria, and D. Resnick, "Disorders in the stumps of amputee patients: MR imaging." *American Journal of Roentgenology*, vol. 171, no. 2, pp. 497–501, Aug. 1998. [Online]. Available: http://www.ajronline.org/doi/abs/10.2214/ajr.171.2.9694483

[48] Q. Sun, H. Tu, G.-G. Xing, J.-S. Han, and Y. Wan, "Ectopic discharges from injured nerve fibers are highly correlated with tactile allodynia only in early, but not late, stage in rats with spinal nerve ligation," *Experimental Neurology*, vol. 191, no. 1, pp. 128–136, Jan. 2005.

[49] B. Nystrm and K.-E. Hagbarth, "Microelectrode recordings from transected nerves in amputees with phantom limb pain," *Neuroscience Letters*, vol. 27, no. 2, pp. 211–216, Dec. 1981. [Online]. Available: http://www.sciencedirect.com/science/article/pii/0304394081902706

[50] R. P. Iacono, J. Linford, and R. Sandyk, "Pain management after lower extremity amputation," *Neurosurgery*, vol. 20, no. 3, pp. 496–500, Mar. 1987.

[51] M. Devor and P. D. Wall, "Plasticity in the spinal cord sensory map following peripheral nerve injury in rats," *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, vol. 1, no. 7, pp. 679–684, Jul. 1981.

[52] A. K. Thompson and J. R. Wolpaw, "Operant conditioning of spinal reflexes: from basic science to clinical therapy," *Frontiers in Integrative Neuroscience*, vol. 8, Mar. 2014. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3957063/

[53] M. J. Teixeira, M. G. d. S. da Paz, M. T. Bina, S. N. Santos, I. Raicher, R. Galhardoni, D. T. Fernandes, L. T. Yeng, A. F. Baptista, and D. C. de Andrade, "Neuropathic pain after brachial plexus avulsion - central and peripheral mechanisms," *BMC Neurology*, vol. 15, May 2015. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4429458/

[54] S. L. Florence and J. H. Kaas, "Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys," *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, vol. 15, no. 12, pp. 8083–8095, Dec. 1995.

[55] C. W. H. Wu and J. H. Kaas, "The effects of long-standing limb loss on anatomical reorganization of the somatosensory afferents in the brainstem and spinal cord," *Somatosensory & Motor Research*, vol. 19, no. 2, pp. 153–163, 2002.

[56] J. Xu and J. T. Wall, "Rapid changes in brainstem maps of adult primates after peripheral injury," *Brain Research*, vol. 774, no. 12, pp. 211–215, Nov. 1997. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0006899397817064

[57] J. D. Churchill, L. L. Arnold, and P. E. Garraghty, "Somatotopic reorganization in the brainstem and thalamus following peripheral nerve injury in adult primates," *Brain Research*, vol. 910, no. 1-2, pp. 142–152, Aug. 2001.

[58] V. S. Ramachandran, D. Rogers-Ramachandran, and M. Stewart, "Perceptual correlates of massive cortical reorganization," *Science (New York, N.Y.)*, vol. 258, no. 5085, pp. 1159–1160, Nov. 1992.

[59] H. Flor, W. Mhlnickel, A. Karl, C. Denke, S. Grsser, R. Kurth, and E. Taub, "A neural substrate for nonpainful phantom limb phenomena," *Neuroreport*, vol. 11, no. 7, pp. 1407–1411, May 2000.

[60] S. M. Grsser, W. Mhlnickel, M. Schaefer, K. Villringer, C. Christmann, C. Koeppe, and H. Flor, "Remote activation of referred phantom sensation and cortical reorganization in human upper extremity amputees," *Experimental Brain Research*, vol. 154, no. 1, pp. 97–102, Jan. 2004.

[61] M. J. Giummarra, S. J. Gibson, N. Georgiou-Karistianis, and J. L. Bradshaw, "Central mechanisms in phantom limb perception: the past, present and future," *Brain Research Reviews*, vol. 54, no. 1, pp. 219–232, Apr. 2007.

[62] P. Schwenkreis, B. Pleger, B. Cornelius, U. Weyen, R. Dertwinkel, M. Zenz, J. P. Malin, and M. Tegenthoff, "Reorganization in the ipsilateral motor cortex of patients with lower limb amputation," *Neuroscience Letters*, vol. 349, no. 3, pp. 187–190, Oct. 2003.

[63] M. I. Garry, A. Loftus, and J. J. Summers, "Mirror, mirror on the wall: viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability," *Experimental Brain Research*, vol. 163, no. 1, pp. 118–122, May 2005.

[64] J. C. Forst, D. C. Blok, J. P. Slopsema, J. M. Boss, L. A. Heyboer, C. M. Tobias, and K. H. Polasek, "Surface electrical stimulation to evoke referred sensation," *Journal of Rehabilitation Research and Development*, vol. 52, no. 4, pp. 397–406, 2015.

[65] C. S. McCabe, R. C. Haigh, P. W. Halligan, and D. R. Blake, "Referred sensations in patients with complex regional pain syndrome type 1," *Rheumatology (Oxford, England)*, vol. 42, no. 9, pp. 1067–1073, Sep. 2003.

[66] M. Soler, H. Kumru, J. Vidal, R. Pelayo, J. Tormos, F. Fregni, X. Navarro, and A. Pascual-Leone, "Referred sensations and neuropathic pain following spinal cord injury," *Pain*, vol. 150, no. 1, pp. 192–198, Jul. 2010. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3540745/

[67] C. I. Moore, C. E. Stern, C. Dunbar, S. K. Kostyk, A. Gehi, and S. Corkin, "Referred phantom sensations and cortical reorganization after spinal cord injury in humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 26, pp. 14 703–14 708, Dec. 2000. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC18982/

[68] R. Melzack, "The McGill Pain Questionnaire: Major properties and scoring methods," *PAIN*, vol. 1, no. 3, pp. 277–299, Sep. 1975. [Online]. Available: http://www.sciencedirect.com/science/article/pii/0304395975900445

[69] W. Trotter and H. M. Davies, "Experimental studies in the innervation of the skin," *The Journal of Physiology*, vol. 38, no. 2-3, pp. 134–246.1, Feb. 1909. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1533644/

[70] G. D. Shukla, S. C. Sahu, R. P. Tripathi, and D. K. Gupta, "A psychiatric study of amputees," *The British Journal of Psychiatry: The Journal of Mental Science*, vol. 141, pp. 50–53, Jul. 1982.

[71] J. H. Kashani, R. G. Frank, S. R. Kashani, S. A. Wonderlich, and J. C. Reid, "Depression among amputees," *The Journal of Clinical Psychiatry*, vol. 44, no. 7, pp. 256–258, Jul. 1983.

[72] R. H. Dworkin, D. C. Turk, K. W. Wyrwich, D. Beaton, C. S. Cleeland, J. T. Farrar, J. A. Haythornthwaite, M. P. Jensen, R. D. Kerns, D. N. Ader, N. Brandenburg, L. B. Burke, D. Cella, J. Chandler, P. Cowan, R. Dimitrova, R. Dionne, S. Hertz, A. R. Jadad, N. P. Katz, H. Kehlet, L. D. Kramer, D. C. Manning, C. McCormick, M. P. McDermott, H. J. McQuay, S. Patel, L. Porter, S. Quessy, B. A. Rappaport, C. Rauschkolb, D. A. Revicki, M. Rothman, K. E. Schmader, B. R. Stacey, J. W. Stauffer, T. von Stein, R. E. White, J. Witter, and S. Zavisic, "Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations," *The Journal of Pain: Official Journal of the American Pain Society*, vol. 9, no. 2, pp. 105–121, Feb. 2008.

[73] J. Katz, "Psychophysiological contributions to phantom limbs," *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, vol. 37, no. 5, pp. 282–298, Jun. 1992.

[74] J. Katz and R. Melzack, "Pain 'memories' in phantom limbs: review and clinical observations," *Pain*, vol. 43, no. 3, pp. 319–336, Dec. 1990.

[75] T. Blgestad, S. Pallesen, J. Grnli, N. K. Y. Tang, and I. H. Nordhus, "How Perceived Pain Influence Sleep and Mood More Than The Reverse: A Novel, Exploratory Study with Patients Awaiting Total Hip Arthroplasty," *Frontiers in Psychology*, vol. 7, p. 1689, 2016.

[76] W. H. Sweet, ""Phantom" sensations following intraspinal injury," *Neurochirurgia*, vol. 18, no. 5, pp. 139–154, Sep. 1975.

[77] J. W. Tsao, S. B. Finn, and M. E. Miller, "Reversal of phantom pain and handtoface remapping after brachial plexus avulsion," *Annals of Clinical and Translational Neurology*, vol. 3, no. 6, pp. 463–464, May 2016. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4892000/

[78] B.-C. Son and S.-W. Ha, "Phantom Remodeling Effect of Dorsal Root Entry Zone Lesioning in Phantom Limb Pain Caused by Brachial Plexus Avulsion," *Stereotactic and Functional Neurosurgery*, vol. 93, no. 4, pp. 240–244, 2015.

[79] T.-m. Qiu, L. Chen, Y. Mao, J.-s. Wu, W.-j. Tang, S.-n. Hu, L.-f. Zhou, and Y.-d. Gu, "Sensorimotor cortical changes assessed with resting-state fMRI following total brachial plexus root avulsion," *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 85, no. 1, pp. 99–105, Jan. 2014.

[80] C. B. Parry, "Pain in avulsion lesions of the brachial plexus," *Pain*, vol. 9, no. 1, pp. 41–53, Aug. 1980.

[81] R. A. Sherman, J. G. Arena, C. J. Sherman, and J. L. Ernst, "The mystery of phantom pain: Growing evidence for psychophysiological mechanisms," *Biofeedback and Self-regulation*, vol. 14, no. 4, pp. 267–280, Dec. 1989. [Online]. Available: http://link.springer.com/article/10.1007/BF00999118

[82] R. Melzack and P. D. Wall, "Pain mechanisms: a new theory," *Science (New York, N.Y.)*, vol. 150, no. 3699, pp. 971–979, Nov. 1965.

[83] L. M. Mendell, "Constructing and Deconstructing the Gate Theory of Pain," *Pain*, vol. 155, no. 2, pp. 210–216, Feb. 2014. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009371/

[84] R. Melzack, "From the gate to the neuromatrix," *Pain*, vol. Suppl 6, pp. S121–126, Aug. 1999.

[85] P. D. Wall, "The gate control theory of pain mechanisms. A re-examination and re-statement," *Brain: A Journal of Neurology*, vol. 101, no. 1, pp. 1–18, Mar. 1978.

[86] R. Melzack, "Phantom limbs," *Scientific American*, vol. 266, no. 4, pp. 120–126, Apr. 1992.

[87] ——, "Phantom limbs and the concept of a neuromatrix," *Trends in Neurosciences*, vol. 13, no. 3, pp. 88–92, Mar. 1990.

[88] M. Lotze, H. Flor, W. Grodd, W. Larbig, and N. Birbaumer, "Phantom movements and pain. An fMRI study in upper limb amputees," *Brain: A Journal of Neurology*, vol. 124, no. Pt 11, pp. 2268–2277, Nov. 2001.

[89] T. Yanagisawa, R. Fukuma, B. Seymour, K. Hosomi, H. Kishima, T. Shimizu, H. Yokoi, M. Hirata, T. Yoshimine, Y. Kamitani, and Y. Saitoh, "Induced sensorimotor brain plasticity controls pain in phantom limb patients," *Nature Communications*, vol. 7, p. 13209, Oct. 2016.

[90] P. Srs, S. Knecht, C. Bantel, T. Imai, R. Wsten, C. Pantev, B. Ltkenhner, H. Brkle, and H. Henningsen, "Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography," *Neuroscience Letters*, vol. 298, no. 3, pp. 195–198, Feb. 2001.

[91] L. Nikolajsen, S. Ilkjaer, K. Krner, J. H. Christensen, and T. S. Jensen, "The influence of preamputation pain on postamputation stump and phantom pain," *Pain*, vol. 72, no. 3, pp. 393–405, Sep. 1997.

[92] A. J. Harris, "Cortical origin of pathological pain," *Lancet (London, England)*, vol. 354, no. 9188, pp. 1464–1466, Oct. 1999.

[93] C. Johnson, "Research Tools for the Measurement of Pain and Nociception," *Animals: an open access journal from MDPI*, vol. 6, no. 11, Nov. 2016.

[94] E. C. Huskisson, "Measurement of Pain," *The Lancet*, vol. 304, no. 7889, pp. 1127–1131, Nov. 1974. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0140673674908848

[95] R. Dar, D. Ariely, and H. Frenk, "The effect of past-injury on pain threshold and tolerance," *Pain*, vol. 60, no. 2, pp. 189–193, Feb. 1995.

[96] G. L. Wasner and J. A. Brock, "Determinants of thermal pain thresholds in normal subjects," *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, vol. 119, no. 10, pp. 2389–2395, Oct. 2008.

[97] H. P. Lacey, A. Fagerlin, G. Loewenstein, D. M. Smith, J. Riis, and P. A. Ubel, "Are they really that happy? Exploring scale recalibration in estimates of well-being," *Health psychology : official journal of the Division of Health Psychology, American Psychological Association*, vol. 27, no. 6, pp. 669–675, Nov. 2008. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3744864/

[98] M. P. Jensen, D. G. Smith, D. M. Ehde, and L. R. Robinsin, "Pain site and the effects of amputation pain: further clarification of the meaning of mild, moderate, and severe pain," *Pain*, vol. 91, no. 3, pp. 317–322, Apr. 2001.

[99] D. Bouhassira, N. Attal, J. Fermanian, H. Alchaar, M. Gautron, E. Masquelier, S. Rostaing, M. Lanteri-Minet, E. Collin, J. Grisart, and F. Boureau, "Development and validation of the Neuropathic Pain Symptom Inventory," *Pain*, vol. 108, no. 3, pp. 248–257, Apr. 2004.

[100] S. Mackey, I. Carroll, B. Emir, T. K. Murphy, E. Whalen, and L. Dumenci, "Sensory Pain Qualities in Neuropathic Pain," *The journal of pain : official journal of the American Pain Society*, vol. 13, no. 1, pp. 58–63, Jan. 2012. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3249485/

[101] B. S. Galer and M. P. Jensen, "Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale," *Neurology*, vol. 48, no. 2, pp. 332–338, Feb. 1997.

[102] S. J. Krause and M.-M. Backonja, "Development of a neuropathic pain questionnaire," *The Clinical Journal of Pain*, vol. 19, no. 5, pp. 306–314, Oct. 2003.

[103] D. Bouhassira, N. Attal, H. Alchaar, F. Boureau, B. Brochet, J. Bruxelle, G. Cunin, J. Fermanian, P. Ginies, A. Grun-Overdyking, H. Jafari-Schluep, M. Lantri-Minet, B. Laurent, G. Mick, A. Serrie, D. Valade, and E. Vicaut, "Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)," *Pain*, vol. 114, no. 1-2, pp. 29–36, Mar. 2005.

[104] M. Bennett, "The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs," *Pain*, vol. 92, no. 1-2, pp. 147–157, May 2001.

[105] C. Sommer, H. Richter, J. P. Rogausch, J. Frettlh, M. Lungenhausen, and C. Maier, "A modified score to identify and discriminate neuropathic pain: a study on the German version of the neuropathic pain symptom inventory (NPSI)," *BMC Neurology*, vol. 11, p. 104, Aug. 2011. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3180265/

[106] Y. Matsubayashi, K. Takeshita, M. Sumitani, Y. Oshima, J. Tonosu, S. Kato, J. Ohya, T. Oichi, N. Okamoto, and S. Tanaka, "Psychometric Validation of the Japanese Version of the Neuropathic Pain Symptom Inventory," *PLoS ONE*, vol. 10, no. 11, Nov. 2015. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4658188/

[107] I. Gilron, C. P. N. Watson, C. M. Cahill, and D. E. Moulin, "Neuropathic pain: a practical guide for the clinician," *CMAJ : Canadian Medical Association Journal*, vol. 175, no. 3, pp. 265–275, Aug. 2006. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1513412/

[108] D. G. Blazer, R. C. Kessler, K. A. McGonagle, and M. S. Swartz, "The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey," *The American Journal of Psychiatry*, vol. 151, no. 7, pp. 979–986, Jul. 1994.

[109] M. J. M. Alviar, T. Hale, and M. Dungca, "Pharmacologic interventions for treating phantom limb pain," *The Cochrane Database of Systematic Reviews*, vol. 10, p. CD006380, Oct. 2016.

[110] C. Eccleston, L. Hearn, and A. C. d. C. Williams, "Psychological therapies for the management of chronic neuropathic pain in adults," *The Cochrane Database of Systematic Reviews*, no. 10, p. CD011259, Oct. 2015.

[111] G. Tan, M. P. Jensen, J. I. Thornby, and B. F. Shanti, "Validation of the Brief Pain Inventory for chronic nonmalignant pain," *The Journal of Pain: Official Journal of the American Pain Society*, vol. 5, no. 2, pp. 133–137, Mar. 2004.

[112] K. A. Raichle, T. L. Osborne, M. P. Jensen, and D. Cardenas, "The reliability and validity of pain interference measures in persons with spinal cord injury," *The Journal of Pain: Official Journal of the American Pain Society*, vol. 7, no. 3, pp. 179–186, Mar. 2006.

[113] T. L. Osborne, K. A. Raichle, M. P. Jensen, D. M. Ehde, and G. Kraft, "The reliability and validity of pain interference measures in persons with multiple sclerosis," *Journal of Pain and Symptom Management*, vol. 32, no. 3, pp. 217–229, Sep. 2006.

[114] J. Katz and R. Melzack, "The McGill Pain Questionnaire: Development Psychometric Properties, and Usefulnes of the Long Form, Short Form, and Short Form-2," in *Handbook of Pain Assessment*, 3rd ed., D. C. Turk and R. Melzack, Eds. New York, US: The Guilford Press, 2010, pp. 45–66. [Online]. Available: http://site.ebrary.com/lib/alltitles/docDetail.action?docID=10430943

[115] M. Von Korff, J. Ormel, F. J. Keefe, and S. F. Dworkin, "Grading the severity of chronic pain," *Pain*, vol. 50, no. 2, pp. 133–149, Aug. 1992.

[116] H. Flor, T. Elbert, S. Knecht, C. Wienbruch, C. Pantev, N. Birbaumer, W. Larbig, and E. Taub, "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, vol. 375, no. 6531, pp. 482–484, Jun. 1995.

[117] M. W. Legro, G. D. Reiber, D. G. Smith, M. del Aguila, J. Larsen, and D. Boone, "Prosthesis evaluation questionnaire for persons with lower limb amputations: assessing prosthesis-related quality of life," *Archives of Physical Medicine and Rehabilitation*, vol. 79, no. 8, pp. 931–938, Aug. 1998.

[118] J. Zhao, X. Guo, X. Xia, W. Peng, W. Wang, S. Li, Y. Zhang, and L. Hu, "Functional Reorganization of the Primary Somatosensory Cortex of a Phantom Limb Pain Patient," *Pain Physician*, vol. 19, no. 5, pp. E781–786, Jul. 2016.

[119] T. T. Liu and L. R. Frank, "Efficiency, power, and entropy in event-related FMRI with multiple trial types. Part I: theory," *NeuroImage*, vol. 21, no. 1, pp. 387–400, Jan. 2004.

[120] T. T. Liu, "Efficiency, power, and entropy in event-related fMRI with multiple trial types. Part II: design of experiments," *NeuroImage*, vol. 21, no. 1, pp. 401–413, Jan. 2004.

[121] A. Eklund, T. E. Nichols, and H. Knutsson, "Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 28, pp. 7900–7905, Jul. 2016. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4948312/

[122] R. A. Sherman, C. J. Sherman, and N. G. Gall, "A survey of current phantom limb pain treatment in the United States," *Pain*, vol. 8, no. 1, pp. 85–99, Feb. 1980.

[123] R. A. Sherman, "Published treatments of phantom limb pain," *American Journal of Physical Medicine*, vol. 59, no. 5, pp. 232–244, Oct. 1980.

[124] A. J. Vernadakis, H. Koch, and S. E. Mackinnon, "Management of neuromas," *Clinics in Plastic Surgery*, vol. 30, no. 2, pp. 247–268, Apr. 2003. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0094129802001049

[125] R. A. Sherman, C. J. Sherman, and L. Parker, "Chronic phantom and stump pain among American veterans: results of a survey," *Pain*, vol. 18, no. 1, pp. 83–95, Jan. 1984.

[126] C. M. Mortimer, R. J. M. MacDonald, D. J. Martin, I. R. McMillan, J. Ravey, and W. M. Steedman, "A focus group study of health professionals' views on phantom sensation, phantom pain and the need for patient information," *Patient Education and Counseling*, vol. 54, no. 2, pp. 221–226, Aug. 2004.

[127] R. A. Sherman, C. J. Sherman, and G. M. Bruno, "Psychological factors influencing chronic phantom limb pain: an analysis of the literature," *Pain*, vol. 28, no. 3, pp. 285–295, Mar. 1987.

[128] S. W. Wartan, W. Hamann, J. R. Wedley, and I. McColl, "Phantom pain and sensation among British veteran amputees," *British Journal of Anaesthesia*, vol. 78, no. 6, pp. 652–659, Jun. 1997.

[129] C. L. Wu, P. Tella, P. S. Staats, R. Vaslav, D. A. Kazim, U. Wesselmann, and S. N. Raja, "Analgesic effects of intravenous lidocaine and morphine on postamputation pain: a randomized double-blind, active placebo-controlled, crossover trial," *Anesthesiology*, vol. 96, no. 4, pp. 841–848, Apr. 2002.

[130] C. L. Wu, S. Agarwal, P. K. Tella, B. Klick, M. R. Clark, J. A. Haythornthwaite, M. B. Max, and S. N. Raja, "Morphine versus Mexiletine for Treatment of Postamputation Pain," *Anesthesiology*, vol. 109, no. 2, pp. 289–296, Aug. 2008. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2654208/

[131] M. Bone, P. Critchley, and D. J. Buggy, "Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study," *Regional Anesthesia and Pain Medicine*, vol. 27, no. 5, pp. 481–486, Oct. 2002.

[132] D. G. Smith, D. M. Ehde, M. A. Hanley, K. M. Campbell, M. P. Jensen, A. J. Hoffman, A. B. Awan, J. M. Czerniecki, and L. R. Robinson, "Efficacy of gabapentin in treating chronic phantom limb and residual limb pain," *Journal of Rehabilitation Research and Development*, vol. 42, no. 5, pp. 645–654, Oct. 2005.

[133] U. Eichenberger, F. Neff, G. Sveticic, S. Bjrgo, S. Petersen-Felix, L. Arendt-Nielsen, and M. Curatolo, "Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds," *Anesthesia and Analgesia*, vol. 106, no. 4, pp. 1265–1273, table of contents, Apr. 2008.

[134] R. Ben Abraham, N. Marouani, and A. A. Weinbroum, "Dextromethorphan mitigates phantom pain in cancer amputees," *Annals of Surgical Oncology*, vol. 10, no. 3, pp. 268–274, Apr. 2003.

[135] L. R. Robinson, J. M. Czerniecki, D. M. Ehde, W. T. Edwards, D. A. Judish, M. L. Goldberg, K. M. Campbell, D. G. Smith, and M. P. Jensen, "Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study," *Archives of Physical Medicine and Rehabilitation*, vol. 85, no. 1, pp. 1–6, Jan. 2004.

[136] J. Halbert, M. Crotty, and I. D. Cameron, "Evidence for the optimal management of acute and chronic phantom pain: a systematic review," *The Clinical Journal of Pain*, vol. 18, no. 2, pp. 84–92, Apr. 2002.

[137] J. W. Tupper and D. M. Booth, "Treatment of painful neuromas of sensory nerves in the hand: A comparison of traditional and newer methods," *The Journal of Hand Surgery*, vol. 1, no. 2, pp. 144–151, Sep. 1976. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0363502376800081

[138] A. B. Swanson, N. R. Boeve, and R. M. Lumsden, "The prevention and treatment of amputation neuromata by silicone capping," *The Journal of Hand Surgery*, vol. 2, no. 1, pp. 70–78, Jan. 1977. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0363502377800130

[139] M. Kon and J. J. Bloem, "The treatment of amputation neuromas in fingers with a centrocentral nerve union," *Annals of Plastic Surgery*, vol. 18, no. 6, pp. 506–510, Jun. 1987.

[140] J. Barber and R. Albert-Pampl, "Centrocentral anastomosis of the proximal nerve stump in the treatment of painful amputation neuromas of major nerves," *Journal of Neurosurgery*, vol. 79, no. 3, pp. 331–334, Sep. 1993.

[141] S. E. Mackinnon, A. L. Dellon, A. R. Hudson, and D. A. Hunter, "Alteration of neuroma formation by manipulation of its microenvironment," *Plastic and Reconstructive Surgery*, vol. 76, no. 3, pp. 345–353, Sep. 1985.

[142] S. E. Mackinnon and A. L. Dellon, "Results of treatment of recurrent dorsoradial wrist neuromas," *Annals of Plastic Surgery*, vol. 19, no. 1, pp. 54–61, Jul. 1987.

[143] J. M. Souza, J. E. Cheesborough, J. H. Ko, M. S. Cho, T. A. Kuiken, and G. A. Dumanian, "Targeted Muscle Reinnervation: A Novel Approach to Postamputation Neuroma Pain," *Clinical Orthopaedics and Related Research*, vol. 472, no. 10, pp. 2984–2990, Oct. 2014. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4160494/

[144] M. I. Johnson, M. R. Mulvey, and A.-M. Bagnall, "Transcutaneous electrical nerve stimulation (TENS) for phantom pain and stump pain following amputation in adults," *The Cochrane Database of Systematic Reviews*, vol. 8, p. CD007264, Aug. 2015.

[145] R. L. Rauck, S. P. Cohen, C. A. Gilmore, J. M. North, L. Kapural, R. H. Zang, J. H. Grill, and J. W. Boggs, "Treatment of post-amputation pain with peripheral nerve stimulation," *Neuromodulation: Journal of the International Neuromodulation Society*, vol. 17, no. 2, pp. 188–197, Feb. 2014.

[146] M. Tilak, S. A. Isaac, J. Fletcher, L. T. Vasanthan, R. S. Subbaiah, A. Babu, R. Bhide, and G. Tharion, "Mirror Therapy and Transcutaneous Electrical Nerve Stimulation for Management of Phantom Limb Pain in Amputees - A Single Blinded Randomized Controlled Trial," *Physiotherapy Research International: The Journal for Researchers and Clinicians in Physical Therapy*, vol. 21, no. 2, pp. 109–115, Jun. 2016.

[147] J. Katz and R. Melzack, "Auricular transcutaneous electrical nerve stimulation (TENS) reduces phantom limb pain," *Journal of Pain and Symptom Management*, vol. 6, no. 2, pp. 73–83, Feb. 1991.

[148] H. Flor, C. Denke, M. Schaefer, and S. Grsser, "Effect of sensory discrimination training on cortical reorganisation and phantom limb pain," *The Lancet*, vol. 357, no. 9270, pp. 1763–1764, Jun. 2001. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S014067360004890X

[149] W. F. Agnew, D. B. McCreery, T. G. Yuen, and L. A. Bullara, "Evolution and resolution of stimulation-induced axonal injury in peripheral nerve," *Muscle & Nerve*, vol. 22, no. 10, pp. 1393–1402, Oct. 1999.

[150] D. B. McCreery, T. G. Yuen, W. F. Agnew, and L. A. Bullara, "A characterization of the effects on neuronal excitability due to prolonged microstimulation with chronically implanted microelectrodes," *IEEE transactions on bio-medical engineering*, vol. 44, no. 10, pp. 931–939, Oct. 1997.

[151] M.-C. Lu, C.-Y. Ho, S.-F. Hsu, H.-C. Lee, J.-H. Lin, C.-H. Yao, and Y.-S. Chen, "Effects of electrical stimulation at different frequencies on regeneration of transected peripheral nerve," *Neurorehabilitation and Neural Repair*, vol. 22, no. 4, pp. 367–373, Aug. 2008.

[152] S. F. Cogan, K. A. Ludwig, C. G. Welle, and P. Takmakov, "Tissue damage thresholds during therapeutic electrical stimulation," *Journal of Neural Engineering*, vol. 13, no. 2, p. 021001, 2016. [Online]. Available: http://stacks.iop.org/1741-2552/13/i=2/a=021001

[153] Y. A. Patel and R. J. Butera, "Differential fiber-specific block of nerve conduction in mammalian peripheral nerves using kilohertz electrical stimulation," *Journal of Neurophysiology*, vol. 113, no. 10, pp. 3923–3929, Jun. 2015. [Online]. Available: http://jn.physiology.org/content/113/10/3923

[154] D. Prodanov, E. Marani, and J. Holsheimer, "Functional electric stimulation for sensory and motor functions: progress and problems," *Biomedical Reviews*, vol. 14, no. 0, pp. 23–50, Dec. 2003. [Online]. Available: http://press.mu-varna.bg/ojs/index.php/bmr/article/view/107

[155] D. B. McCreery, W. F. Agnew, T. G. Yuen, and L. A. Bullara, "Damage in peripheral nerve from continuous electrical stimulation: comparison of two stimulus waveforms," *Medical & Biological Engineering & Computing*, vol. 30, no. 1, pp. 109–114, Jan. 1992.

[156] ——, "Relationship between stimulus amplitude, stimulus frequency and neural damage during electrical stimulation of sciatic nerve of cat," *Medical & Biological Engineering & Computing*, vol. 33, no. 3 Spec No, pp. 426–429, May 1995.

[157] S. Brunelli, G. Morone, M. Iosa, C. Ciotti, R. De Giorgi, C. Foti, and M. Traballesi, "Efficacy of progressive muscle relaxation, mental imagery, and phantom exercise training on phantom limb: a randomized controlled trial," *Archives of Physical Medicine and Rehabilitation*, vol. 96, no. 2, pp. 181–187, Feb. 2015.

[158] V. S. Ramachandran and D. Rogers-Ramachandran, "Synaesthesia in phantom limbs induced with mirrors," *Proceedings. Biological Sciences*, vol. 263, no. 1369, pp. 377–386, Apr. 1996.

[159] C. Mercier and A. Sirigu, "Training with virtual visual feedback to alleviate phantom limb pain," *Neurorehabilitation and Neural Repair*, vol. 23, no. 6, pp. 587–594, Aug. 2009.

[160] V. W. Priganc and S. W. Stralka, "Graded Motor Imagery," *Journal of Hand Therapy*, vol. 24, no. 2, pp. 164–169, Apr. 2011. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0894113010002061

[161] G. L. Moseley, "Graded motor imagery for pathologic pain: a randomized controlled trial," *Neurology*, vol. 67, no. 12, pp. 2129–2134, Dec. 2006.

[162] K. J. Bowering, N. E. O'Connell, A. Tabor, M. J. Catley, H. B. Leake, G. L. Moseley, and T. R. Stanton, "The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis," *The Journal of Pain: Official Journal of the American Pain Society*, vol. 14, no. 1, pp. 3–13, Jan. 2013.

[163] K. Limakatso, L. Corten, and R. Parker, "The effects of graded motor imagery and its components on phantom limb pain and disability in upper and lower limb amputees: a systematic review protocol," *Systematic Reviews*, vol. 5, p. 145, 2016. [Online]. Available: http://dx.doi.org/10.1186/s13643-016-0322-5

[164] K. L. Macuga and S. H. Frey, "Neural representations involved in observed, imagined, and imitated actions are dissociable and hierarchically organized." *NeuroImage*, vol. 59, no. 3, pp. 2798–2807, Feb. 2012.

[165] D. C. Turk, J. Audette, R. M. Levy, S. C. Mackey, and S. Stanos, "Assessment and Treatment of Psychosocial Comorbidities in Patients With Neuropathic Pain," *Mayo Clinic Proceedings*, vol. 85, no. 3 Suppl, pp. S42–S50, Mar. 2010. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2844010/

[166] K. Yoshida, J. Malec, C. Comoglio, K. Mosier, R. Lontis, K. Larsen, X. Navarro, and W. Jensen, "Evaluation of the Effect of Sensory Feedback on Phantom Limb Pain in Multi-center Clinical Trials," in *Converging Clinical and Engineering Research on Neurorehabilitation II*, ser. Biosystems & Biorobotics, J. Ibez, J. Gonzlez-Vargas, J. M. Azorn, M. Akay, and J. L. Pons, Eds.   Springer International Publishing, 2017, no. 15, pp. 725–730, dOI: 10.1007/978-3-319-46669-9_119. [Online]. Available: http://link.springer.com/chapter/10.1007%2F978-3-319-46669-9_119

[167] F. Baker, M. Denniston, J. Zabora, A. Polland, and W. N. Dudley, "A POMS short form for cancer patients: psychometric and structural evaluation," *Psycho-Oncology*, vol. 11, no. 4, pp. 273–281, Aug. 2002.

[168] R. I. Parker, K. J. Vannest, and J. L. Davis, "Effect size in single-case research: a review of nine nonoverlap techniques," *Behavior Modification*, vol. 35, no. 4, pp. 303–322, Jul. 2011.

[169] J. Cohen, *Statistical power analysis for the behavioral sciences*, 2nd ed.   Hillsdale, NJ: Erlbaum, 1988.

[170] R. I. Parker and K. Vannest, "An improved effect size for single-case research: nonoverlap of all pairs," *Behavior Therapy*, vol. 40, no. 4, pp. 357–367, Dec. 2009.

[171] D. Bouhassira, S. Wilhelm, A. Schacht, S. Perrot, E. Kosek, G. Cruccu, R. Freynhagen, S. Tesfaye, A. Lled, E. Choy, P. Marchettini, J. A. Mic, M. Spaeth, V. Skljarevski, and T. Tlle, "Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study," *Pain*, vol. 155, no. 10, pp. 2171–2179, Oct. 2014.

[172] R. J. Little, R. DAgostino, M. L. Cohen, K. Dickersin, S. S. Emerson, J. T. Farrar, C. Frangakis, J. W. Hogan, G. Molenberghs, S. A. Murphy, J. D. Neaton, A. Rotnitzky, D. Scharfstein, W. J. Shih, J. P. Siegel, and H. Stern, "The Prevention and Treatment of Missing Data in Clinical Trials," *The New England journal of medicine*, vol. 367, no. 14, pp. 1355–1360, Oct. 2012. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3771340/

[173] K. MacIver, D. M. Lloyd, S. Kelly, N. Roberts, and T. Nurmikko, "Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery," *Brain*, vol. 131, no. 8, pp. 2181–2191, Aug. 2008.

[174] D. W. Tan, M. A. Schiefer, M. W. Keith, J. R. Anderson, J. Tyler, and D. J. Tyler, "A neural interface provides long-term stable natural touch perception," *Science Translational Medicine*, vol. 6, no. 257, p. 257ra138, Oct. 2014.

[175] K. Kroenke, R. L. Spitzer, and J. B. W. Williams, "The PHQ-9," *Journal of General Internal Medicine*, vol. 16, no. 9, pp. 606–613, Sep. 2001. [Online]. Available: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1495268/

[176] J. T. Farrar, J. P. Young, L. LaMoreaux, J. L. Werth, and R. M. Poole, "Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale," *Pain*, vol. 94, no. 2, pp. 149–158, Nov. 2001.

[177] "CFR - Code of Federal Regulations Title 21." [Online]. Available: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=882.5890

APPENDICES

A. THE EPIONE EXTRACTION PROGRAM USER GUIDE

A.1 Introduction and Purpose

The purpose of the EPIONE Extraction Program (EEP) is to extract the raw data generated by the EPIONE Psychophysical Platform (PsyP) and conduct the initial analysis on the psychophysical data. This program compiles, analyzes, and tabulates the results for a subject of the EPIONE consortium clinical study. This user guide is to be used with EEP software version 1.0.x (v1.0.x) and has been validated up to version 3.1.15 of the PsyP. The EEP can be used with four psychophysical data types generated during the EPIONE common clinical protocol (CCP); this includes the brief pain inventory (BPI), neuropathic pain symptom inventory (NPSI), profile of mood states - short form (POMS-SF), and visual analog scale (VAS).

A.2 Operation

A.2.1 Installation

Download the EPIONE Data Extraction installer. You will need admin rights to complete the installation process. After you begin the installer will ask where you want to save the program. If you do not have MATLAB® Runtime already installed on your machine the installer will proceed by adding this to the installation process. The final steps are accepting the terms of the MATLAB® Runtime License agreement and initiating installation.

A.2.2 Getting Started

The EEP allows the the data analyst to compile and analyze a subject's data following the completion of the EPIONE CCP. Figure A.1 shows version 1.0.0 of the software's front panel. The organization of the program is mostly in order of work flow. This subsection will go through, step-by-step, how to use the program. While these steps can be completed in any order, the order is meant to be intuitive for the user.
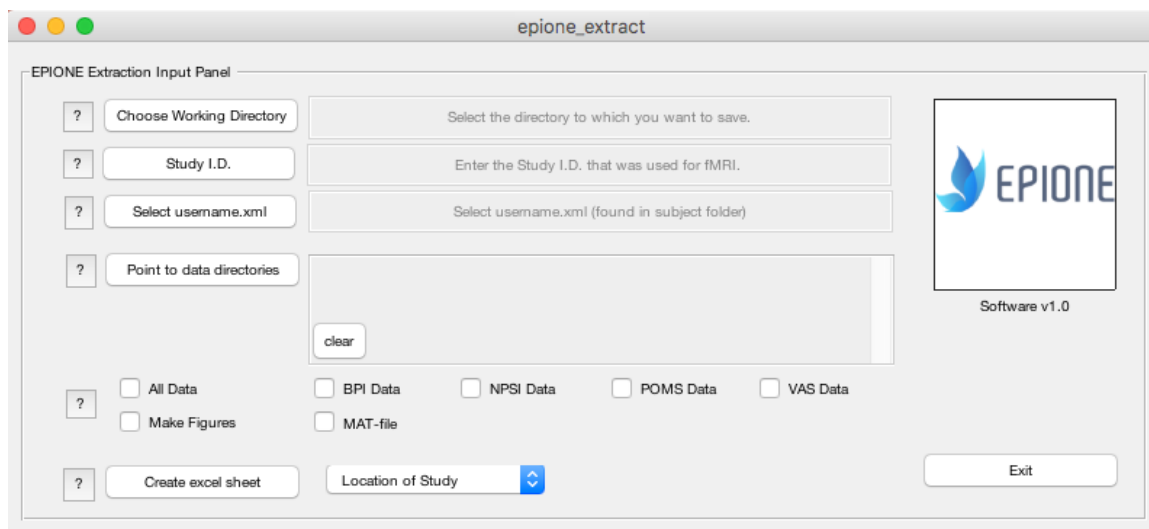

Fig. A.1. The EPIONE Extraction Input Panel at startup

The basic workflow involves identifying the working directory, specifying the Study ID, selecting the username.xml file, pointing to the data directory, picking the data to be saved, and selecting the study location. Throughout the process workflow, the user can select the button with the question mark next to the area where help is needed and a new window will open with some helpful details.

Step 1: Choose Working Directory

Clicking on *Choose Working Directory* will open a new window. This can be used to select the folder in which to save the output file; this also serves as home directory

for the rest of the processing. Each time the user attempts to open a file, the program will use the selected working directory as the starting point.
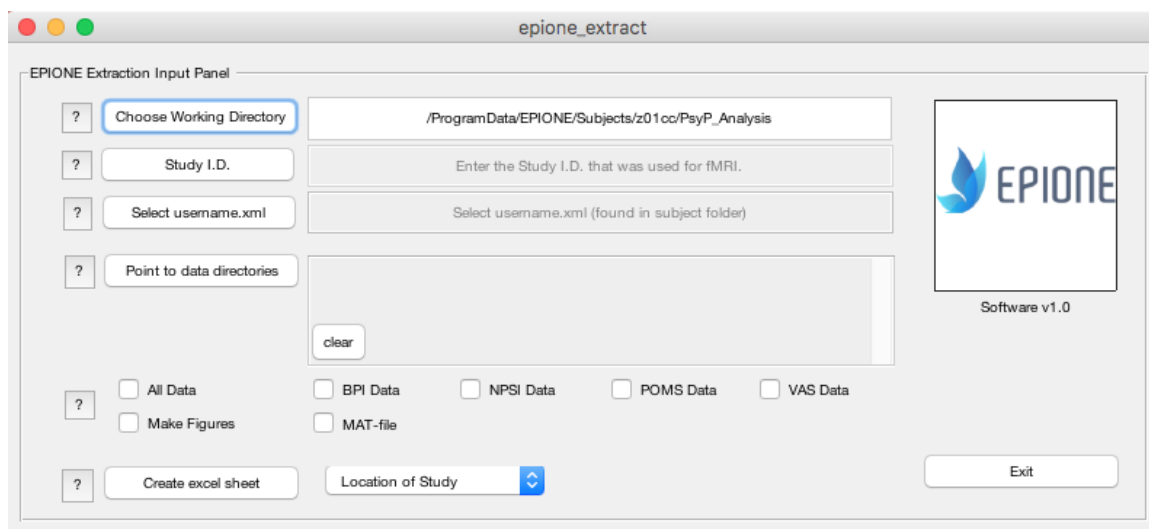

Fig. A.2. Choosing the working directory where output data will be saved.

It is recommended not to use the desktop as the working directory. Depending on the options selected, up to 13 files can be generated, including one Excel® file, one mat-file, one log-file for debugging, five MATLAB® figure files, and 5 scalable vector graphic (SVG) figure files. In Figure A.2 a file called PsyP_Analysis in the subject's natural Psychophysical Platform data folder.

Step 2: Input Study ID

The study ID is very important for linking a subject's psychophysical data to his/her fMRI data. The study ID should be the same as what was given during the fMRI, which is not necessarily the ID that is given by the Psychophysical Platform. It is recommended for the ID to be a random string of 6 alphanumeric characters to de-identify the data. If necessary use a separate document to keep track of study IDs generated by the Psychophysical Platform and the ID for data analysis. Clicking on the *Study I.D.* brings up the window shown in Figure A.3.
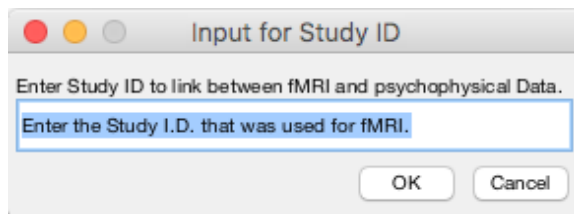
Fig. A.3. Specifying the subject I.D.

After the window pops up, the user enters the study ID, and clicks *OK*, the input panel will display the user entered study ID. If the ID is incorrect, simply click the *Study I.D.* button again and re-enter the appropriate study ID.

Step 3: Select Username.xml File

The username.xml file is found within the subject specific folder. An example of the typical file path for this file is: /ProgramData/EPIONE/Subjects/z01cc/, where z01cc should be replaced by the subject's Psychophysical Platform username. Note the ProgramData directory is typically hidden in the windows C-drive. The username.xml file for this example case would be z01cc.xml. Clicking the *Select username.xml* button on the input panel opens another window to browse to the appropriate directory. Note, there are other, similar xml-files also existing in this directory; however, only the z01cc.xml file should be selected. If the wrong file is selected simply click the *Select username.xml* button again and select the appropriate file. Only one file can be selected at any given time. If the subject folder structure is maintained, the next step is simplified. The EEP will recognize if the data directory exists and will automatically fill in the next field. If this data directory is correct and is the only data directory Step 4 can be skipped.

Step 4: Point to Data Directories

Just like with choosing the working directory, pressing the *Point to data directories* button will open a window to browse from the working directory to the folder containing the subject's data (or the data directory). If your data is in separate folders, multiple directories can be entered, one at a time, by clicking the *Point to data directories* button and pointing to each folder individually. Each data directory will be listed in the input panel window. Psychophysical Platform data is typically found in .../z01cc/Questnr directory. In most cases all of the subject's data should be contained within this folder. Data files have the .mat extension. Each selected directory will be listed in the window to the right of the *Point to data directories* button. If an incorrect directory is selected, select the directory in the list of data directories and click *clear*. This will remove the selected directory. After selecting the username.xml file and pointing to the data directories, the input panel should resemble Figure A.4.
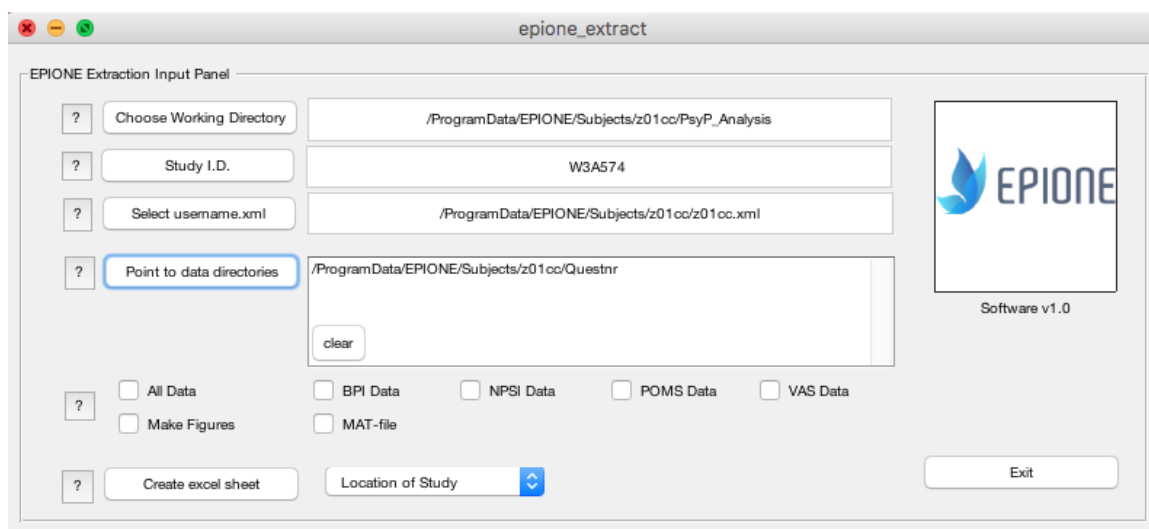

Fig. A.4. Selecting the subject specific data files for processing

Step 5: Select the Data to be Saved

Select the data you want to save by checking the box next to each measure type. Toggling the *All Data* box will select or deselect all four data measure types (BPI, NPSI, POMS, and VAS). These can be requested independently if desired. Note, that the *VAS* checkbox will also save the Nonoverlap of All Pairs (NAP) data. Furthermore, for the sake of convenience, the EEP can generate preliminary figures in the form of scalable vector graphics (SVGs) and MATLAB® figure files (FIGs). If the user prefers to create his or her own figures, the average, maximum, and minimum values for each questionnaire type can be saved to a mat-file, but can also be found within the Excel® output file. For every measure selected by the user, the statistics are saved for each analysis period (pre-therapy, therapy week-1, etc.). Note, for group analysis in the EEP - Group Analysis Module, the data should be saved in the mat-file format. See Appendix B for more details.

Step 6: Specify Location of Study

There are two options for this drop down menu; the user must select one to continue to processing. If the questionnaires were administered in Danish, the user should select *Denmark* as the location of study; otherwise, the user should select *Other Site.* Upon completing Step 6, the input panel should resemble Figure A.5.

Step 7: Create Excel® Sheet

To create the output file, select *Create Excel® sheet.* Depending on the amount of data for a given subject, the data requested for processing by the user, and the system specifications of the machine processing the data, output files should be available in just a few minutes. Observe the progress bar during processing for reference. This will create an .xls file in the working directory (selected in step 1), in addition to a log file (used for debugging), and additional files at the user's request (such as figures or mat-
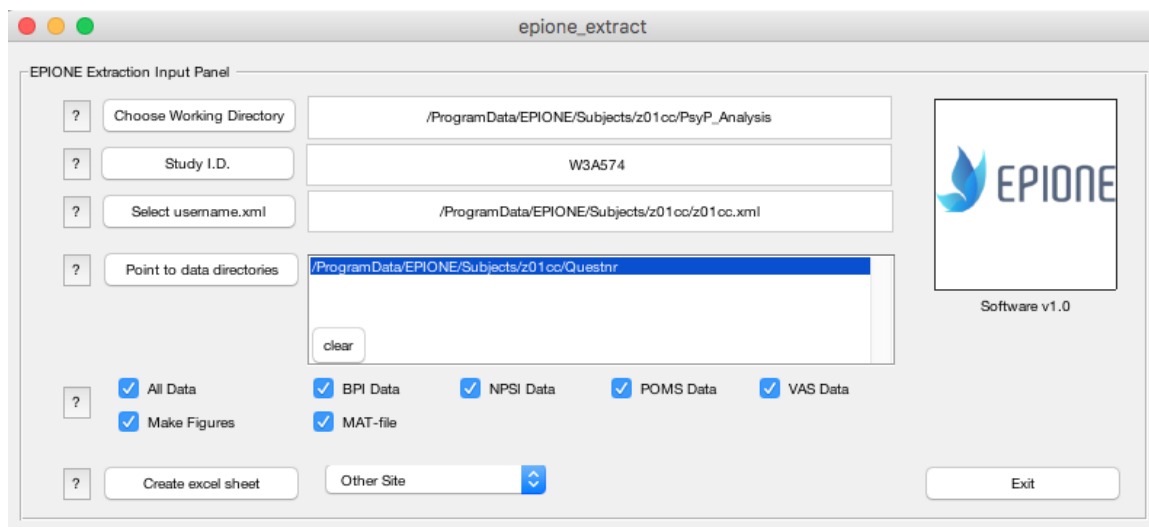
Fig. A.5. The input panel prior to processing data

file). The file name will be displayed in the successful extraction pop up window. All data files will be named in the following format: PsyPdata_studyID_ABCDEF.xls, where ABCDEF is a string of six random, alphanumeric characters. Figure A.6 demonstrates the pop-up window that is displayed if extraction is successful. Once this window is displayed the user can close the program and investigate the output files or continue processing another subject's data.
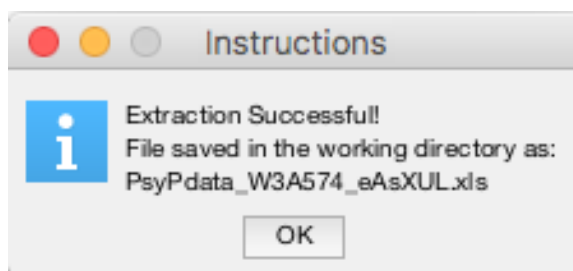

Fig. A.6. Successfully extracting data is indicated by the EEP

Note, upon clicking *Create Excel® sheet*, the button is disabled until the EEP has completed processing the requested data. This is to protect the integrity of the data and to avoid interrupting the software. While every effort has been made to anticipate and prevent user-errors, some errors are simply unpredictable. Should an

unanticipated error occur, the *Create Excel*® *sheet* button may or may not be re-enabled. If it is not re-enabled the button will still visibly toggle, but processing will not begin (as would be indicated by a progress bar). To alleviate this issue, simply close and re-open the EEP.

Step 8: Exit

You may exit the EEP at any time by clicking the *Exit* button, or clicking the red *X* button in the corner of the window. Note, because of the brevity of entering the file locations, there is no method of saving entries in this program, so exiting will lose any settings. However, The log-file generated during processing contains a list of all of the settings selected. This allows the user to review or even repeat previous extractions if necessary.

A.2.3   Output Files and Analysis

The output Excel® file has several tabs/sheets of data. Because of restrictions of MATLAB®, Excel®, and computer operating systems, three empty sheets will appear at the front of each output file. These can be deleted at any time. The first relevant sheet is *Results*. This displays the final results calculated by the program for the primary and secondary instruments. For VAS the scores are displayed as NAP scores. For NPSI and POMS, the scores are displayed as difference scores. For this sheet and all others, only the data selected in the input panel will be available. Furthermore, if a measure is not selected (e.g. if the *VAS* checkbox is not checked), the measure specific sheets will not be available in the output file (e.g. NAP tables).

Following the *Results* sheet is the *Tables* sheet. This contains the average, minimum, and maximum values for a given period for each selected score. Periods are broken up into the following groups: Pre-therapy, Therapy week-1, Therapy week-2, Therapy week-3, Therapy week-4, Outcome, and Follow-Up. In the case of the

NAP scores, the Outcome and Follow-Up phases are combined into the Post-Therapy period score. This is to take advantage of the multiple comparisons.

NAP tables are provided for each of the three VAS measures (0-hour, 1-hour, 24-hour). The scores displayed in the *Results* sheet are calculated by averaging the NAP in each therapy week (or post-therapy period). The *Schedule* sheet shows the dates for the subject entering each phase. If the program could not find the date, *DNE* (Does Not Exist) is displayed. The remaining sheets simply display the data in different formats. The *Binned* format separates the data into column groups for the sake of the readability. This allows the reader to understand how the data was organized for analysis at a quick glance. This should be used to evaluate how scores were broken up to get the week to week effect size displayed in the *Results* sheet. The data is also displayed in the *Raw* sheets. These contain the timestamp and scores (for BPI and VAS) or timestamp, subscores, and question scores (for NPSI, and POMS).

The mat-file contains repeated information from the *Tables* sheet of the Excel® file. The purpose of the mat-file is to get the data in an easily accessible format. Included in the mat-file are the average, maximum, and minimum for each instrument for each period as described previously. In addition two other variables containing the difference between the average and minimum for each index and for the difference between the average and maximum for each index allow one to quickly create bar graphs with max-min error bars in MATLAB®.

The effect size can be calculated by referring to Table A.1 and Table A.2. These effect size thresholds are elaborated on in section 2.4, which discusses the background of how results are calculated as well as these limits for effect. In regards to the NAP the limits are for a two sided test of effect per the recommendations of Parker and Vannest [170].

The thresholds for effect size for the secondary measures (NPSI and POMS-SF) and for the BPI interference scale (BPI-IS) exploratory measure are in Table A.2.

Table A.1. The VAS-NAP thresholds for measuring effect size.

NAP Thresholds	Effect
$0 - 0.07$	Large/Strong Negative
$0.08 - 0.33$	Medium/Moderate Negative
$0.34 - 0.66$	None
$0.67 - 0.92$	Medium/Moderate Positive
$0.93 - 1$	Large/Strong Positive

Table A.2. The thresholds for effect size utilize Cohen's *d*. For more details on how these thresholds were established, see Chapter 3.

Questionnaire	Subscale Name	Subscale Range	Strong Negative Effect ($d = -0.8$)	Medium Negative Effect ($d = -0.5$)	Medium Positive Effect ($d = 0.5$)	Strong Positive Effect ($d = 0.8$)
	General Activity		2.4	1.5	−1.5	−2.4
	Mood		2.4	1.5	−1.5	−2.4
	Mobility		2.5	1.5	−1.5	−2.5
BPI-IS	Normal Work	$0 - 10$	2.5	1.5	−1.5	−2.5
	Relationships		2.4	1.5	−1.5	−2.4
	Sleep		2.7	1.7	−1.7	−2.7
	Enjoyment of life		2.8	1.8	−1.8	−2.8
	Total		2.1	1.3	−1.3	−2.1
NPSI	Burning Pressing Paroxysmal Evoked Paresthesia/ dysesthesia	$0 - 10$	2	1	−1	−2
	Total	$0 - 100$	16	10	−10	−16
	Anger	$7 - 35$				
	Confusion	$5 - 25$				
POMS-SF	Depression	$8 - 40$	3	2	−2	−3
	Fatigue	$5 - 25$				
	Tension	$6 - 30$				
	Vigor	$6 - 30$	−4	−2	2	4

B. THE GROUP ANALYSIS MODULE USER GUIDE

B.1   Introduction and Purpose

The purpose of the EPIONE Extraction Program - Group Analysis Module (EEP-GAM) is to generate group results from subject data created by the EEP. This module compiles, runs preliminary analysis, and tabulates results for a group configured by the user. This user guide is to be used with the GAM software version 1.0.x (v1.0.x) and has been validated up to version 3.1.15 of the PsyP. The GAM can be used with the four psychophysical data types generated during the EPIONE common clinical protocol (CCP); this includes the brief pain inventory (BPI), neuropathic pain symptom inventory (NPSI), profile of mood states - short form (POMS-SF), visual analog scale (VAS), and Nonoverlap of all pairs (NAP).

B.2   Operation

B.2.1   Installation

No installation is needed to run the GAM. This module runs in the MATLAB$^{\circledR}$ Standard Suite, provided by MathWorks, Inc.

B.2.2   Getting Started

To begin simply download the module specific MATLAB$^{\circledR}$ files and click the files to open the input panel. The GAM allows the the data analyst to compile and analyze group data following the completion of the EPIONE CCP and initial processing in the EEP. Figure B.1 shows version 1.0.0 of the software tool's front panel. The organization of the program is mostly in order of work flow. This subsection will go

through, step-by-step, how to use the GAM. While these steps can be completed in any order, the order is meant to be intuitive for the user.

Fig. B.1. The Group Analysis Module Input Panel at startup

The basic workflow involves specifying the Subject Codes specifying the Group IDs, selecting the subject data, picking the data to be saved, and selecting a save directory.

Step 1: Adding Subjects to the Workspace

The table in the workspace is for creating the analysis table. The analysis table specifies the subject codes, group IDs, and location of the subject data. To begin filling in the analysis table click on the cell below *Subject_Code*. This allows the user to type in the subject code, which can be alphanumeric. To add the group name for a subject click on the corresponding cell under the *Group_ID* column and type in the

group ID. The group IDs are case-sensitive and can be alphanumeric. An example of this is demonstrated in Figure B.2.
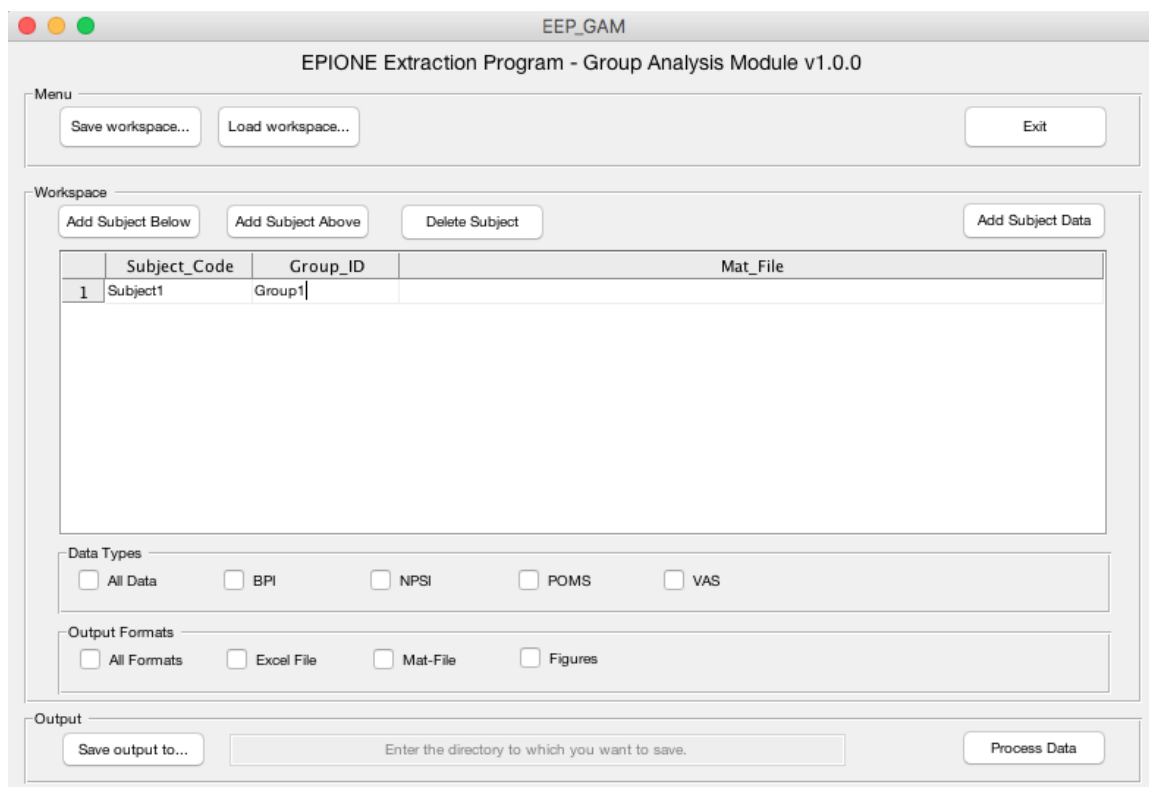

Fig. B.2. Users can add subject codes and group IDs by typing into the analysis table.

To finish adding a subject to the analysis table, select the corresponding cell under the *Mat_File* column and click the *Add Subject Data* button. A separate window pops up to select the subject's mat-file generated during processing in the EEP.

Add or Remove Subjects

Additional subjects can be added to or removed from the analysis table by using the *Add Subject Below* or *Add Subject Above* buttons, which is demonstrated in Figure B.3. If you want to remove a subject, select a cell in the subject line of the analysis table and select the *Delete Subject* button.
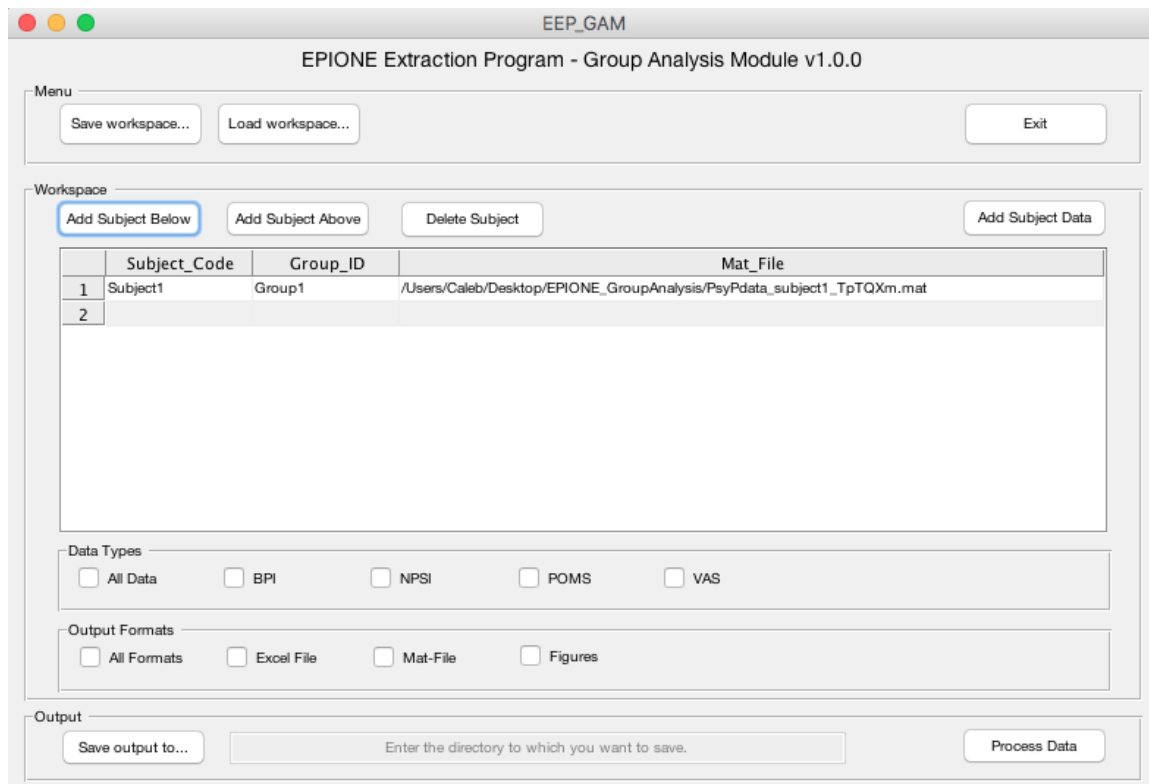
Fig. B.3. Adding and removing subjects from the group analysis table is simple with the navigation buttons.

Step 3: Select the Data to be Saved

Select the data you want to save by checking the box next to each data type. Toggling the *All Data* box will select or deselect all four data types (BPI, NPSI, POMS, and VAS). These can be requested independently, if desired. Note, that the *VAS* checkbox will also save the NAP data. For the sake of convenience, the GAM can generate preliminary figures in the form of scalable vector graphics (SVGs) and MATLAB® figure files (FIGs) by selecting the *Figures* format. If the user prefers to create his or her own figures, the group average, maximum, minimum, standard deviation, and n values for each questionnaire type can be saved to a mat-file. The mat-file also contains the average, maximum, and minimum for each subject as well. This information can also be found within the Excel® output file if the *Excel®* checkbox is selected. Toggling the *All Formats* selects or deselects all of the output formats. For

every measure selected by the user, the statistics are saved for each analysis period (pre-therapy, therapy week-1, etc.).

Step 4: Specify the Save Directory

It is recommended not to use the desktop as the working directory. Depending on the options selected, up to 64 files can be generated for each group specified in the analysis table, including one Excel® file, one mat-file, 31 FIGs, and 31 SVGs. In Figure B.4 a folder called GroupResults is selected as the location for saving output files.
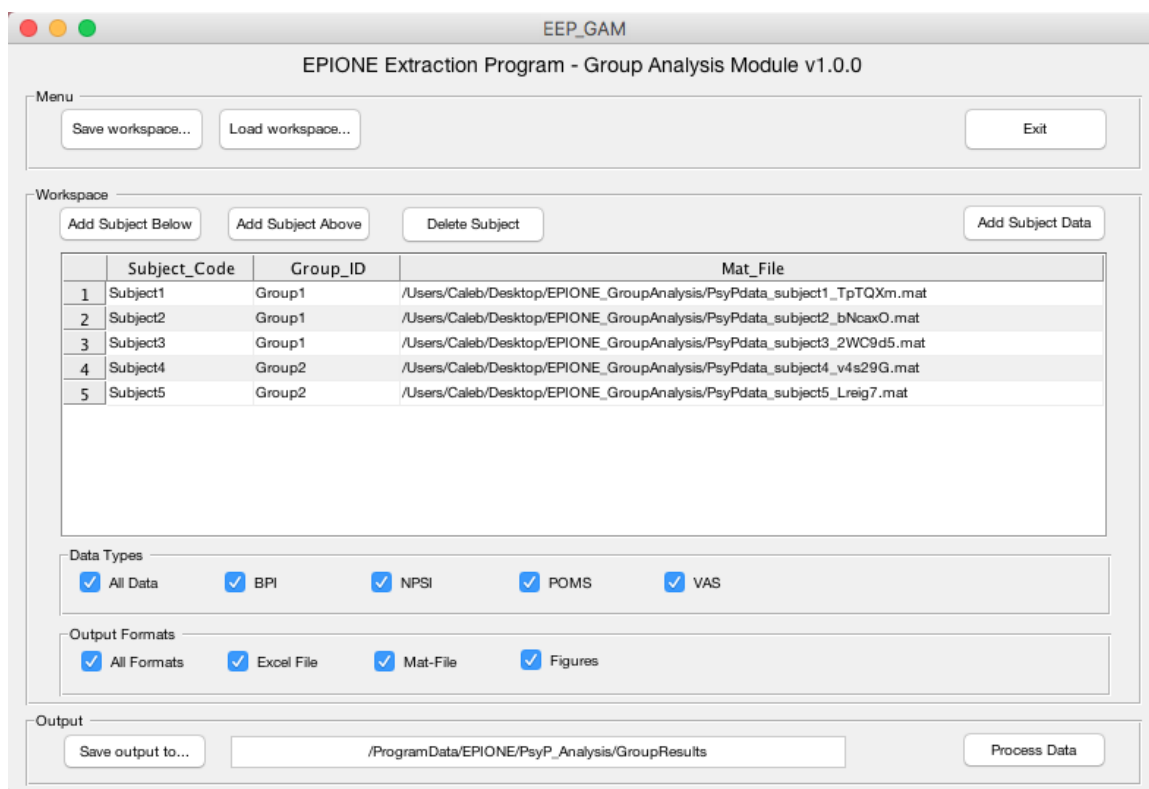

Fig. B.4. All information is entered into the GAM input panel and the user is ready for processing.

Step 5: Process Data

To create the output file, select *Process Data*. Depending on the amount of data for a given subject, the data requested for processing by the user, and the system specifications of the machine processing the data, output files should be available in just a few minutes. Observe the progress bar during processing for reference. The GAM will create files at the user's request in the following order. Excel® files are created first, mat-files second, and figures last. Data types are also sequential: BPI, NPSI, POMS, VAS, NAP. Before moving on to the next format or data type, the module will process each group. Once the module is done processing data a window pops up stating group analysis is successful. All data files will be named in the following format: PsyPdata_Group_GroupID_DataType_ABCDEF.xls, where ABCDEF is a string of six random, alphanumeric characters. Figure B.5 demonstrates the pop-up window that is displayed if group analysis is successful. Once this window is displayed the user can close the program and investigate the output files or continue processing another subject's data.
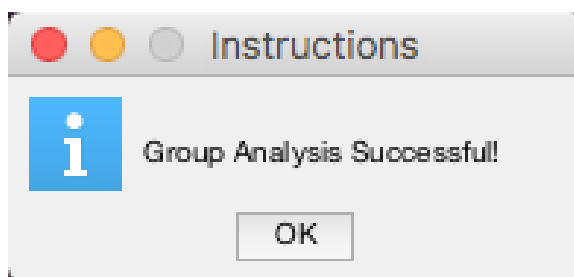

Fig. B.5. Successfully extracting data is indicated by the GAM.

Step 6: Saving and Loading the Workspace (optional)

Before or after processing the workspace can be saved for future use. To save the workspace click the *Save workspace...* button. The workspace is saved as a mat-file. To load the workspace click the *Load the workspace...* button and select the mat-file previously saved.

Step 7: Exit

You may exit the EEP at any time by clicking the *Exit* button, or clicking the red X button in the corner of the window. Note, if the workspace is not saved there is no way to recover work.

B.2.3 Output Files and Analysis

The output Excel$^{\circledR}$ file has several tabs/sheets of data. Because of restrictions of MATLAB$^{\circledR}$, Excel$^{\circledR}$, and computer operating systems, three empty sheets will appear at the front of each output file. These can be deleted at any time. The first relevant sheet is *Results*. This displays the final results calculated by the GAM for the BPI, NPSI, POMS-SF, and NAP. For the primary instrument, VAS, the effect is displayed as NAP scores. For BPI, NPSI and POMS, the scores are displayed as difference scores. For this sheet and all others, only the data selected in the input panel will be available. Furthermore, if a measure is not selected (e.g. if the *VAS* checkbox is not checked), the measure specific sheets will display N/A in the Excel$^{\circledR}$ file.

Following the *Results* sheet are the data type specific sheets. These sheets contains group data along with the average, minimum, and maximum values for each subject in the group. The group data saved in this sheet is the average, minimum, maximum, standard deviation, and n. The n table shows the number of subjects used for each group score. This is useful especially if a subject is missing data. Periods are broken

up according to the following time periods: Pre-therapy, Therapy week-1, Therapy week-2, Therapy week-3, Therapy week-4, Outcome, and Follow-Up. In the case of the NAP scores, the Outcome and Follow-Up phases are combined into the Post-Therapy period score. This is to take advantage of the multiple comparisons.

The mat-file contains the same information as the Excel® file. The purpose of the mat-file is to get the data in an easily accessible format. Included in the mat-file are the average, maximum, and minimum for each instrument for each period as described previously.

The effect size can be calculated by referring to Table A.1 and Table A.2. These effect size thresholds are elaborated on in section 2.4, which discusses the background of how results are calculated as well as these limits for effect. In regards to the NAP the limits are for a two sided test of effect per the recommendations of Parker and Vannest [170].

C. EPIONE EXTRACTION PROGRAM CHANGE LOGS

C.1 EPIONE Extraction Program Change Log

C.1.1 Preface

The EPIONE Extraction Program (EEP) Change Log tracks changes for released versions of the EEP. EEP versions are in the $M.m_a.m_b$ format where M denotes major changes to the software, m_a denotes minor changes to the software that evoke a different user experience, and m_b specifies minor changes to the software that do not change how the user interacts with the software, i.e. minor backend changes. Major changes could involve several additional features at once, significant bugs, etc. Examples of minor changes include bugs that do not affect data quality, background features to optimize the program, background features for system integration, or additional features that do not significantly alter the user experience. Importance level is determined based on the detectability, the stage of the project, effects on data quality, and how many clinical sites are affected. Affected parties refers to which clinical sites are affected by the change.

C.1.2   v1.0.2 - Currently Released Version

Updates from Previous Version

Changed cutoff date for POMS data import correction. Previous versions use v3.1.15 of the psychophysical platform as the cutoff date when it should be v3.1.17. This issue stems from known software differences in the psychophysical platform for data entry and interpretation. POMS questions are supposed to range 1-5 and in some scenarios 1s were encoded as 0s. For Danish POMS the values ranged 0-4 instead of 1-5. This was corrected in v3.2.0 of the psychophysical platform.

Importance Level

Moderate Importance.

Effects on Data Quality or Accuracy

POMS data from previous versions is effected for all sites only if data collected after v3.1.15 and before v3.2.0 of the Psychophysical Platform. Otherwise, data is unaffected.

Recommended Activities

Update to latest version. Rerun POMS data if data collected after v3.1.15 and before v3.2.0. Otherwise, no action required.

Affected Parties

All

C.1.3 v1.0.1 - Retired Version

Updates from Previous Version

Added NAP data to mat-file output. This allows data to be passed into the group analysis module.

Importance Level

Low Importance.

Effects on Data Quality or Accuracy

None.

Recommended Activities

Update to latest version. If you want to run group analysis this version is required.

Affected Parties

All.

C.1.4 v1.0.0 - Retired Version

Updates from Previous Version

First release.

Importance Level

N/A

Effects on Data Quality or Accuracy

N/A

Recommended Activities

N/A

Affected Parties

N/A

C.2 Group Analysis Module Change Log

C.2.1 Preface

The EPIONE Extraction Program - Group Analysis Module (GAM) Change Log tracks changes for released versions of the GAM. GAM versions are in the $M.m_a.m_b$ format where M denotes major changes to the module, m_a denotes minor changes to the software that evoke a different user experience, and m_b specifies minor changes to the software that do not change how the user interacts with the software, i.e. minor backend changes. Major changes could involve several additional features at once, significant bugs, etc. Examples of minor changes include bugs that do not affect data quality, background features to optimize the program, background features for system integration, or additional features that do not significantly alter the user experience. Importance level is determined based on the detectability, the stage of the project, effects on data quality, and how many clinical sites are affected. Affected parties refers to which clinical sites are affected by the change.

C.2.2 v1.0.0 - Currently Released Version

Updates from Previous Version

First release.

Importance level

N/A

Effects on Data Quality or Accuracy

N/A

Recommended Activities

N/A

Affected Parties

N/A