Aus dem Friedrich-Baur-Institut an der Neurologischen Klinik und Poliklinik

Klinikum der Ludwig-Maximilians-Universität München

Anwendung der peripheren elektrischen Stimulation bei Gesunden und Schlaganfallpatienten und die Auswirkungen auf die somatosensorisch evozierten Potenziale

Dissertation

zum Erwerb des Doktorgrades der Humanbiologie

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

Marko Mijic

aus

Gradacac, Bosnien und Herzegovina

Jahr

2023

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

Erster Gutachter:	Prof. Dr. med. Benedikt Schoser
Zweiter Gutachter:	Prof. Dr. Stephan Kröger
Dritter Gutachter:	Prof. Dr. Wolfgang Müller-Felber

Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 17.10.2023

Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

Marko Mijic
Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Anwendung der peripheren elektrischen Stimulation bei Gesunden und Schlaganfallpatienten und die Auswirkungen auf die somatosensorisch evozierten Potenziale

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München 17.10.2023
Ort, Datum

Marko Mijic
Unterschrift Doktorand

Inhaltsverzeichnis

Liste der Abkürzungen I

Liste der Veröffentlichungen II

Beitrag zu Papier I III

Beitrag zu Papier II IV

Verzeichnis der Abbildungen V

1. Einleitung

1.1. Schlaganfall

1.2. Somatosensorisch evozierte Potenziale

1.2.1. Subkortikale und kortikale SEP-Komponenten des Nervus medianus der oberen Extremität

1.2.2. Subkortikale und kortikale SEP-Komponenten des Nervus tibialis der unteren Extremität

1.3. Fußheberschwäche und funktionelle (periphere) Elektrostimulation

1.4. Problemstellung

2. Zusammenfassung

3. Abstract

4. Publikation I

5. Publikation II

6. Literaturverzeichnis

8. Danksagung

9. Lebenslauf

Abkürzungsverzeichnis

EEG Elektroenzephalogramm

SEP Somatosensorisch evozierte Potenziale

EP Evozierte Potenziale

NT Nervus tibialis

NM Nervus medianus

NU Nervus ulnaris

UE Untere Extremität

OE Obere Extremität

DGKN Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN) e.V.

FHS Fußheberschwäche

MRC Medical Research Council's scale for muscle strength

FES Funktionelle Elektrostimulation

PES Periphere elektrische Stimulation

MEP Motorisch evozierte Potenziale

TMS Transkranielle Magnetstimulation

fMRI Funktionelle Magnetresonanztomographie

Publikationsliste

Mijic M, Jung A, Schoser B, Young P. Use of peripheral electrical stimulation on healthy individual and patients after stroke and its effects on the somatosensory evoked potentials. A systematic review. Front Neurol. 2022 Nov 18;13:1036891. doi: 10.3389/fneur.2022.1036891. PMID: 36468059; PMCID: PMC9716063.

Mijic M, Schoser B, Young P. Efficacy of functional electrical stimulation in rehabilitating patients with foot drop symptoms after stroke and its correlation with somatosensory evoked potentials-a crossover randomised controlled trial. Neurol Sci. 2022 Dec 21. doi: 10.1007/s10072-022-06561-3. PMID: 36544079.

Beitrag zu den Veröffentlichungen

1.1 Beitrag zu Publikation I

Für die erste Veröffentlichung habe ich das Studienprotokoll, die Methodik, die Validierung sowie die formale Analyse mit Unterstützung von Prof. Dr. Benedikt Schoser und Prof. Dr. Peter Young entworfen. Ich habe alle statistischen Tests und Datenanalysen durchgeführt und das Manuskript geschrieben. Herr Andres Jung unterstützte mich mit dem Softwaresystem "Rayyan" bei der Datenerfassung und Datenauswertung. Darüber hinaus begleitete mich Herr Andres Jung durch die gesamte systematische Auswertung. Alle Studienschritte wurden mit Prof. Dr. Benedikt Schoser und Prof. Dr. Peter Young besprochen, um von ihrem fachlichen Wissen zu profitieren. Ebenso wurde auf den TAC-Treffen das Studienprotokoll auch Prof. Dr. Stephan Körger, Genomische Physiologie der LMU, zur Diskussion vorgestellt. Als korrespondierender Autor habe ich den ersten Entwurf der vorliegenden Arbeit verfasst und an alle anderen Autoren zur Überarbeitung geschickt und dann eingereicht.

1.2 Beitrag zu Publikation II

Für die zweite Publikation, für die ich ebenfalls als Hauptautor fungierte, habe ich mit Unterstützung von Prof. Dr. Benedikt Schoser und Prof. Dr. Peter Young das Studienprotokoll, die Methodik, die Validierung und die formale Analyse konzipiert. Dabei hat mich Prof. Dr. Benedikt Schoser als Supervisor meines Dissertationsprozesses bei der Konzeption eines geeigneten und validierten Studienprotokolls unterstützt. Außerdem habe ich von seinen Anweisungen zur Auswertung und Darstellung der Ergebnisse profitiert. Prof. Dr. Peter Young unterstützte mich bei experimentellen Testverfahren, Validierung und Formalanalyse mit seiner Expertise. Ebenso wurde auf den TAC-Treffen das Studienprotokoll auch Prof. Dr. Stephan Körger, Genomische Physiologie der LMU, zur Diskussion vorgestellt. Darüber hinaus unterstützte mich Prof. Dr. Peter Young bei allen Forschungsschritten durch seine Supervision. Das Manuskript wurde von beiden Co-Autoren zweimal begutachtet und dann von mir eingereicht.

Abbildungen:

Abbildung 1. SEP-Aufzeichnungskanäle des Nervus tibialis (links) und des Nervus medialis (rechts)

Abbildung 2. Das funktionelle Elektrostimulationsgerät "L300 Go System".

1. Einleitung

1.1. Schlaganfall

Alljährlich gibt die American Heart Association in Zusammenarbeit mit den Center for Disease Control and Prevention, den National Institutes of Health und anderen US Regierungsstellen statistische Daten über die jährliche Häufigkeit von Schlaganfällen heraus [1]. Weltweit leiden jährlich etwa 15 Millionen Menschen an einem Schlaganfall, was zu 5 Millionen Todesfällen und weiteren 5 Millionen Menschen mit dauerhaften Behinderungen führt [1]. Pro Jahr treten in Deutschland 200.000 erstmalige Schlaganfälle und 70.000 wiederholte Schlaganfälle auf [2]. Der Schlaganfall ist eine zentralnervöse neurologische Störung. Man unterscheidet zwei pathophysiologsich abgrenzbare Typen, den ischämischen Schlaganfall, der mit ca. 85 % der häugigere Subtyp ist, und einen hämorrhagischen Schlaganfall, den man in 15 % der Fälle nachweisen kann [3,4]. Dem ischämische Schlaganfall liegt ein temporärer oder dauerhafter Verschluss von hirnversorgenden Arterien zu Grunde. Durch thrombotisches Blutmaterial wird eine hirnversorgende Arterie verschlossen. Infolgedessen werden die umliegende Nervenzelllen durch eine komplexe kaskade der Unterversorgung geschädigt. Dies führt u.a. zu einem plötzlichen Absterben von Nervenzellen aufgrund von Sauerstoffmangel und anderen molekularen Mechanismen. Im Gegensatz dazu wird der hämorrhagische Schlaganfall durch intrazebebrale Blutungen oder Aneurysmatablutungen verursacht [3]. Im Folgenden wird der Begriff Schlaganfall für beide Formen, den ischämischen und den hämorrhagischen Schlaganfall, verwendet.

1.2. Somatosensorisch evozierte Potenziale

1951 wurden die ersten somatosensorisch evozierten Potenziale (SEP) von George Dawson bei Menschen aufgezeichnet [5]. In den späten 1960er Jahren wurden somatosensorisch evozierte Potenziale bei bestimmten chirurgischen Eingriffen zum zerebralen Monitoring eingesetzt [6]. Heute werden SEP routinemäßig zur Bewertung der somatosensorischen Bahn verwendet und sind ein

wichtiges ergänzendes diagnostisches Verfahren neben der Anamnese, der neurologischen Untersuchung und der Bildgebung [7].

Ein evoziertes Potenzial (EP) ist eine elektrische Aktivitätsänderung des Nervensystems als Reaktion auf eine externe Stimulation. Im Gegensatz zum Elektroenzephalogramm (EEG), das konstante und spontan wechselnde elektrische Aktivität des Gehirns anzeigt, ist das EP zeitlich mit dem Beginn der Stimulation korreliert und besteht aus einer Reihe von elektrischen Wellen, die für jede Stimulationsart charakteristisch und definiert sind. Für klinische Tests werden visuelle, auditive und somatosensorische Stimulationen verwendet [8].

Bei den SEPs handelt es sich um zeitlich festgelegte Potenziale, die durch elektrische Stimulation der sensorischen oder gemischten peripheren Nerven entstehen und entlang der somatosensorischen Großfaserbahn (dorsale Säule - medialer Lemniskus) aufgezeichnet werden. SEPs zeichnen die Übertragung eines elektrischen Signals/Aktionspotenzials zwischen den Aufzeichnungsstellen entlang der Nervenbahn auf und ermöglichen so die Identifizierung von Abnormitäten, die eine Läsion lokalisieren können. Die elektrische Stimulation über die peripheren Nerven erzeugt vorhersagbare SEPs mit bestimmten Werten (Amplitude und Latenzzeit), die auf den verwendeten Aufzeichnungssequenzen basieren [7].

Bei der SEP der oberen Extremität (OE) wird der Nervus medianus (NM) oder der Nervus ulnaris (NU) am Handgelenk stimuliert und bei der SEP der unteren Extremität (UE) wird der Nervus tibialis (NT) am Fußgelenk oder der Nervus peroneus an der poplitealen Beuge stimuliert [8]. Abbildung 1 zeigt die in der vorliegenden zweiten Studie verwendeten Aufzeichnungstechniken.

Detaillierte Aufzeichnungstechniken wurden von verschiedenen Autoren beschrieben [6–8]. Diese beinhalten geringe Unterschiede in den einzelnen technischen Verfahrensschritten. Die meisten Autoren folgen jedoch den Richtlinien der American Clinical Neurophysiology Society [10] oder der International Federation of Clinical Neurophysiology [11], und für Deutschland der Deutsche Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung (DGKN) e.V. [12].

1.2.1. Subkortikale und kortikale SEP-Komponenten des Nervus medianus der oberen Extremität

Der N13/P14 (je nach Aufnahmemontage/Kanälen) wird von dorsalen Säulenfasern des Cuneatus generiert, die am Nucleus cuneatus in der unteren Medulla ankoppeln und sich als medialer Lemniskus nach der Kreuzung mit dem Cervicomedullarium fortsetzen. Es ist ein subkortikales Fernfeldpotential, das mit Hilfe von Kopfhautelektroden aufgezeichnet wird. Es hat eine weite Verbreitung auf der Kopfhaut und spiegelt wahrscheinlich die Aktivität im kaudalen mittleren Lemniskus wider [11–13].

N20 spiegelt die Aktivierung des Handbereichs des primären kortikalen somatosensorischen Rezeptionsgebietes durch die thalamokortikalen Anteile [11,12]. N20 wird mit einer bipolaren Methode aufgezeichnet, um die weit verbreiteten Fernfeldsignale (z. B. P14 und N18) von der primären kortikalen Aktivität zu unterscheiden, die über der zentroparietalen Region kontralateral zum stimulierten NM aufgezeichnet wird [16].

1.2.2. Subkortikale und kortikale SEP-Komponenten des Nervus tibialis der unteren Extremität

N34/N35 repräsentieren ein subkortikal erzeugtes Fernfeldpotential, das von einer Fpz-Elektrode aufgezeichnet wird und wahrscheinlich analog zu N18/N20 nach NM-Stimulation ist [15,16]. Es spiegelt voraussichtlich postsynaptische Aktivität aus mehreren Generatorquellen im Hirnstamm und möglicherweise im Thalamus wider [7].

P37/P40 spiegelt die Aktivierung des primären kortikalen somatosensorischen Rezeptionsbereichs der UE wider. N50/P60 weisen einen geringen negativen/positiven Peak auf, wodurch sie zusammen mit P40 die typische W-Konfiguration des primären somatosensorischen Komplexes nach Reizung der NT zeigen [9].

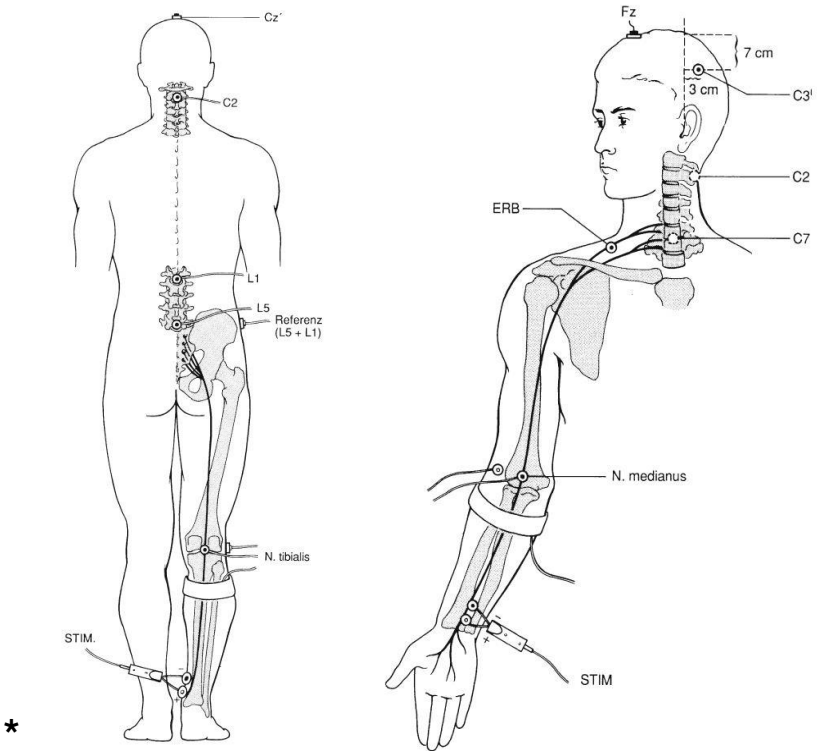


Abbildung 1. SEP-Aufzeichnungskanäle des Nervus tibialis (links) und des Nervus medianus (rechts) * Quelle [19]

1.3. Fußheberschwäche und funktionelle (periphere) Elektrostimulation

Liberson [20] beschrieb 1961 als Erste den unmittelbaren Nutzen des Fußheberstimulators. Eine Fußheberschwäche (FHS) verursacht häufig eine pathologische Gangstörung, die durch eine Lähmung oder erhebliche Schwäche der Dorsalflexionsmuskeln des Fußgelenks verursacht wird. Charakteristisch ist die Unfähigkeit, eine ausreichende Dorsalflexion zu erzielen, um während der Schwungphase des Gangs einen ausreichenden Abstand vom Boden zu erreichen [21]. FHS ist auch durch eine unkontrollierte Plantarflexion unmittelbar nach dem ersten Kontakt gekennzeichnet [22].

In den letzten zehn Jahren zeigte sich, dass die funktionelle Elektrostimulation (FES) beim Training von Geh- und Armbewegungen bei Schlaganfallpatienten oder Personen mit einer inkompletten Läsion des Rückenmarks wirksam eingesetzt werden kann. Die therapeutische FES wird überwiegend in Rehabilitationszentren nach der Verletzung oder dem Krankheitsbeginn angesetzt. Teilweise

wird es auch bei den Patienten zu Hause nach der Entlassung aus der Rehabilitationseinrichtung eingesetzt [23].

In der Literatur finden sich mehrere Bezeichnungen für die periphere Elektrostimulation (PES): die transkutane elektrische Nervenstimulation (TENS) [22-25], FES [26–29], die kutane Elektrostimulation [32], die somatosensorische Stimulation [33], die neuromuskuläre Elektrostimulation [32, 33] oder die Kombination der Begriffe "perkutan" und "Neuromodulation".

*

Abbildung 2. Das funktionelle Elektrostimulationsgerät „The 300 Go System“ *Quelle [36]

Sheffler und Chae [37] befassten sich ausführlich mit dem Einsatz der Elektrostimulation bei dem motorischen Lernen. Sie beschrieben drei Arten der Stimulation, die für das motorische Lernen zur Verfügung stehen: FES, Elektromyografie- oder biofeedbackvermittelte FES und die Anwendung von Neuroprothesen. Im ersten Fall ist der Patient ein passiver Teilnehmer am FES-Training und es ist kein kognitiver Einsatz erforderlich. Bei der zweiten Art des Trainings werden afferenzbasierte Feedbackinformationen mit FES-induzierten repetitiven Bewegungen kombiniert. Beim Training mit verschiedenen Orthesen können funktionelle Aufgaben durchgeführt werden [23]. Die verschiedenen FES-Begriffe, die in der vorliegenden Übersicht beschrieben sind, lassen sich einem oder mehreren der von Sheffler und Chae [37] beschriebenen Stimulationstypen zuordnen. Darüber hinaus wird bei allen Stimulationsarten dieselbe Technik verwendet: Platzierung von Oberflächenelektroden auf der Haut, die über sensomotorischen Nervenstrukturen liegen, Aufbau eines elektrischen Feldes zwischen zwei Elektroden und Ionen und die Erzeugung einer Elektrizität im Gewebe. Im folgenden

Text wird ausschließlich der Begriff FES verwendet. In einigen Fällen könnte jedoch der Begriff PES den elektrischen Stimulationsprozess treffender beschreiben.

1.4. Problemdarstellung

Es wurde angenommen, dass eine somatosensorische Stimulation in Form von elektromyographisch ausgelöster neuromuskulärer Elektrostimulation des peripheren Nervs funktionelle Veränderungen der motorischen Leistung bei Schlaganfallpatienten beeinflussen könnte. Zusätzlich könnte es zu Veränderungen der kortikalen Erregbarkeit kommen [21,33].

In mehreren Studien wurde bereits festgestellt, dass sich die Laufgeschwindigkeit, die Kraftausdauer und die Koordination von Schlaganfallpatienten durch den Einsatz von FES verbessert haben [21,37–39]. Weiterhin deuten die Studien an Schlaganfallpatienten, in denen FES eine willkürliche Kontraktion für eine bestimmte Bewegung oder Aufgabe auslösen [29–31,41], auf eine positive Beziehung und Korrelation mit Bewertungen der motorischen Funktion hin. Diese Hypothese wird durch die Ergebnisse einer Meta-Analyse über die motorische Erholung von OE-Funktionen bei Schlaganfall [42] und die therapeutischen Auswirkungen der Peronealstimulation auf den Gang und die motorische Erholung [39] unterstützt.

Diese Modalität wird auch für die motorische kortikale Aktivität durch die Aufzeichnung motorisch evozierter Potenziale (MEP) [40–42], transkranielle Magnetstimulation (TMS) [43,44] oder funktionelle Magnetresonanztomographie (fMRI) übertragen. Andererseits wurde der Einfluss von FES auf die somatosensorische Funktion im klinischen Kontext und in der Forschung auf dem Gebiet der Schlaganfallrehabilitation häufig übersehen. Die Vorhersage der motorischen Erholung von UE und OE bei Schlaganfallpatienten basiert im Allgemeinen auf der klinischen Untersuchung [48]. Die Prognose basiert in der Regel auf dem klinischen Eindruck, der klinische und chronologische Faktoren wie die Schwere des Schlaganfalls und das Alter einbezieht [49].

Darüber hinaus können Neurologen nur dann feststellen, ob ihre Prognosen in der kritischen Behandlungsphase zutreffen, wenn sie ihre Patienten routinemäßig nach einigen Monaten erneut untersuchen [49]. Dieser Aspekt kann zu unterschiedlichen Einschätzungen der Prognose führen, die sich auch in der Entlassungsplanung widerspiegeln [50]. Nach Feys und Kollegen [48] ist die Kombination aus motorischem Index und SEPs vor allem in der akuten Phase des Schlaganfalls am besten geeignet, ein Ergebnis zu prognostizieren, da neurophysiologische Messungen allein nur von begrenztem Wert für die Vorhersage eines langfristigen Effekts sind. Die Ergebnisse von Kato und Kollegen [49], die bei Patienten mit hämorrhagischen Infarkten die SEPs der NM und der NT untersuchten, ergaben, dass 60 von 65 OE (92,3%) und 50 von 62 der UE (80,6%) Abweichungen in den SEPs-Messungen aufwiesen. Diese Ergebnisse weisen darauf hin, dass SEP-Messungen, die Latenzen, Schwellenwerte und evozierte Reaktionen bei hohen Stimulatorintensitäten, eine hohe Zuverlässigkeit aufweisen und nur eine kleine Stichprobengröße erfordern, um eine Studie angemessen auswerten zu können. Daher scheint die Validierung der SEP als neues neurophysiologisches Standardinstrument zur Beurteilung der Rehabilitationsprognose nach Schlaganfall sinnvoll zu sein.

Urasaki und Kollegen [27] fanden heraus, dass die dorsale Säule (medialer Lemniskus) die Hauptrolle bei der sensorischen Verstärkung im zentralen Nervensystem spielt und dass FES dieses Verstärkungsphänomen im medialen Lemniskusbahn unterdrückt. Der Einsatz von FES als Intervention zur Überprüfung der SEP als neues neurophysiologisches Standardinstrument könnte daher eine hervorragende Methode zur Beobachtung von Veränderungen in den kortikalen somatosensorischen Bahnen darstellen.

Zwischen motorischen und somatosensorischen Hirnarealen bestehen wichtige anatomische Verbindungen. Motorische kortikale Areale erhalten direkten Input vom primären und sekundären somatosensorischen Kortex. Umgekehrt erhalten somatosensorische Areale direkte kortikale Inputs aus dem primären motorischen Kortex, dem prämotorischen Kortex und dem supplementären motorischen Areal [42,50]. Eine Veränderung der somatosensorischen Funktion im Zusammenhang mit motorischem Lernen scheint ein natürliches Nebenprodukt dieser anatomischen Konnektivität zu sein [42,50].

Ein weiterer Beweis dafür liefert Rocchi und Kollegen [52] in der Studie „High frequency somatosensory stimulation increases sensori-motor inhibition“ wo durch die Bewertung der motorischen Funktion und Kontrolle, die mit den Veränderungen der SEP-Komponenten bei gesunden Teilnehmern korrespondieren. Die hochfrequente repetitive somatosensorische Stimulation führt zu einer verbesserten Leistung in Verhaltenstests und trägt zu einer besseren Leistung bei räumlichen Wahrnehmungsaufgaben hinzu. Dennoch beeinträchtigt die hochfrequente repetitive somatosensorische Stimulation auch die Hemmung der kurzen Latenz in M1 (primär motorische Cortex). Zusammengenommen könnten diese Veränderungen in S1 (somatosensorische Cortex) und M1 den berichteten Verbesserungen der manuellen motorischen Leistung zugrunde liegen [52].

Diese Kenntnisse deuten darauf hin, dass die FES die somatosensorische Reaktion in die motorischen Bereiche des Gehirns verlagern kann. Andererseits könnte die Hypothese aufgestellt werden, dass die FES indirekt Veränderungen in den motorischen Hirnarealen erfassen kann.

Sollten die SEPs empfindlich genug sein, um selbst kleine Veränderungen im Aktionspotenzial bei kortikaler neuronaler Netze nach einem Schlaganfall zu erkennen, könnten damit die Auswirkungen der entsprechenden sensorischen Therapien eingesetzt werden. Möglicherweise lassen sich mit ihr die Effekte von sensorischen Therapien (Kältetherapie, Thermotherapie, taktile Ergotherapie oder robotergestützte taktile Therapie) direkt beurteilen.

Die Auswirkungen von FES auf die somatosensorische kortikale Repräsentation bei gesunden Probanden müssen noch gründlich untersucht werden, da nur wenig über die funktionellen Eigenschaften von abweichenden und typischen Reaktionen in verschiedenen sensorischen Gehirn-Modalitäten bekannt ist [53]. Diese Kontroverse über sensorische Veränderungen und kortikale Plastizität besteht auch bei Schlaganfallpatienten fort, und Veränderungen der kortikal-motorischen Übertragbarkeit bleiben weiterhin unklar [54].

Die Rolle von FES bei der Veränderung von Latenzen und Amplituden des SEP bei gesunden Probanden oder deren Auswirkung auf die Verbesserung pathologischer SEPs durch FES in der motorischen Rehabilitation nach Schlaganfall ist bisher nicht bekannt.

Ein wesentliches Ziel der vorliegenden Dissertation war es, die Evidenz zur sensomotorischen Diagnostik und zu Veränderungen der SEP-Komponenten nach der FES-Behandlung auf klinische Zusammenhänge zu untersuchen. Für einen klinischen Therapieansatz könnte der Einfluss von Veränderungen im SEP als ein Prädiktor für die Rehabilitationsprognose nach dem Schlaganfall genutzt werden. Um diese Hypothese zu bestätigen, wurde eine systematische Übersichtsarbeit durchgeführt.

Im zweiten Teil der Dissertation wurde eine randomisierte kontrollierte Crossover-Studie durchgeführt, um Veränderungen der pathologischen Latenzen und Amplituden der SEPs, die durch eine akute subkortikale und kortikale Läsion nach einem Schlaganfall verursacht wurden, nach einer zweiwöchigen FHS-Behandlung mit einer FES-Neuroprothese zu ermitteln. Zusätzlich wurden bei einer unbehandelten Kontrollgruppe gesunder Erwachsener wiederholte SEP-Messungen durchgeführt, die nur der Auswertung der Ergebnisse dienten.

Das endgültige Ziel war es, die festgestellten SEP-Änderungen mit der Effizienz einer zweiwöchigen FES-Neuroprothesen-Intervention in Bezug auf die Verbesserung der FHS zu korrelieren, die anhand eines 10-Meter-Gehtests und der Stärke der Dorsalflexion unter Verwendung der Skala für Muskelstärke des Medical Research Council (MRC) [55] zwischen den beiden Schlaganfallgruppen gemessen wurde. Zudem wurde eine Korrelation zwischen den SEP-Änderungen und den Ergebnissen des 10-Meter-Gehtests und der Stärke der Dorsalflexion MRC zwischen den Schlaganfallgruppen hergestellt.

2. Zusammenfassung:

Nur wenige Studien haben die somatosensorisch evozierte Potenziale (SEP) genutzt, um die kortikale Neuroplastizität und die Rehabilitationsprognose bei Schlaganfallpatienten nach der Anwendung der funktionellen Elektrostimulation (FES) zu untersuchen. Das Hauptziel meiner Studie war es, systematisch zu überprüfen, ob FES eine Rolle bei der Veränderung der Latenzen und Amplituden von SEPs bei gesunden Probanden oder bei den Patienten nach einem Schlaganfall darstellt. Weiterhin suchte ich nach einer Korrelation zwischen sensorischen und motorischen Funktionstests und den Veränderungen der SEP-Latenzen und Amplituden. Folgende Datenbanken wurden durchsucht: Pubmed/MEDLINE, Scopus/ScienceDirect, Web of Science/Clarivate, Cochrane Library, The Physiotherapy Evidence Database (PEDro), und ClinicalTrials.gov. Die Titel und Abstracts sowie die Volltexte der Studien wurden von zwei unabhängigen Autoren anhand von im Vorfeld festgelegten Kriterien auf ihre Eignung geprüft. Es wurden alle Studien, die sich auf die Behandlung der oberen oder unteren Extremitäten oder des Rumpfes mit FES, inkludiert. Die systematische Suche resultierte in insgesamt 11344 Studien, von denen nur 10 evaluiert wurden. Ich konnte keinen ausreichenden Nachweis finden, dass das SEP als Indikator für eine Prognose der Rehabilitation nach einem Schlaganfall nützlich ist. Ich fand jedoch einen Zusammenhang zwischen verschiedenen sensorischen und motorischen Funktionsbewertungen und Veränderungen der SEP-Komponenten. Die Schlaganfallstudien mit FES, die eine willkürliche Kontraktion für eine bestimmte Bewegung oder Aufgabe initiieren, deuten auf eine positive Beziehung und Korrelation mit den Bewertungen der motorischen Funktion hin. Es könnte darauf hinweisen, dass FES eine positive Auswirkung auf die sensorische Reorganisation hat, was sich in der Veränderung der SEP-Amplitude und -Latenz widerspiegelt. Das Ausmaß der Konnektivität zwischen SEP und kortikaler Plastizität lässt sich bisher nicht feststellen. Um diese Hypothese zu bestätigen, haben wir ein randomisiertes, kontrolliertes zwei-Perioden-Crossover-Design mit gesunden Probanden und Schlaganfallpatienten durchgeführt.

Meine zweite Studie analysierte Veränderungen der pathologischen SEP-Latenzen und Amplituden nach einem akuten Schlaganfall nach zweiwöchiger Rehabilitation mit FES. Die Veränderungen der SEPs wurden auch mit der FES-Intervention bei Schlaganfall-Symptomen der Fußheberschwäche (FHS) korreliert, die anhand des 10-Meter-Gehtests und der Stärke der Dorsalflexion im Fußgelenk bewertet wurden. Gruppe A erhielt die FES direkt, während Gruppe B nach zwei Wochen behandelt wurde. Zudem wurden in der unbehandelten Kontrollgruppe gesunder Erwachsener in den gleichen Zeitabständen wie bei den Schlaganfallpatienten wiederholte SEP-Messungen durchgeführt. Die statistische Analyse (ANOVA) zeigte eine signifikante Abnahme der SEP-Latenzen des paretischen Nervus tibialis (NT) in den Schlaganfallgruppen nach der Intervention, gefolgt von einer Abnahme der SEP des nicht-paretischen NT im Vergleich zur Kontrollgruppe der gesunden Erwachsenen. Darüber hinaus wurde in den Schlaganfallgruppen eine Zunahme der Kraft des FHS und eine Verringerung der Kadenz beobachtet. Wir fanden eine moderate Korrelation (r=0,50-0,70) zwischen der Latenzzeit des nicht-paretischen NT und der Schrittkadenz in den Schlaganfallgruppen nach der FES-Zeit. Der pathologische Gang wurde verändert und das afferente SEP-Feedback verbesserte sich nach der FES-Intervention.

3. Abstract:

A small number of studies used somatosensory evoked potentials (SEP) to demonstrate changes in cortical sensory function in healthy subjects or to assess cortical plasticity and rehabilitation prognosis in stroke patients following an functional electrical stimulation (FES) intervention. The main objective of first study was to systematically investigate whether FES is involved in altering SEP latency and amplitude in healthy subjects and stroke survivors. We also searched for correlations between sensory and motor assessments and SEP component changes in the included studies. Databases of interest were: Scopus (ScienceDirect) , Pubmed (MEDLINE), Web of Science, The Physiotherapy Evidence Database (PEDro), Cochrane Library, and ClinicalTrials.gov. A priori eligibility criteria were used to screen titles, abstracts, and reports for eligibility. There were no limitations regarding the treatment of the upper extremity, lower extremity, or trunk with FES. The last systematic search resulted in 11344 entries. However, only ten of these were evaluated. There was insufficient evidence for using SEP to predict rehabilitation prognosis after stroke. However, we did find a correlation linking the assessment of sensory and motor function and the changes in the components of the SEPs. Moreover, a positive relationship and correlation with motor function assessments in stroke studies using FES, which initiates a voluntary contraction used for a specific movement or task, was found. However, the degree of connectivity between the SEP and cortical plasticity remains elusive. To confirm this hypothesis, we conducted a randomised, controlled, two-period crossover study with stroke patients and healthy volunteers. The second study examined changes in pathological SEP latencies and amplitudes following an acute stroke after two weeks of rehabilitation with FES. Changes in SEPs between the stroke groups were also correlated with FES therapy intervention for foot drop stroke symptoms, assessed by the 10-metre walk test and strength of dorsal flexion in the foot ankle. Group A received the FES directly, while group B was treated after two weeks. Moreover, repeated SEP measurements were evaluated in the untreated control group of healthy adults at the same interval as for stroke groups. The statistical measures (ANOVA) showed a significance decrease in paretic tibial nerve SEP latencies in stroke groups after the intervention, tracked by a decrease in non-paretic tibial nerve SEP comparing to the control

group of healthy adults. Furthermore, increasing of foot drop strength and reducing the cadence in stroke groups was found. We found a moderate correlation (r=0.50-0.70) between non-paretic tibial nerve latency N50 and step cadence in stroke groups after the FES time. The pathological gait was modified with improved SEP afferent feedback following the FES intervention.

4. Paper I.

Front Neurol. 2022 Nov 18;13:1036891. doi: 10.3389/fneur.2022.1036891.

Use of peripheral electrical stimulation on healthy individual and patients after stroke and its effects on the somatosensory evoked potentials. A systematic review.

Mijic Marko [1], Jung Andres [2], Schoser Benedikt [1], Young Peter [3]

Affiliations

[1] Department of Neurology, Friedrich-Baur-Institute, Klinikum der Universität, Ludwig-Maximilians-University, Munich, Germany,

[2] Institute of Health Sciences, Universität zu Lübeck, Luebeck, Germany,

[3] Clinic for Neurology, Medical Park, Bad Feilnbach, Germany

PMID: 36468059; PMCID: PMC9716063.

frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 18 November 2022
DOI 10.3389/fneur.2022.1036891

OPEN ACCESS

EDITED BY
Carlos Luque-Moreno,
University of Seville, Spain

REVIEWED BY
Auwal Abdullahi,
Bayero University Kano, Nigeria
Manuel Albornoz-Cabello,
Sevilla University, Spain

*CORRESPONDENCE
Marko Mijic
marko.mijic@med.uni-muenchen.de

SPECIALTY SECTION
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

RECEIVED 05 September 2022
ACCEPTED 20 October 2022
PUBLISHED 18 November 2022

CITATION
Mijic M, Jung A, Schoser B and Young P (2022) Use of peripheral electrical stimulation on healthy individual and patients after stroke and its effects on the somatosensory evoked potentials. A systematic review. *Front. Neurol.* 13:1036891. doi: 10.3389/fneur.2022.1036891

Use of peripheral electrical stimulation on healthy individual and patients after stroke and its effects on the somatosensory evoked potentials. A systematic review

Marko Mijic[1]*, Andres Jung[2], Benedikt Schoser[1] and Peter Young[3]

[1]Department of Neurology, Friedrich-Baur-Institute, Klinikum der Universität, Ludwig-Maximilians-University, Munich, Germany, [2]Institute of Health Sciences, Universität zu Lübeck, Luebeck, Germany, [3]Clinic for Neurology, Medical Park, Bad Feilnbach, Germany

Introduction: To date, a few studies have used somatosensory evoked potentials (SEP) to demonstrate cortical sensory changes among healthy subjects or to estimate cortical plasticity and rehabilitation prognosis in stroke patients after peripheral electrical stimulation (PES) intervention. The primary aim was to systematically review whether PES has a role in changing latencies and amplitudes of SEPs in healthy subjects and stroke patients. Moreover, we searched for a correlation between sensory and motor function assessments and changes in SEP components of included studies.

Methods: The following databases were searched: Pubmed/MEDLINE, Scopus/ScienceDirect, Web of Science/Clarivate, Cochrane Library, The Physiotherapy Evidence Database (PEDro), and ClinicalTrials.gov. Titles and abstracts, as well as full-text reports, were screened for eligibility by two independent reviewers according to a priori defined eligibility criteria. There were no study limitations concerning the treatment of the upper limb, lower limb, or torso with PES.

Results: The final systematic search resulted in 11,344 records, however only 10 were evaluated. We could not find enough evidence to confirm use of SEP as a predictor to estimate the rehabilitation prognosis after stroke. However, we found a correlation between different sensory and motor function assessments and changes in SEP components. The stroke studies involving PES that initiate a voluntary contraction used for a specific movement or task indicate a positive relationship and correlation to assessments of motor function. It could be indicated that PES have a predictive impact of sensory reorganization, as mirrored by the change in SEP amplitude and latency. However, it is not possible to verify the degree of connectivity between SEP and cortical plasticity. To confirm this hypothesis, we propose the conduction of randomized controlled trials in healthy volunteers and stroke patients.

Systematic review registration: https://doi.org/10.17605/OSF.IO/U7PSY.

KEYWORDS

peripheral electrical stimulation, somatosensory evoked potentials (SEP), stroke rehabilitation, sensory and motor recovery, somatosensory cortex

Introduction

Peripheral electric stimulation (PES) is a rehabilitative technology that uses electrical currents to the peripheral nerves. It has been proposed that somatosensory stimulation in the form of electromyographically triggered neuromuscular electrical stimulation to the peripheral nerve can influence functional measures of motor performance in stroke patients and can additionally produce changes in cortical excitability (1, 2). In this way, PES provides restoration of walking or arm movements in individuals with complete or incomplete spinal cord injury, stroke, or other upper motor neuron lesion (2–4).

The literature offers multiple terms for peripheral electrical stimulation: transcutaneous electric nerve stimulation (TENS) (5–8), functional electrical stimulation (9–12), cutaneous electrical stimulation (13), somatosensory stimulation (14), neuromuscular electrical stimulation (1, 15) or combination of terms "percutaneous" and "neuromodulation".

Sheffler and Chae (16) devoted important consideration to the use of electrical stimulation for motor relearning. They described three types of electrical stimulation available for motor learning: functional electrical stimulation (FES), electromyography or biofeedback mediated FES, and application of neuroprostheses. In the first case the patient is a passive participant in the FES training and no cognitive investment is necessary. The second type of exercises combines afferent feedback information with FES induced repetitive movements. During training with neuroprosthesis, functional tasks can be performed (2). The multiple PES terms used in the present review can be classified into one or more stimulation types described by Sheffler and Chae. Furthermore, for all terms the same technique is being used: placing surface electrodes on the skin overlaying sensory-motor nerve structures, establishing an electric field between two electrodes and ions, generating a current in the tissue. In the following text, only the term PES will be used exclusively.

In many studies, it has been found that the stroke patient's walking speed, endurance, and coordination improved with the use of PES (2, 17–19). The same modality on motor cortical excitability is described by recording motor evoked potentials (20–22), transcranial magnetic stimulation (23, 24) or fMRI (1, 25). On the other hand, the influence of PES on somatosensory function has been frequently overlooked in clinical context and research in the field of stroke rehabilitation (15). Prediction of upper limb (UL) and lower limb (LL) motor recovery in stroke patients is generally based on clinical examination (26). The prognosis is typically based on clinical impression, incorporating clinical and demographic factors such as stroke severity and age (27). Moreover, clinicians cannot know whether the prognoses they make at the acute stage are correct unless they do not routinely assess each of their patients several months later (27). This gestalt approach can produce differing opinions about prognosis and these seem to produce variation in discharge planning (28). According to Feys et al. (26) the combination of the motor score and somatosensory evoked potentials (SEPs) is best able to predict an outcome especially in the acute stroke phase, since neurophysiological measures alone are of limited value in predicting a long-term effect. The finding by Kato et al. (29) who examined the SEPs of the median and the tibial nerves in patients with hemorrhagic lesions, confirmed that 60 out of 65 arms (92.3%) and 50 out of 62 legs (80.6%) showed abnormalities in SEPs. These findings may indicate SEP measures quantifying latencies, thresholds, and evoked responses at high stimulator intensities had high reliability and require small sample sizes to power a study adequately (30). Therefore, the validation of SEP as a new standard neurophysiological tool for assessing the rehabilitation prognosis after stroke seems a reasonable decision.

SEPs are time-locked potentials evoked by electric stimulation of the sensory or mixed peripheral nerves and recorded along with the large fiber somatosensory (dorsal column–medial lemniscus) pathway. SEPs record transmission of an electrical signal/action potential between recording sites along the impulse pathway, thereby allowing the identification of abnormalities that help to localize a lesion (31).

Urasaki et al. (8) found that the dorsal column nucleus has the main role in CNS sensory amplification and that PES suppresses this amplification phenomenon in the medial lemniscus pathway. Consequently, use of PES as an intervention to verify SEP as a new standard neurophysiological tool could be a good method to observe changes in cortical somatosensory pathways.

The effects of PES on somatosensory cortical representation in healthy subjects have not been fully investigated yet, since little is known about the functional features of mismatch deviant and standard responses across different sensory brain modalities (32). This controversy of sensory changes and cortical plasticity persists in stroke patients and changes in corticomotor excitability still remains elusive (33).

To our knowledge, the role of PES in changing latencies and amplitudes of SEPs in healthy subjects or whether effects of PES aiming at motor rehabilitation after stroke have an impact on the improvement of pathological SEPs have not yet been studied. Furthermore, one of the aims of the present study was to examine the evidence on sensorimotor assessment and changes in SEP components after PES treatment for clinical correlations, so that SEP can be used at best as a predictor for estimating rehabilitation prognosis after stroke.

Abbreviations: PES, peripheral electrical stimulation; TENS, transcutaneous electric nerve stimulation; FES, functional electrical stimulation; SEP, somatosensory evoked potentials; UL, upper limb; LL, lower limb; CNS, central nerve system; MEP, motor evoked potential; FIM, Functional Independence Measure; NIH, National Institutes of Health; RCT, randomized controlled trial.

TABLE 1 PICO criteria.

P	Patient/Subjects	Healthy subjects Stroke patients
I	Intervention	Transcutaneous electric nerve stimulation, functional electrical stimulation, cutaneous electrical stimulation, somatosensory stimulation, neuromuscular electrical stimulation or combination of terms "percutaneous" and "neuromodulation"
C	Comparison	No PES intervention, placebo, inactive intervention, or waiting-list
O	Outcome	Latency and amplitude of somatosensory evoked potentials

Materials and methods

The study protocol was prospectively registered at the open science framework (OSF) with the registration DOI: https://doi.org/10.17605/OSF.IO/YW6PT on the 14th of March 2021 and an update protocol was registered in OSF (https://doi.org/10.17605/OSF.IO/U7PSY) on the 27th of August 2022. The PICO (34) model was implemented to answer the primary clinical questions: Do the effects of PES on motor rehabilitation in post-stroke patients have an impact on the latencies and amplitudes of pathological SEPs and does PES alter the latencies and amplitudes of SEPs in healthy subjects? (Table 1).

This systematic review was conducted using "The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement 2020" (35) and followed recommendations from the Cochrane handbook (36).

Study selection

A team of four healthcare professionals, including two physiotherapists (MM, AJ), and two physicians (PY, BS), established the study's aim, its primary outcome measures, the search strategy, and its eligibility criteria. The search construct consisted of two main subjects: peripheral electric stimulation and somatosensory evoked potentials. The following databases were searched: Pubmed/MEDLINE, Scopus/ScienceDirect, Web of Science/Clarivate, Cochrane library database, The Physiotherapy Evidence Database (PEDro), and ClinicalTrials.gov. The cut-off date of the search was the 28th of August 2022.

Because only 8 eligible studies were identified with the initial search, it was decided to repeat the search, include additional databases, use a revised search strategy, and publish an update registration protocol (see above). All search strategies (from the first search and from the update search) can be found in each registration protocol in OSF. Screening of all articles published in English and German was performed independently by two authors (MM, AJ) using the Rayyan QCRI software (37) and no automation tools were used in the process. The research team defined inclusion and exclusion criteria in advance. Reference sections of relevant review and research articles were used to identify additional pertinent articles. The full text of articles identified by the title and/or abstract as possibly applicable was retrieved, and the final decision on the inclusion was made by both reviewers independently. Disagreements between reviewers were resolved by consulting a third and fourth reviewers (PY, BS). The mesh term SEP was introduced in 1982 by PubMed, consequently the search time limit was set from January of the same year. If required, additional information was requested from the article authors. Data regarding the number of probands, study design, duration of treatments, and PES adjustments (Table 2) were extracted from each report. In addition, the researchers evaluated all found cortical latencies and amplitudes of SEPs fragments. The data of SEP fragments from healthy individuals and from patients with stroke regarding PES are presented separately to avoid misunderstanding of the evaluated fragments (Tables 3, 4).

Exclusion/inclusion criteria

All type of non-randomized and randomized intervention studies were included. Moreover, intervention studies with no control group were also included since it was anticipated that the available data to answer the research question would be limited. No restrictions were set with regard to the body parts treated (UL, LL or torso) with PES. Studies in which only electroacupuncture was used were excluded since the piercing through dermis can affect additional neurological afferent pathways associated with pain giving misleading SEP results (43). Studies that measured SEP only during the intervention without follow-up measure were excluded since the study search is limited on SEP use as a change predictor. No limits were set regarding the outcome measures used to determine motor impairment and/or functional performance. Data from abstracts, letters, pilot studies, case studies and review articles were excluded from the study. Studies involving children and animals were not considered either. No limitations were applied regarding the type of stroke (ischemic or hemorrhagic), the time elapsed since the last occurrence, or the stroke location. In the text, the term stroke is used for both, ischemic and hemorrhagic stroke. The studies which focused on the effect of electrical stimulation on any of the following conditions were excluded:

TABLE 2 Peripheral electrical stimulation effect—characteristic summary.

Study	Study design	Healthy or stroke population; no. of participants	Duration of treatments	Location of peripheral electrical stimulation	Form of stimulation; pulse amplitude; pulse duration; pulse frequency	Outcome measures
Studies made on healthy volunteers						
Ashton et al. (6)	Case-matched study; three group; pre-post test	32 healthy volunteers; Group A/Placebo (11n); Group B/TENS (10n); Group C/Aspirin (11n)	TENS 5 cycles randomly varied between 30 and 33 stimuli ∼5 min duration	TENS with two 8 cm^2—disposable electrodes were placed on the ventral surface of the forearm between the elbow and the wrist.	Monophasic electric shock stimulation; Not Provided (individual); 0.2 ms; 100 Hz	Not provided
Cogiamanian et al. (38)	One-group; pre-post test	12 healthy volunteers; Group A/(12n) tsDCS + (5n) (Placebo) same volunteers as in group A	Transcutaneous spinal (anodal and cathodal) direct current stimulation for 15 min	2 pair of saline-soaked synthetic sponge electrodes placed on tenth thoracic spinal vertebra and other above the right shoulder.	Constant current pulses; 2.5 mA; Not provided; Not provided	Not provided
Schabrun et al. (33)	(Crossover model) One-group; pre post test	13 healthy volunteers; Motor Movement PES Intervention and Sensory PES 100 Hz Interventions	Each subject participated in two sessions (30 min of PES) separated by at least 72 h	On each occasion, a different electrical stimulation intervention was administered to the right ABP	Constant current pulses; **1.** Motor movement: Stimulus intensity set to sufficient to induce a mid-range thumb abduction; 0.1 ms; 30 Hz; **2.** Sensory 100 Hz: set at the point where the subject first reported perception of the stimulus; 0.1 ms; 100 Hz	TMS, MEP, EEG
Kang et al. (39)	(Crossover model) one-group; pre-post test	20 healthy volunteers; Sham TENS 2 Hz; TENS 2 Hz EA	The application of sham TENS, 2 Hz TENS and 2 Hz EA lasted for 15 min	Sham TENS and TENS electrodes were placed on the fibular side of the tibial tuberosity (electrode size is not provided)	Bidirectional symmetric square-wave pulses; 12 to 24 mA; Not provided; 2 Hz	Not provided
Rocchi et al. (40)	One-group; pre-post test	15 healthy volunteers	Subjects underwent 45 min of HF-RSS	Stimulation was delivered separately to the third phalanx of the right and left thumb and index finger using surface electrodes separated by 0.5 cm (anode placed distally to the cathode)	Constant current stimulator in the form of square-wave pulses; Not provided (individual); 200 μs; 20 Hz	TMS, STDT, tactile spatial acuity and short intracortical inhibition

(Continued)

10.3389/fneur.2022.1036891

TABLE 2 (Continued)

Study	Study design	Healthy or stroke population; no. of participants	Duration of treatments	Location of peripheral electrical stimulation	Form of stimulation; pulse amplitude; pulse duration; pulse frequency	Outcome measures
Zarei et al. (41)	Case-matched study two group; pre-post test	40 healthy volunteers; Group A/(20n) TENS; Group B (20n) (Placebo)	TENS two blocks of 40 trials applied for 20 min	The electrical pulses were delivered through the same electrodes (4 × 4.6 cm) as used in the SEP procedure (left-MN of the non-dominant hand)	Constant current stimulator in the form of square-wave pulses below the motor threshold (individual); 1 ms; 100 Hz	EEG
Studies made on stroke population						
Bao et al. (12)	Retrospective case-matched study two groups; pre-post	Group A / BWSTT / 90 stroke patients; Group B / FES plus BWSTT/ 90 stroke patients	Group A / BWSTT for 30 min daily; Group B / FES for 45 min twice a day, plus BWSTT for 30 min daily for 8 weeks	FES of paretic leg 6 cm X 9 cm and 4 cm x 4 cm electrodes four output channels and a one-foot switch	Bidirectional symmetry square-wave pulses; 15 mA; 0.3 ms; 30 Hz	Walking speed, step length, step cadence, LL-fMa, CSS, 10MWt, TBT and MEP
Peurala et al. (13)	Case-matched study three-group; pre-post test	Group A / 32 stroke patients, active treatment of the paretic hand; Group B / 19 stroke patients, active treatment of the paretic foot; Group C/8 stroke patients, placebo treatment in the paretic hand	Group A and B active FES for 20 min twice a day Group C Placebo for 21 days	Cutaneous stimulation of paretic hand or paretic foot treatment 6 cm diameter electrode *via* glove/sock electrode	Monophasic constant current twin pulses; Not provided (individual); Not provided; 50 Hz	MMAS, 10MWt, paretic limb function, limb skin sensation
Giaquinto et al. (42)	Case-matched study two-group; pre-post test	Group A / 20 stroke patients; Group B / 82 stroke patients (control group)	Twice a day (morning and afternoon)	Target or non-target stimulation of the impaired or non-impaired hand, shoulder or hip using feedback system (electrode size is not provided)	Constant current pulses; 25 mA, above the threshold; 0.1 ms; Not provided;	CT scan and/or NMR, FIM, CIRS 14 and EEG signals
Tashiro et al. (15)	Case-matched study one-group; pre-post test	23 stroke patients	HANDS therapy system, applied for 8 h each day for 21 days	A hybrid electrode (10 mm diameter) for EMG detection and stimulation was placed on the belly of the affected EDC. An electrode (10 mm) for stimulation was placed on the affected EIP.	Not provided; Not provided (individual); Not provided (individual); Not provided (individual)	SWMT, TLT, FMA, MAS, SIAS, and MAL-14

BWSTT, Body Weight-Supported Treadmill Training; FES plus BWSTT, Functional Electrical Stimulation plus Body Weight-Supported Treadmill Training; FES, Functional Electrical Stimulation; tsDCS, Transcutaneous spinal (anodal and cathodal) direct current stimulation: MEP, Magnetic Evoked Potential; LL-fMa, Fugl-Meyer Lower-limb Scale; CSS, Composite Spasticity Scale; 10MWt, 10-Meter Walk Test; TBT, Tinetti Balance Test; MMAS, Modifed Motor Assessment Scale; NMR, Nuclear Magnetic Resonance; CT scan, Computed Tomography; FIM, Functional Independence Measure; CIRS 14, Cumulative Illness Rating Scale; EEG, Electroencephalography; HANDS, Hybrid Assistive Neuromuscular Dynamic Stimulation; EDC, Extensor Digitorum Communis; EIP, Extensor Indicis Propris; SWMT, Semmes–Weinstein Monofilament Test; TLT, Thumb Localizing Test; FMA, Fugl-Meyer Assessment for the UL; SIAS, Stroke Impairment Assessment Set; MAS, Modified Ashworth Scale; Mal-14, Motor Activity Log-14; TENS, Transcutaneous Electrical Nerve Stimulation; EA, Electroacupuncture; PES, Peripheral Electrical Stimulation; ABP, Abductor Pollicis Brevis; TMS, Transcranial Magnetic Stimulation; HF-RSS, High Frequency Repetitive Somatosensory Stimulation; STDT, Somatosensory Temporal Discrimination Threshold.

10.3389/fneur.2022.1036891

TABLE 3 Latencies and Amplitudes of SEP Components—Pre–Posttest—Studies made on healthy volunteers.

Study/sample size	SEP components (latencies and amplitudes)	Test time/follow-up and statistical analysis	Significant effects
Ashton et al. (6) 32 healthy volunteers	MN at the wrist, troughs and peaks utilizing latency criterion of: P1:60-100 msec, N1:100-160 msec, P2: 160-260 msec, N2 and P3: 260-360 msec	Pretreatment/- 15 min Post-I/0 min Post-II/+15 min Post-III/30 min Post-IV / +45 min 1-way ANOVA and 2-way ANOVA	Consideration of means showed a decrease of N1P2 amplitude and increase of N1 latency in the TENS group as compared to placebo or aspirin group. For the SEP total excursion measure, a significant effect occurred in the time epoch 30 min post-treatment ($F = 3.92$, $df = 2, 29$, $P < 0.05$) and a marginal effect in the last time epoch 45 min post-treatment ($F = 2.79$, $df = 2, 29$, $0.10 > P > 0.05$).
Cogiamanian et al. (38) 12 healthy volunteers	The SEP of MN at the wrist: P14, N20 latency and amplitudes and TN SEPs at the ankle: N9, N22, P30, P39, latency and amplitudes	Baseline Post-I/0 min Post-II/+20 min 1-way ANOVA and 2-way ANOVA Post hoc analysis	Compering changes in TN and MN SEPs after anodal tsDCS over the thoracic spinal cord con- firmed that P30 component elicited by TN stimulation decreased by 49% in amplitude (baseline 0.78 ± 0.12 lV, T0 0.40 ± 0.07 lV; *t*- test: $p = 0.01$), but remained statistically unchanged in latency (baseline 28.8 ± 0.67 ms, T0 28.5 ± 0.57 ms; *t*-test: $p =$ NS). After thoracic tsDCS all the median nerve SEP components remained unchanged (P14 amplitude: baseline 0.68 ± 0.10 lV, T0 0.70 ± 0.04 lV; *t*-test: $p =$ NS; P14 latency: baseline 13.9 ± 0.48 ms, T0 13.7 ± 0.48 ms; *t*-test: $p =$ NS).
Kang et al. (39) 20 healthy volunteers	The SEP of MN at the wrist: N13, N20, P25, N30 latency and amplitudes	Baseline During the stimulation period Post-I / + 20 min 1-way ANOVA and Scheffe's post hoc correction	EA demonstrated a higher mean amplitude in N20 during the stimulation and post- stimulation periods compared with baseline. In N30 the difference only appeared during the stimulation period when treated with EA. These effects were not observed when subjects were treated with sham TENS or 2 Hz TENS. No significant differences were observed in other components of MN-SEPs, either for mean latency or amplitude.
Schabrun et al. (33) 13 healthy volunteers	The SEP of MN at the wrist: peak-to-peak amplitudes: P14-N20, N20-P25, P25-N33, N13, N9 and latencies N9, N14 and N20	Before and after completion of the stimulation period 1-way ANOVA Linear regression analyses Where appropriate, *post-hoc* tests were performed	Neither motor or sensory PES induced a change in the latency of the N13/N20 1. Motor movement: Motor PES increased the amplitude N20-P25 (*post-hoc* pre vs. post $p = 0.007$,) no change in the P14-N20 (*post-hoc* pre vs. post $p = 0.34$) or P25-N33 (*post-hoc* pre vs. post $p = 0.77$) components. 2. Sensory 100 Hz: Sensory PES increased the amplitude of P14-N20 (*post-hoc* pre vs. post $p = 0.01$,) and reduced P25-N33 (*post-hoc* pre vs. post $p = 0.001$) The N20-P25 component was unchanged by sensory PES (*post-hoc* pre vs. post $p = 0.34$).
Rocchi et al. (40) 15 healthy volunteers	Digital nerves of the right index finger were stimulated The UL SEPs: amplitudes: P14, N20-P25 and N20 peak latency	Before and 5 min after the completion of the 45 min stimulation period 2-way ANOVA and dependent Student's *t*-test	HF-RSS increased the amplitude of N20-P25 ($p < 0.001$) and P14 ($p < 0.001$) immediately after HF-RSS was applied. No changes in N20 or P14 latency were observed (p values of all *t*- tests > 0.05)
Zarei et al. (41) 40 healthy volunteers	The SEP of MN at the hand: N100, P200, and N400 latency and amplitudes	Baseline Post-I / 0 min Post-II/+30 min Post-III/60 min 2-way ANOVA Where appropriate, *post-hoc* tests were performed	The magnitude of N100, P200 waves, and theta and alpha band power was significantly suppressed following the TENS intervention. The suppression of the magnitude of the N100 wave lasted at least an hour. However, the effects of TENS on the magnitude of P200 only remained for 30 min after the intervention.

MN, Median nerve; TENS, Transcutaneous Electrical Nerve Stimulation; EA, Electroacupuncture; UL, Upper limb; HF-RSS, High Frequency Repetitive Somatosensory Stimulation; LL, Lower limb; TN, Tibial nerve; tsDCS, Transcutaneous Spinal (anodal and cathodal) Direct Current Stimulatio.

10.3389/fneur.2022.1036891

TABLE 4 Latencies and Amplitudes of SEP Components—Pre–Posttest –Studies made on stroke population.

Study/sample size	SEP components (latencies and amplitudes)	Test time/follow-up and statistical analysis	Significant effects
Bao et al. (12) 90 stroke patients	Not provided	Baseline, end of week 8 Paired *t*-tests and McNemar tests, 1-way ANOVA, χ2 tests	Significant differences in latency and peak value of SEP between the two groups at the end of the eighth week ($p < 0.05$), but not at baseline ($p > 0.05$).

	Latency (ms)			Peak (μV)		
	Baseline	**8 weeks**	**P value**	**Baseline**	**8 weeks**	**P value**
Group A	43.7±5.56	38±3.6	P<0.05	1.44±0.52	2.13±0.51	P<0.05
Group B	44.1±6.97	27.3±5.36	P<0.01	1.53±0.46	2.94±0.59	P<0.01
P-value	0.89	P<0.01		0.7	P<0.01	

Peurala et al. (13) 59 stroke patients	The SEP of MN at the wrist: N20, N30, N60, (patients with hand stimulation treatment) and TN SEPs at the ankle: P40, N80, (patients with foot stimulation treatment)	Baseline, end of week 3 Paired samples *t*-test, nonparametric Wilcoxon and marginal homogenity test	SEP normality classification improved significantly in paretic UL ($p < 0.01$) and in paretic LL ($p < 0.05$) in the stimulated group (n = 51) after 3 weeks of rehabilitation.

Hand SEP* (n = 8)	**Before**	**After**	**Foot SEP* (n = 19)**	**Before**	**After**
1	0	0	1	0	2
2	3	3	2	10	10
3	5	5	3	9	7

*SEP: 1, normal; 2, minor change; 3, abnormal

Giaquinto, et al. (42) 102 stroke patients	The UL SEP N20 latency, affected and unaffected side	Baseline, end of week 8 Mann–Whitney *U*-test, Student's *t*-test, Spearman correlation	The mean amplitude N20 on the affected side increased compared to the baseline. Latencies did not change.

	N20: Mean Amplitude SD		N20: Mean Latencies and SD	
	Unaffected Hemisphere	**Affected Hemisphere**	**Unaffected Hemisphere**	**Affected Hemisphere**
Before	−3.4 μV (1.5)	−1.8 μV (1.4) df = 18, *t* = 3.716, *P* = 0.002	20.5ms (1.5)	17.7ms (7.9) df = 18, *t* = 1.489, ns
After (1.3)	−3.4 μV	−2.6 μV (1.2) df = 16, *t* = −2.270, *P* = 0.003	20.1ms (1.2)	19.2ms (5.1) df = 16, *t* = 0.735, ns
Before and after comparison	df = 016, *t* = 0.363, ns df = 16, *t* = 4.932, *P* = 0.0001			

(Continued)

10.3389/fneur.2022.1036891

TABLE 4 (Continued)

Study/sample size	SEP components (latencies and amplitudes)	Test time/follow-up and statistical analysis	Significant effects
Tashiro et al. (15) 23 stroke patients	NI(N20), PI(P25), NII(N33), PII(P45), NIII(N60) of the MN at the wrist and N31, P35, N42, P53, N66 of the TN at the ankle	Baseline, end of week 3; Wilcoxon signed-rank tests Student's *t*-test	The Wilcoxon signed-rank test indicated that the number of cortical peaks significantly increased in the MN, but not in the TN in the non-paretic side (MN, $p = 0.008$; TN, $p = 0.11$). No significant changes in the MN between peak latencies of central SEP peaks and N18. Remarkable differences were detected in shortening of the latency between NI(N20) – PII(P45) after the intervention.

MN, Median nerve; TENS, UL, Upper limb; HF-RSS, High Frequency Repetitive Somatosensory Stimulation; LL, Lower limb; TN, Tibial nerve.

spinal cord injuries, Parkinson's disease, multiple sclerosis, pain or cranial nerve. Furthermore, the studies that used transcranial direct current stimulation, transcranial magnetic stimulation, or deep brain stimulation were excluded.

Methodological quality

The Cochrane risk of bias in non-randomized studies (ROBINS-I) tool developed by Sterne et al. (44) was used to assess the risk of bias of observational studies that compare health effects of two or more interventions. ROBINS-I is a tool for evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions from studies that did not use randomization to allocate units (individuals or clusters of individuals) to comparison groups. ROBINS-I'S fundamental underlying principle is to compare the risk of bias associated with the current evaluated non-randomized trial with a target randomized controlled trial (RCT) hypothesized to be conducted with the same group of participants, even though this RCT may not be feasible or ethical (45). The ROBINS-I tool includes seven domains to assess the risk of bias that may arise in a non-randomized study: (1) bias due to confounding; (2) bias in selection of participants into the study; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in measurement of outcomes (or detection bias); (7) bias in selections of the reported results. The categories for risk of bias judgments are Low risk, Moderate risk, Serious risk and Critical risk. The risk of bias is first assessed for each domain, and then the overall judgement of the study's risk of bias is made (44).

The "Quality Assessment Tool for Before-After (Pre-post)" developed by the National Institutes of Health (NIH) was used to rate the methodological quality of pre-post studies without a control group (46). The questions in the NIH quality assessment tool were designed to help reviewers focus on the key concepts for evaluating the internal validity of a study. Critical appraisal of a study involves considering the potential for selection bias, information bias, measurement bias, or confounding. Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues addressed throughout the tool which can be found in Table 5. High risk of bias translates to a rating of poor quality; low risk of bias translates to a rating of fair and good quality (46).

The overall certainty of evidence and strength of recommendation was assessed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE handbook) methodology (47). According to the GRADE approach, the evidence is graded as high, moderate, low, or very low certainty of evidence. Furthermore, a body of evidence from observational studies begins with a low certainty of evidence-rating which could be downgraded due to five reasons: risk of bias, indirectness, inconsistency, imprecision

TABLE 5 Methodological quality of included studies according to the "Quality Assessment Tool for Before-After (Pre-post)".

	Studies made on healthy volunteers				Study made on stroke population
	Cogiamanian et al. (38)	Schabrun et al. (33)	Kang et al. (39)	Rocchi et al. (40)	Tashiro et al. (15)
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No	No	No	No	Yes
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	No	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes	Not reported	Not reported	Not reported	Yes
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Not reported	Yes	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests were done that provided *p*-values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes	No	Yes	Yes	No
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No	NA	NA	NA	NA
Quality rating	Fair	Fair	Poor	Fair	Good

and publication bias (36). There are three factors that permit rating up the certainty of evidence: large magnitude of an effect, dose-response gradient, and effect of plausible residual confounding (47).

Results

The systematic search resulted in 11,351 references. The search from Pubmed/MEDLINE database resulted in 2,963 records, Scopus/ScienceDirect database resulted in 1,882 records, Cochrane library database resulted in 4,176 records, Web of Science/Clarivate resulted in 4,877 records and the database PEDro resulted in 10 records. The registry ClinicalTrials.gov was searched manually, and four studies were included for further evaluation. We excluded 2,561 duplicate studies using Rayyan QCRI software (37). Based on the titles and abstracts 69 reports were included for full-text reading. Additionally, six articles were found after the screening of reference lists. Ten articles were included in the review after applying the inclusion and exclusion criteria. The search process is presented in the PRISMA flow diagram (Figure 1).

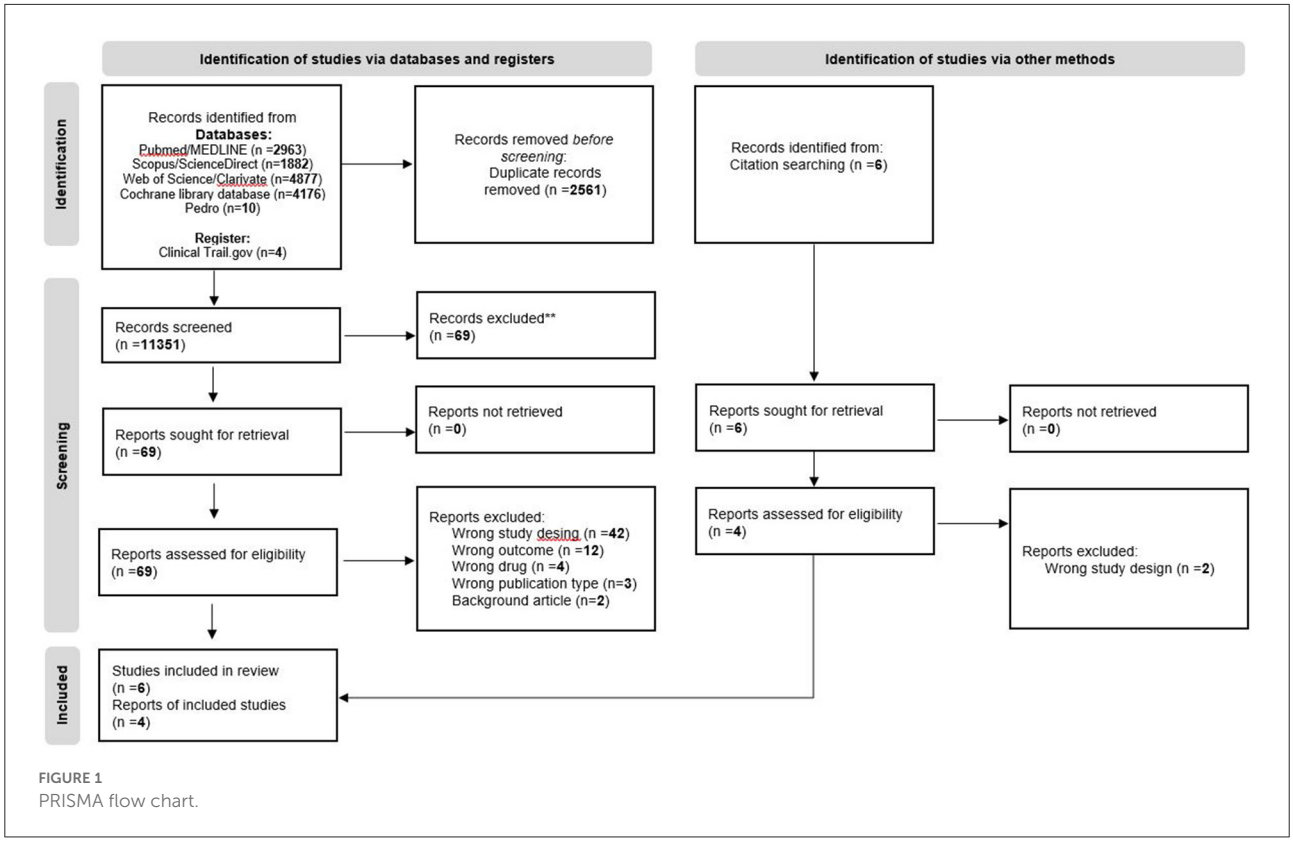


FIGURE 1
PRISMA flow chart.

Intervention procedure and the time frame between the SEP measurements

The different forms of stimulation, stimulation devices, location of PES, amplitude, duration, and frequency pulse as well as test time and follow-up of SEP were examined in each study. All data are summarized in Table 2. The total amount of participants in the reviewed studies was 496. Of these, 364 were stroke patients and 132 were healthy participants. Five studies involved one (12, 41, 42) or two (6, 13) control groups. The study by Kang et al. (39) applied: Sham TENS, 2Hz TENS or 2Hz electroacupuncture and the study from Schabrun et al. (33) applied Motor Movement PES or Sensory PES 100 Hz intervention. On the other hand Tashiro et al. (15) used SEP of the tibial nerve as a reference to SEP for the median nerve and Cogiamanian et al. (38) measured five subjects from the first group a second time using sham stimulation. A wide range of sensory-motor assessments was used to examine the effect of PES in studies of stroke patients and healthy participants (Table 2). The assessment of SEP in two studies on stroke patients (12, 42) was performed at baseline and 8 weeks post PES intervention. In the other two studies (13, 15) the assessment was performed at baseline and 3 weeks post PES intervention. The SEP in healthy participants in all six studies was assessed before, at baseline, and 0,15/20/30/45/60 min after the intervention (6, 33, 38–41). In the majority of studies on stroke patients the SEP measurements were performed on the median nerve. In the study by Peurala et al. (13) SEPs on the UL were performed in those patients who received hand stimulation and SEPs on the LL were performed in those patients who received foot stimulation while in the study from Tashiro et al. (15) SEPs from tibial nerves were used as a control measurement. Bao et al. (12) reported an improvement of latency and peak value of SEPs between the two groups at the end of the 8th week without further explanation of how the measurement was performed. No study showed a loss of peaks after the intervention. Details about SEP changes in latencies and amplitudes components can be found in Tables 3, 4. The following body location were stimulated with PES: tenth thoracic spinal vertebra (38), shoulder (38, 42), arm, hand or fingers (6, 13, 15, 33, 40–42), lower limb and foot (12, 13, 39) and hip (42). The found data about stimulation form, stimulation devices, location of PES, amplitude, duration, and frequency pulse as well as test time and follow-up of SEP could not be standardized so we decided to analyzed data separately.

Methodological quality of included studies

Five non-randomized studies (6, 12, 13, 41, 42) with serious to moderate risk of bias (Figure 2) and five pre-post studies (15, 33, 38–40) without a control group with poor to good methodological quality (Table 5) were included and assessed

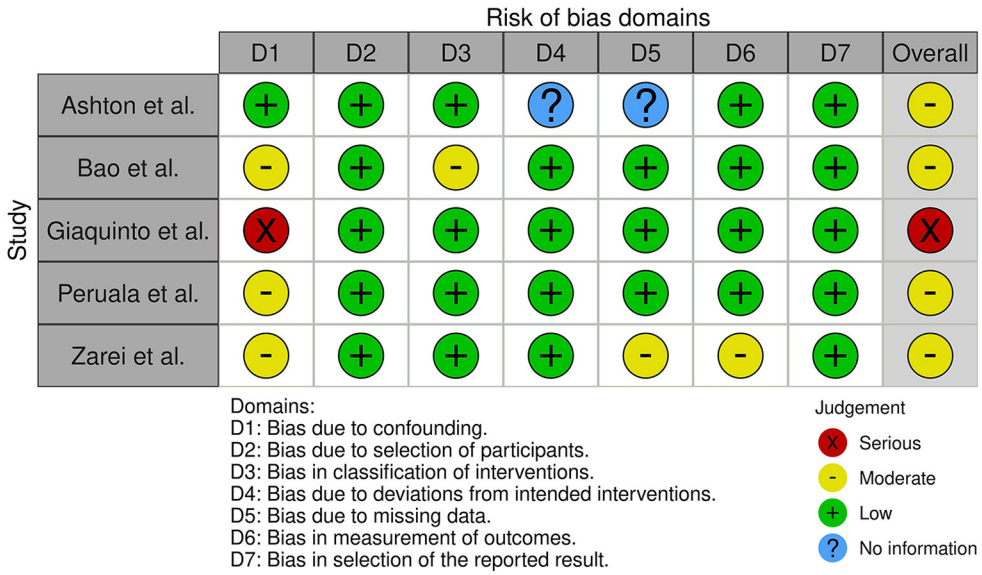


FIGURE 2
Results of the ROBINS-I tool to assess risk of bias domains.

in the present review. No randomized trials were found. Low overall risk of bias in non-randomized trials, which can be compared to a well-performed randomized trial, was not found in any of the included studies (6, 12, 13, 41, 42). Due to the fact that the Robins-I tool uses strict criteria to evaluate confounding bias, one study was classified as having serious risk of bias (42). Four studies were evaluated as having moderate risk of bias because the data was collected retrospectively (12), insufficient information was given about the potential confounding bias (13, 41), or no explanation of the source of information about intervention status was reported (6). In accordance with the NIH tool, one pre-post study had good (15), tree studies had fair (33, 38, 40), and one had poor (39) methodological quality. The eligibility criteria and the outcome measures were prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants, except for the study by Kang et al. (39). According to the NIH tool, the sample size should be large enough to provide confidence in the findings and outcome assessors should be blinded to the participants' exposures, and interventions. Only the study by Tashiro et al. (15) managed to meet these important criteria.

The overall certainty of evidence was very low for all outcomes (Supplementary Table 1). All available evidence was downgraded for limitations in study design and risk of bias (6, 12, 13, 15, 33, 38–42), imprecision (6, 12, 13, 15, 33, 38–42), or indirectness (6, 12, 39, 41) to very low certainty of evidence. There were no legit reasons to rate up the certainty of evidence. Thus, there is insufficient evidence for or against the use of SEP to monitor therapeutic effects.

Synthesis of results

It was planned to perform a meta-analysis, if enough homogenous data were available, using mean difference and random effects model. However, quantitative synthesis was not possible due to limited and heterogenous eligible studies. Therefore, a qualitative synthesis was performed. Table 6 features a summary of SEP latency and amplitude outcomes in studies using same measurement instruments.

Discussion

Studies made on healthy volunteers

By evaluating motor function and control, corresponding to changes in SEP components in healthy participants, the study by Rocchi et al. (40) suggested that high frequency repetitive somatosensory stimulation leads to improved performance in behavioral tests of temporal discrimination and contributes to improved performance in tests of spatial detection. Nevertheless, high frequency repetitive somatosensory stimulation also affects short-latency inhibition in M1. Together these changes in S1 and M1 may underlie reported improvements in manual motor performance (40). The correlation in healthy individuals between SEP and similar neurophysiological procedures as described in the study by Schabrun et al. (33). The magnitude and direction of the change in corticomotor excitability induced by sensory and motor PES was positively correlated with the difference in the cortical SEP components ($r = 0.71$, p

TABLE 6 SEP latency and amplitude outcomes synthesis in studies using same measurement instruments.

Outcomes/study	Measurement instruments	Significant effects
Studies made on stroke population		
Amp N20/P25/UL (13, 15, 42)	The UL SEP N20 amplitude was recorded using surface electrodes placed in anatomically identified locations of the hand area of the primary somatosensory cortex. Affected and unaffected side was measured.	The signal amplitude N20 **increased**. Student's *t*-test ($P = 0.0001$) (42) SEP normality classification **improved** significantly in paretic UL. Paired samples *t*-test ($p < 0.01$) (13) The number of cortical peaks **increased** significantly The Wilcoxon signed-rank test ($p = 0.008$) (15)
Lat N20/UL (13, 15, 42)	The UL SEP N20 latency was recorded using surface electrodes placed in anatomically identified locations of the hand area of the primary somatosensory cortex. Affected and unaffected side was measured.	Latencies **did not change**. Student's *t*-test ($p > 0.05$) (42) SEP normality classification **improved** significantly in paretic UL. Paired samples *t*-test ($p < 0.01$) (13) **No significant changes** between peak latencies ($p > 0.05$) (15)
Amp P40/LL (12, 13)	Not provided (12) The TN SEP P40 amplitude was recorded using surface electrodes placed in anatomically identified locations of the LL area of the primary somatosensory cortex. Affected and unaffected side was measured (13)	The signal amplitude N20 **increased**. Paired samples *t*-test ($p < 0.05$) (12) SEP normality classification **improved** significantly in paretic LL. Paired samples *t*-test ($p < 0.05$) (13)
Lat P40/LL (12, 13)	Not provided (12) The TN SEP P40 latency was recorded using surface electrodes placed in anatomically identified locations of the LL area of the primary somatosensory cortex. Affected and unaffected side was measured (13)	Latency **improved** after intervention. Paired *t*-tests ($p < 0.05$) (12) SEP normality classification **improved** significantly in paretic LL. Paired samples *t*-test ($p < 0.05$) (13)
Studies made on stroke population		
Amp N20/P25/UL (33, 38–40)	The UL SEP and N20/P25 amplitude was recorded using surface electrodes placed in anatomically identified locations of the hand area of the primary somatosensory cortex.	The signal amplitude **decreased**. paired *t*-tests $p = 0.01$ (38) **No significant differences** observed in amplitude. One-way analysis of variance shown as mean±SD (39) Motor PES **increased** the amplitude (*post-hoc* pre vs. post $p = 0.007$,) (33) The signal amplitude **increased**. Dependent *t*-tests were ($p < 0.001$) (40)
Amp N100/UL (6, 41)	The EEG signals was recorded during the sensory evoked potential (SEP) phases.	The signal amplitude **decreased.** 2-way ANOVA ($P > 0.05$) (6) The magnitude was significantly **decreased**. 2-way ANOVA ($P > 0.05$) (41)
Lat N100/UL (6, 41)	The EEG signals was recorded during the sensory evoked potential (SEP) phases.	Latency **increased** after intervention. 2-way ANOVA ($P > 0.05$) (6) Latencies **did not change**. 2-way ANOVA ($P > 0.05$) (41)

UL, Upper limb; LL, Lower limb; Amp, Amplitude: Lat, Latency.

< 0.001), as confirmed by linear regression between cortical SEP components (N20-P25 and P25-N33) and corticomotor excitability motor evoked potential (MEP) amplitude. Similar changes as already described in the study from Rocchi et al. (40) showed a correlation between PES, high-frequency oscillations analysis and N20-P25 recovery curve. The first conclusion considered from the obtained results is a good validity between SEP, TMS and its correlation with PES. In other terms, not only

somatosensory brain areas are affected through PES. Moreover, the motoric brain regions are part of this process. Despite those fact it is necessary to note that all studies made on healthy volunteers assess SEP maximum 1 h after PES and that the studies (38, 41) showed selectively reduced amplitudes in primary somatosensory cortex direct after stimulation. However, we did not identify enough data to provide a clear relationship between SEP and motor performance subsequently to PES in healthy individuals. The lack of observation studies over extended periods of time is the main problem when it comes to drawing a clear conclusion about the impact of PES on SEP.

Studies made on stroke patients

In the stroke study (13) SEP and Modified Motor Assessment Scale results were not compared, but both measures showed improvement. Moreover, in a study (42) significant negative correlation between the time interval for the appearance of somatosensory event-related potentials and the functional independence measure (FIM) score at the time of discharge ($r = -0.53$, $p < 0.01$). The study on stroke patients by Tashiro et al. (15) observed significant improvements in behavioral assessment scores for proprioception followed by PES interventions. We could conclude that assessments of motor performance correspond to changes in SEP components in UL and LL. Additionally, the studies on stroke patients involving PES that initiate a voluntary contraction used for a specific movement or task (12, 13, 15, 42), indicate a positive relationship and correlation to assessments of motor function. This hypothesis is supported by findings in a meta-analysis on stroke motor recovery of UL functions (48) and therapeutic effects of peroneal stimulation on gait and motor recovery (18). Moreover, simple sensory stimulation, unrelated to the movement, was of limited functional value for motor recovery for the rehabilitation of the hand in stroke patients and no correlation was described (49).

SEP results in healthy subjects compared to stroke patients

Somatosensory event-related potentials accompanied with SEP in a study from Giaquinto et al. (42) were adequate to follow changes in primary somatosensory area N20. The Bao et al. (12) found significantly improved latency and peak value of SEP and MEP. Furthermore, those changes respond to sensory and motor nerve conduction velocity at the end of the 8 week ($p < 0.05$). This finding indicates the relevance of evaluating electrophysiological methods and may verifies the use of SEP in stroke patients. All SEP set on stroke patients demonstrated several subcortical or cortical reorganization changes after treatment with PES on the paretic side. However, an unrelated time frame and insufficient data were collected to analyze the relationship between the form of stimulation, pulse amplitude, pulse duration, or location of stimulation and changes in SEP. Perhaps it should be emphasized that in stroke studies in which high pulse amplitude inducing muscle contraction was delivered, the increase of amplitude N20-P25 (15, 42) was seen. The same was observed in healthy participants (33, 40). In order to confirm this hypothesis, we suggest conduction of randomized controlled study on healthy subjects and stroke patients using standard SEP procedure define by Muzyka et al. (31), and clearly described used PES parameter. Based on the GRADE approach to assess the quality of evidence, no outcome that provided a strong recommendation was found. There is thus far insufficient evidence to support a decision for or against use of SEP to monitor therapeutic effects and the results of this analysis cannot be generalizable.

It is known that there are substantial anatomical interconnections linking the brain's motor and somatosensory regions. Cortical motor areas receive direct inputs from primary and second somatosensory cortex and inversely, somatosensory areas get direct cortical inputs from primary motor cortex, premotor cortex, and from supplementary motor area (21, 50). A change in somatosensory function in association with motor learning would seem to be a natural by-product of this anatomical connectivity (21, 50). Findings in this review suggest that PES may shift the response of somatosensory to motor areas of the brain. On the other hand, it could be hypothesized that SEP can indirectly recognize the changes in motor area of the brain. Moreover, it appears that SEPs have sufficient sensitivity to detect even the smallest changes in action potential of neural cortical network after stroke and is probably able to assess the effect of various sensory therapies: cryotherapy, thermotherapy, occupational tactile therapy, or robotic tactile therapy more directly.

Limitations of the study

First, we cannot confirm that all PES studies were identified because the meaning of the term "peripheral electrical stimulation" varies widely and is understood differently. We tried to minimize this limitation by searching more databases. Second, we were aware that EEG measurement can also be used to record SEP, and the lack of keywords and terms to describe this process limited our desire to include all of these studies. However, we used the term "evoked potentials" to increase the number of studies identified in our database search and to include studies using EEG. We also tried to use all PES terms indexed in PubMed to find an optimal data set and minimize this limitation.

Conclusion

From the results of this review, the repetitive task-oriented treatment enriched with PES could likely become a different approach to be applied in stroke patients to improve daily living activities since we have hints that PES may impact changes in motor neuroplasticity. We suggest that more studies (especially RCTs) should be conducted to evaluate whether SEP measures can be used to monitor the therapeutic effects of PES in the rehabilitation of stroke patients, as there is insufficient evidence to do so but SEP remains a promising tool to estimate rehabilitation prognosis after stroke.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MM, AJ, BS, and PY contributed to conception and design of the study. MM organized the database and wrote the first draft of the manuscript. MM and AJ performed the qualitative analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

Acknowledgments

We appreciate the help of Prof. Stephan Kröger from Ludwig-Maximilians-University Munich, Institute for Physiology and Prof. Joachim Liepert, head of the Department of Neurorehabilitation Kliniken Schmieder Allensbach, for critical reading of the article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1036891/full#supplementary-material

References

1. Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey LL, Lojovich JM, Carey JR. Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Exp Brain Res.* (2004) 154:450–60. doi: 10.1007/s00221-003-1695-y

2. Bajd T, Crt M, Munih M. Functional electrical stimulation with surface electrodes. *J Autom Control.* (2008) 18:3–9. doi: 10.2298/JAC0802003B

3. Marquez-Chin C, Popovic MR. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. *Biomed Eng Online.* (2020) 19:34. doi: 10.1186/s12938-020-00773-4

4. Moll I, Vles JSH, Soudant DLHM, Witlox AMA, Staal HM, Speth LAWM, et al. Functional electrical stimulation of the ankle dorsiflexors during walking in spastic cerebral palsy: a systematic review. *Dev Med Child Neurol.* (2017) 59:1230–6. doi: 10.1111/dmcn.13501

5. Laufer Y, Elboim-Gabyzon M. Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review. *Neurorehabil Neural Repair.* (2011) 25:799–809. doi: 10.1177/1545968310397205

6. Ashton H, Golding JF, Marsh VR, Thompson JW. Effects of transcutaneous electrical nerve stimulation and aspirin on late somatosensory evoked potentials in normal subjects. *Pain.* (1984) 18:377–86. doi: 10.1016/0304-3959(84)90050-2

7. Golding JF, Ashton H, Marsh R, Thompson JW. Transcutaneous electrical nerve stimulation produces variable changes in somatosensory evoked potentials, sensory perception and pain threshold: clinical implications for pain relief. *J Neurol Neurosurg Psychiatry.* (1986) 49:1397–406. doi: 10.1136/jnnp.49.12.1397

8. Urasaki E, Wada SI, Yasukouchi H, Yokota A. Effect of transcutaneous electrical nerve stimulation (TENS) on central nervous system amplification of somatosensory input. *J Neurol.* (1998) 245:143–8. doi: 10.1007/s004150050194

9. Straudi S, Baroni A, Mele S, Craighero L, Manfredini F, Lamberti N, et al. Effects of a robot-assisted arm training plus hand functional electrical stimulation on recovery after stroke: a randomized clinical trial. *Arch Phys Med Rehabil.* (2020) 101:309–16. doi: 10.1016/j.apmr.2019.09.016

10. Gandolla M, Ward NS, Molteni F, Guanziroli E, Ferrigno G, Pedrocchi A. The neural correlates of long-term carryover following functional electrical stimulation for stroke. *Neural Plast.* (2016) 2016:4192718. doi: 10.1155/2016/4192718

11. Berenpas F, Weerdesteyn V, Geurts AC, Van Alfen N. Long-term use of implanted peroneal functional electrical stimulation for stroke-affected gait: the effects on muscle and motor nerve. *J Neuroeng Rehabil.* (2019) 16:1–10. doi: 10.1186/s12984-019-0556-2

12. Bao X, Luo JN, Shao YC, Tang ZQ, Liu HY, Liu H, et al. Effect of functional electrical stimulation plus body weight-supported treadmill training for gait rehabilitation in patients with poststroke: a retrospective case-matched study. *Eur J Phys Rehabil Med.* (2020) 56:34–40. doi: 10.23736/S1973-9087.19.05879-9

13. Peurala SH, Pitkänen K, Sivenius J, Tarkka IM. Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clin Rehabil.* (2002) 16:709–16. doi: 10.1191/0269215502cr543oa

14. Sawaki L, Wu CWH, Kaelin-Lang A, Cohen LG. Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. *Stroke.* (2006) 37:246–7. doi: 10.1161/01.STR.0000195130.16843.ac

15. Tashiro S, Mizuno K, Kawakami M, Takahashi O, Nakamura T, Suda M, et al. Neuromuscular electrical stimulation-enhanced rehabilitation is associated with not only motor but also somatosensory cortical plasticity in chronic stroke patients: an interventional study. *Ther Adv Chronic Dis.* (2019) 10:204062231988925. doi: 10.1177/2040622319889259

16. Sheffler LR, Chae J. Neuromuscular electrical stimulation in neurorehabilitation. *Muscle Nerve.* (2007) 35:562–90. doi: 10.1002/mus.20758

17. Stein RB, Everaert DG, Thompson AK, Su Ling Chong, Whittaker M, Robertson J, et al. Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. *Neurorehabil Neural Repair.* (2010) 24:152–67. doi: 10.1177/1545968309347681

18. Dunning K, O'Dell MW, Kluding P, McBride K. Peroneal stimulation for foot drop after stroke. *Am J Phys Med Rehabil.* (2015) 94:649–64. doi: 10.1097/PHM.0000000000000308

19. Popović DB. Advances in functional electrical stimulation (FES). *J Electromyography Kinesiol.* (2014) 24:795–802. doi: 10.1016/j.jelekin.2014.09.008

20. Everaert DG, Thompson AK, Su Ling Chong, Stein RB. Does functional electrical stimulation for foot drop strengthen corticospinal connections? *Neurorehabil Neural Repair.* (2010) 24:168–77. doi: 10.1177/1545968309349939

21. Tinazzi M, Zarattini S, Valeriani M, Romito S, Farina S, Moretto G, et al. Long-lasting modulation of human motor cortex following prolonged transcutaneous electrical nerve stimulation (TENS) of forearm muscles: Evidence of reciprocal inhibition and facilitation. *Exp Brain Res.* (2005) 161:457–64. doi: 10.1007/s00221-004-2091-y

22. Mima T, Oga T, Rothwell J, Satow T, Yamamoto JI, Toma K, et al. Short-term high-frequency transcutaneous electrical nerve stimulation decreases human motor cortex excitability. *Neurosci Lett.* (2004) 355:85–8. doi: 10.1016/j.neulet.2003.10.045

23. Fernandez-del-Olmo M, Alvarez-Sauco M, Koch G, Franca M, Marquez G, Sanchez JA, et al. How repeatable are the physiological effects of TENS? Clin Neurophysiol. 2008;119(8):1834–9. doi: 10.1016/j.clinph.2008.04.002

24. Kofler M, Fuhr P, Leis AA, Glocker FX, Kronenberg MF, Wissel J, et al. Modulation of upper extremity motor evoked potentials by cutaneous afferents in humans. *Clin Neurophysiol.* (2001) 112:1053–63. doi: 10.1016/S1388-2457(01)00540-5

25. Zheng X, Chen D, Yan T, Jin D, Zhuang Z, Tan Z, et al. A randomized clinical trial of a functional electrical stimulation mimic to gait promotes motor recovery and brain remodeling in acute stroke. *Behav Neurol.* (2018) 2018:8923520. doi: 10.1155/2018/8923520

26. Feys H, Van Hees J, Bruyninckx F, Mercelis R, De Weerdt W. Value of somatosensory and motor evoked potentials in predicting arm recovery after a stroke. *J Neurol Neurosurg Psychiatry.* (2000) 68:323–31. doi: 10.1136/jnnp.68.3.323

27. Stinear CM, Smith M-C, Byblow WD. Prediction tools for stroke rehabilitation. *Stroke.* (2019) 50:3314–22. doi: 10.1161/STROKEAHA.119.025696

28. Cormier DJ, Frantz MA, Rand E, Stein J. Physiatrist referral preferences for postacute stroke rehabilitation. *Medicine.* (2016) 95:e4356. doi: 10.1097/MD.0000000000004356

29. Kato H, Sugawara Y, Ito H, Onodera K, Sato C, Kogure K. Somatosensory evoked potentials following stimulation of median and tibial nerves in patients with localized intracerebral hemorrhage: correlations with clinical and CT findings. *J Neurol Sci.* (1991) 103:172–8. doi: 10.1016/0022-510X(91)90160-9

30. Brown KE, Lohse KR, Mayer IMS, Strigaro G, Desikan M, Casula EP, et al. The reliability of commonly used electrophysiology measures. *Brain Stimul.* (2017) 10:1102–11. doi: 10.1016/j.brs.2017.07.011

31. Muzyka IM, Estephan B. Somatosensory evoked potentials. *Handb Clin Neurol.* (2019) 160:523–40. doi: 10.1016/B978-0-444-64032-1.00035-7

32. Zhao C, Valentini E, Hu L. Functional features of crossmodal mismatch responses. *Exp Brain Res.* (2014) 233:617–29. doi: 10.1007/s00221-014-4141-4

33. Schabrun SM, Ridding MC, Galea MP, Hodges PW, Chipchase LS. Primary sensory and motor cortex excitability are co-modulated in response to peripheral electrical nerve stimulation. *PLoS ONE.* (2012) 7:1–7. doi: 10.1371/journal.pone.0051298

34. Eriksen MB, Frandsen TF. The impact of PICO as a search strategy tool on literature search quality: a systematic review. *J Med Libr Assoc.* (2018) 106:420–31. doi: 10.5195/jmla.2018.345

35. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

36. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ WV, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3.* (2022). Available online at: www.training.cochrane.org/handbook (assessed September 1, 2022).

37. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev.* (2016) 5:1–10. doi: 10.1186/s13643-016-0384-4

38. Cogiamanian F, Vergari M, Pulecchi F, Marceglia S, Priori A. Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. *Clin Neurophysiol.* (2008) 119:2636–40. doi: 10.1016/j.clinph.2008.07.249

39. Kang YT, Liao YS, Hsieh CL. Different effects of transcutaneous electric nerve stimulation and electroacupuncture at ST36-ST37 on the cerebral cortex. *Acupunct Med.* (2015) 33:36–41. doi: 10.1136/acupmed-2014-010650

40. Rocchi L, Erro R, Antelmi E, Berardelli A, Tinazzi M, Liguori R, et al. High frequency somatosensory stimulation increases sensori-motor inhibition and leads to perceptual improvement in healthy subjects. *Clin Neurophysiol.* (2017) 128:1015–25. doi: 10.1016/j.clinph.2017.03.046

41. Zarei AA, Jadidi AF, Lontis ER, Jensen W. Short-term suppression of somatosensory evoked potentials and perceived sensations in healthy subjects following tens. *IEEE Trans Biomed Eng.* (2021) 68:2261–9. doi: 10.1109/TBME.2021.3051307

42. Giaquinto S, Mascio M, Fraioli L. The physiopathological bases of recovery processes: The bases of stroke rehabilitation. The cassino project. *Clin Exp Hypertens.* (2002) 24:543–53. doi: 10.1081/CEH-120015331

43. Liu S, Wang ZF, Su YS, Ray RS, Jing XH, Wang YQ, et al. Somatotopic organization and intensity dependence in driving distinct NPY-expressing sympathetic pathways by electroacupuncture. *Neuron.* (2020) 108:436–50.e7. doi: 10.1016/j.neuron.2020.07.015

44. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* (2016) 355:4–10. doi: 10.1136/bmj.i4919

45. Schünemann HJ, Cuello C, Akl EA, Mustafa RA, Meerpohl JJ, Thayer K, et al. GRADE guidelines: 18. How ROBINS-I and other tools to assess risk of bias in nonrandomized studies should be used to rate the certainty of a body of evidence. *J Clin Epidemiol.* (2019) 111:105–14. doi: 10.1016/j.jclinepi.2018.01.012

46. National Institutes of Health. *Quality Assessment Tool for Before-After Studies.* (2014). Available online at: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort (accessed September 1, 2022).

47. Schünemann H, Brozek J, Guyatt G, Oxman A. *Handbook for Grading the Certainty of Evidence and the Strength of Recommendations Using the GRADE Approach.* Hamilton, ON: GRADE Working Group 2013 (2013).

48. Bolton DAE, Cauraugh JH, Hausenblas HA. Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: a meta-analysis. *J Neurol Sci.* (2004) 223:121–7. doi: 10.1016/j.jns.2004.05.005

49. Hummelsheim H, Maier-Loth ML, Eickhof C. The functional value of electrical muscle stimulation for the rehabilitation of the hand in stroke patients. *Scand J Rehabil Med.* (1997) 29:3–10.

50. Nasir SM, Darainy M, Ostry DJ. Sensorimotor adaptation changes the neural coding of somatosensory stimuli. *J Neurophysiol.* (2013) 109:2077–85. doi: 10.1152/jn.00719.2012

5. Paper II.

Neurol Sci. 2022 Dec 21. doi: 10.1007/s10072-022-06561-3.

Efficacy of functional electrical stimulation in rehabilitating patients with foot drop symptoms after stroke and its correlation with somatosensory evoked potentials-a crossover randomised controlled trial

Mijic Marko [1], Schoser Benedikt [1], Young Peter [2]

Affiliations

[1] Department of Neurology, Friedrich-Baur-Institute, Klinikum der Universität, Ludwig-Maximilians-University, Munich, Germany,

[2] Clinic for Neurology, Medical Park, Bad Feilnbach, Germany

doi: 10.1007/s10072-022-06561-3. PMID: 36544079.

Free PMC article

ORIGINAL ARTICLE
Neurological Sciences
https://doi.org/10.1007/s10072-022-06561-3

Efficacy of functional electrical stimulation in rehabilitating patients with foot drop symptoms after stroke and its correlation with somatosensory evoked potentials—a crossover randomised controlled trial

Marko Mijic[1] · **Benedikt Schoser**[1] · **Peter Young**[2]

Received: 2 October 2022 / Accepted: 12 December 2022

Abstract

Objective The connectivity between somatosensory evoked potentials (SEPs) and cortical plasticity remains elusive due to a lack of supporting data. This study investigates changes in pathological latencies and amplitudes of SEPs caused by an acute stroke after 2 weeks of rehabilitation with functional electrical stimulation (FES). Furthermore, changes in SEPs and the efficacy of FES against foot drop (FD) stroke symptoms were correlated using the 10-m walk test and foot–ankle strength.

Methods A randomised controlled two-period crossover design plus a control group (group C) was designed. Group A ($n=16$) was directly treated with FES, while group B ($n=16$) was treated after 2 weeks. The untreated control group of 20 healthy adults underwent repeated SEP measurements for evaluation only.

Results The repeated-measures ANOVA showed a decrease in tibial nerve (TN) P40 and N50 latencies in group A after the intervention, followed by a decline in non-paretic TN SEP in latency N50 ($p<0.05$). Moreover, compared to groups B and C from baseline to 4 weeks, group A showed a decrease in paretic TN latency P40 and N50 ($p<0.05$). An increase in FD strength and a reduction in step cadence in group B ($p<0.05$) and a positive tendency in FD strength ($p=0.12$) and step cadence ($p=0.08$) in group A were observed after the treatment time. The data showed a moderate ($r=0.50$–0.70) correlation between non-paretic TN latency N50 and step cadence in groups A and B after the intervention time.

Conclusion The FES intervention modified the pathological gait in association with improved SEP afferent feedback. Registered on 25 February 2021 on ClinicalTrials.gov under identifier number: NCT04767360.

Keywords Functional electrical stimulation · Neuroprostheses · Somatosensory evoked potentials · Stroke rehabilitation · Sensory and motor recovery

Abbreviations

PES	Peripheral electrical stimulation
FES	Functional electrical stimulation
SEPs	Somatosensory evoked potentials
UL	Upper limb
LL	Lower limb
MN	Median nerve
TN	Tibial nerve
FD	Foot drop
MRC	Manual muscle testing grading systems

Introduction

In our previous systematic review [1], we searched for studies using somatosensory evoked potentials (SEPs) to demonstrate cortical sensory changes in healthy subjects or to estimate cortical plasticity and rehabilitation prognosis in stroke patients after peripheral electrical stimulation (PES) intervention.

SEPs are time-locked potentials evoked by electric stimulation of the sensory or mixed peripheral nerves and recorded along the large-fibre somatosensory (dorsal column–medial lemniscus) pathway [2]. Measures of SEP

✉ Marko Mijic
Marko.Mijic@med.uni-muenchen.de

[1] Department of Neurology, Friedrich-Baur-Institute, Klinikum der Universität, Ludwig-Maximilians-University, Munich, Germany

[2] Clinic for Neurology, Medical Park, Reithof 1, 83075 Bad Feilnbach, Germany

Published online: 21 December 2022

latencies, thresholds and evoked responses at high stimulator intensities have the highest reliability and require the smallest sample sizes to power a study adequately [3].

PES is a rehabilitative technology that uses electrical currents to the peripheral nerves. It has been proposed that somatosensory stimulation in the form of electromyographically triggered neuromuscular electrical stimulation to the peripheral nerve can influence functional measures of motor performance in stroke patients and produce changes in cortical excitability [4, 5]. The literature offers multiple terms for PES: transcutaneous electric nerve stimulation [6–9], functional electrical stimulation (FES) [10–14], cutaneous electrical stimulation [15], somatosensory stimulation [16], neuromuscular electrical stimulation [4, 17] or a combination of the terms 'percutaneous' and 'neuromodulation'. Sheffler and Chae [14] gave serious consideration to the use of electrical stimulation for motor relearning under the term 'functional electrical stimulation' instead of PES. They described three types of electrical stimulation available for motor learning: cyclic functional electrical stimulation (FES), electromyography- or biofeedback-mediated FES, and application of neuroprostheses. In the first case, the patient is a passive participant in the FES training, and no cognitive investment is necessary. The second type of exercise combines afferent feedback information with FES-induced repetitive movements. During training with a neuroprosthesis, functional tasks can be performed [5]. All interventions use the same technique, placing surface electrodes on the skin overlaying sensory-motor nerve structures, establishing an electric field between two electrodes through a medium containing dissolved ions and generating a current in the tissue. Hereinafter, only the term FES will be used.

Our previous review found a correlation between different FES types and changes in SEP components. However, verifying the degree of correlation between SEPs and cortical plasticity was not possible. An interesting finding was that the stroke studies involving FES that initiated a voluntary contraction used for a specific movement or task indicated a positive relationship and correlation with assessments of motor function [13, 15, 17, 18]. Moreover, in stroke studies, patients suffering from foot drop (FD) [13, 15] caused by subcortical or cortical lesions showed remarkable increases in walking speed, endurance and coordination after the application FES. FD is a common gait impairment derived from this pathology and consists of paralysis or significant weakness of the ankle dorsiflexor muscles. It is characterised by the inability to achieve adequate dorsiflexion to obtain a sufficient distance from the ground during the swing phase of gait [19]. FD is also characterised by uncontrolled plantar flexion immediately after initial contact [20].

Therefore, for this trial, the decision was made to apply neuroprosthetic FES using the L300 Go system [21] in patients suffering from post-stroke FD caused by an acute subcortical and cortical lesion. The L300 Go system was designed to improve gait in people suffering from FD and knee flexion or extension in individuals with muscle weakness caused by stroke. The system communicates wirelessly to deliver electrical pulses over the common peroneal nerve and to the motor point of the anterior tibialis muscle, causing ankle dorsiflexion in the swing phase of gait to prevent FD. The effectiveness of eliciting muscle contraction force depends on the electrical stimulation signal's amplitude, duration, frequency and waveform. The external pulse generator can activate one or two stimulation channels, depending on the cuff type and electrode pre-set [21].

The degree of correlation between SEP and cortical plasticity remained elusive due to a lack of supporting data in previous studies. However, neurophysiological measures may also have predictive value. According to Feys et al. [22], the combination of the motor score and somatosensory evoked potentials (SEPs) is best able to predict an outcome, especially in the acute phase of stroke, since neurophysiological measures alone are of limited value in predicting a long-term effect. Moreover, predictive accuracy is substantially improved by using electric measures and clinical variables [22]. Previous research by Kato et al. [23], who examined the SEPs of the median nerve (MN) and tibial nerve (TN) in patients with haemorrhagic brain lesions, reported that 60 out of 65 arms (92.3%) and 50 out of 62 legs (80.6%) showed abnormalities in SEPs [23]. To overcome this hurdle, we performed a short-term crossover randomised controlled intervention using FES and SEPs in patients with acute stroke.

Our primary aim was to detect changes in pathological latencies and amplitudes of SEPs caused by an acute subcortical and cortical poststroke lesion after a 2-week FES neuroprosthesis FD treatment by observing two stroke groups during intervention and non-intervention times. In addition, an untreated control group of healthy adults underwent repeated SEP measurements for evaluation only.

The second aim was to correlate the detected SEP changes with the efficacy of a 2-week FES neuroprosthesis intervention in improving FD weakness as measured by a 10-m walking test and the strength of dorsal flexion using manual muscle testing grading systems (MRC) [24] between the two stroke groups. Furthermore, we correlated SEP changes with the results of the 10-m walking test and the strength of dorsal flexion MCR between stroke groups.

Methods

Study approval and the study protocol

A randomised clinical sequential two-period crossover-design protocol was constructed. The PICO [25] model

was implemented to answer the primary clinical question (online data 1) https://osf.io/3dsu6. The study protocol was registered at ClinicalTrials.gov under the identifier number NCT04767360 on 25 February 2021, and data collection ended on 19 October 2021. All participants signed written consent forms. The study was approved by the ethics committee of the Ludwig-Maximilians-Universität München. All examinations were performed as part of a 4-week inpatient neurological rehabilitation in the neurological clinic at Medical Park, Reithof Park, Bad Feilnbach, Germany. The sample size was calculated in a pilot study in a homogeneous population of patients with nearly identical impairments.

Furthermore, 20 healthy subjects underwent a non-interventional second measurement 4 weeks after baseline to determine the maximum fluctuation in the latencies and amplitudes of subcortical and cortical components and in statistical methods for evaluating SEP differences between stroke groups. Thirty-two participants with acute stroke were registered. One patient was excluded due to a repeat stroke, and one healthy volunteer was excluded because of exceeding the timeframe between SEP assessments. Each patient was randomised using https://www.random.org and then began two separate consecutive treatment periods. For the first 2 weeks, group A was directly treated with FES, while group B was treated without FES. After this first 2-week period, group A and group B switched. Group C (healthy participants) received no intervention during the treatment periods. Initially, the ethics commission did not approve the randomised trial with only an intervention group and a control stroke group; therefore, the decision was made to design a crossover study, including a third group with healthy volunteers.

Patients

The patients were diagnosed with either ischaemic or haemorrhagic stroke within the past 6 months. In this text, the term 'stroke' is used for both ischaemic and haemorrhagic stroke. Stroke was confirmed by cerebral computed tomography or magnetic resonance imaging. The inclusion and exclusion criteria were according to the study by Stein et al. [26] and were adapted for our setting. The inclusion criteria for patients were as follows: (1) adults between the ages of 18 and 75 years; (2) inadequate ankle dorsiflexion during the swing phase of gait; (3) inadequate limb clearance as a result of this inadequate ankle dorsiflexion; (4) medically stable condition for at least 1 week following the last episode of stroke; (5) medical clearance to participate with the expectation that current medication can be maintained without change for the next 4 weeks; (6) adequate minimal stability at the ankle during stance with stimulation; (7) adequate cognitive and communication function to give informed consent; (8) the ability to understand the training instructions, use the device, and give adequate feedback; (9) the ability to walk at least 10 m with or without an assistive device. The exclusion criteria eliminated patients with (1) lower motor neuron injury; (2) severe cardiac diseases such as myocardial infarction, congestive heart failure or the need for a demand pacemaker; (3) other electrical stimulation devices in use; (4) hip or knee prostheses made of metal on the lower limb; and (5) epilepsy, autoimmune diseases or tumours.

Outcomes

The baseline information included age, sex, time of onset, time since stroke and side of stroke lesion. The duration of the entire study examinations was 30 min (including inclusion questionnaires and functional assessments). Sufficient breaks were given between the motor tests. The following motor practical assessments were carried out: ankle dorsiflexion strength measured by MRC classification of muscle imbalance patterns and force produced by voluntary contractions and a 10-m walking test as quickly as possible. The MRC grading system provides the following grades: (0) the ankle is paralysed; (1) only a trace or flicker of muscle contraction is seen or felt; (2) muscle movement is possible with gravity eliminated; (3) muscle movement is possible against gravity; (4) muscle strength is reduced, but movement against resistance is possible; (5) the ankle has normal strength. The 10-m walking test was performed without the FES, and the patient was allowed to use a cane or other walking aid. The same assistive device was used in all sets.

Pedometer records of the steps made with FES were saved for further assessment at the end of a 2-week treatment from the L300 Go System. All data, including SEP, were assessed at baseline, week 2 pre- or post-intervention, and from baseline to week 4. The evaluation of SEP, the 10-m walking test and the measurement of ankle dorsiflexion strength by MRC was made by clinical experts blinded to participants' clinical information.

Electrophysiological assessment

The neurological assessment SEPs were recorded from the bilateral MN and TN using a Neurowerk EMG two-channel device by the methods described by Muzyka and Estephan [2]. The standard values for MN and TN were determined for 30 healthy subjects before the start of the study.

The latencies of several components for the MN (N13, N20, P25) and TN (N35, P40, N50) were evaluated, together with central nerve conduction in the MN (P25–N13) and TN (N50–N35). Furthermore, the amplitudes of N20/P25 in the MN and N35/P40 in TN were measured. A detailed description of the SEP measurement process and the measured TN/MN components of the primary somatosensory complex can

be found (online data 2) https://osf.io/n3ckg. The SEP was measured at least 1 h after FES therapy.

Intervention

The intervention group received FES therapy of at least 30 min five times per week. A trained physiotherapist performed the FES therapy and assessments. The following measurements were performed under FES treatment: gait training, balance exercises, and strength exercises while standing and walking, including staircase walking. Groups A and B received the same standard therapies: physiotherapy, resistance training therapy and treadmill therapy. The muscle contraction force elicited by FES was adjusted by setting the amplitude, duration, frequency and waveform of the electrical stimulation signal. Each parameter was set individually depending on the gait parameter quality (Table 1).

Statistical analyses

Statistical analyses were performed using STATISTICA software (version 10; Tulsa, OK, USA). All data were normally distributed, as evaluated using the Shapiro−Wilks test. To compare pre-test–post-test improvement with the two therapy protocols at each follow-up point between the groups, group (2 levels) × time (2 levels) repeated-measures ANOVA was used. We used dependent *t* tests to evaluate pre-test–post-test improvement within groups, and the Pearson correlation coefficient was computed to assess the linear relationship between variables. A positive or negative correlation coefficient was considered high if its absolute value was between 0.70 and 0.90, moderate if its absolute value was between 0.50 and 0.70, and low if its absolute value was below 0.50 [27]. A p value of ≤ 0.05 was considered statistically significant for all analyses, and the 95% confidence interval for the mean difference was calculated for each dependent variable. No significant difference among groups was found in sex, age, time of onset or time since stroke (Table 2).

Results

Repeated-measures ANOVA found significant differences between group A and groups B and C (healthy probands) in the changes from baseline to the 2-week examination, consisting of decreased latencies of P40 [$F(2, 37) = 7.70$, $p = 0.001$] and N50 [$F(2, 37) = 3.19$, $p = 0.052$] as well as central nerve conduction velocity [N50–N35: $F(2, 37) = 3.35$, $p = 0.045$] on the affected side. However, in the same period, there were also significant decreases in group A compared to groups B and C in the N50 latency of the non-paretic TN SEP [$F(2, 37) = 8.02$, $p = 0.001$], and as a result of this change, a decrease in central nerve conduction velocity at N50–N35 [$F(2, 37) = 4.21$, $p = 0.022$] was observed. No increase was found in the N35–P40 amplitude of the paretic TN [$F(2, 37) = 1.88$, $p = 0.166$] in the first 2 weeks in group A, B or C. Furthermore, the changes in the paretic TN between 2 and 4 weeks at each of the analysed latencies and amplitudes did not differ among groups A, B and C ($p > 0.05$). An interesting difference was found between group A and groups B and C from baseline to 4 weeks in the decreases in P40 [$F(2, 37) = 4.71$, $p = 0.014$] and N50 [$F(2, 37) = 3.96$, $p = 0.027$] latency in the paretic TN. Important statistically significant changes in the peak latency of SEPs between group A, group B and group C can be found in Fig. 1, and the remaining differences in the SEP variables can be found in Supplementary material 1.

When we examined only group A to group B between baseline and week 2 with *F*-tests of the N35, P40 and N50 latency, N50–N35 central nerve conduction velocity, and N35–P40 amplitude values of the paretic TN, significant changes could not be found ($p > 0.05$). However, positive tendencies were found in the P40 [$F(1, 19) = 2.63$, $p = 0.120$] latency value and central nerve conduction velocity N50–N35 [$F(1, 19) = 2.16$, $p = 0.157$]. In addition, FES was not found to improve pathological latencies or amplitudes in any observed segment between group B and group A between week 2 and week 4 ($p > 0.05$). However, a positive tendency in N35–P40 amplitude could be observed [$F(1, 19) = 2.83$, $p = 0.108$].

Table 1 FES stimulation parameters* (Bioness L300 Go)

	Group A	Group B
Intensity (strength of stimulation)	42.71 mA ± 18.78*	41.84 mA ± 15.53*
Phase duration (length of time of the pulse)	200 or 300 µs	200 or 300 µs
Pulse rate (frequency of stimulation)	30 to 50 Hz, in 5-Hz steps	30 to 50 Hz, in 5-Hz steps
Type of electrode: *quick fit* (one channel) or *steering* (two channel) stimulation	14 patients/quick fit 2 patients/steering	13 patients/quick fit 2 patients/steering
Waveform	Symmetric	Symmetric

*Values are given as the mean values with standard deviations

Table 2 Patient characteristics and descriptive data

	Group A	Group B
Age, years	61.50 ± 9.01*	61.60 ± 8.96*
Sex	12 males, 4 females	12 males, 3 females
Type of stroke	3 × Pontine infarct, left 1 × Pontine infarct, right 4 × Middle cerebral artery infarct, left 1 × Bihemispheric middle cerebral artery infarct media 1 × Capsula interna infarct, left 1 × Incomplete medial infarct, right 1 × Cortical ischaemia (no further diagnosis description) 1 × Precentral gyrus infarct 1 × Bilateral cerebral haemorrhage 1 × Capsula interna haemorrhage, left 1 × Cerebellar haemorrhage, right	6 × Pontine infarct, left 1 × Pontine infarct, right 4 × Middle cerebral artery infarct, left 1 × Middle cerebral artery infarct, right 1 × Precentral gyrus infarct, right 1 × Anterior choroidal artery infarct, left 1 × Frontoparietal cerebral haemorrhage, left
Time since stroke, days	25.33 ± 14.02*	31.93 ± 15.76*
Hemiparetic side	15 Rt, 1 Lt	15 Rt
Dominant hand affected	13	11
Steps taken with FES	28,849 ± 23,056	25,657 ± 22,753

*Values are given as the mean values with standard deviations

The pre-intervention–post-intervention strength increase in dorsiflexion of the paretic foot ankle between weeks 2 and 4, as measured by MRC classification, significantly differed in group B compared to group A by repeated-measures ANOVA [$F(1, 29) = 4.36$, $p = 0.045$]. Moreover, a positive tendency was found in group A compared to group B between baseline and 2 weeks after the intervention [$F(1, 29) = 2.50$, $p = 0.124$]. *F*-Statistics showed no effects of FES on time or steps in the 10-m walking test between groups A and B in the first 2 weeks ($p > 0.05$). However, a difference was found in the step cadence decrease between group B and group A between weeks 2 and 4 [$F(1, 29) = 4.79$, $p = 0.036$], and there was a positive tendency from baseline to 4 weeks between group A and B [$F(1, 29) = 3.10$, $p = 0.08$]. Groups A and B did not show any changes in the 10-m walking test time in any measurement period. The significant differences between groups A and B from baseline to week 2 and week 4 are shown in Fig. 2.

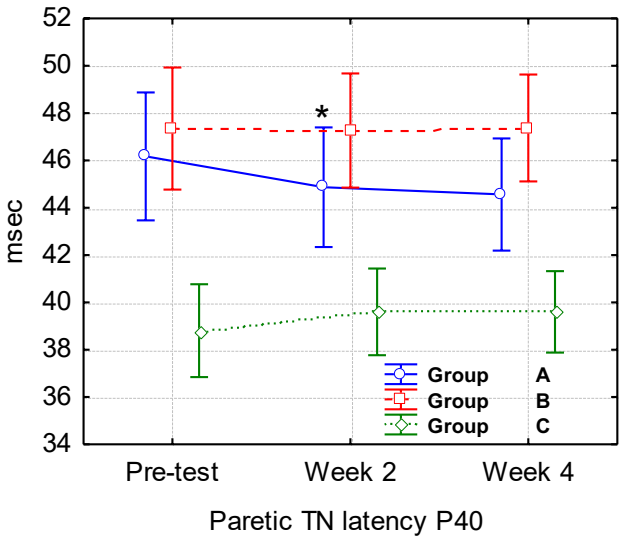
An essential factor to mention is that a dependent *t* test within groups showed significant changes in 10-m walking test in both groups in the first 2 weeks, in time as well as in cadence ($p < 0.05$); by contrast, in weeks 2 to 4, those differences were not found. Nevertheless, the dependent *t* test shows a remarkable increase in strength within both groups in the first 2 weeks of inpatient intervention ($p < 0.05$) compared to weeks 2 to 4, when this difference was not found ($p > 0.05$).

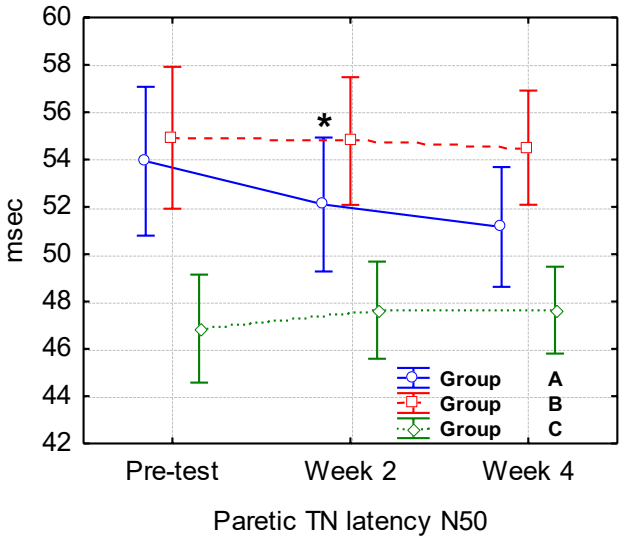
Clinical neurophysiologists were initially unable to evaluate TN SEPs of ten patients and MN SEPs in two patients because SEP amplitudes were absent due to subcortical or cortical lesions. Those patients were excluded from the calculations of the SEP *F*-statistics and correlation data. Four patients recovered cortical evoked peaks that could not be evaluated initially. None of the patients without cortical SEP peaks showed complete recovery of MRC foot drop. Five patients showed reduced foot drop MRC weakness even though TN SEP on the paretic side indicated an increase in TN cortical latency. Two patients initially indicated MRC weakness in the non-paretic (ipsilesional) foot and ankle in dorsiflexion/plantar flexion.

A moderate correlation from baseline to week 2 between the variables [N50 TN non-paretic latency] and [10-m walking cadence] in group A, $r(10) = 0.65$, $p < 0.05$, was found. In addition, a moderate correlation was observed in groups A and B at baseline to week 4 between the variables [N50 TN non-paretic latency] and [10-m walking steps], $r(21) = 0.52$, $p < 0.05$. A correlation matrix with SEP variables and FD weakness parameters can be found in Supplementary material 2.

Discussion

FES is a standard inpatient neurological intervention for stroke patients with FD. Due to this ethical consideration, denying patients the right to be involved in FES therapy was not an option. Therefore, the decision was made to construct a crossover design. Including the third group with healthy volunteers was required for three reasons. First, finding the maximal relative difference between healthy individuals for





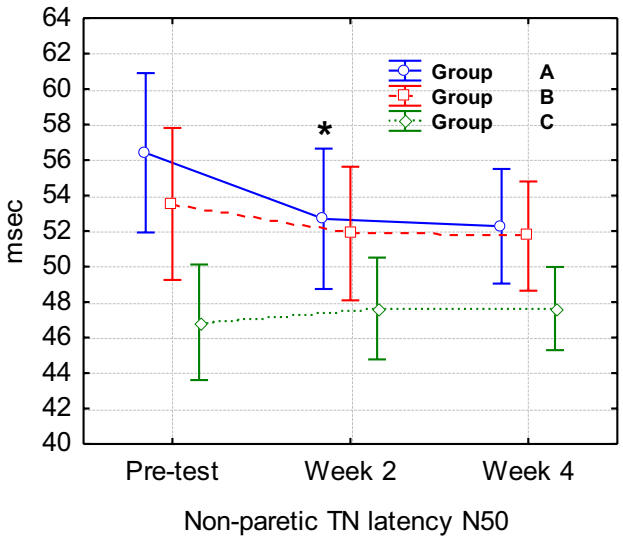
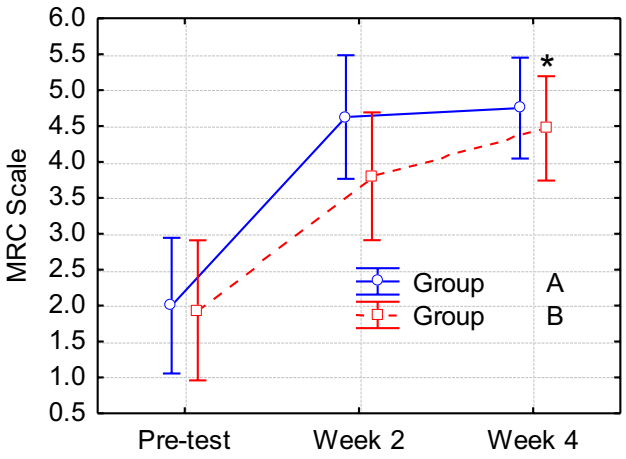


Fig. 1 Variation of TN SEP latency: P40 and N50 of the paretic limb ▶ and N50 of the non-paretic limb. Vertical bars denote 95% confidence intervals for means. *Comparison of group A to groups B and C from baseline to 2 weeks: decrease in paretic TN P40 latency: $F(2, 37) = 7.70$, $p = 0.001$; decrease in paretic TN N50 latency: $F(2, 37) = 3{,}1937$, $p = 0.05254$; and decrease of non-paretic TN latency N50: $F(2, 37) = 8.02$, $p = 0.001$

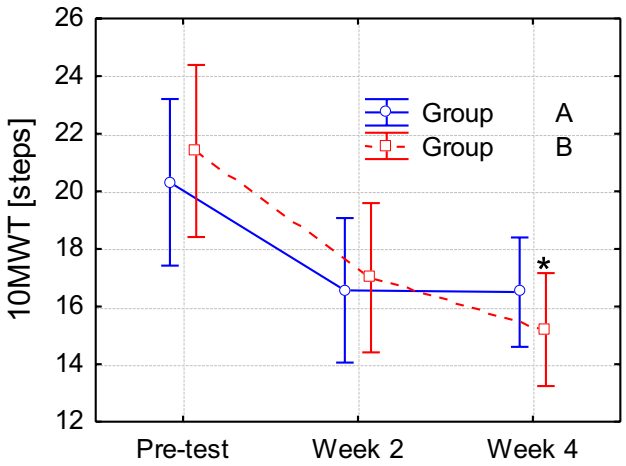
the SEP amplitude and latencies between 4 weeks of measurements is necessary. This gives us information about the standard deviation and sensibility of SEP measurement. Second, the third group increased the number of study participants with minimal detected SEP variation, increasing the validity of the results. Finally, no previous study compared stroke patients and healthy individuals by measuring SEP differences.

Following the interventions, SEP changes found in group A (time since stroke, 25.33 ± 14.02 days) support the hypothesis that post-stroke functional recovery occurred primarily over the first 30 days, with moderate recovery continuing for 30–90 days [28]. However, we are aware of confounding bias created due to spontaneous recovery and endogenous plasticity, which occurs most intensively in the first weeks after stroke [29, 30]. Moreover, few human studies have explicitly sought to test whether intense training early after stroke can augment spontaneous biological recovery [29]. Some retrospective studies on stroke populations suggest that early initiation of rehabilitation is associated with better outcomes [31–33]. These studies had similar confounding to this trial because patients involved in rehabilitation are generally sicker and more severely affected and thus less likely to improve regardless of the timing of care [34]. The time from stroke to rehabilitation inclusion in our study for group B was 31.93 ± 15.76 days, which might mean that the intervention is too late [35]. These results can be substantiated with a dependent *t* test within groups, which showed significant changes in 10-m walking time in both groups in the first 2 weeks, in time and steps cadence ($p < 0.05$) as well as in increase of strength, compared to weeks 2 to 4, where those differences were not found ($p > 0.05$).

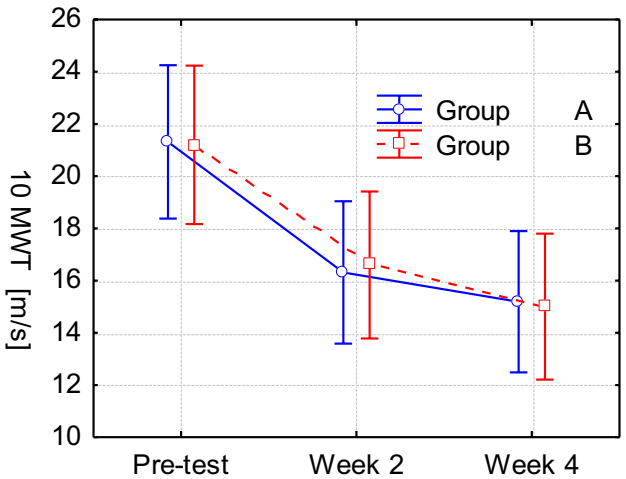
LL hemiparesis was found independent of whether the lesions were cortical, subcortical or in the brainstem. Nevertheless, the pathology of SEP in the primary cortical somatosensory complex of the paretic foot can be observed independent of the height of the lesion within the brain. This phenotype was previously explained by Krakauer and Carmichael [29] and Kato et al. [23]. In our case, 11 patients had left/right pons infarcts, and 11 had left/right middle cerebral artery infarcts. It seems that the SEP recordings along the projection fibre pathway (dorsal column–medial lemniscus) allow the identification of abnormalities independent of the lesion location. The researchers considered the spontaneous physical recovery process, which is far more prominent in the acute phase



Dorsal flexion strength in the paretic ankle between Group A and Group B



10-metre walking test in steps [cadence] between Group A and Group B



10-metre walking test in time [m/s] between Group A and Group B

Fig. 2 Variation of the motor skill parameters: FD strength and 10-m walk test results (number of steps and time). Vertical bars denote 0.95 confidence intervals for means. *Significant difference in the pre- to post-intervention increase in strength (MRC) in the paretic ankle in dorsal flexion between group B and group A, weeks 2 and 4: [$F(1, 29) = 4.36$, $p = 0.045$] and in steps [cadence] decrease between group B and group A between weeks 2 and 4: [$F(1, 29) = 4.79$, $p = 0.036$]. No effects of FES in 10-m walking test time [s] between groups A and B ($p > 0.05$)

of stroke than in the chronic phase [29], and that found minimal variance in paretic TN cortical peaks P40 and N50 could be attributed to those changes. On the other hand, detected changes in TN SEP could not be found in MN SEP, even though 19 patients showed at least one pathological latency (N20, P25) or amplitude (N20/P25) in the primary somatosensory cortex of the UL. Moreover, those variations could not be observed in the norm data obtained by healthy subjects and maximal deviation given by Muzyka and Estephan [2]. Independently, all patients demonstrated at least one form of subcortical or cortical reorganisation upstream of the TN, reflected in latency or amplitude, after treatment with FES.

No patient showed a loss or decrease in TN cortical peaks after the FES intervention, which could be generated as a result of aggravation or as already described in studies [7, 36, 37] in which the use of FES decreased cortical somatosensory amplitudes. Analysing common values of healthy subjects with stroke patients, all patients showed at least one pathology in loss of cortical waves, delay in peak latencies (N35/P40/N50) or reduction in amplitude (N35/P40). These results correspond to the outcome obtained in the study from Kato et al. [23]. Finally, the lack of SEP changes by examining group A to group B without healthy subjects is probably caused by the number of cases and the short assessment timeframe. However, a positive tendency seen in several components supports our opinion that there is an influence of FES on SEP.

The dependent *t* test found improvements in both cadence and time in the 10-m walking test in both groups during 4-week inpatient neurological rehabilitation. Moreover, the dependent *t* test showed a remarkable increase in strength in both groups. These results were expected because, in addition to FES, all patients received other standard therapies as well: physiotherapy, resistance training therapy, treadmill therapy and activities of daily living training. The MRC scale data (Fig. 1) show that group A recovered faster within the first 2 weeks and group B in the second 2 weeks in the paretic feet ankle in dorsal flexion strength. Five patients showed recovery in FD strength measured by MRC classification even though the TN SEPs of the paretic side still indicated an increase in TN cortical latency and amplitude. Moreover, FD was still obtained, and sufficient distance

from the ground during the swing phase of gait was clinically not visible. A study by Bao et al. [13] reported that LL strength is necessary but insufficient to produce recovery of voluntary control of coordinated and rhythmic movements in patients poststroke. Recovery of joint mobility and rhythmic movements should not be omitted due to their impact on the recovery of central nervous system motor control function [13]. This statement indicates that reduced coordination and rhythmic foot movement can be more affected and take longer to recover, whereas strength in FD recovers more quickly in the first weeks after stroke. These results are similar to the data found in our study.

Interestingly, group A showed no improvement in steps taken in the 10-m walking test between weeks 2 and 4, during which no intervention was given. This showed that using individual adjusted FES on stroke patients could help reduce this impairment by providing an electrical stimulus in the average gait rhythm pace. Furthermore, a moderate correlation between changes in the variable [N50 TN non-paretic latency] and the variable [10-m walking test in cadence/group A], $r(10) = 0.65$, $p < 0.05$, over intervention time was found. These data, in addition to changes in TN SEP N50 latency on the non-paretic side, could reveal the influence of the ipsilateral side on cortical reorganisation after stroke. Moreover, ipsilateral foot weakness was found in two patients. This phenomenon was already described by Xu et al. [38] on maximal voluntary contraction force in the unaffected side/hand. We remain careful about further statements on the influence and changes found in non-paretic SEP latency N50 since the cortical reference electrode of the TN for the right and left sides is in a single recording location, and lower subcortical changes cannot be evaluated using this measuring method. Last, FD recovery was observed only in patients with retained SEPs. The correlation between SEP and gait parameters after intervention time in both groups demonstrated a relationship between sensory and motor brain areas. It is known that there are substantial anatomical interconnections linking the brain's motor and somatosensory regions. Cortical motor areas receive direct inputs from the primary and second somatosensory cortex. Conversely, somatosensory areas receive direct cortical inputs from the primary motor cortex, premotor cortex and supplementary motor area [39, 40]. A change in somatosensory function associated with motor learning would seem to be a natural by-product of this anatomical connectivity [39, 40]. The findings in this study suggest that FES may shift the somatosensory response to the brain's motor areas. On the other hand, it could be hypothesised that SEP can indirectly recognise changes in the brain's motor area.

Furthermore, SEPs have sufficient sensitivity to detect even the smallest changes in the action potential of cortical neural networks after stroke. They can probably be used to assess the effect of various sensory therapies—cryotherapy, thermotherapy, occupational tactile therapy or robotic tactile therapy—in a direct manner. Nevertheless, it would be essential for future studies to assess the influence of FES using a combination of SEP with different neurophysiological measures, such as transcranial magnetic stimulation [40–42] or laser-evoked potentials [43], which have already shown good prognostic value. There is a reasonable proposition that a combination of neurophysiological measures could provide high correlation in the prediction of upper limb (UL) and lower limb (LL) motor recovery in stroke patients [41, 42, 44, 45].

Study limitations

The patients and the therapist were unblinded during the therapy. We did not include a group that underwent FES only. However, the data from the MN SEP can be considered compensation from our point of view. Moreover, we had healthy volunteers to minimise this bias. We evaluated outcomes only up to week 4 after the intervention; thus, long-term outcomes are still needed to substantiate our results further. We cannot exclude the possibility of selection bias because we used strength inclusion criteria. High technical performance in carrying out SEP measurements and evaluations is necessary to interpret variability in pathological cortical peaks. Even though clinical experts were masked to participants' clinical information, additional patient data would reduce the bias caused by manual cortical peaks cursor adjustment.

Conclusion

After a short-term neuroprosthetic FES intervention, we found an improvement in pathological gait function (time, number of steps and reduction of FD weakness). Correlating with the clinical improvement, changes in afferent SEP feedback were observed. This indicates that FES should be included in the stroke rehabilitation process as early as possible. The SEP measurement procedure is time consuming and susceptible to error, and it requires a highly knowledgeable clinician. Our findings indicate the importance of assessing electrophysiological methods and verifying the application of SEP by stroke patients.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s10072-022-06561-3.

Funding Open Access funding enabled and organized by Projekt DEAL.

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval The study was approved bythe local ethics committee.

Informed consent Informed consent was obtained from patients or their family members including the consent of publication.

References

1. Mijic M, Jung A, Schoser B, Young P (202) Use of peripheral electrical stimulation on healthy individual and patients after stroke and its effects on the somatosensory evoked potentials. A systematic review. Front Neurol 18(13):1036891. https://doi.org/10.3389/fneur.2022.1036891
2. Muzyka IM, Estephan B (2019) Somatosensory evoked potentials, 1st ed., vol. 160. Elsevier B.V,. https://doi.org/10.1016/B978-0-444-64032-1.00035-7
3. Brown KE et al (2017) The reliability of commonly used electrophysiology measures. Brain Stimul 10(6):1102–1111. https://doi.org/10.1016/j.brs.2017.07.011
4. Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey LL, Lojovich JM, Carey JR (2004) Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. Exp Brain Res 154(4):450–460. https://doi.org/10.1007/s00221-003-1695-y
5. Bajd T, Crt M, Munih M (2008) Functional electrical stimulation with surface electrodes. J Autom Control 18(2):3–9. https://doi.org/10.2298/jac0802003b
6. Laufer Y, Elboim-Gabyzon M (2011) Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review. Neurorehabil Neural Repair 25(9):799–809. https://doi.org/10.1177/1545968310397205
7. Ashton H, Golding JF, Marsh VR, Thompson JW (1984) Effects of transcutaneous electrical nerve stimulation and aspirin on late somatosensory evoked potentials in normal subjects. Pain 18(4):377–386. https://doi.org/10.1016/0304-3959(84)90050-2
8. Golding JF, Ashton H, Marsh R, Thompson JW (1986) Transcutaneous electrical nerve stimulation produces variable changes in somatosensory evoked potentials, sensory perception and pain threshold: clinical implications for pain relief. J Neurol Neurosurg Psychiatry 49(12):1397–1406. https://doi.org/10.1136/jnnp.49.12.1397
9. Urasaki E, Wada S, Yasukouchi H, Yokota A (1998) Effect of transcutaneous electrical nerve stimulation (TENS) on central nervous system amplification of somatosensory input. J Neurol 245(3):143–148. https://doi.org/10.1007/s004150050194
10. Straudi S et al (2020) Effects of a robot-assisted arm training plus hand functional electrical stimulation on recovery after stroke: a randomized clinical trial. Arch Phys Med Rehabil 101(2):309–316. https://doi.org/10.1016/j.apmr.2019.09.016
11. Gandolla M, Ward NS, Molteni F, Guanziroli E, Ferrigno G, Pedrocchi A (2016)The neural correlates of long-term carryover following functional electrical stimulationfor stroke. Neural Plast 2016. https://doi.org/10.1155/2016/4192718
12. Berenpas F, Weerdesteyn V, Geurts AC, Van Alfen N (2019) Long-term use of implanted peroneal functional electrical stimulation for stroke-affected gait: the effects on muscle and motor nerve. J Neuroeng Rehabil 16(1):1–10. https://doi.org/10.1186/s12984-019-0556-2
13. Bao X et al (2020) Effect of functional electrical stimulation plus body weight-supported treadmill training for gait rehabilitation in patients with poststroke: a retrospective case-matched study. Eur J Phys Rehabil Med 56(1):34–40. https://doi.org/10.23736/S1973-9087.19.05879-9
14. Sheffler LR, Chae J (2007) Neuromuscular electrical stimulation in neurorehabilitation. Muscle Nerve 35(5):562–590. https://doi.org/10.1002/mus.20758
15. Peurala SH, Pitkänen K, Sivenius J, Tarkka IM (2002) Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. Clin Rehabil 16(7):709–716. https://doi.org/10.1191/0269215502cr543oa
16. Sawaki L, Wu CWH, Kaelin-Lang A, Cohen LG (2006) Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. Stroke 37(1):246–247. https://doi.org/10.1161/01.STR.0000195130.16843.ac
17. Tashiro S et al (2019) Neuromuscular electrical stimulation-enhanced rehabilitation is associated with not only motor but also somatosensory cortical plasticity in chronic stroke patients: an interventional study. Ther Adv Chronic Dis 10:204062231988925. https://doi.org/10.1177/2040622319889259
18. Giaquinto S, Mascio M, Fraioli L (2002) The physiopathological bases of recovery processes: the bases of stroke rehabilitation. The cassino project. Clin Exp Hypertens 24(7–8):543–553. https://doi.org/10.1081/CEH-120015331
19. Melo PL, Silva MT, Martins JM, Newman DJ (2015) Technical developments of functional electrical stimulation to correct drop foot: sensing, actuation and control strategies. Clin Biomech 30(2):101–113. https://doi.org/10.1016/j.clinbiomech.2014.11.007
20. Hanft A, Hall JR, Kapila DT (2011) A guide to preventative offloading of diabetic foot ulcers, Podiatry Today. https://www.hmpgloballearningnetwork.com/site/podiatry/guide-preventative-offloading-diabetic-foot-ulcers. Accessed 20 Dec 2022
21. Bioness Europe BV (2021) *L300 Go Clinician's Guide*. Zwijndrecht: Bioness Europe B.V., [Online]. Available: www.bioness.com
22. Feys H, Van Hees J, Bruyninckx F, Mercelis R, De Weerdt W (2000) Value of somatosensory and motor evoked potentials in predicting arm recovery after a stroke. J Neurol Neurosurg Psychiatry 68(3):323–331. https://doi.org/10.1136/jnnp.68.3.323

23. Kato H, Sugawara Y, Ito H, Onodera K, Sato C, Kogure K (1991) Somatosensory evoked potentials following stimulation of median and tibial nerves in patients with localized intracerebral hemorrhage: correlations with clinical and CT findings. J Neurol Sci 103(2):172–178. https://doi.org/10.1016/0022-510X(91)90160-9
24. Vanhoutte EK et al (2012) Modifying the Medical Research Council grading system through Rasch analyses. Brain 135(5):1639–1649. https://doi.org/10.1093/brain/awr318
25. Eriksen MB, Frandsen TF (2018) The impact of PICO as a search strategy tool on literature search quality: a systematic review. J Med Libr Assoc 106(4):420–431. https://doi.org/10.5195/jmla.2018.345
26. Stein RB et al (2006) A multicenter trial of a footdrop stimulator controlled by a tilt sensor. Neurorehabil Neural Repair 20(3):371–379. https://doi.org/10.1177/1545968306289292
27. Mukaka MM (2012) Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J 24(3):69–71
28. Duncan PW, Goldstein LB, Matchar D, Divine GW, Feussner J (1992) Measurement of motor recovery after stroke outcome assessment and sample size requirements. Stroke 23(8):1084–1089. https://doi.org/10.1161/01.STR.23.8.1084
29. Krakauer ST, Carmichael JW (2017) Broken movement: the neurobiology of motor recovery after stroke. The MIT Press, Cambridge, Massachusetts, MA, p 288
30. Kwakkel G, Kollen B, Twisk J (2006) Impact of time on improvement of outcome after stroke. Stroke 37(9):2348–2353. https://doi.org/10.1161/01.STR.0000238594.91938.1e
31. Wylie CM (1970) The value of early rehabilitation in stroke. Geriatrics 25(5):107–113
32. Feigenson JS, McDowell FH, Meese P, McCarthy ML, Greenberg SD (1977) Factors influencing outcome and length of stay in a stroke rehabilitation unit. Part 1. Analysis of 248 unscreened patients—medical and functional prognostic indicators. Stroke 8(6):651–656. https://doi.org/10.1161/01.str.8.6.651
33. Kotila M, Waltimo O, Niemi ML, Laaksonen R, Lempinen M (1984) The profile of recovery from stroke and factors influencing outcome. Stroke 15(6):1039–1044. https://doi.org/10.1161/01.str.15.6.1039
34. Ween JE, Alexander MP, D'Esposito M, Roberts M (1996) Factors predictive of stroke outcome in a rehabilitation setting. Neurology 47(2):388–392. https://doi.org/10.1212/wnl.47.2.388
35. Norvang OP et al (2018) Time spent lying, sitting, and upright during hospitalization after stroke: a prospective observation study. BMC Neurol 18(1):138. https://doi.org/10.1186/s12883-018-1134-0
36. Cogiamanian F, Vergari M, Pulecchi F, Marceglia S, Priori A (2008) Effect of spinal transcutaneous direct current stimulation on somatosensory evoked potentials in humans. Clin Neurophysiol 119(11):2636–2640. https://doi.org/10.1016/j.clinph.2008.07.249
37. Zarei AA, Jadidi AF, Lontis ER, Jensen W (2021) Short-term suppression of somatosensory evoked potentials and perceived sensations in healthy subjects following tens. IEEE Trans Biomed Eng 68(7):2261–2269. https://doi.org/10.1109/TBME.2021.3051307
38. Xu J et al (2017) Separable systems for recovery of finger strength and control after stroke. J Neurophysiol 118(2):1151–1163. https://doi.org/10.1152/jn.00123.2017
39. Nasir SM, Darainy M, Ostry DJ (2013) Sensorimotor adaptation changes the neural coding of somatosensory stimuli. J Neurophysiol 109(8):2077–2085. https://doi.org/10.1152/jn.00719.2012
40. Tinazzi M et al (2005) Long-lasting modulation of human motor cortex following prolonged transcutaneous electrical nerve stimulation (TENS) of forearm muscles: evidence of reciprocal inhibition and facilitation. Exp Brain Res 161(4):457–464. https://doi.org/10.1007/s00221-004-2091-y
41. Everaert DG, Thompson AK, Chong SL, Stein RB (2010) Does functional electrical stimulation for foot drop strengthen corticospinal connections? Neurorehabil Neural Repair 24(2):168–177. https://doi.org/10.1177/1545968309349939
42. Mima T et al (2004) Short-term high-frequency transcutaneous electrical nerve stimulation decreases human motor cortex excitability. Neurosci Lett 355(1–2):85–88. https://doi.org/10.1016/j.neulet.2003.10.045
43. Timofeeva MA, Ar'kov VV, Andreev RA, Trushkin EV, Tonevitsky AG (2011) Changes in parameters of laser-induced potentials after transcutaneous electroneurostimulation. Bull Exp Biol Med 150(4):479–480. https://doi.org/10.1007/s10517-011-1173-7
44. Stein R, Everaert D, Chong S, Thompson A (2007) Using FES for foot drop strengthens cortico-spinal connections. PA USA, Philadelphia
45. Stein RB et al (2010) Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders. Neurorehabil Neural Repair 24(2):152–167. https://doi.org/10.1177/1545968309347681

6. Literaturverzeichnis

[1] E. J. Benjamin *et al.*, “Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association.,” *Circulation*, vol. 135, no. 10, pp. e146–e603, Mar. 2017, doi: 10.1161/CIR.0000000000000485.

[2] R. Koch-Institut, “Wie steht es um unsere Gesundheit?,” no. Kapitel 2. Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung, 2015, doi: 10.17886/rkipubl-2015-003-2.

[3] D. Kuriakose and Z. Xiao, “Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives,” *Int. J. Mol. Sci.*, vol. 21, no. 20, p. 7609, Oct. 2020, doi: 10.3390/ijms21207609.

[4] T. D. Musuka, S. B. Wilton, M. Traboulsi, and M. D. Hill, “Diagnosis and management of acute ischemic stroke: speed is critical,” *CMAJ*, vol. 187, no. 12, pp. 887–893, Sep. 2015, doi: 10.1503/cmaj.140355.

[5] K. Inoue, T. Shirai, T. Harada, Y. Mimori, and M. Matsumoto, “[Somatosensory evoked potentials/fields--exploration of brain function].,” *Rinsho Byori.*, vol. 52, no. 1, pp. 77–80, Jan. 2004.

[6] V. Gugino and R. J. Chabot, “Somatosensory evoked potentials,” *International Anesthesiology Clinics*, vol. 28, no. 3. pp. 154–164, 1990, doi: 10.1097/00004311-199002830-00005.

[7] I. M. Muzyka and B. Estephan, *Somatosensory evoked potentials*, 1st ed., vol. 160. Elsevier B.V., 2019.

[8] T. Yamada, M. Yeh, and J. Kimura, “Fundamental principles of somatosensory evoked potentials,” *Phys. Med. Rehabil. Clin. N. Am.*, vol. 15, no. 1, pp. 19–42, 2004, doi: 10.1016/S1047-9651(03)00100-1.

[9] H. Buchner, *Praxisbuch Evozierte Potenziale*. Stuttgard: Georg Thieme Verlag KG, 2014.

[10] “Guideline 9D: Guidelines on short-latency somatosensory evoked potentials.,” *J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc.*, vol. 23, no. 2, pp. 168–179, Apr. 2006, doi: 10.1097/00004691-200604000-00013.

[11] G. Cruccu *et al.*, “Recommendations for the clinical use of somatosensory-evoked potentials,” *Clin. Neurophysiol.*, vol. 119, no. 8, pp. 1705–1719, 2008, doi: https://doi.org/10.1016/j.clinph.2008.03.016.

[12] D. W. U.Walter, H.Hinrichs, S. Brandt, M. Kaps, S Förderreuther, W. Müllges, H.-C. Hansen, “Empfehlungen der Deutschen Gesellschaft für Klinische Neurophysiologie und Funktionelle Bildgebung zur Diagnostik des irreversiblen Hirnfunktionsausfalls - Richtlinie der Kommission Hirntod,” DGKN, Berlin, 2015.

[13] J. E. Desmedt and G. Cheron, “Central somatosensory conduction in man: Neural generators and interpeak latencies of the far-field components recorded from neck and right or left scalp and earlobes,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 50, no. 5, pp. 382–403, 1980, doi: https://doi.org/10.1016/0013-4694(80)90006-1.

[14] F. Mauguière and J. Courjon, “The origins of short-latency somatosensory evoked potentials in humans,” *Ann. Neurol.*, vol. 9, no. 6, pp. 607–611, 1981, doi: https://doi.org/10.1002/ana.410090616.

[15] R. G. Emerson, M. Seyal, and T. A. Pedley, “Somatosensory evoked potentials following median nerve stimulation. I. The cervical components.,” *Brain*, vol. 107 (Pt 1, pp. 169–182, Mar. 1984, doi: 10.1093/brain/107.1.169.

[16] J. E. Desmedt and G. Cheron, “Non-cephalic reference recording of early somatosensory potentials to finger stimulation in adult or aging normal: differentiation of widespread N18 and contralateral N20 from the prerolandic p22 and N30 components,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 52, no. 6, pp. 553–570, 1981, doi: https://doi.org/10.1016/0013-4694(81)91430-9.

[17] M. Seyal, R. G. Emerson, and T. A. Pedley, “Spinal and early scalp-recorded components of the somatosensory evoked potential following stimulation of the posterior tibial nerve,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 55, no. 3, pp. 320–330, 1983, doi: 10.1016/0013-4694(83)90210-9.

[18] E. K. Lee and M. Seyal, “Generators of short latency human somatosensory-evoked potentials recorded over the spine and scalp.,” *J. Clin. Neurophysiol. Off. Publ. Am. Electroencephalogr. Soc.*, vol. 15, no. 3, pp. 227–234, May 1998, doi: 10.1097/00004691-199805000-00006.

[19] C. W. H. Stöhr, M. J.Dichgans,U. W. Buettne, *Evozierte Potenziale*. Augsburg, Germany: Springer, Berlin, Heidelberg, 2005.

[20] W. T. Liberson, H. J. Holmquest, D. Scot, and M. Dow, “Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients.,” *Arch. Phys. Med. Rehabil.*, vol. 42, pp. 101–105, Feb. 1961.

[21] P. L. Melo, M. T. Silva, J. M. Martins, and D. J. Newman, “Technical developments of functional electrical stimulation to correct drop foot: Sensing, actuation and control strategies,” *Clin. Biomech.*, vol. 30, no. 2, pp. 101–113, 2015, doi: 10.1016/j.clinbiomech.2014.11.007.

[22] A. Hanft, J.R., Hall, D.T., Kapila, “A guide to preventative offloading of diabetic foot ulcers,” *Podiatry Today*, 2011. Available: https://www.hmpgloballearningnetwork.com/site/podiatry/guide-preventative-offloading-diabetic-foot-ulcers.

[23] T. Bajd, M. Crt, and M. Munih, “Functional electrical stimulation with surface electrodes,” *J. Autom. Control*, vol. 18, no. 2, pp. 3–9, 2008, doi: 10.2298/jac0802003b.

[24] Y. Laufer and M. Elboim-Gabyzon, “Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review,” *Neurorehabil. Neural Repair*, vol. 25, no. 9, pp. 799–809, 2011, doi: 10.1177/1545968310397205.

[25] H. Ashton, J. F. Golding, V. R. Marsh, and J. W. Thompson, “Effects of transcutaneous electrical nerve stimulation and aspirin on late somatosensory evoked potentials in normal subjects,” *Pain*, vol. 18, no. 4, pp. 377–386, 1984, doi: 10.1016/0304-3959(84)90050-2.

[26] J. F. Golding, H. Ashton, R. Marsh, and J. W. Thompson, “Transcutaneous electrical nerve stimulation produces variable changes in somatosensory evoked potentials, sensory perception and pain threshold: Clinical implications for pain relief,” *J. Neurol. Neurosurg. Psychiatry*, vol. 49, no. 12, pp. 1397–1406, 1986, doi: 10.1136/jnnp.49.12.1397.

[27] E. Urasaki, S. I. Wada, H. Yasukouchi, and A. Yokota, “Effect of transcutaneous electrical nerve stimulation (TENS) on central nervous system amplification of somatosensory input,” *J. Neurol.*, pp. 143–148, 1998, doi: 10.1007/s004150050194.

[28] S. Straudi *et al.*, “Effects of a Robot-Assisted Arm Training Plus Hand Functional Electrical Stimulation on Recovery After Stroke: A Randomized Clinical Trial,” *Arch. Phys. Med. Rehabil.*, vol. 101, no. 2, pp. 309–316, 2020, doi: 10.1016/j.apmr.2019.09.016.

[29] M. Gandolla, N. S. Ward, F. Molteni, E. Guanziroli, G. Ferrigno, and A. Pedrocchi, “The Neural Correlates of Long-Term Carryover following Functional Electrical Stimulation for Stroke,” *Neural Plast.*, vol. 2016, 2016, doi: 10.1155/2016/4192718.

[30] F. Berenpas, V. Weerdesteyn, A. C. Geurts, and N. Van Alfen, “Long-term use of implanted peroneal functional electrical stimulation for stroke-affected gait: The effects on muscle and motor nerve,” *J. Neuroeng. Rehabil.*, vol. 16, no. 1, pp. 1–10, 2019, doi: 10.1186/s12984-019-0556-2.

[31] X. Bao *et al.*, “Effect of functional electrical stimulation plus body weight-supported treadmill training for gait rehabilitation in patients with poststroke: A retrospective case-matched study,” *Eur. J. Phys. Rehabil. Med.*, vol. 56, no. 1, pp. 34–40, 2020, doi: 10.23736/S1973-9087.19.05879-9.

[32] S. H. Peurala, K. Pitkänen, J. Sivenius, and I. M. Tarkka, “Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke,” *Clin. Rehabil.*, vol. 16, no. 7, pp.

709–716, 2002, doi: 10.1191/0269215502cr543oa.

[33] L. Sawaki, C. W. H. Wu, A. Kaelin-Lang, and L. G. Cohen, “Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke,” *Stroke*, vol. 37, no. 1, pp. 246–247, 2006, doi: 10.1161/01.STR.0000195130.16843.ac.

[34] S. Tashiro *et al.*, “Neuromuscular electrical stimulation-enhanced rehabilitation is associated with not only motor but also somatosensory cortical plasticity in chronic stroke patients: an interventional study,” *Ther. Adv. Chronic Dis.*, vol. 10, p. 204062231988925, Jan. 2019, doi: 10.1177/2040622319889259.

[35] T. J. Kimberley, S. M. Lewis, E. J. Auerbach, L. L. Dorsey, J. M. Lojovich, and J. R. Carey, “Electrical stimulation driving functional improvements and cortical changes in subjects with stroke,” *Exp. Brain Res.*, vol. 154, no. 4, pp. 450–460, 2004, doi: 10.1007/s00221-003-1695-y.

[36] Bioness Europe B.V., *L300 Go Clinician’s Guide*. Zwijndrecht: Bioness Europe B.V., 2021.

[37] L. R. Sheffler and J. Chae, “Neuromuscular electrical stimulation in neurorehabilitation.,” *Muscle Nerve*, vol. 35, no. 5, pp. 562–590, May 2007, doi: 10.1002/mus.20758.

[38] R. B. Stein *et al.*, “Long-term therapeutic and orthotic effects of a foot drop stimulator on walking performance in progressive and nonprogressive neurological disorders,” *Neurorehabil. Neural Repair*, vol. 24, no. 2, pp. 152–167, 2010, doi: 10.1177/1545968309347681.

[39] K. Dunning, M. W. O’Dell, P. Kluding, and K. McBride, “Peroneal Stimulation for Foot Drop after Stroke,” *Am. J. Phys. Med. Rehabil.*, vol. 94, no. 8, pp. 649–664, 2015, doi: 10.1097/PHM.0000000000000308.

[40] D. B. Popović, “Advances in functional electrical stimulation (FES),” *Journal of Electromyography and Kinesiology*, vol. 24, no. 6. Elsevier Ltd, pp. 795–802, Dec. 01, 2014, doi: 10.1016/j.jelekin.2014.09.008.

[41] S. Giaquinto, M. Mascio, and L. Fraioli, “The physiopathological bases of recovery processes: The bases of stroke rehabilitation. The cassino project,” *Clin. Exp. Hypertens.*, vol. 24, no. 7–8, pp. 543–553, 2002, doi: 10.1081/CEH-120015331.

[42] D. A. E. Bolton, J. H. Cauraugh, and H. A. Hausenblas, “Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: A meta-analysis,” *J. Neurol. Sci.*, vol. 223, no. 2, pp. 121–127, 2004, doi: 10.1016/j.jns.2004.05.005.

[43] D. G. Everaert, A. K. Thompson, Su Ling Chong, and R. B. Stein, “Does functional electrical stimulation for foot drop strengthen corticospinal connections?,” *Neurorehabil. Neural Repair*, vol. 24, no. 2, pp. 168–177, 2010, doi: 10.1177/1545968309349939.

[44] M. Tinazzi *et al.*, “Long-lasting modulation of human motor cortex following prolonged transcutaneous electrical nerve stimulation (TENS) of forearm muscles: Evidence of reciprocal inhibition and facilitation,” *Exp. Brain Res.*, vol. 161, no. 4, pp. 457–464, 2005, doi: 10.1007/s00221-004-2091-y.

[45] T. Mima *et al.*, “Short-term high-frequency transcutaneous electrical nerve stimulation decreases human motor cortex excitability,” *Neurosci. Lett.*, vol. 355, no. 1–2, pp. 85–88, 2004, doi: 10.1016/j.neulet.2003.10.045.

[46] M. Fernandez-del-Olmo *et al.*, “How repeatable are the physiological effects of TENS?,” *Clin. Neurophysiol.*, vol. 119, no. 8, pp. 1834–1839, 2008, doi: 10.1016/j.clinph.2008.04.002.

[47] M. Kofler *et al.*, “Modulation of upper extremity motor evoked potentials by cutaneous afferents in humans,” *Clin. Neurophysiol.*, vol. 112, no. 6, pp. 1053–1063, 2001, doi: 10.1016/S1388-2457(01)00540-5.

[48] H. Feys, J. Van Hees, F. Bruyninckx, R. Mercelis, and W. De Weerdt, “Value of somatosensory and motor evoked potentials in predicting arm recovery after a stroke,” *J. Neurol. Neurosurg. Psychiatry*, vol. 68, no. 3, pp. 323–331, 2000, doi:

10.1136/jnnp.68.3.323.

[49] C. M. Stinear, M.-C. Smith, and W. D. Byblow, “Prediction Tools for Stroke Rehabilitation,” *Stroke*, vol. 50, no. 11, pp. 3314–3322, Nov. 2019, doi: 10.1161/STROKEAHA.119.025696.

[50] D. J. Cormier, M. A. Frantz, E. Rand, and J. Stein, “Physiatrist referral preferences for postacute stroke rehabilitation.,” *Medicine (Baltimore).*, vol. 95, no. 33, p. e4356, Aug. 2016, doi: 10.1097/MD.0000000000004356.

[51] S. M. Nasir, M. Darainy, and D. J. Ostry, “Sensorimotor adaptation changes the neural coding of somatosensory stimuli,” *J. Neurophysiol.*, vol. 109, no. 8, pp. 2077–2085, 2013, doi: 10.1152/jn.00719.2012.

[52] L. Rocchi *et al.*, “High frequency somatosensory stimulation increases sensori-motor inhibition and leads to perceptual improvement in healthy subjects,” *Clin. Neurophysiol.*, vol. 128, no. 6, pp. 1015–1025, 2017, doi: 10.1016/j.clinph.2017.03.046.

[53] C. Zhao, E. Valentini, and L. Hu, “Functional features of crossmodal mismatch responses,” *Exp. Brain Res.*, vol. 233, no. 2, pp. 617–629, 2014, doi: 10.1007/s00221-014-4141-4.

[54] S. M. Schabrun, M. C. Ridding, M. P. Galea, P. W. Hodges, and L. S. Chipchase, “Primary Sensory and Motor Cortex Excitability Are Co-Modulated in Response to Peripheral Electrical Nerve Stimulation,” *PLoS One*, vol. 7, no. 12, pp. 1–7, 2012, doi: 10.1371/journal.pone.0051298.

[55] E. K. Vanhoutte *et al.*, “Modifying the Medical Research Council grading system through Rasch analyses,” *Brain*, vol. 135, no. 5, pp. 1639–1649, 2012, doi: 10.1093/brain/awr318.

7. Danksagung

Lieber Herr Prof. Dr. Young, Herr Prof. Dr. Schoser und Herr Prof. Dr. Kröger, ich bin sehr dankbar für die Kommentare und das konstruktive Feedback. Außerdem möchte ich mich dafür bedanken, dass Sie mir die Möglichkeit gegeben haben, selbstständig zu arbeiten.

Vielen Dank an meine Frau Monika für die harte Zeit während meiner Promotion. Ich werde es nie vergessen.

Ich nehme mir die Erlaubnis und schreibe diesen Abschnitt in meiner Muttersprache, damit meine Eltern ihn verstehen können. "Draga mama Biserka i tata Mladen, iako nisam uvijek razumio vaše odgojno obrazovne metode, uspijeli ste stvaviti na noge moja tri brata Igora, Tomislava, Josipa i mene. Želim vam od srce zahvaliti na tome."

Besonderen Dank an Prof. Toso Marsic, Dr. Durdica Marosevic, Andres Jung, Nathalie Walter, Ivan (Dama) Damjanovic, Josip, Tomislav, Igor und Janja Mijic, die immer da waren, wenn ich sie brauchte. Vielen Dank an alle meine Freunde und Familie für die Unterstützung meiner Arbeit!