UNIVERSITAT DE BARCELONA

Enriched Music-supported Therapy and motivational factors in chronic stroke rehabilitation

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2024

Agradecimientos

Al mirar atrás en el tiempo me pregunto qué sería de mí si no hubiese decidido embarcarme en esta aventura llamada *doctorado*. Los siete años que llevo en investigación han sido un constante e intenso aprendizaje tanto a nivel académico como personal. El 30 de octubre de 2020, mientras hacía mi primera matrícula, no me imaginaba la cantidad de retos intelectuales, personas interesantes, y lugares encantadores que me iba a aportar tomar esa decisión. Si estás leyendo esto significa que has formado parte de mi proceso y que me has acompañado, ayudado, e inspirado, de alguna manera u otra, en el desarrollo de esta tesis. Así pues, qué menos que unas palabras de agradecimiento…

El principal causante de que estas líneas existan es el **Dr. Antoni Rodríguez Fornells**. Toni, gracias por darme la oportunidad de unir mis dos pasiones. Siete líneas no son suficientes para agradecer todo lo que he aprendido, vivido, y experimentado a partir de todas las puertas que me has abierto y caminos que me has mostrado. Gracias por confiar en mí, escucharme, guiarme, y apoyarme. Tu motivación contagiosa inspira y planta semillas de curiosidad a todos los que tenemos el honor de estar bajo tu supervisión. Gracias por crear del laboratorio un lugar en el que crecer y desarrollarse. Si puedo imaginar mi futuro profesional lleno de proyectos sobre música, cognición, y terapia, es gracias a ti.

La segunda causante a la que agradecer la existencia de esta tesis es la **Dra. Jennifer Grau Sánchez**. Jenny, gràcies pel teu suport, comprensió, i ànims durant tots aquests anys. Gràcies per estar sempre disposada a xerrar del que necessités i per ajudar-me a confiar en la meva feina. Fer aquesta tesi al teu costat m'ha fet el recorregut molt més planer. Gràcies per tot el que m'has ensenyat sobre recerca clínica i per obrir-me les portes de la EUIT. Em sento privilegiada d'haver sigut la teva primera estudiant de doctorat i haver continuat tota la feina que vas fer sobre rehabilitació per ictus i teràpia musical.

La mayor parte mi tesis ha sido posible gracias a un equipo enorme de profesionales a los que admiro y agradezco su trabajo. **Dr. Josep Lluis Arcos**, gràcies per treballar sempre amb curiositat i pel suport constant amb l'app durant tot el projecte. **Dra. Esther Duarte**, gràcies per tota l'ajuda i per fer-me sentir com a casa a l'*Hospital de l'Esperança*. **Anna Palumbo**, **Dr. Alan Turry**, and **Dr. Preety Raghavan**, thank you for welcoming me in the US and teaching me about your incredible work on music therapy and rehabilitation. **Myriam** y **Mafe**, gracias por hacer más amenas todas las horas que pasamos en el hospital evaluando a pacientes. Disfruté mucho de ese periodo de mi doctorado y fue muy bonito y didáctico compartirlo con vosotras. **Xim**, gràcies per fer que tot sembli més fàcil, per les converses sobre la vida, i per deixar-me guanyar sempre les apostes. **Dr. David Sánchez-Pinsach** i al **Dr. Jesús Cerquies**, gràcies per tota la vostra feina en aquest projecte. Thank you also **Dr. Thomas Münte** and **Dr. Teppo Särkämö** for your valuable contributions on this work. Este proyecto tampoco habría sido viable sin los **participantes** de los estudios. A todos y todas vosotras quería daros las gracias, no sólo por hacer posible la realización de esta tesis, sino también por enseñarme el significado de fuerza, voluntad, y vitalidad después de que vuestra vida diera un vuelco de 180º. Detrás de los resultados de esta tesis hay historias de superación admirables. Gracias por enseñarme tanto y compartir la música conmigo.

Tengo que admitir que nunca pensé en incluir un estudio que no fuera sobre música en mi tesis, pero con Adrià y Aida fue todo lo contrario a tedioso. **Adrià**, gràcies per tot el que m'has ensenyat, per la teva humilitat, i per la teva ajuda incessant fins a resoldre tots els problemes. Em vas treure la por a programar i em vas ajudar molt a confiar en la meva feina, i això sempre t'ho agrairé. **Aida**, és un plaer treballar amb algú amb el teu entusiasme. Gràcies per tot el que he après amb tu sobre anhedònia.

Me considero demasiado afortunada de haber realizado mi trabajo en *Brainvitge,* un lugar que siento como mi segunda casa y que me ha rodeado de personas maravillosas. Començaré per la primera que em va rebre als passadissos del *lab* i em va supervisar els meus primers anàlisis i escrits científics. **Neus**, gràcies per animar-me des del primer dia a seguir a on acabava d'entrar. Recordo quan em parlaves, mentre rascàvem caps envoltats d'elèctrodes, sobre la qualitat científica i humana que hi ha a *Brainvitge*. Ara, uns anys més tard, puc afirmar que tenies tota la raó. Gràcies per tot el que vam compartir i tot el que em vas ensenyar. Els dies a les escoles passant EEGs sempre els recordaré amb carinyo i felicitat. La meva feina tampoc hagués sigut possible sense la incondicional ajuda del **Joan Rodríguez** i el **David Cucurell**. Joan, gràcies per tot. Hem compartit tantes coses durant aquests anys que no sé ni per on començar (però òbviament començaré pel menjar): sushi, pizza, sopa de miso, més de 60 trajectes en cotxe, més de 30 cases visitades, innumerables fotos, concerts de música clàssica, *esnórquel*, un *esquéip rum* d'on per poc no surto viva... Coincidir amb tu a *Brainvitge* ha sigut, en resum, una *fantasia*. David, gràcies per tota l'ajuda i la teva constant predisposició a resoldre amb interès i humilitat tots els problemes tècnics i intel·lectuals.

Gràcies també a totes i tots els de la 1.7 passats i presents, amb qui he compartit uns quants seminaris a part de dinars. Gràcies als meus *germans* de PhD, la **Gemma** i el **Guillem**, per la vostra companyia, ajuda, i suport durant tots aquests anys, i especialment aquests últims mesos. Ha sigut un plaer compartir en paral·lel amb vosaltres aquest camí des de l'inici fins al final. Gemma, gràcies per fer del *lab* un lloc tan acollidor omplint les parets de fotos i la cuina de dolços, i per fer-me viure des de més a prop l'encantador món de les *manualitats*. Guillem, gràcies per fer aquesta experiència més divertida i lleugera fent-me plorar del riure i incrementant-me un xic la meva tolerència als ensurts. Gràcies a la **Claudia A**, per ser un gran exemple d'amabilitat i humilitat. La teva arribada al *lab* el va convertir en un lloc encara millor. I al **Marc B**, per ser company i amic dins i fora del *lab*. Gràcies per la teva inesgotable bona vibra i tanta música compartida. Gràcies a la **Lucía**, **Polina**, **Víctor**, **Anna G**, i **Khalil**, per compartir amb mi el camí de la recerca. Y por último y no menos importante, un gracias muy especial a todas esas doctoras a las que admiro y han sido para mí un gran ejemplo a seguir: **Dra. Marta M**, **Dra. Ana Z**, **Dra. Patricia L**, **Dra. Alba G**, **Dra. Laura F**, **Dra. Lucía V**, y **Dra. Claudia P**. En un mundo donde es fácil caer en el síndrome de la impostora, vosotras siempre me habéis inspirado profundamente a continuar por este camino.

Y siguiendo con mis queridísimas personas de *Brainvitge*... **Marta S**, my *partner in dance*, gracias por tanta música y experiencias compartidas, por siempre decirme las palabras más sabias, por darme fuerza en los momentos difíciles, y por enseñarme a mirar la vida con pragmatismo y optimismo. Gracias por tu amistad y por inspirarme tanto a nivel científico como personal. Estar lejos de ti significa echarte de menos, pero sentirte cerca (¡no puedo esperar a nuestro reencuentro en cualquier parte del mundo!). **Bianca**,

pocos meses fueron suficientes para forjar una amistad que me acompaña allá donde voy. Gracias por compartir conmigo conversaciones llenas de matices y planes estimulantes en los que siempre hay cabida para un par de botellas de *Vichy Catalan*. Admiro tu capacidad de disfrutar intensamente los pequeños y grandes placeres de la vida y de llenar de alegría cada sala en la que entras. Gràcies també al **Joan T**, per compartir amb mi tants espais més enllà de *Brainvitge*, per crear la major indústria d'*Stickers*, i per ensenyar-me conceptes de totes les generacions. Gràcies per la teva amistat, pel teu suport, i per totes les converses, des dels temes més profunds als més banals. Gracias a **Paula LG**, the *coolest artist and data scientisit* I've ever known. Compartir *lab* con una persona que irradia tanto arte siempre me ha hecho sentir como en casa. Gracias por tu amistad y por demostrarme con un disfraz de *pollo a l'ast* y con otro de *calçot* que la creatividad no tiene límites. A **Audrey**, mi otra compi de "*thesis submission*", gracias por todas las risas y por tu incesante energía positiva y contagiosa que levanta montañas. Haces que el *lab* sea un lugar más brillante, divertido, y emocionante. **Brian**, gracias por tu naturalidad desde el día 0, por los paseos en patines, y por siempre enseñarme *random facts*. Thanks to **Eylül** and **Judit** for inspiring me to seek scientific experiences abroad and for our meetings in random places around the world. Thanks also to **Vicky** and **Daniela** for bringing fresh air to the lab and making it an even more special space. **Ieva**, thank you for all our lovely language exchanges filled with both random and personal topics. **Dr. Clem François**, gracias por las conversaciones sobre música e investigación que tuvimos antes de que yo empezara el doctorado. Sin duda me motivaste a seguir por aquí. A tota la resta de gent de *Brainvitge* amb qui he compartit una conversa, dinar, congrés, calçotada, o festa de Nadal, gràcies: **Dra. Ruth de Diego-Balaguer**, **Dra. Estela Càmara**, **Dr. Lluis Fuentemilla**, **Dr. Josep Marco-Pallarés**, **Dra. Mireia Hernández**, **Dr. Xavi Rifà-Ros**, **Dr. Pablo Ripollés**, **Dr. Ernest Mas-Herrero**, **Dr. Alberto Ara**, **Dra. Elena Koulaniga**, **Dra. Asia Sierpowska**, **Dra. Helena Alicart**, **Dr. Alexis Pérez-Bellido**, **Dr. Jeison Parra-Tíjaro**, **Dr. Joan Orpella**, **Dra. Berta Nicolás**, **Dra. Clara García-Gorro**, **Dr. Francesco Giannelli**, **Dr. Xiongbo Wu**, **Dr. Carles Falcón**, **Dr. Ludo Saint-Amour**, **Anna Gasa**, **Pablo Marcos**, i **Helena Pardina**.

A mis amigas y amigos del máster de *Research in Behaviour and Cognition* y de *Mundet*, gracias por compartir nuestras alegrías y penas mientras se investiga. Os admiro mucho y os agradezco por haber hecho mi camino más llevadero entre risas, confidencias, y debates. **Martina**, gracias por ser un pilar en mi vida, por celebrar mis logros como si fueran tuyos y amortiguar mis caídas donde sea que me encuentre. Tu presencia ha sido esencial para que pudiese seguir adelante en los momentos más duros de mi doctorado. Gracias por tu mirada justa y comprensiva, y por recordarme las veces que haga falta todo de lo que soy capaz cuando me olvido. **Pancho**, si existiese la reencarnación estoy segura de que éramos amigos en una vida pasada. Gracias infinitas por tu presencia. Gracias por tu apoyo, por tus bromas, y por compartir tantas horas de *co-working* como de conciertos y karaokes. **Enrico**, gracias por una amistad tan bella. Gracias por compartir, analizar, y debatir conmigo múltiples puntos de vista, y por enseñarme tu enorme sensibilidad por la vida, la comida, la ciencia, la música, y el cine. Gracias también por las risas, *obvio*. **Marc D**, gràcies per tot el que hem compartit aquests anys, des de plans a *Barcelona* i *Creixell*, fins a *Astúries*, *Hèlsinki*, i el nostre estimat *Mèxic*. En tots aquests llocs tinc records amb tu plens de riures, música, i converses sobre la vida. Gràcies per ser xarxa de suport i zona segura. Y a mi otra compi de aventuras *mexicanas*, **Laia**, gracias por inspirarme a nivel tanto personal como científico. Desde que te conozco, admiro tu capacidad de gestionar la vida con cabeza y humor, siempre con las palabras justas, necesarias, y graciosas cuando la situación lo requiere. Y para finalizar con mis *compitruenos mexicanos*, un gracias tan grande como los abrazos que da ella, **Laura**. Gracias por ser ejemplo de fuerza y resiliencia. Gracias por todo lo que hemos compartido y por todo tu soporte durante estos años, especialmente en uno de los momentos más complicados de mi doctorado. Gracias también a **Cris**, por hacernos afortunadas a todas las personas que hemos tenido el placer de conocerte en nuestros últimos años de doctorado. Gracias por tu inmensa empatía y por traer luz a *Mundet*. **Stella**, gracias por tu gran cariño, por apoyarme tanto en todo lo que he hecho, por todas nuestras conversaciones, y por los viajes que hemos vivido juntas a lo largo de estos años. Al **Marc S**, gràcies per ser no només un gran amic, si no el millor compi de sala a *Mundet*. Gràcies per sempre transmetre'm calma i energia positiva. A l'**Adrià**, gràcies per totes les experiències compartides; la teva amabilitat i humilitat sempre m'han inspirat a ser millor persona. **Carlos**, gracias por la buena compañía en todos los planes y por las conversaciones sobre *personalidad*. **Josué**, gracias por los *breaks* compartidos y por hacer que la estadística parezca fácil. And *last but not least*, gracias a **José**, **Robinson**, **Ari**, **Gaël**, **Jaume**, **Marta**, **Gemma F**, **Borja**, y **Laura M**, por cruzarse en mi camino e inspirarme siendo ejemplos de inteligencia y constancia.

A mis amistades del máster de *Musicoterapia*, **Maribel**, **Carolina**, **Mónica**, **Vittoria**, **Antonella**, **Clara**, **Aseel**, **Jazziel**, **Alejandro**, y **Giancarlo**, gracias por compartir con el mundo vuestro gran corazón y por enseñarme a tener una perspectiva holística de la disciplina más bonita.

El doctorado me ha llevado a vivir en una ciudad que nunca me imaginé: *Aarhus*. Mi experiencia en esta ciudad danesa fue transformadora a muchos niveles y me rodeó de personas brillantes. Quiero agradecer primero de todo al **Dr. Boris Kleber**, por abrirme las puertas al *Center for Music in the Brain (MIB)*, por apoyarme, y por coger con entusiasmo nuevos proyectos. Gràcies també a la **Dra. Anna**, per sempre fer-me sentir com a casa. *MIB* is a magical place full of people who share two passions with me: music and neuroscience. The best gift this *lab* has given me is the friendship with my dear **Dr. Sànder Celma-Miralles**. Sànder, no tinc paraules per agrair tot el que m'has aportat i ajudat durant els meus últims mesos de doctorat. Les hores de cafè amb tu em donaven anys de vida. Gràcies per escoltar-me i donar-me els millors consells. Ets un gran científic i encara (si cap) millor persona. Thanks to my friends from the *big temporary room* **Tamar**, **Marcelo**, **Dhwani**, and **Ferran**, for being the sweatiest colleagues I could have ever imagined. After several days talking about my thesis, you can finally read it! Thanks also to the other *MIB* members with whom I shared a seminar, a dinner, a concert, or a foosball match, for inspiring me in many ways: **Dr. Peter Vuust**, **Dr. Bjørn Petersen**, **Dr. Peter Keller**, **Dr. Cecilie Møller**, **Dr. Kira Vibe Jespersen**, **Dr. Massimo Lumacca**, **Dr. Thomas Matthews**, **Dr. Victor Pando-Naude**, **Dr. Jan Stupacher**, **Dr. Mattia Rosso**, **Dr. Leonardo Bonetti**, **Silvia**, **Rebecca**, **Teresa**, **Nasia**, **Paul**, **Pelle**, **Olivia**, **Mathias**, **Gemma**, **Alberte**, **Tina**, and **Hella**.

Mi estancia en *Aarhus* también me hizo coincidir con una gran amiga e investigadora (y antigua *Brainvitgera*!): **Analú**, gracias por tu soporte, por compartir cada paso, y por ser familia a tantos *kms* de

distancia. Nuestro reencuentro fue de lo más bonito de mi año. Gracias también a **Ane** y a **Silvia**, por las cenas, las risas, y por darme tanta fuerza en los últimos meses. Al **Víctor**, el català més danès que conec. Gràcies pels ànims i pel teu exemple de disciplina i perseverança. I also want to thank my *Sabar Family*, **Ida**, **David**, **Arka**, **Amdy**, **Mo'Thiam**, **Jens Peter**, **Casper**, **Freya**, **Katleen**, and **Gianmario**, for creating one of the spaces that made me happiest in *Aarhus* and for giving me strength on the days I lacked energy. *West African rhythms* were the soundtrack of my thesis writing. Por último, gracias a mis queridísimas *postdocs* **Esme** y **Lía**, por aconsejarme, cuidarme, y ayudarme a ver la luz en los días en los que todo se me hizo más cuesta arriba.

También agradecer a las personas que aparecieron en mi vida mucho antes de la tesis y han sido un gran soporte hasta el día de hoy. A **María**, con quien descubrí el significado de la palabra *amistad*. Gracias por compartir la vida conmigo, hermana. Me lleno de amor cada vez que hablas con orgullo sobre mí. A **Judit** y **Cris**, gracias por todo lo que hemos vivido juntas, por vuestro apoyo con todas las decisiones que tomo, y por escucharme tantas horas sobre investigación como si para vosotras también fuera lo más interesante. A les meves amigues de *Biologia*, **Maria**, **Judith**, **Jess**, **Àlex** i **Rita**, per recolzar-me, animar-me, i inspirar-me. Sense la vostra presència des de la carrera tampoc hauria arribat fins aquí. És un orgull que sigueu les primeres persones amb qui vaig estudiar i compartir la ciència, i que puguem seguir veient-nos créixer personal i professionalment. Gracias también a mi profesora de piano **Elbi** y a mis compañeras **Silvia**, **Carolina**, **Majo**, **Carlitos**, **Marcos**, y **Debby**, por apoyar mi proyecto musical durante el doctorado. El piano ha sido mi mayor aliado a lo largo de estos años, y compartirlo con vosotras ha sido todo un privilegio.

Mi más profundo agradecimiento va para las personas sin las cuales tampoco existiría esta tesis: mis padres **Mercedes González** y **Jordi Segura**, y mi hermano **Eric Segura**. Gracias por darme todos los recursos necesarios para seguir un camino que me haga feliz, y por apoyarme incondicionalmente durante este reto intelectual y personal. Os agradezco a los tres por haberme rodeado siempre de música, arte, y cultura. Para mí sois una inspiración, y vuestro orgullo hacia mí me llena el corazón. Os quiero y admiro muchísimo. Eric, gracias por enseñarme la importancia de la creatividad, la sensibilidad, la humildad, y del querer bien. Gracias por toda tu ayuda con los aspectos técnicos para las sesiones de musicoterapia y por crear la portada de tesis más bonita que podía imaginar. Papa, gracias por confiar en todas las decisiones que tomo, y por enseñarme el significado de trabajo constante y comprometido. Mama, gracias por guiarme y ayudarme a desarrollar mi mejor versión, por enseñarme a ser libre y feliz, y por hacer que la música siempre nos acompañe. Eres la que más de cerca ha vivido esta tesis y sin ti no hubiese sido capaz de llevarla a cabo como lo he hecho. Gracias también a mis **tías**, **primas**, y **primos** por siempre interesaros en lo que estaba haciendo con tanto cariño y amor.

Por último, nombrar a la **música**, ese estímulo abstracto causante de que yo me dedique a la ciencia, que siempre me saca de mi zona de comfort, y que hace mi vida extremadamente más entretenida y bonita.

A mi madre

Table of contents

List of abbreviations

ADL	Activities of Daily Living
AE	Affected Extremity
AES-I	Apathy Evaluation Scale - Informant Version
AES-S	Apathy Evaluation Scale - Self-Rated Version
AI	Artificial Intelligence
ARAT	Action Research Arm Test
ASD	Agile Software Development
BBT	Box and Block Test
BDI-II	Beck Depression Inventory-II
CAHAI	Chedoke Arm and Hand Activity Inventory
CONSORT	Consolidated Standards of Reporting Trials
DALYs	Disability-Adjusted Life-Years
EEG	Electroencephalography
eMST	Enriched Music-supported Therapy
FMA-UE	Fugl-Meyer Assessment for Upper Extremity
fMRI	Functional Magnetic Resonance Imaging
GRASP	Graded Repetitive Arm Supplementary Program
ICF	International Classification of Functioning, Disability and Health
MCID	Minimally Clinically Important Difference
MDC	Minimal Detectable Change
MIDI	Musical Instrument Digital Interfance
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRCS	Medical Research Council Scale
MST	Music-supported Therapy
NAE	Non-Affected Extremity
NHPT	Nine Hole Pegboard Test
OT	Occupational Therapy
PT	Physiotherapy
POMS	Profile of Mood States
PSD	Post-Stroke Depression
QoL	Quality of Life
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Controlled Trial
TMS	Transcranial Magnetic Stimulation
TR	Telerehabilitation
WHO	World Health Organization
3D	Three dimensional

Abstract

More than half of stroke survivors in the chornic phase still experience upper-limb motor deficits that limit their daily activities and community participation. This ongoing disability can significantly impact their sense of autonomy, social interaction, occupational identity, and overall quality of life. Despite the rising prevalence of stroke, access to rehabilitation in the chronic phase remains limited, representing a major unmet need in this population. Developing accessible, community-based interventions is thus crucial to maintaining or improving the physical and mental health of chronic stroke survivors while alleviating the burden on healthcare systems.

Music-supported Therapy (MST) is a widely studied intervention for treating post-stroke hemiparesis through standardized instrumental training, adhering to rehabilitation principles such as mass repetition and gradual increase of difficulty. In addition, the program benefits from the audio-motor coupling activation and motivational effects provided by music. MST has consistently been shown to improve upper-limb motor functions, neuroplasticity, emotional well-being, and quality of life in subacute and chronic stroke patients. However, it did not demonstrate superior effectiveness compared to conventional motor therapy in enhancing motor function. To increase the accessibility and effectiveness of chronic stroke rehabilitation, we designed an enriched version of MST (eMST) by integrating socio-motivational and learning components proven to enhance the reacquisition of motor skills. This redesigned program was adapted for home use, incorporating both self-training and group music therapy sessions to foster autonomy and socialization, crucial factors in rehabilitation. We also increased training intensity and introduced new percussion instruments, upper-limb movements, and rhythmic patterns to further enhance motor recovery. To facilitate the intervention, we developed a tablet-based app with gamification strategies that provides instructions for conducting the home-based self-training eMST sessions.

This doctoral thesis aimed to evaluate the effectiveness of eMST in chronic stroke rehabilitation and explore the presence of anhedonia, a condition characterized by diminished sensitivity to everyday pleasures that may hinder engagement in rehabilitation. The thesis comprises four studies with different research designs to address these goals. In **Study 1**, we refined the MST app based on the feedback from chronic stroke patients, who confirmed the usability of the latest version of the app. After 30h of home-based training over 10 weeks, participants demonstrated clinically relevant upper-limb improvements, increased velocity in piano performance, high adherence, and no safety concerns, confirming the feasibility of the home-based eMST. In **Study 2**, we developed a clinical trial protocol to compare the effectiveness of eMST to a conventional home-based rehabilitation program for chronic stroke survivors. We designed a pragmatic parallel-group randomized controlled trial to assess

the benefits of eMST when implemented as planned as well as accounting for patients who dropped out to evaluate its effectiveness under real-world conditions. The primary outcome was upper-limb functionality, and secondary outcomes included other motor and cognitive functions, emotional well-being, QoL, self-regulation and self-efficacy. Both interventions were designed to provide 40 hours of training over 10 weeks, with the eMST intervention comprising 30 hours of self-training sessions and 10 hours of group sessions. Evaluation points were established before and after the intervention, and at three-month follow-up to assess lasting effects. In **Study 3**, we tested the effectiveness of eMST in chronic stroke rehabilitation compared to a conventional program. For the first time, we demonstrated that eMST outperformed conventional rehabilitation in both motor and emotional outcomes. The eMST group showed greater improvements in upper-limb motor impairment after the intervention, which were maintained after three months, as well as in upper-limb functionality and motor performance during daily tasks at follow-up. These gains were observed regardless of clinical, demographic, or personal factors. Notably, motor improvements occurred in both participants who completed the interventions as planned and those who dropped out, indicating real-world benefits. The lack of association between participants' level of musical hedonia and their motor improvements in the music intervention suggests that other factors, such as social interaction or gamification strategies, may have a greater impact on motor recovery. The eMST intervention also led to reduced anger and apathy, increased positive emotions, and enhanced community participation. Furthermore, participants found the sessions more fun and enjoyable compared to the control intervention. In **Study 4**, we measured the presence of anhedonia in subacure and chronic stroke survivors, and we found significantly higher levels compared to healthy controls. This difference remained even after accounting for the influence of other related negative emotions, indicating a distinct role for anhedonia after stroke. The prevalence of anhedonia was 20%, regardless of stroke etiology, lesion location, affected hemisphere, or time since the stroke, suggesting a potential effect of post-stroke low-grade chronic inflammation that disrupts the mesolimbic pathway. Furthermore, anhedonia was associated with older age, anger, and fatigue in chronic stroke survivors, highlighting its emotional impact in this stroke phase.

In conclusion, eMST is a more effective and engaging alternative to conventional rehabilitation, improving motor function, emotional well-being, and quality of life in chronic stroke survivors. Given the high prevalence of anhedonia, which can reduce motivation for rehabilitation, the development of accessible, cost-effective, and community-based programs like eMST are essential to support long-term physical and mental health of stroke survivors while reducing the burden on healthcare systems.

Resum

Més de la meitat dels supervivents d'ictus a la fase crònica continuen presentant dèficits motors a les extremitats superiors que limiten les seves activitats diàries i la seva participació en la comunitat. Aquesta discapacitat permanent pot contribuir significativament a la seva pèrdua d'autonomia, interacció social, identitat ocupacional i qualitat de vida en general. Tot i la creixent prevalença de l'ictus, l'accés a la rehabilitació en la fase crònica és limitat, el què representa una necessitat no coberta preocupant per a aquesta població. Per tant, el desenvolupament d'intervencions accessibles i basades en la comunitat és crucial per mantenir o millorar la salut física i mental dels supervivents d'ictus crònic i alleugerir la càrrega sobre els sistemes de salut.

La Teràpia amb suport Musical (MST) és una intervenció àmpliament estudiada per al tractament de l'hemiparèsia post-ictus a través d'un entrenament instrumental que s'ajusta als principis de rehabilitació, com la repetició massiva i l'augment gradual de la dificultat. A més, el programa es beneficia de l'activació de la connexió àudio-motora i dels efectes motivacionals que proporciona la música. La MST ha demostrat de manera consistent millorar les funcions motores de les extremitats superiors, la neuroplasticitat, el benestar emocional i la qualitat de vida en pacients amb ictus subagut i crònic. No obstant això, no ha demostrat una efectivitat superior en comparació amb una teràpia motora convencional en la millora de funcions motores. Per augmentar l'accessibilitat i l'efectivitat de la rehabilitació de l'ictus a la fase crònica, vam dissenyar una versió enriquida de la MST (eMST) integrant components socio-motivacionals i d'aprenentatge que han demostrat potenciar la readquisició d'habilitats motores. Aquest programa redissenyat es va adaptar per a ús domiciliari, incorporant sessions d'autoentrenament i grupal de teràpia musical per fomentar l'autonomia i la socialització, factors crucials en la rehabilitació. També vam augmentar la intensitat de l'entrenament i vam introduir nous instruments de percussió, moviments de les extremitats superiors i patrons rítmics per maximitzar la recuperació motora. Per facilitar la intervenció, vam desenvolupar una aplicació per tauleta electrònica amb estratègies de gamificació que proporciona instruccions per a la realització de les sessions d'autoentrenament d'eMST a casa.

Aquesta tesi doctoral tenia com a objectiu avaluar l'efectivitat de l'eMST en la rehabilitació d'ictus crònic i explorar la presència d'anhedonia, una condició caracteritzada per la pèrdua de sensibilitat als plaers quotidians que pot dificultar la participació en la rehabilitació. La tesi comprèn quatre estudis amb diferents dissenys per abordar aquests objectius. A l'**Estudi 1**, vam refinar l'aplicació MST basant-nos en els comentaris dels pacients d'ictus crònics, que van confirmar la usabilitat de la darrera versió de l'aplicació. Després de 30 hores d'entrenament a casa durant 10 setmanes, els participants van demostrar millores clíniques rellevants en les extremitats superiors, així com un augment de la

velocitat en els exercicis de piano, alta adherència al programa i cap preocupació de seguretat, confirmant la viabilitat de completar l'eMST a casa. A l'**Estudi 2**, vam desenvolupar un protocol d'assaig clínic per comparar l'efectivitat de l'eMST amb un programa de rehabilitació convencional domiciliari per supervivents d'ictus crònic. Vam dissenyar un assaig controlat aleatoritzat de grups paral·lels i pragmàtic per avaluar els beneficis de l'eMST tenint en compte tant els pacients que van completar la teràpia com estava planificat, com els que van abandonar, per tal de demostrar la seva efectivitat en condicions reals. L'objectiu principal va ser millorar la funcionalitat de les extremitats superiors, i els objectius secundaris incloïen millorar altres funcions motores i cognitives, el benestar emocional, la qualitat de vida, l'autoregulació i l'autoeficàcia dels pacients. Ambdues intervencions es van dissenyar per proporcionar 40 hores d'entrenament durant 10 setmanes, amb l'eMST comprenent 30 hores de sessions d'autoentrenament i 10 hores de sessions grupals. Els punts d'avaluació es van establir abans i després de la intervenció i a un seguiment de tres mesos per avaluar els efectes a llarg termini. A l'**Estudi 3**, vam provar l'efectivitat de l'eMST en la rehabilitació d'ictus crònic en comparació amb un programa convencional. Per primera vegada, vam demostrar que l'eMST pot superar la rehabilitació convencional en la millora tant de funcions motores com de benestar emocional. Els participants del grup eMST van mostrar majors millores en la discapacitat motora de l'extremitat superior després de la intervenció, les quals es van mantenir al cap de tres mesos, així com en la funcionalitat de les extremitats superiors i el rendiment motor en les tasques diàries a llarg termini. Aquests guanys motors es van produir independentment dels factors clínics, demogràfics, o personals. Aquests guanys motors es van produir independentment dels factors clínics, demogràfics o personals. És important destacar que tant els participants que van completar les intervencions com aquells que les van abandonar abans de finalitzar-les van presentar millores motores, proporcionant evidència sobre els beneficis d'aquesta teràpia en circumstàncies reals. La manca d'associació entre el nivell d'hedonia musical dels participants i les seves millores motores en la intervenció musical suggereix que altres factors, com la interacció social o les estratègies de gamificació, poden tenir un impacte més gran en la recuperació motora. La intervenció eMST també va conduir a una reducció de la ràbia i l'apatia, un augment de les emocions positives, i una major participació a la comunitat. A més, els participants van trobar les sessions més divertides i agradables en comparació amb la intervenció control. A l'**Estudi 4**, vam mesurar la presència d'anhedònia en supervivents d'ictus subagut i crònic, i vam trobar nivells significativament més alts en comparació amb els controls sans. Aquesta diferència es va mantenir fins i tot després de controlar la influència d'altres emocions negatives relacionades, indicant el paper diferenciat de l'anhedònia després de l'ictus. La prevalença d'anhedonia va ser del 20%, independentment de l'etiologia de l'ictus, la localització de la lesió, l'hemisferi afectat, o el temps transcorregut després l'ictus, suggerint un efecte potencial de la inflamació crònica de baix grau post-ictus que altera la via mesolímbica. A més, l’anhedonia es va associar amb l'edat avançada, la ira i la fatiga en els participants amb ictus crònic, ressaltant el seu impacte emocional en aquesta fase de l'ictus.

En conclusió, l'eMST és una alternativa més efectiva i atractiva a la rehabilitació convencional, millorant la funció motora, el benestar emocional, i la qualitat de vida dels supervivents d'ictus crònic. Donada l’alta prevalença d’anhedonia, que pot reduir la motivació per a la rehabilitació, el desenvolupament de programes accessibles, rendibles, i basats en la comunitat com l'eMST és essencial per millorar l’estat físic i mental dels supervivents d'ictus a llarg termini i reduir la càrrega sobre els sistemes de salut.

General Introduction

1. General Introduction

1.1 Stroke: a cause of long-term disability

1.1.1 Global burden of stroke

Stroke is a cerebrovascular and non-communicable disease that represents a major cause of death and long-term disability worldwide. The World Health Organization (WHO) estimates that stroke affects around 15 million people each year, resulting in 5 million deaths and leaving another 5 million permanently disabled. Globally, stroke ranks as the second-leading cause of death, the third-leading cause of death and disability combined, and the leading cause of disability-adjusted life-years lost (DALYs) among neurological disorders (GBD 2019 Stroke Collaborators, 2021). In 2021, stroke affected around 11.9 million individuals, leading to 7.3 million deaths, 160.5 million DALYs, and 93.8 million prevalent cases worldwide (Institute for Health Metrics and Evaluation, 2021). The global burden of stroke is rising due to population growth, aging, and increase in prevalence of modifiable risk factors, particularly in low- and middle-income countries (Katan & Luft, 2018). From 1990 to 2019, there was a notable rise in stroke incidence (70%), prevalence (85%), mortality (43%), and DALYs (32%) (see Figure 1.1). During this period, the fastest-growing risk factor was high body-mass index, underscoring the importance of a healthy and active lifestyle as a preventive measure (GBD 2019 Stroke Collaborators, 2021). In addition, age-standardized mortality and DALYs were higher in males compared to females, while age-standardized incidence rates did not differ between sexes (GBD 2019 Stroke Collaborators, 2021).

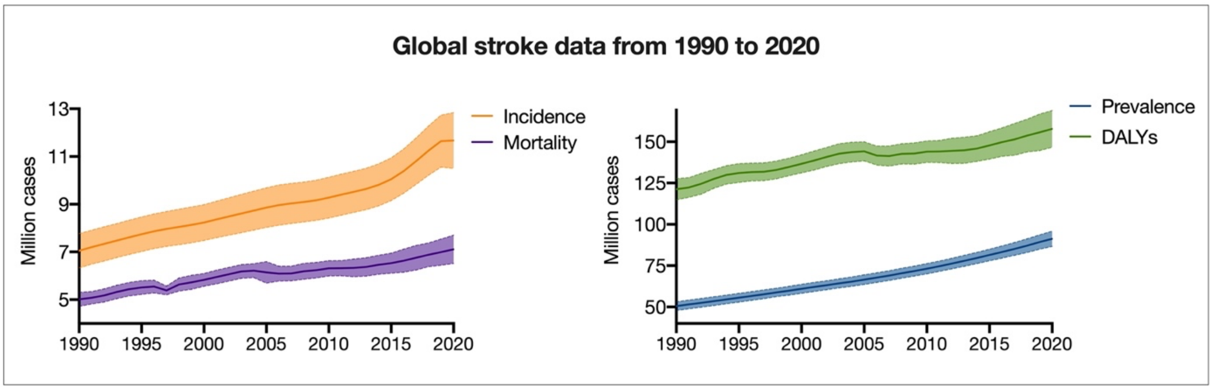


Figure 1.1. Global stroke data from 1990 to 2020.
This figure displays the annual absolute counts of new stroke cases, stroke-related deaths, prevalent stroke cases, and disability-adjusted life years lost (DALYs) from 1990 to 2020, with shaded 95% uncertainty interval. Source: Institute for Health Metrics and Evaluation, 2021.

Long-term projections for Europe estimate that between 2017 and 2047, stroke incidence and prevalence will increase by 3%-27%, while deaths and DALYs will decline by 17%-33%. This shift from mortality to morbidity will significantly raise the number of people living with stroke, thus increasing the associated human and economic burden (Wafa et al., 2020). In 2019, the global economic impact of stroke was approximately €1833 billion, accounting for 1.66% of all direct and indirect costs and around 4% of total healthcare expenditures in Western countries (Gerstl et al., 2023; Wafa et al., 2020). With an aging population, these costs are expected to rise drastically, intensifying the financial and workload burdens on the working-age population (Wafa et al., 2020). Economic costs include hospital expenses, rehabilitation and psychological therapies, transportation for hospital visits, home assistance, home modifications, assistive products, and lost wages both for patients who are unable to work and for family members or friends who reduce their working hours to provide care (Strilciuc et al., 2021; Tziaka et al., 2024). Given the significant and growing impact of stroke on our society, it is crucial to develop cost-effective preventive and rehabilitation strategies to mitigate its burden.

1.1.2 Functional and affective consequences after stroke

Stroke is an unexpected event that can profoundly impact an individual's physical and psychological states. It occurs when the blood flow in the brain is interrupted by a clot blocking a vessel (i.e., ischemic stroke) or a ruptured vessel causing bleeding (i.e., hemorrhagic stroke). This interruption deprives brain regions of the oxygen and nutrients necessary for maintenance and function, resulting in permanent neurological damage that affects different functions depending on the lesion's location (Jung, 2017; Mohr et al., 1997; Pessoa, 2008).

The most common functional consequence after stroke is motor impairment (Langhorne et al., 2009; Siddique et al., 2009). Around 85% of stroke survivors experience hemiparesis or hemiplegia, characterized by one-sided weakness or paralysis (Siddique et al., 2009; Teasell et al., 2009). Upper-limb motor deficits are particularly prevalent, including slowness, tremor, lack of coordination, and loss of strength, precision, and dexterity (Feys et al., 1998; Pomeroy et al., 2011). Somatosensory impairments, characterized by reduced ability to perceive touch, pressure, temperature, and pain, also impact motor control (Carey et al., 2018; Johansson & Westling, 1984; Sullivan & Hedman, 2008; Winward et al., 2007). Alterations in proprioception and sensory feedback reduce the accuracy of information about body position and movement, impairing motor planning and real-time performance adjustments. This hinders object manipulation, maintaining appropriate force during grasp, and relearning movements, among others motor tasks (Moore & Barnett, 2012; Uysal & Düger, 2020). Language and cognitive impairments are also usual after stroke, affecting speaking, auditory comprehension, reading, writing, attention, information processing speed, memory, orientation, and executive functions (Lingo VanGilder et al., 2020; Moore & Barnett, 2012). Visual impairments may also occur, ranging from simple visual field issues to higher-order visual cognition deficits (Hepworth et al., 2016; Sullivan & Hedman, 2008).

Noteworthy, stroke can lead to a detrimental psychological impact. The most common stroke-related mood disorder is post-stroke depression (PSD), affecting 55% of individuals at some point of the disease, especially within the first year (Medeiros et al., 2020). The etiology of PSD has been attributed to both neural (i.e., disruption of limbic-cortical pathways related to emotional processing) (Medeiros et al., 2020; Vataja et al., 2001) and situational factors related to stroke (i.e., sudden disability and loss of autonomy) (Kneebone, 2000). Depressive symptoms include sadness, emptiness, hopelessness, guilt, worthlessness, irritability, restlessness, fatigue, and anhedonia (Kouwenhoven et al., 2011). Importantly, PSD is linked to higher mortality, greater long-term disability, reduced QoL, and increased suicidal ideation (Medeiros et al., 2020).

Apathy and anxiety are also common after stroke, with reported rates of 11%-57% and 14%-21%, respectively (Sagen et al., 2010). Notably, depression, apathy, and anxiety persist in approximately 30% of individuals several years after stroke (Hartman-Maeir et al., 2007; Sagen-Vik et al., 2022). Apathetic individuals do not usually exhibit typical depressive symptoms, but both apathy and depression share the symptom of reduced motivation and goal-directed behavior. This prevents patients from participating in rehabilitation programs and exacerbates functional impairments (Moore & Barnett, 2012; Ramasubbu et al., 1998). Anhedonia, characterized by a diminished sensitivity to everyday pleasures, has been described as both a symptom of depression and an enduring behavioral trait that contributes to its development. This psychological condition is crucial for engaging in rewarding activities, and its presence might also reduce motivation to complete rehabilitation programs and maintain an active and healthy lifestyle after stroke (Verrienti et al., 2023). Despite their detrimental impact, depression and particularly anhedonia remain understudied and undertreated in the stroke population (Medeiros et al., 2020). Addressing this gap is thus essential to preventing further declines in physical and mental health among stroke survivors.

1.1.3 Autonomy and participation in chronic stroke

Our health is influenced by both biological and environmental factors. Similarly, our functional autonomy not only depends on our physical and mental states but also on external barriers that either facilitate or hamper activity completion. To address the interaction between health, functioning, and contextual factors in recovery, the World Health Organization (WHO) developed the International Classification of Functioning, Disability and Health (ICF). This framework categorizes human functioning into three domains: body structure and function (e.g., movement), activity (e.g., eating), and participation (e.g., dining out), which are further complemented by personal and environmental factors (e.g., motivation and social support) (see Figure 1.2) (ICF, World Health Organization, 2001; Vargus-Adams & Majnemer, 2014). In stroke rehabilitation, the ICF framework helps identify of neurological impairments, individual activity limitations, interpersonal participation restrictions, and personal and environmental factors that may enhances or hinder recovery (Jung, 2017).

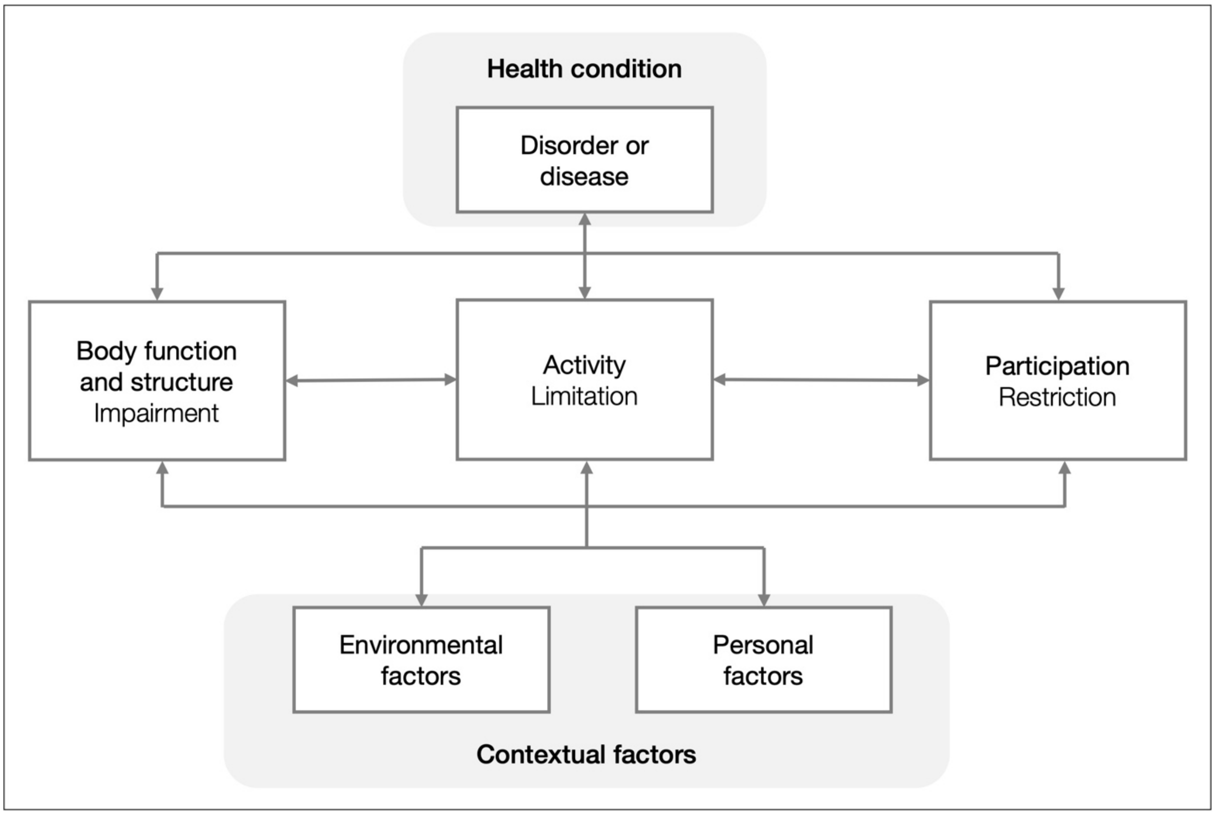


Figure 1.2. The International Classification of Functioning, Disability and Health.
This scheme represents the elements constituting human functioning: body structure and function, activity, and participation. Health conditions and contextual factors influence these elements, leading to impairments, limitations and restrictions. Adapted from: World Health Organization, 2001.

The chronic phase of stroke begins six months after onset, when stroke-induced endogenous plasticity plateaus and functional impairments become apparently permanent (Jung, 2017; Kwakkel et al., 2004). About 50%-80% of chronic stroke individuals still exhibit residual upper-limb motor deficits (Ingram et al., 2021; Kwakkel et al., 2003; Lee et al., 2015), which hinder movement (e.g., picking up objects) (Hatem et al., 2016) and thus affect the completion of activities of daily living (ADL) (Rafsten et al., 2019). Indeed, residual motor deficits are the strongest predictor of autonomy in chronic stroke (Moore & Barnett, 2012). Around 50% of individuals in this stage of the disease are limited in ADL, with 25% requiring support from caregivers (Hartman-Maeir et al., 2007). Notably, lower performance in basic and instrumental ADL has been observed between two- and fifteen-years after stroke without significant differences across years, underscoring the chronic nature of stroke-related disability (Hartman-Maeir et al., 2007; Teasdale & Engberg, 2005).

Reduced autonomy in completing ADL restricts individuals' participation the years following a stroke (Aked et al., 2024; Palstam et al., 2019). Participation is defined as the involvement in various life situations such as family, work, and community (ICF, World Health Organization, 2001), and entails completing activities that are purposeful and meaningful to an individual's life (Boop et al., 2020). From five- to ten-years after stroke, 30%-65% of individuals experience diminished participation compared to pre-stroke, particularly in complex and social everyday activities (Singam et al., 2015). Given the influence of daily participation on our self-identity, many individuals with disability prioritize being part of different life situations over body functions (Palstam et al., 2019; Van Der Zee et al., 2013; Vargus-Adams & Majnemer, 2014). On this basis, chronic stroke rehabilitation focuses on enhancing individuals' autonomy and participation rather than solely improving body functions (Borschmann & Hayward, 2020).

1.1.4 Occupational identity and life satisfaction

The long-term disability experienced by many stroke survivors prevents them from participating in meaningful daily activities that were integral to their pre-stroke routines, ranging from essential tasks to personal desires and societal roles (Hartman-Maeir et al., 2007). Approximately 72% of chronic stroke individuals report a lack of significant and meaningful activities in their daily lives (Mayo et al., 2002). This hinders them from recognizing and expressing themselves as occupational beings, thereby disrupting their occupational identity (Bergström et al., 2017; Boop et al., 2020). A recently developed model describes the process of post-stroke occupational identity disruption in three stages: i) factors influencing it, ii) how it is experienced, and iii) coping mechanisms (see Figure 1.3). The influencing factors (stage 1) include perceived bodily impairments, loss of life control, diminished occupational roles, and altered social interactions, leading to dependence, reduced self-worth, unmet goals, and feelings of emptiness. As occupational identity starts to deteriorate (stage 2), individuals may experience self-devaluation, resulting in frustration, sadness, and feelings of uselessness. In response to occupational identity disruption (stage 3), some stroke survivors reinvent their occupational selves by finding new ways to participate and derive meaning, which can restore feelings of usefulness and self-worth. For example, a carpenter who can no longer perform their pre-stroke work due to reduced dexterity and physical strength might become a woodworking instructor and continue to apply their knowledge through their preserved skills. However, diminished self-confidence due to an inability to perform certain tasks may result in social withdrawal to avoid failure in previous occupations. This maladaptive response increases social isolation and reinforces a negative feedback loop that exacerbates occupational identity disruption (Martin-Saez & James, 2021).

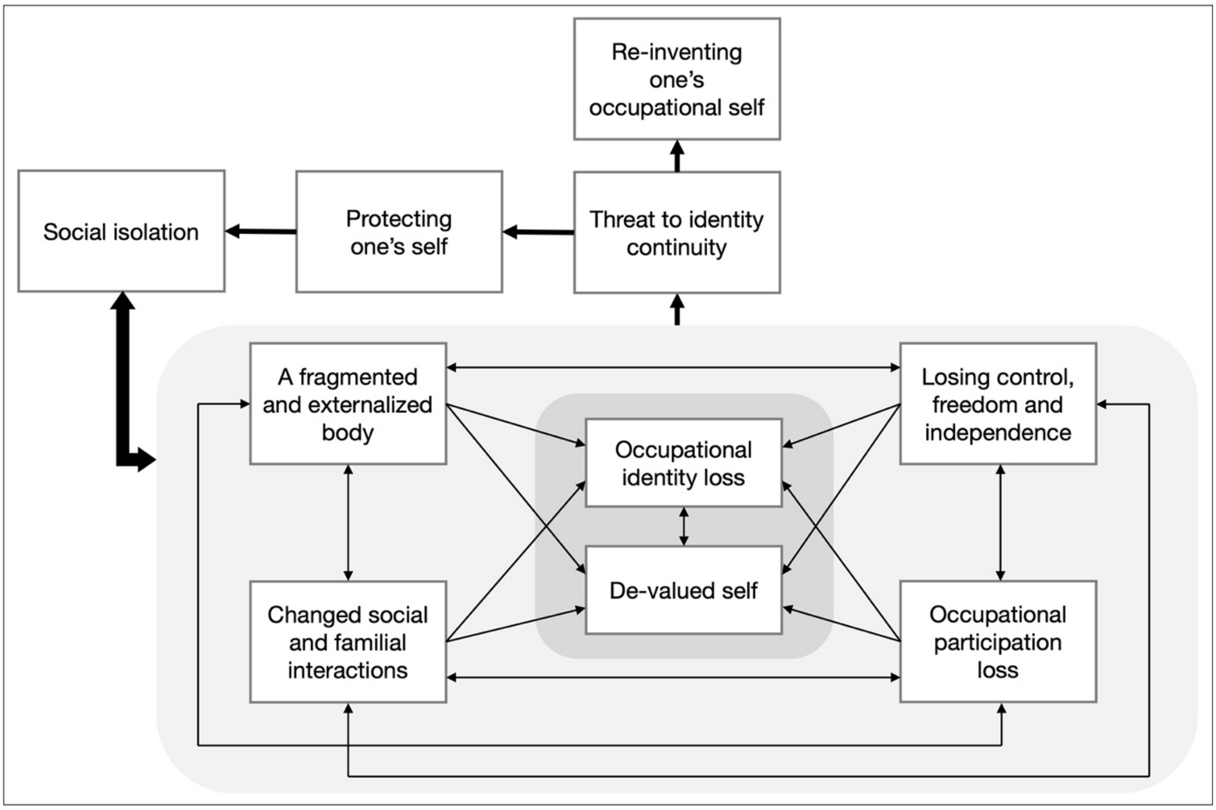


Figure 1.3. Conceptual model of occupational identity disruption after stroke.
This scheme represents the three stages constituting occupational identity disruption: 1) factors influencing the occupational disruption (inside the light grey shade), 2) occupational identity loss and de-valuated self (inside the dark grey shade), and 3) individuals' responses to this disruption, which may be directed towards either the re-invention of the occupational self or social withdrawal. Adapted from: Martin-Saez and James, 2021.

Given the social nature of humans, our psychological health is profoundly influenced by the quality of our interpersonal relationships (Mellor et al., 2008). Social isolation and loneliness are linked to boredom, a state of dissatisfaction attributed to inadequately stimulating situations (An et al., 2023). Chronic stroke survivors often experience boredom because are socially isolated and/or their abilities are insufficient to meet situational demands, leading them to withdraw from activities where they lack companionship or feel overwhelmed. In turn, retreating from community participation exacerbates loneliness, reflecting its bidirectional relationship with boredom (An et al., 2023). Noteworthy, both boredom and loneliness are triggers for depression and can deeply contribute to emotional distress and life dissatisfaction after stroke (An et al., 2023; Mellor et al., 2008; Spaeth et al., 2015; Spruyt et al., 2018). Indeed, longitudinal studies have shown that stroke survivors within the first three years after onset usually experience lower life satisfaction and increased psychiatric symptoms compared to healthy individuals, highlighting the detrimental impact of stroke on subjective well-being (Hartman-Maeir et al., 2007).

1.1.5 Needs of stroke survivors

The high prevalence of long-term disability after stroke leads to significant physical and psychological needs that must be addressed to help individuals resume their pre-stroke lives (McNamara & Dalton, 2024). A recent systematic review reported that 62% of stroke survivors present at least one unmet need after six months, increasing to 81% after two years, underscoring the importance of long-term stroke care (Lin et al., 2021). According to the ICF framework, unmet needs can be associated with bodily impairments, activity limitations, participation restrictions, and environmental barriers. Notably, the most common long-term unmet needs after stroke are related to environmental factors, particularly with healthcare services and social care (Chen et al., 2019; Lin et al., 2021). About half of stroke survivors experience a lack of stroke-related information and rehabilitation services during the chronic phase, which are often limited or discontinued (Hotter et al., 2018; Moore & Barnett, 2012). Importantly, this makes survivors and their informal caregivers feel abandoned by health organizations when they return to the community (Lin et al., 2021). Transport accessibility is another significant environmental unmet need, restricting around 32% of stroke survivors from participating in community activities (Chen et al., 2019; McNamara & Dalton, 2024).

Poor physical and mental health are also serious concerns among chronic stroke survivors. The primary physical unmet need is motor function impairment, followed by fatigue and spasticity. Regarding mental health concerns, the most common unmet needs include limited leisure time, difficulties with self-care, cognitive impairments, low mood, and reduced social engagement (Lin et al., 2021). Additionally, common mood disorders after stroke, such as depression, apathy, and anhedonia, are often underdiagnosed and undertreated. For example, while approximately half of stroke survivors experience PDS, only about 5% are diagnosed and treated in clinical practice, likely due to symptom overlap with functional impairments caused by the stroke. Nevertheless, depressive symptoms can be managed even if functional deficits persist, highlighting the need for routine emotional assessments in post-stroke clinical care (Medeiros et al., 2020).

Among all needs, those related to rehabilitation access, community participation, physical impairment, and socialization are the strongest predictors of QoL (Chen et al., 2019; McNamara & Dalton, 2024; Shaik et al., 2024). This highlights the critical importance of providing ongoing stroke rehabilitation programs that promote socialization and physical activity (Hotter et al., 2018). The WHO acknowledges that health outcomes result from complex interactions among biological, psychological, and social factors, and emphasizes the importance of addressing the emotional and social needs of stroke survivors (Cott et al., 2007). However, the unaffordability of adequate clinical infrastructure and personnel, particularly in rural and remote areas, impede effective chronic stroke care (Katan & Luft, 2018; Moore & Barnett, 2012). Moreover, individuals with lower income and poorer functionality report greater unmet rehabilitation needs, which correlate with worse functional outcomes (McNamara & Dalton, 2024; Shaik et al., 2024). Therefore, developing accessible, cost-effective, and community-based programs is essential to support chronic stroke survivors in maintaining or improving physical and cognitive functions while covering their socio-emotional needs (Steultjens et al., 2003).

1.2 New proposals for stroke rehabilitation

1.2.1 Community-based therapies for chronic stroke

Returning home after hospital discharge poses significant challenges for most chronic stroke survivors, who must adapt their lives to new physical and mental conditions without post-hospital care. Indeed, the impact of stroke-related disability usually becomes truly evident when patients return to home and community settings, where they encounter environmental barriers that were absent in the hospital (Magwood et al., 2020). Notably, common unmet needs impacting stroke survivors' QoL post-discharge include access to rehabilitation, community participation, mobility, and socialization (Chen et al., 2019; McNamara & Dalton, 2024; Shaik et al., 2024). Therefore, community-based programs are essential to increase rehabilitation opportunities that help chronic stroke individuals reintegrate into community life while potentiating their autonomy and social interaction (Cott et al., 2007; Magwood et al., 2020; Zeng et al., 2023).

Community-based rehabilitation encompasses a range of multisectoral interventions aimed at providing therapeutic services within individuals' home or in community facilities (e.g., health centers, rehabilitation clinics, non-profit stroke associations) across rural, urban, and suburban settings. The interventions are provided both individually and in group by healthcare professionals that offer occupational, physical, speech, psychological, and art therapy, as well as education on stroke care and management to patients and caregivers (Zeng et al., 2023). In an earlier study, Pang et al. (2006) conducted a randomized controlled trial (RCT) to evaluate the effectiveness of a community-based exercise program aimed at improving upper-limb motor recovery and functional abilities in individuals with chronic stroke. Sixty participants were randomly assigned to one of two intervention groups: arm or leg. Both groups underwent three one-hour weekly sessions of either arm or leg self-directed motor exercises for 19 weeks. The interventions were conducted in a community hall with 9-12 participants and supervised by a physical therapist, an occupational therapist, and an exercise instructor. The results showed significant motor improvements in the trained extremity for both groups, with the arm group exhibiting greater improvements compared to the leg group. Notably, the motor gains achieved by the arm group were comparable to those observed in other effective therapies, such as constraint-induced (CI) movement therapy or robot-assisted exercise training previously documented in chronic stroke cases (Pang et al., 2006).

Recent reviews have also reported several benefits of community-based programs contributing to emotional well-being and QoL after stroke. Crucially, these practices potentiate individuals' sense of autonomy, connectedness, social inclusion, self-enjoyment, self-expression, self-efficacy, active lifestyle, optimism, coping, and life satisfaction (Magwood et al., 2020; Zeng et al., 2023). Furthermore, treatments involving psychosocial factors have demonstrated to decrease depression and apathy after stroke (Medeiros et al., 2020). While interventions completed in community settings facilities social interaction, those completed at home foster feelings of belonging and safety (Marcheschi et al., 2018).

Community-based programs are cost-effective, reducing travel distance, staff needs, and associated costs, which is especially important given the financial challenges that stroke survivors often face. This approach thus provides chronic stroke survivors with ongoing care from interdisciplinary teams and supports their reintegration into community life, potentially contributing to their long-term mental and physical health (Zeng et al., 2023).

1.2.2 The importance of leisure after stroke

After hospital discharge, the discontinuity of a rehabilitation routine, therapist guidance, and lack of health education programs led chronic stroke survivors or their caregivers with the primary responsibility for maintaining their physical and mental health (Hotter et al., 2018). However, various factors such as motor and cognitive impairments, diminished self-efficacy and self-regulation, older age, lack of social support, low income, and limited opportunities for participating in diverse activities hinder individuals from leading an active lifestyle (Ashe et al., 2009; Morris et al., 2015). Prior studies have shown that stroke survivors tend to spend more time in sedentary behavior one-year post-onset compared to healthy age-matched controls (Galea et al., 2015; Lin et al., 2021). This inactivity significantly contributes to the decline in motor and cognitive functions between one- and six-years after stroke, reducing their autonomy, participation, and emotional well-being (Jung, 2017; Lo et al., 2022; Wondergem et al., 2017). In contrast, those who maintain an active lifestyle after stroke show improved functional mobility, muscle strength, depressive symptoms, participation in valued activities, identity continuity, and QoL, as well as reduced risk of further strokes (Billinger et al., 2014; Moore & Barnett, 2012). Therefore, it is crucial for stroke survivors to adopt a healthy and active lifestyle post-discharge in order to maintain optimal physical and mental health (Morris et al., 2015). Nevertheless, individuals with higher levels of disability and/or older age often perceive physical activity as too effortful with minimal restorative outcomes. For these individuals, reducing sedentary behavior instead of engaging in physical activity may be more practical and beneficial (Moore & Barnett, 2012; Morris et al., 2015; Wondergem et al., 2017). Given the numerous environmental (e.g., lack of health promotion programs) and personal barriers (e.g., diminished self-regulation and motor function) that impede stroke survivors from maintaining an active lifestyle, it is key to develop strategies that provide meaningful, goal-oriented, and motivating activities that facilitate community participation for individuals in the chronic phase of stroke (Morris et al., 2015).

In this context, leisure activities, defined as non-obligatory activities that are intrinsically motivating and engaged in during discretionary time (i.e., not related to obligatory occupations such as work, self-care, or sleep) seem an appropriate and affordable solution to promote mental and physical activity in stroke survivors. Leisure activities offer fun, relaxation, enjoyment, self-expression, achievement, self-determination, sense of belonging, and life satisfaction (O'Sullivan & Chard, 2010). In the long-term, leisure can foster a strong sense of engagement and participation in life, reducing boredom and social isolation, and contributing to overall well-being and QoL (An et al., 2023; Hartman-Maeir et al., 2007; O'Sullivan & Chard, 2010; Teasdale & Engberg, 2005). In the stroke population, leisure activities have been demonstrated to enhance motor and cognitive functions, community participation, and emotional and social well-being (Brunborg & Ytrehus, 2014; Dorstyn et al., 2014; Lin et al., 2021; Palstam et al., 2019). Through leisure, stroke individuals can find new meaningful activities that help re-establish functional, social, and occupational identity after stroke, promoting a more active lifestyle that benefits physical and mental health (Brunborg & Ytrehus, 2014; Dorstyn et al., 2014; Morris et al., 2015; Teasdale & Engberg, 2005).

Previous RCTs on leisure therapy have yielded varied outcomes, probably due to differences in program content. Drummond and Walker (1995) compared the effectiveness of a home-based leisure rehabilitation program with home-based occupational therapy (OT) and no treatment in individuals with acute and subacute stroke post-hospital discharge. The leisure program involved detailed discussions with a therapist about participants' hobbies and interests and the importance of maintaining them, while the OT intervention focused on improving independence in ADL. After three and six months of intervention, the leisure therapy group showed significantly higher rates of social and leisure activity participation, along with improved psychological well-being at three months, compared to the other groups (Drummond & Walker, 1995). Later, Parker et al. (2001) conducted a multicenter RCT comparing the effects of leisure therapy versus conventional OT on mood, leisure participation, and ADL independence in chronic stroke survivors. The leisure therapy consisted of practicing specific leisure activities. After six months of intervention and an additional six-month follow-up, no significant differences were found between groups, but the leisure therapy led to improvements in all outcomes, and the OT showed improved mood and ADL independence (Parker et al., 2001). Finally, Desrosiers et al. (2007) evaluated a home-based leisure education program aimed at integrating meaningful leisure activities into the lives of individuals with chronic stroke living in the community. Compared to a control group that engaged in discussions on non-leisure topics, the leisure education group reported significant improvements in leisure participation, satisfaction, and depressive symptoms after 8-12 weeks of one-hour weekly sessions (Desrosiers et al., 2007).

Qualitative reviews indicate that many individuals ten-years after stroke find new meaningful activities that enable them to focus on stimulating tasks and social interactions despite their disability (Brunborg & Ytrehus, 2014). Considering the high prevalence of inactivity among stroke survivors (Dorstyn et al., 2014), community-based leisure programs are a suitable solution to enhance their engagement in meaningful and motivating activities, improving their occupational functioning and QoL (O'Sullivan & Chard, 2010; Wulf & Lewthwaite, 2016).

1.2.3 Tele-rehabilitation and gamification strategies for stroke

Access to both hospital and community-based rehabilitation programs is often constrained by limited infrastructure, personnel, and transportation resources (Magwood et al., 2020). Technological advancements have facilitated the development of innovative healthcare strategies to improve rehabilitation accessibility and reduce stroke-related burdens. In particular, telerehabilitation (TR) addresses resource limitations by enabling remote assessment, intervention, education, and consultation via internet-based video calls, mobile apps, and sensors. TR extends stroke care beyond the clinical setting post-discharge, helping to maintain or enhance individuals' functionality and reduce long-term disability (Boop et al., 2020; Lai et al., 2004; Laver et al., 2020). A key advantage of TR is its ability to increase therapy dosage without requiring face-to-face supervision, making it especially beneficial for individuals who live in rural and remote areas, have restricted mobility, or are on low incomes (Laver et al., 2020). The COVID-19 pandemic underscored the utility of TR in maintaining rehabilitation services while minimizing infection risks, inactivity, and social isolation, particularly among geriatric patients (Oh-Park et al., 2021). Recent Cochrane reviews affirm TR's effectiveness in enhancing physical and language functions and promoting motivation and adherence comparable to in-clinic rehabilitation (Laver et al., 2020; Nikolaev et al., 2022).

Given its flexibility, TR is particularly well-suited for home-based rehabilitation, offering high accessibility and comfort (Tamayo-Serrano et al., 2018). However, maintaining motivation for autonomous home-based sessions can be challenging for stroke survivors due to the repetitive nature of exercises (Tosto-Mancuso et al., 2022). Incorporating motivating elements is thus a promising solution to enhance engagement and adherence in home-based self-training sessions. In this context, adding gamification strategies in rehabilitation tasks presents a promising solution, as they were indeed designed to increase engagement amongst game-player in the general population. Gamification employs game elements that induce rewards like points, achievements, rankings, trophies, or discovery of secrets or new information to transform mundane tasks into motivating and engaging activities (Jung et al., 2016; Tamayo-Serrano et al., 2018).

In stroke rehabilitation, gamification can make repetitive tasks more enjoyable, increasing the likelihood of sustained intervention adherence both at home and in clinical settings (Tamayo-Serrano et al., 2018). The most common gamification element used in therapy is the point system (i.e., a score based on individuals' performance), that provides positive feedback and encourages progress (Tamayo et al., 2012; Wulf & Lewthwaite, 2016). This feedback, whether visual or auditory, shifts the focus from the daunting goal of full recovery to smaller achievable milestones, which enhances engagement (Jacobs et al., 2013; Jung et al., 2016). An example of visual feedback is a graph showing the proportion of good and bad trials after a game session, informing individuals about their performance progress over time (Flores et al., 2008). Gamified therapy systems also adapt tasks to the individual's ability level, making them challenging yet achievable, which further encourages adherence (Jung et al., 2016). Notably, previous studies have demonstrated that gamified rehabilitation systems improve compliance, usability, and enjoyment, thereby enhancing motor and cognitive functions with lasting effects, independence in ADL, participation, and social interaction (Tamayo-Serrano et al., 2018; Tosto-Mancuso et al., 2022).

Within gamified rehabilitation systems, videogame-based therapies, consisting of playing games where the actions are controlled by electronic devices, are increasingly used in stroke rehabilitation. These interventions have shown benefits in motor and cognitive functions, autonomy in ADL, socialization, and depression treatment (Amorim et al., 2020; Saposnik et al., 2016; Tamayo-Serrano et al., 2018). Notably, they are more motivating and engaging and lead to higher adherence rates compared to standard therapy. Indeed, neuroimaging studies have shown that playing videogames affects neural processing in the ventral striatum, which is involved in reward processing and motivation (Tosto-Mancuso et al., 2022). Recent multicentric RCTs have highlighted the effectiveness of videogame-based therapies for motor recovery after stroke. Ali et al. (2024) demonstrated that the ArmAble™ gamified rehabilitation system, which provides games that mimic ADLs, significantly enhances motor recovery in acute and subacute stroke survivors after just two weeks compared to task-based training. Importantly, participants found ArmAble™ to be user-friendly, enjoyable, meaningful, and highly motivating (Ali et al., 2024). Gauthier et al. (2022) evaluated the VIGoROUS program, a self-managed home-based videogame therapy, in chronic stroke recovery. After three weeks, VIGoROUS demonstrated similar improvements in motor speed and function as its TR-supported version (i.e., with telehealth visits), conventional rehabilitation, and CI movement therapy, with benefits lasting six months. Notably, both self-managed and TR-based VIGoROUS enhanced everyday arm use more effectively than conventional therapy and were comparable to CI therapy, with the TR-supported version of VIGoROUS showing the greatest benefits. The authors suggested that frequent therapist feedback in TR sessions is a potentially efficient and cost-effective approach to support self-managed rehabilitation (Gauthier et al., 2022).

Advances in technology have also enabled the combination of gamified systems with robot-assisted therapy, where mechanical devices assist voluntary movements, enhancing the quality and intensity of training (Moore & Barnett, 2012). In robot-enabled gamified neurorehabilitation, limb movements control actions in video games, with robotic support improving adaptability and effectiveness. While robotic rehabilitation has shown benefits in arm function and muscle strength (Tosto-Mancuso et al., 2022), the largest RCT on robot-assisted training for the upper limb after stroke (RAULTS), found no superiority in completion of ADL over a dose-matched usual care. In this context, combined approaches with functionally oriented therapies may offer better outcomes (Rodgers et al., 2019).

Another promising approach is immersive virtual reality (VR), where rehabilitation games are played in computer-generated, three-dimensional environments using VR glasses and headsets (Rogante et al., 2010; Tamayo-Serrano et al., 2018). Immersive VR allows safe practice of activities that may be unsafe in the real world (Tosto-Mancuso et al., 2022), and it has been shown to improve upper-limb functions, enjoyment, motivation, and adherence compared to conventional rehabilitation (Amorim et al., 2020). Immersive VR also provides real-time feedback and multisensory cues that can facilitate cortical reorganization and proprioception (Saposnik & Levin, 2011). The only meta-analysis on immersive VR for stroke rehabilitation indicated significant benefits in treating upper- and lower-limb deficits in chronic stroke patients, with a trend toward greater improvements compared to conventional therapies (Palacios-Navarro & Hogan, 2021).

In conclusion, TR programs with gamification strategies show potential for minimizing treatment discontinuity post-discharge, offering chronic stroke survivors effective and engaging interventions without physical barriers (Amorim et al., 2020; Magwood et al., 2020). These programs can augment clinical practice and reduce the overall stroke burden (Zeng et al., 2023).

1.2.4 Optimized learning for functional improvement

Given the high prevalence of motor impairment following stroke, rehabilitation research has focused particularly on the neural mechanisms underlying motor recovery and the factors that enhance it. A key principle in rehabilitation states that the reacquisition of motor skills requires a learning process, which allows for lasting neural and behavioral changes throughout life (Moore & Barnett, 2012; Nudo, 2007). Motor learning theories developed with healthy individuals suggest that long-term motor skill acquisition is driven by interactions among brain regions involved in reward, attention, and memory consolidation through dopaminergic pathways (Dayan & Cohen, 2011; Draganski & May, 2008). According to these theories, the learning-based model of rehabilitation proposes that training must be task-specific and goal-driven for an effective reacquisition of motor functions after stroke (Kitago & Krakauer, 2013; Moore & Barnett, 2012; Nudo, 2007). Goal-driven tasks involve setting a target or outcome and maintaining a focus on the actions required to achieve it. This promotes attentional processing and active problem solving in respond to environmental demands, which are crucial for achieving functional improvements (Fishman et al., 2021; Kitago & Krakauer, 2013; Posner et al., 2014). In addition, the trained task must have real-world relevance for the individual. Having meaningful goals associated with motor practice increases individuals' motivation to complete the entire training. In this context, the achievement of the desired goal will provoke a reward, a key element in motor skill learning (Chun & Turk-Browne, 2007; Dorstyn et al., 2014; Moore & Barnett, 2012).

Motivation is defined as an individual's orientation towards behaviors that are anticipated to be rewarding and can be influenced by both internal and external factors. While intrinsic motivation stems from positive thoughts and affective responses driven by the pleasure and interest in an activity (e.g., running for enjoyment), extrinsic motivation arises from external rewards driven by social rules or environmental conditions (e.g., running to lose weight) (Verrienti et al., 2023). Intrinsic motivation drives behaviors aimed at satisfying basic psychological needs, including autonomy (i.e., having choice and control over one's environment), competence (i.e., experiencing oneself as capable), and relatedness (i.e., having relationships where one feels respected and cared). According to the Self-Determination Theory (SDT), fulfilling these needs allow individuals to achieve optimal functioning, social development, and well-being (Swanson & Whittinghill, 2015; Verrienti et al., 2023; Wulf & Lewthwaite, 2016). Notably, prior research has demonstrated that individuals with physical impairments recover more effectively when they are highly motivated (Maclean & Pound, 2000). Attention, the ability to focus on a task or stimulus despite conflicting inputs, is also critical for sensory processing (Moore & Barnett, 2012). This cognitive function guides the brain in prioritizing relevant information for task performance, which is also crucial for the learning process (Posner et al., 2014). Indeed, attention-based rehabilitation programs have shown to improve behavioral outcomes and neural reorganization after stroke (Moore & Barnett, 2012). Intrinsic motivation and attention are thus critical factors to consider in post-stroke rehabilitation practices.

The most recently proposed motor learning theory called Optimizing Performance Through Intrinsic Motivation and Attention for Learning (OPTIMAL) delves deeply into the motivational and attentional factors that significantly enhance motor skill acquisition (Wulf & Lewthwaite, 2016). Based on previous research, this theory suggests that our sense of competence can be met by enhanced expectancies in future motor performance. If we expect success in our performance, which represents a predicted reward, our level of confidence will increase, and our performance will thus improve. Performance expectancies are enhanced by positive feedback, positive affect, and perceived task difficulty. Receiving information about the good trials in the performance increases self-efficacy and feelings of satisfaction, contributing to our sense of competence and positive affect. Positive feedback acts as a reinforcer (e.g., feeling of success) when the desired skill is performed, which increases the likelihood of repeating the movement and thus enhances performance, in comparison with negative feedback (Saemi et al., 2012). Experiencing positive affect during motor activity also enhances agency, performance expectations, and decreases perception in task difficulty, consequently fostering the sense of competence (Gentsch & Synofzik, 2014). During motor performance, autonomy is the sense of control over certain aspects of the motor training. The OPTIMAL theory suggests that providing opportunities for deciding about these aspects (e.g., material used, exercise order, schedule) boosts the sense of agency and self-efficacy, thus fulfilling the need for autonomy. Moreover, the active involvement in the learning process promotes deeper processing and enhances skill acquisition (Wulf & Lewthwaite, 2016).

Prior evidence has stated that linking goals to specific actions during motor training, which is known as goal-action coupling, facilitates motor performance and contributes to effective learning (Lohse et al., 2014; Porter et al., 2010). The OPTIMAL model underlines the benefits of adopting an external focus on the task goal (i.e., the intended movement effect) rather than an internal focus on body movements. An internal attentional focus induces a conscious type of motor control that can interfere with automatic motor processes and constrain the motor system. Especially if the individual has low performance expectations, a focus on voluntary movements can increase anxiety and negative affect (McKay et al., 2015). In contrast, an external focus to the task goal allows for unconscious, fast, and reflexive control of movements (Pascua et al., 2015), which has shown to promote movement effectiveness (e.g., accuracy in hitting a target) and efficiency (e.g., optimal coordination of movements to achieve maximum force) (Marchant et al., 2009). The ease of movements and consequent successful performance enhance expectancies for positive outcomes, which helps fulfil the sense of competence and increase motivation to be focused on the task (Wulf & Lewthwaite, 2016).

The OPTIMAL theory scheme (see Figure 1.4) shows how enhanced expectations, autonomy-supportive conditions, and an external attentional focus contribute to the efficient goal-action coupling, which prepares the motor system for task execution and achievement of the desired goal. The consequent successful motor performance improves self-efficacy and performance expectations. The anticipation of success, along with feelings of competence and autonomy, and the actual success during motor training, serve as inherent rewards that stimulate dopamine release. Importantly, dopamine not only aids in the consolidation of trained movements but also enhances intrinsic motivation, which drives individuals to complete the whole training, thereby maximizing motor learning and functional recovery after stroke (Wulf & Lewthwaite, 2016).

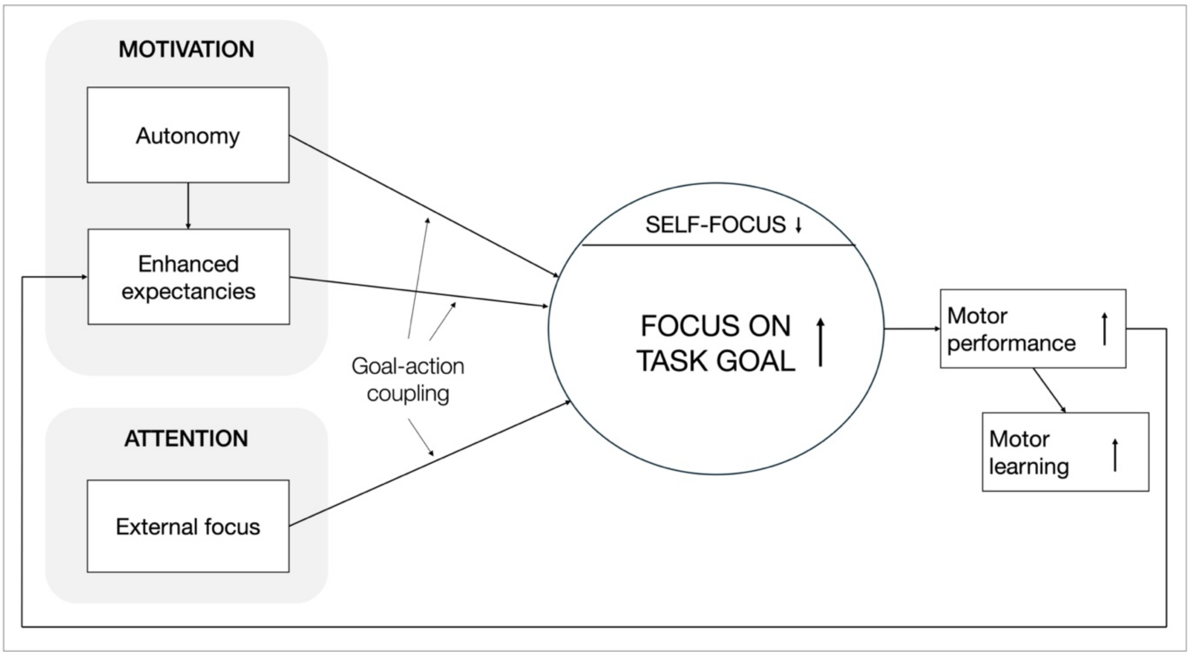


Figure 1.4. Schematic of the OPTIMAL theory of motor learning.
By modulating aspects of the motor training that increase motivation and attention, goal-action coupling is enhanced. This leads to performing movements with a focus on the task goal, which improves motor performance and maximizes learning. Adapted from Wulf & Lewthwaite, 2016.

Prior motor learning theories also suggest that training must be intense, varied, guided, individualized, progressively challenging, and enriched (Moore & Barnett, 2012). While mass repetitions strength existing neural connections and reinforce plasticity (Van der Lee, 2001; Wittenberg et al., 2003), task variation promotes generalization and transfer of skills to daily activities, enhancing post-stroke recovery (Maier et al., 2019). To maximize the benefits of the remaining elements, the OPTIMAL theory should be considered in rehabilitation practices. Guidance involves providing task instructions and modelling, consisted of demonstrating the desired skill. According to the OPTIMAL model, adopting an autonomy-supportive approach in instructional language and modelling type (e.g., offering choices or minimal cues) will potentiate individuals' sense of volition and self-efficacy. Furthermore, the perceived task difficulty can be modified by adapting the task to individuals' motor function levels. Two strategies for doing so are task shaping, which reinforces approximations of a desired skill, and chaining, which reinforces sequential steps of more complex skills. Prompting, the incorporation of cues that help performance initiation, also diminishes task difficulty. As the individual improves in motor performance, it is crucial to gradually increase difficulty, which supports differentiation of complex stimuli and long-term retention, while maintaining an achievable challenge for the individual (Wulf & Lewthwaite, 2016). Fading, which involves removing cues or physical support, also allows for a gradual increase in difficulty. Lastly, motor recovery benefits from an enriched environment, a stimulating context that engages physical, cognitive, and social functions, providing a multisensory training that boosts individuals' attention and intrinsic motivation (Kitago & Krakauer, 2013; Livingston-Thomas et al., 2016; Maier et al., 2019).

1.3 Music as a health intervention

1.3.1 Music, health, and well-being

Most humans can affirm that music has a great positive effect on them. With the advent of affordable technology, people nowadays can instantly select soundtracks that help regulate their thoughts and emotions to manage daily challenges in various activities and situations (Stige, 2012). The beneficial effects of music on our wellbeing have been recognized throughout history, from documented 30,000-year-old shamanic healing practices and affirmations by philosophers like Plato, to the benefits reported by nurses treating World War II soldiers, which marked the beginning of the therapeutical use of music as a recognized discipline (Ruud, 2000; Västfjäll et al., 2012).

In the last decades, the relationship between music, health, and wellbeing has been increasingly studied. The WHO defines health as a state of complete physical, mental, and social well-being, emphasizing the significant role that cultural activities and social relationships play in our health. Music has demonstrated numerous benefits for both mental and physical health across all ages, in both healthy and clinical populations. It significantly enhances our subjective well-being, boosting daily positive emotions, sense of meaning, life satisfaction, and overall QoL. Engaging in musical activities can also foster self-esteem, confidence, autonomy, and self-worth, which are crucial for mental health, reducing stress, anxiety, and the risk of depression. The social nature of music is a key factor in its benefits. Compared to other activities, those involving music promote quicker social bonding, reducing isolation and loneliness, and strengthening social support networks (Fancourt & Finn, 2019). These outcomes improve communication and relationships, and contribute to the development of self- and group-identities (Raglio & Oasi, 2015). Moreover, music engagement offers opportunities to learn new skills, enhancing motor and cognitive functions in an enjoyable context (Fancourt & Finn, 2019).

According to WHO, music activities can be applied as enriched interventions that elicit psychological, physiological, social, and behavioral responses that contribute to emotional, sensory-motor, and cognitive improvements. These benefits have led to the development of music-based interventions, which use music as a tool to achieve specific health goals by adjusting its elements (e.g., tempo, rhythm, melody, harmony, and lyrics) to meet individual needs. Music-based interventions fall into two categories: receptive (e.g., listening to music) and active (e.g., creating or improvising music, playing an instrument, or singing) (Sihvonen et al., 2017). Among all music-based interventions, music therapy differs by being conducted by trained professionals who provide tailored music experiences and therapeutic relationships (Magee et al., 2017). A wide range of music-based interventions have shown benefits across a broad spectrum of clinical populations, including those with psychiatric and neurodevelopmental disorders like depression and autism, as well as neurological and degenerative diseases like stroke, dementia, and Parkinson's disease. They have also been effective in cancer treatment and palliative care, alleviating anxiety and stress before surgeries, and reducing pain perception during and after medical procedures. Music-based interventions have thus demonstrated significant therapeutic value across diverse healthcare settings (Raglio & Oasi, 2015; Sihvonen et al., 2017). Compared to conventional interventions, the intrinsic aesthetic beauty, creative expression, and social interaction fostered by music activities drives the intrinsic motivation for engaging in them beyond health goals. In addition, they have shown equivalent or greater cost-effectiveness, targeting multiple health-promoting factors and being adaptable to diverse cultural backgrounds (Fancourt & Finn, 2019).

1.3.2 The stimulating and enjoyable nature of music

From an evolutionary perspective, numerous theories have sought to explain why music, despite not being essential for human survival, is ubiquitous in our daily life across cultures, social contexts, ages, and genders. A 35,000-year-old bone flute is proof that in the origins of our species, we were already predisposed to make music (Mehr et al., 2019, 2021). For this to be possible, thousands of years of evolution shaped our neural organization, enabling us to perceive, produce, and enjoy the complex rhythmic, melodic, and harmonic structure of music from birth without prior training (Zatorre & Salimpoor, 2013). Our inherent capacity to process music thus indicates that musical behaviors have always been evolutionarily advantageous.

Several prior studies have demonstrated the multimodal stimulation that music provides, engaging simultaneously multiple brain areas responsible for auditory, sensory-motor, cognitive, visual, and emotional functions. When listening to music, the auditory cortex processes both basic sound features (e.g., pitch, volume, and timbre) and more complex aspects (e.g., melody, harmony, and rhythm) by interacting with systems in the frontal, temporal, parietal, and limbic regions (Zatorre et al., 2007). The interaction between auditory and limbic systems is crucial for deriving pleasure from music, which in turn drives our intrinsic motivation to incorporate this abstract stimulus into our lives (Mehr et al., 2021; Zatorre & Salimpoor, 2013). The so-called mesolimbic regions constitute the reward system, responsible for producing hedonic responses to pleasurable stimuli. The two core areas of the reward system are the ventral tegmental area and nucleus accumbens. The former sends dopaminergic projections to the latter, which elicit reward and pleasure responses to specific behaviors, reinforcing them (Salimpoor et al., 2009; Zatorre & Salimpoor, 2013). Therefore, although listening to music is not biologically adaptive like eating or having sex, our reward system ensures that music remains a pleasurable and persistent aspect of human life (Koehler & Neubauer, 2020; Mas-Herrero et al., 2013; Zatorre & Salimpoor, 2013).

The pleasure derived from music is strongly linked to its ability to evoke emotions and enhance mood (Corrigall & Schellenberg, 2013; Juslin & Västfjäll, 2008; Salimpoor et al., 2009; Zatorre & Salimpoor, 2013). Emotionally evocative music activates the reward system, which projects information to subcortical and cortical areas through mesolimbic and mesocortical dopaminergic pathways (Salimpoor et al., 2011). These areas, including the amygdala, hippocampus, orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex, are responsible for mood regulation, motivation, memory, learning, attention, decision-making, and executive functions. Importantly, the connection between the nucleus accumbens and the aforementioned areas allows for the integration of emotional and rewarding responses with cognitive processes (Corrigall & Schellenberg, 2013; Salimpoor et al., 2009; Zatorre & Salimpoor, 2013). The mechanisms underlying music-induced emotions include emotional contagion, episodic memory, and musical expectancy. Humans have the inherent ability to perceive emotional expressions in music (e.g., happiness, characterized by fast tempo and high pitch) and mimic it internally due to its similarity to emotional speech. Music can also evoke emotions by triggering memories associated with those emotions. Additionally, rhythmic and harmonic patterns in music can confirm or violate listener expectations, leading to emotional and rewarding responses through predictable and surprising events (Bianco et al., 2019; Corrigall & Schellenberg, 2013; Juslin & Västfjäll, 2008). These mechanisms help regulate mood, providing enjoyment, comfort, relaxation, and stress relief, thus making music a valuable part of daily life (Mas-Herrero et al., 2013).

Music performance activates various motor areas, including the primary motor cortex, premotor cortex, supplementary motor area, cerebellum, and basal ganglia, which are responsible for controlling, planning, and coordinating voluntary and complex movements. Feedforward and feedback interactions between auditory and motor systems are crucial for the timing, sequencing, and spatial organization of movements. In feedforward processes, tonal and rhythmic information is sent from auditory to motor regions for planning and executing movements to play the correct notes on time. In feedback processes, the motor output is perceived as auditory input, allowing for monitoring and real-time motor adjustments during music performance (Zatorre et al., 2007). The parietal lobe is also involved in spatial processing and sensory integration, helping maintain spatial awareness of the instrument and coordinate hand-eye movements essential for playing (Johnson et al., 1996). The limbic system, interacting with the motor system, also plays a crucial role in the acquisition of motor functions (Doyon et al., 2003).

Besides dopamine, other neurochemicals are regulated during music engagement. Listening to music increases serotonin, which plays a significant role in arousal and mood regulation, and decreases cortisol levels, reducing stress and inflammatory immune responses (Chanda & Levitin, 2013; Fancourt & Finn, 2019; Moraes et al., 2018). High cortisol levels in individuals with acute stroke are associated with larger infarct volumes, higher depression risk, poor prognosis, and fatal outcomes, highlighting music's potential as a preventive health tool (Barugh et al., 2014). Oxytocin and endogenous opioid also play key roles in modifying social attitudes and promoting social bonding during musical activities (Chanda & Levitin, 2013; Tarr et al., 2014). Indeed, another well-supported evolutionary theory posits that music fosters social bonding, a crucial factor for our survival (Savage et al., 2021). Humans establish social contact through shared musical activities (e.g., concerts), music preferences, and coordinated movements in group settings (e.g., playing or dancing together). In this context, music creates an environment that facilitates social interaction, promoting belonginess and social reward (Boer et al., 2011; Cross & Morley, 2009).

Due to genetic variations, humans exhibit individual differences in music processing, regardless of prior training and exposure (Gingras et al., 2015; Zatorre et al., 2007). Beyond musical preferences (Salimpoor et al., 2009), individuals vary in their abilities to perceive (Correia et al., 2023; Peretz et al., 2003), produce (Gingras et al., 2015; Sloboda, 2000; Zatorre et al., 2007), and derive pleasure from music (Martínez-Molina et al., 2016; Mas-Herrero et al., 2013). While most people enjoy music, a small percentage experience musical anhedonia (Mas-Herrero et al., 2013), finding no pleasure in music due to reduced connectivity between the auditory and reward systems (Martínez-Molina et al., 2016). Despite these individual differences, music remains a central element in human life, traditions, and cultures, enhancing the well-being of those who enjoy it.

1.3.3 Music as a tool in neurorehabilitation

Given the multimodal stimulation and intrinsic reward provided by music, it has been proposed as an effective and engaging tool to stimulate brain functions lost or impaired by neurological diseases (Magee et al., 2017). In non-clinical populations, musical training has shown to induce structural and functional changes among the brain regions required for music processing, known as brain plasticity (Särkämö et al., 2016). Indeed, professional musicians exhibit increased auditory cortex volume, grey-matter concentration in motor cortices, and connectivity between auditory and motor cortices as a function of years of experience (Sihvonen et al., 2017; Zatorre et al., 2007).

Neurorehabilitation relies on brain plasticity, that is, its ability to grow neurites and form new synapses that rebuild the injured networks (Nudo, 2013). Therapeutic strategies aim to stimulate impaired functions by activating preserved brain regions, which has been shown to be facilitated by multimodal stimulation (Sihvonen et al., 2017). In this context, music-based interventions incorporate elements of musical training to promote neuroplastic changes similar to those observed in healthy brains, such as massive repetitions of movements in a goal-driven and enjoyable task. Crucially, these elements promote intrinsic motivation and attention, which are essential for skill learning (Wulf & Lewthwaite, 2016).

Engaging in musical activities activates reward-motivation areas (Ferreri et al., 2019; Salimpoor et al., 2011), which interact with the hippocampal memory system and primary motor cortex through the mesolimbic and mesocortical dopaminergic pathways, respectively. These connections result in enduring structural and functional changes in motor cortices during musical training, facilitating motor skill learning (Hosp et al., 2011; Luft & Schwarz, 2009; Nudo, 2007; Ripollés et al., 2018). Moreover, music engagement activates cognitive functions, such as attention and working memory, which are needed to keep track of timing, melodies, and lyrics (Särkämö et al., 2016). Attention is primarily processed by the prefrontal cortex, which interplays with parietal regions and hippocampal system via dopaminergic projections, allowing the prioritization of task-relevant sensory inputs and enhancing the storage of information (Benchenane et al., 2011; Posner et al., 2014). Multimodal stimulation through music, involving temporally and spatially aligned sensory inputs, enhances impaired neural functions through the attentional processing of multiple sensory streams. These additive attentional effects facilitate compensatory motor and language responses and the maintenance of goal-directed behaviors (Talsma et al., 2010).

To recover motor functions, music-based interventions benefit from the strong link between the auditory and motor systems, which enables the planning and adjustment of movements based on sound stimuli (Sihvonen et al., 2017). For neurological diseases affecting internal action sequencing, auditory-motor coupling provides an external timer that aids in movement execution and motor skill reacquisition through the preserved auditory cortex (Clark et al., 2016; Zatorre et al., 2007). Singing has also shown to enhance pronunciation and word recalling, crucial in the rehabilitation of speech and language functions (Norton et al., 2009), probably due to shared networks for processing rhythm and intonation in both singing and speaking (Patel, 2011). Moreover, the emotional impact of music can improve mood during rehabilitation sessions (Magee et al., 2017; Salimpoor et al., 2009). Finally, music exercises can be completed in socially interactive contexts, making them particularly effective for developing social skills and increasing social participation in the rehabilitation process (Nayak et al., 2000).

All these aspects make music-based interventions a suitable solution for stroke rehabilitation. Prior reviews highlight its effectiveness in enhancing neural plasticity and functional abilities of stroke survivors compared to standard care. These benefits include neural reorganization of motor, language, prefrontal, and limbic areas, contributing to improvements in upper- and lower-limbs motor functions, speech production, object naming, verbal memory, executive functions, focused attention, depressive symptoms, and mood (Fancourt & Finn, 2019; Magee et al., 2017; Pohl et al., 2018; Sihvonen et al., 2017).

1.3.4 Instrumental training for upper-limb motor recovery after stroke

Upper-limb motor dysfunction is the most prevalent consequence in chronic stroke survivors (Pomeroy et al., 2011), highly contributing to the long-term disability in this population (Aked et al., 2024; Palstam et al., 2019). Considering the multiple factors encompassed in music-making beneficial for recovering brain functions (see Figure 1.5), active music-based interventions have been developed in the last decades to maintain or enhance upper-limb functionality after stroke. Among the various forms of music-making, learning to play instruments is considered as the main approach to treat post-stroke hemiparesis since it can incorporate all the elements for an effective rehabilitation process (Grau-Sánchez et al., 2020).

Instrumental training is a task-specific and goal-oriented activity that requires mass repetition of movements in a context for motor learning, all key principles in neurorehabilitation (Van der Lee, 2001; Wittenberg et al., 2003). Playing an instrument is an enjoyable activity where motor skills are trained with the goal of making music, a pleasant outcome that provokes intrinsic reward (Grau-Sánchez et al., 2020). Importantly, it may have real-world relevance for many individuals, in which they can find a new leisure activity that becomes part of their occupational identity and motivates them to bring a mentally and physically active lifestyle (Boop et al., 2020; Martin-Saez & James, 2021).

When playing an instrument, movements need to be precise in time and space, which promotes the integration of multisensory inputs that facilitates learning. The musical instrument is the tool that transforms the motor output into an auditory input, activating the audio-motor interplay that involves fast and precise feedforward and feedback loops (Grau-Sánchez et al., 2020). The rhythmic pattern of music serves as a cue to prompt movement initiation, while the sound produced by the instrument provides real-time feedback that allows instant adjustment of movements (Rodriguez-Fornells et al., 2012). The instrument also represents an external focus of attention, which helps concentrate on the goal (i.e., playing the correct notes on time), contributing to a successful performance and learning (Wulf & Lewthwaite, 2016).

Following the learning-based model of rehabilitation, the musical exercises can be provided with an adapted and gradual increased level of difficulty, tailoring the training to individuals' motor and cognitive needs. In addition, playing different types of instruments and musical pieces allow exercising different types of fine and gross movements in a variability of sequences, contributing to task variability.

During the sessions, therapists can provide instructional language directed to focus the attention on the musical outcome more than the movements, while adopting an autonomy-supportive approach that fosters individuals' self-efficacy. The feedback received by both the therapist and the instrument informs individuals about their performance and represent extrinsic reinforcers. Therapist also provides guidance and modelling, demonstrating the desired movement while using verbal and visual cues for prompting movements, which can be progressively faded out as the individual progresses and achieve the desired goals. When this occurs, feelings of self-efficacy, agency, satisfaction, and positive affect arise as intrinsic rewards. Setting achievable goals and providing opportunities to make choices of different aspects during the sessions increase, respectively, sense of competence and autonomy. If the activity is conducted in group, it can significantly contribute to the sense of relatedness. Meeting these basic psychological needs provides reward, increasing the intrinsic motivation to complete the entire training (Wulf & Lewthwaite, 2016), and contributing to individuals' well-being and psychological health (Koehler & Neubauer, 2020). In addition, music has the capacity to inhibit physiological feedback signals such as fatigue, and induce positive emotional states, making an intense and long training more bearable and enjoyable (Fancourt & Finn, 2019).

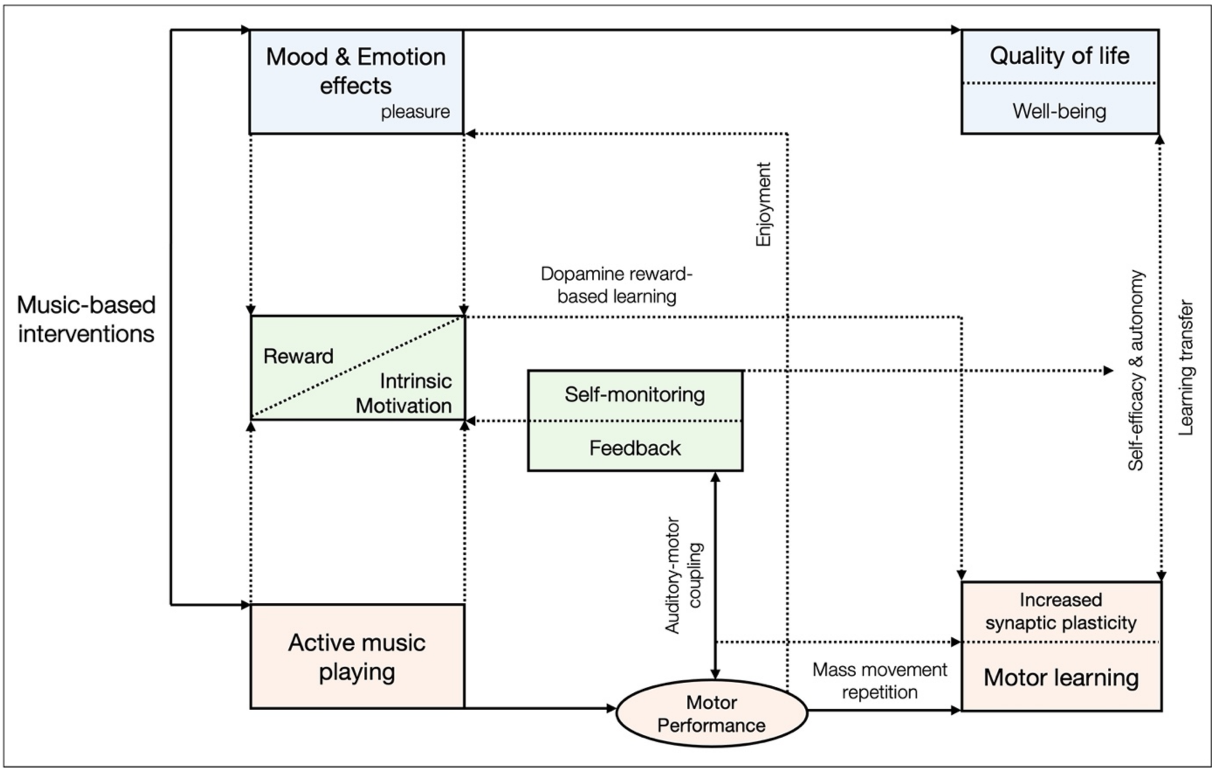


Figure 1.5. Interacting components of active music-based interventions.
Music-making evokes emotion and mood effects that have a direct impact on individual's quality of life and well-being. Playing an instrument requires mass repetition of movements and integration of auditory information, both elements contributing to motor learning. The auditory information serves as feedback that facilitates self-monitoring of the performance, increasing self-efficacy and autonomy. Music also elicits reward responses, promoting enjoyment and intrinsic motivation. This contributes to dopamine release, boosting neural plasticity and learning. Adapted from Grau-Sánchez et al., 2020.

Previously validated active music-based interventions consisted of instrumental training include Music-supported Therapy (Schneider et al., 2007). Music-upper limb therapy-integrated (Raghavan et al., 2016), Therapeutic instrumental music performance (Street et al., 2018), Active music therapy (Raglio et al., 2017), Rhythm- and music-based therapy (Bunketorp-Käll et al., 2017), and rhythm-based instrument-playing (Whitall et al., 2000). Prior clinical trials testing the effectiveness of these interventions compared to conventional physical rehabilitation programs have demonstrated overall improvements in upper-limb fine and gross motor functions, as well as an increase in QoL and positive emotions, and a decrease in negative affect, fatigue, and depressive symptoms after the intervention in both subacute and chronic stroke survivors. In addition, they have shown improved language abilities in subacute participants, and processing speed and mental flexibility in chronic participants. At the neural level, they have reported increased excitability and map reorganization in the affected sensorimotor cortex of subacute and chronic stroke patients, as well as the reestablishment of functional connectivity between auditory and motor regions in chronic stroke patients (Grau-Sánchez et al., 2020; Magee et al., 2017).

1.4 Music-supported Therapy in stroke rehabilitation

1.4.1 Music-supported Therapy intervention

Music-supported Therapy (MST) is one of the most investigated protocols of active music-based interventions to treat post-stroke hemiparesis through instrumental training. The MST program provides a standardized set of musical exercises consisted of playing a keyboard and an electronic drum set with the paretic upper limb to train fine and gross motor skills, respectively (Schneider et al., 2007).

MST is founded on the following rehabilitation principles: i) massive repetition and exercising of finger and arm movements, ii) audio-motor coupling and integration, which reinforces movement through immediate auditory feedback, iii) shaping, by adjusting the complexity of the required movements based on individual's progress, and iv) emotional and motivational effects from the enjoyment of making music and learning a new skill (Schneider et al., 2007; Rodriguez-Fornells et al., 2012).

The drum exercises involve playing note sequences on drum pads labeled 1 to 8 and configured to emit piano tones (G, A, B, C, D, E, F, G‘) instead of drum sounds (see Figure 1.6). The piano exercises involve playing the same note sequences on eight marked white keys of the piano (G, A, B, C, D, E, F, G‘). In the exercise protocol, each finger is associated with a number to indicate the specific finger or combination of fingers required to play each exercise (see Figure 1.6) (Schneider et al., 2007).

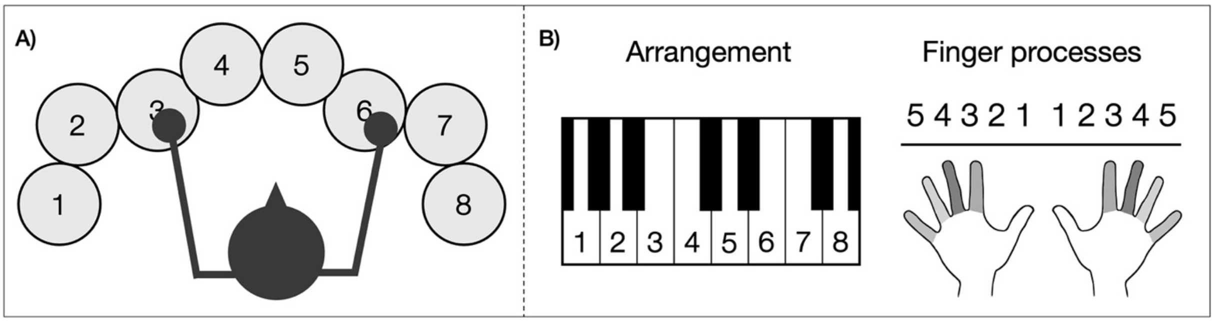


Figure 1.6. Illustration of the drum pads and piano arrangements.
A) Eight drum pads, four for each arm, placed in a semi-circle within reach of the patient. B) Eight notes on the piano to play with the affected hand, using the numbers assigned to each finger. Adapted from the original MST manual by Schneider et al., 2007.

The exercises are organized into ten difficulty levels. The easiest level involves playing a simple scale with individual fingers, while the most advanced level requires performing melodies of children's or folk songs using all five fingers (see examples in Table 1.1). Each successive level increases the number of notes, the sequence complexity and, for piano exercises, also the combination of fingers. Each exercise is repeated until it can be performed smoothly without difficulty (Schneider et al., 2007).

Table 1.1. Three levels of standardized musical exercises from the MST manual.
Examples of exercises for keyboard and electronic drum, categorized into levels 1, 5, 9, showing increasing difficulty. Adapted from the original MST manual by Schneider et al., 2007.

Level	Characteristic	Task	Arrangement	Direction motion	Number of trials	Therapeutic aspects	Finger processes
1 (1 tone)	Individual tones	1	1 2 3 4…	Upward	8	Isolated and controlled movements with each finger	1/2/3/4/5
		2	8 7 6 5…	Downward	8		1/2/3/4/5
		3	1 1 1, 2 2 2…	Repeat 3 times	8		1,1,1/2,2,2/3,3,3…
5 (3 tones)	Interval tone	1	1 2 4, 1 2 5…	Upward	15	Combined movements with 3 neighboring fingers	1,2,3/1,2,4/1,2,5/2,3,5
		2	1 3 4, 1 4 5…	Upward	15		1,2,3/1,3,4/1,4,5/2,4,5
		3	4 3 1, 5 4 1…	Downward	15		4,3,1/5,4,1/5,4,2
		4	4 2 1, 5 2 1…	Downward	15		4,2,1/5,2,1/5,3,2
9 (5 tones)	Interval tone	1	1 3 4 5 6, 1 2 4 5 6…	Upward	12	Combined movements with 5 neighboring fingers	1,2,3,4,5
		2	1 2 3 5 6, 1 2 3 4 6…	Upward	12		1,2,3,4,5
		3	6 5 4 3 1, 6 5 4 2 1…	Downward	12		5,4,3,2,1
		4	6 5 3 2 1, 6 4 3 2 1…	Downward	12		5,4,3,2,1

MST sessions are conducted individually at the hospital and guided by a therapist. The role of the therapist is to demonstrate how the exercises are played, so the individual can subsequently repeat them, as well as to provide physical support to prevent compensatory movements. The training is tailored to individuals' needs by adjusting the number of notes, exercise speed, and the height and proximity of the instruments, excluding one of the instruments if necessary (Schneider et al., 2007).

1.4.2 Benefits of Music-supported Therapy for stroke

For more than ten years, the effectiveness of MST has been studied in individuals with subacute and chronic stroke. A total of fourteen studies have collected behavioral, motor kinetics, and neuroimaging data to assess the benefits of MST in promoting motor recovery among stroke survivors. Secondary outcomes included cognitive functions, mood, and QoL. Table 1.2 provides a summary of all studies on MST for stroke rehabilitation that have been conducted so far, in chronological order. The reported benefits of MST for subacute and chronic stroke individuals are outlined below.

Table 1.2. Summary of studies on MST for stroke rehabilitation.
This table presents the design and results of all studies conducted to date on MST for both subacute and chronic stroke survivors, in chronological order. (RCT: randomized controlled trial; 3D: three dimensional; EEG: electroencephalography; fMRI: magnetic resonance imaging; TMS: transcranial magnetic stimulation; QoL: quality of life; GRASP: Graded Repetitive Arm Supplementary Program; PT: physiotherapy; OT: occupational therapy).

Studies on MST	Design	N and stroke phase	MST	Control group	Motor deficit	Outcomes	Training intensity	MST effects
Schneider et al., 2007	RCT two-armed	20 subacute	Original protocol	Standard care (only)	Moderate	Motor: behavioral tests, and 3D-movement analyzer.	7.5 hours 3 weeks 15 sessions	Improved upper-limb motor function, gross and fine manual dexterity, and speed and quality of movements compared to the control group.
Altenmüller et al., 2009	RCT two-armed	62 subacute	Original protocol	Standard care (only)	Moderate	Motor: behavioral tests, and EEG.	7.5 hours 3 weeks 15 sessions	Improved upper-limb motor function, gross and fine manual dexterity, and speed and quality of movements, correlated to increased activity and neural reorganization in motor regions, compared to the control group.
Rojo et al., 2011	Case-study	1 chronic	Original protocol	No	Mild to moderate	Motor: behavioral tests, fMRI, TMS, and 3D-movement analyzer.	10 hours 4 weeks 20 sessions	Improved paretic upper-limb motor function, movement speed and quality, linked to increased excitability, cortical map reorganization, and functional coupling in motor and auditory areas of the lesioned hemisphere.
Villeneuve et al., 2013	Case series	3 chronic	Home-based piano MST	No	Mild to moderate	Motor: behavioral tests, and movement kinematics.	9 hours 3 weeks 9 sessions	Improved fine and gross manual dexterity and upper-limb functionality after the intervention and at follow-up. Improved note and timing accuracy within and across the training sessions, particularly in the second and third sessions.
Amengual et al., 2013*	Experimental study	20 chronic	Original protocol	14 healthy individuals	Slight to moderate	Motor: behavioral test, TMS, and 3D-movement analyzer.	10 hours 4 weeks 20 sessions	Increased excitability and sensorimotor cortical representation of the paretic hand, correlated with improved upper-limb motor function.
Grau-Sánchez et al., 2013	Experimental study	9 subacute	Original protocol	9 healthy individuals	Mild to moderate	Motor: behavioral test, and TMS. QoL: self-rating questionnaires.	10h 4 weeks 20 sessions	Increased primary motor cortex excitability and motor map displacement, associated with improved upper-limb motor function, gross dexterity, and QoL compared to the control group.
van Vugt et al., 2014	Experimental study	28 subacute	In pairs	MST in turns	Slight to moderate	Motor: behavioral tests, and movement kinematics. Mood: self-rating questionnaires.	5h 3-4 weeks 10 sessions	Both groups improved in fine dexterity and finger-tapping synchronization, with greater gains in the in-turn group. Both showed reduced depression and fatigue, but the in-turn group rated their partner as more sympathetic during therapy.

Studies on MST	Design	N and stroke phase	MST	Control group	Motor deficit	Outcomes	Training intensity	MST effects
Villeneuve et al., 2014	Experimental study	13 chronic	Home-based piano MST	No	Mild to moderate	Motor: behavioral tests, and movement kinematics.	9 hours 3 weeks 9 sessions	Improved fine and gross manual dexterity, upper-limb functionality, and finger movement coordination after the intervention and at a three-week follow-up. Larger improvements in gross manual dexterity were seen in patients with mild paresis, while greater improvements in fine manual dexterity and upper-limb functionality were observed in those with moderate paresis. Many participants reported self-perceived improvements in upper-limb motor functions, mood, and motivation for piano training.
Tong et al., 2015	RCT two-armed	30 subacute and chronic	Original protocol	Muted MST	Moderate	Motor: behavioral tests.	10 hours 4 weeks 20 sessions	Participants in the original MST program showed greater improvement in upper-limb motor function compared to the muted MST group.
Ripollés et al., 2015*	Experimental study	20 chronic	Original protocol	14 healthy individuals	Slight to moderate	Motor: behavioral tests, and fMRI. Cognitive: behavioral tests. Mood, emotional well-being and QoL: self-rating questionnaires.	10 hours 4 weeks 20 sessions	The MST group showed improved upper-limb motor function, gross manual dexterity, and increased fMRI activity and connectivity between auditory and motor regions, unlike the healthy sample. MST participants also showed greater improvements in attention, processing speed, auditory verbal learning, depression, positive affect, family-related QoL, and arousal during the sessions.
van Vugt et al., 2016	RCT two-armed	34 subacute	Original protocol	MST with delayed feedback	Slight to moderate	Motor: behavioral tests, and movement kinematics. Mood: self-rating questionnaires.	5 hours 4 weeks 10 sessions	Both groups improved in all motor outcomes, but the auditory delay group outperformed the normal group in fine dexterity and speed regularity. Both showed reduced depression, anxiety, and fatigue, with progressively improved mood during the intervention.
Grau-Sánchez et al., 2017	Exploratory case study with crossover design	1 chronic	Original protocol	15 healthy individuals	Slight	Motor: behavioral tests, and movement kinematics.	36 hours 16 weeks 24 sessions ABAB reversal design	Keyboard performance and speed tapping improved in the initial weeks, with significant gains in dexterity, motor performance, upper-limb function, grip strength, and reaching kinematics emerging between late first and second treatment periods, with some long-term retention. Dexterity and daily motor task scores remained stable or improved during no-treatment periods.
Fujioka et al., 2018	RCT two-armed	28 chronic	MST with modified percussion exercises	Conventional therapy (GRASP)	Slight to moderate	Motor: behavioral tests. Cognitive: behavioral tests. Mood and QoL: self-rating questionnaires. Musical skills: behavioral test.	30 hours 10 weeks 30 sessions	Neither group improved in motor outcomes, but the MST group showed trends in reduced hand motor impairment and faster upper-limb functionality post-intervention. Both groups showed no cognitive gains but completed the executive function test faster. Both groups had reduced negative affect during the intervention, maintained only in the MST group post-intervention. Both showed trends in improved QoL in emotion and mobility, with significant mobility gains in the GRASP group. Both improved in communication and participation QoL. Only the MST group improved in rhythm discrimination at midpoint.
Grau-Sánchez et al., 2018	RCT two-armed	40 subacute	Original protocol	Conventional therapy (PT and TO)	Mild to moderate	Motor: behavioral tests. Cognitive: behavioral tests.	10 hours 4 weeks 20 sessions	Both groups improved in all motor outcomes, with gains maintained after three months. The MST group outperformed the control group in communication QoL, attention, verbal memory, overall QoL, and had reduced fatigue and negative affect. The control group showed

Studies on MST	Design	N and stroke phase	MST	Control group	Motor deficit	Outcomes	Training intensity	MST effects
						Mood, emotional well-being and QoL: self-rating questionnaires. Musical anhedonia: self-rating questionnaire.		improvement in self-care QoL. MST participants with higher musical hedonia in the sensorimotor component had greater motor gains at follow-up compared to the control group.

*Both studies used the same sample of participants with stroke and healthy participants

1.4.2.1 Effects in subacute stroke

The first MST intervention was tested with subacute stroke patients as a supplementary therapy to conventional treatment (i.e., PT and OT provided at the hospital). After 7.5 hours of MST training over three weeks, participants showed improved upper-limb functionality, gross and fine manual dexterity, and increased speed and quality of movements compared to the control group, which received only standard care. Additionally, 85% of the MST participants reported a high degree of transfer to ADL performance (Schneider et al., 2007). Following these positive results, the authors applied the same study design with a larger group of subacute stroke patients to assess MST's effects on neural reorganization using electroencephalography (EEG). Given the link between increased cortical excitability and event-related desynchronization (ERD) during self-paced movements (Chen et al., 1998). The authors suggested increased activity and neural reorganization in motor regions. These electrophysiological changes correlated with significant improvements in upper-limb motor function, gross and fine manual dexterity, movement speed and quality, and self-perceived generalization of treatment benefits to real-world situations (Altenmüller et al., 2009).

Later, Grau-Sánchez et al., (2013) investigated MST's effects on neuroplastic changes in the sensorimotor cortex of subacute stroke patients using Transcranial Magnetic Stimulation (TMS). After 10 hours of training over four weeks, participants exhibited increased excitability of the primary motor cortex and a displacement in the motor cortex map, which was associated with improved upper-limb functionality and gross manual dexterity compared to healthy controls. Importantly, participants also reported increased health-related QoL after the intervention (Grau-Sánchez et al., 2013).

Considering the social nature of music, Van Vugt et al., (2014) explored whether synchronized playing during MST could enhance upper-limb fine motor functions, using a clinical test assessing dexterity and movement kinematics (index finger-tapping speed and regularity, and metronome-paced finger tapping). They assessed mood states before and after the intervention and tracked mood development throughout the program using a mood scale with faces ranging from very sad to very happy before and after each session. Participants with subacute stroke were divided into a group playing synchronously (in pairs) and a group playing one after the other (in turns). After 5 hours of intervention over four weeks, both groups improved similarly in fine dexterity and finger tapping synchronization without significant differences between them, but individuals playing in turns showed greater improvements. Both groups also reported decreased depression and fatigue post-intervention, but those playing in turns perceived their partners as more sympathetic during the sessions. The authors suggested that improved synchronization resulted from overall improvement in motor dexterity and not the fact of playing synchronously, which might be more challenging and frustrating (Van Vugt et al., 2014).

After observing MST's effects on motor recovery, Tong et al. (2015) conducted a randomized controlled pilot study to determine whether the benefits in motor function were due to the added musical stimulation or simply repeated practice. Thirty participants with subacute and chronic stroke (from 1 to 10 months after stroke) were randomly assigned to either the original MST program or a mute version. After 10 hours of training over four weeks, both groups improved in upper-limb motor function, but those in the original MST group showed significantly greater gains, suggesting the independent role of music in promoting motor recovery (Tong et al., 2015).

Later, Van Vugt et al. (2016) examined the effect of auditory feedback on motor learning by manipulating the timing of the feedback to disrupt error-based learning. Thirty-four individuals with subacute stroke were divided into two groups undergoing MST, each receiving different feedback conditions on the piano: one with immediate feedback (normal group), and the other with delayed feedback (jitter group, with a 100-600ms delay not noticeable to participants). The training intensity and motor assessment battery were identical to those in their previous study (Van Vugt et al., 2014). Both groups improved significantly in all motor outcomes, but the jitter group outperformed the normal group in fine dexterity and speed regularity. The authors proposed that the impaired auditory-motor coupling in stroke patients could make the normal group to correct movement errors that were never committed, leading to less motor gains. However, the lack of integration of auditory feedback online in the jitter group avoided overcorrection and could enhance expectation and awareness of movement outcomes. Both groups also experienced reduced depression, anxiety, and fatigue after the intervention, and mood improvement throughout the intervention (Van Vugt et al., 2016).

Finally, Grau-Sánchez et al. (2018) conducted a RCT to compare MST with conventional therapy (i.e., PT or OT) in subacute stroke patients. Forty participants completed 10 hours of training plus 40 hours of conventional rehabilitation. Evaluations post-intervention and at a 3-month follow-up showed both groups achieved long-term significant improvements in upper-limb functionality, motor impairment, gross and fine manual dexterity, grip strength, and motor performance in daily tasks post-intervention. Differences between groups were observed in QoL, where the MST group reported better self-perceived communication skills post-intervention. MST participants also showed significant improvements in attention, verbal memory, fatigue, negative affect, and overall QoL, whereas the control group only improved in the self-care QoL domain. Notably, MST participants who derived more pleasure from musical activities, especially those involving strong sensorimotor components (e.g., tapping to the beat, dancing), demonstrated greater upper-limb functionality at follow-up compared to the control group (Grau-Sánchez et al., 2018).

1.4.2.2 Effects in chronic stroke

A single-case neuroimaging study by Rojo et al. (2011) was the first to demonstrate that MST can lead to motor gains in the chronic phase, particularly two years post-onset. A woman with chronic stroke underwent 10 hours of training over four weeks and her motor gains were evaluated with functional magnetic resonance imaging (fMRI), TMS, 3D-movement analysis, and behavioral tests. After the intervention, she showed improvements in some domains of upper-limb motor function (grasp, grip, and pinch) but not in gross and fine manual dexterity. These gains were accompanied by increased motor cortex excitability, cortical representation of the paretic hand, and improved speed and quality of hand and finger tapping (Rojo et al., 2011).

To further explore the effects on MST on this population, Villeneuve & Lamontagne (2013) conducted a case series study with three chronic stroke individuals to assess the short- and long-term effects of a home-based self-managed piano training following the MST protocol on their upper-limb functions. The intervention involved home-based, self-managed MST piano exercises using a user-friendly MIDI program called Synesthesia, which replaces traditional sheet music with a simplified score (i.e., each note represented by a colored stick above a virtual piano). After 9 hours of training over three weeks, all three participants showed improvements in fine and gross manual dexterity, as well as upper-limb functionality, which were sustained at a three-week follow-up. Participants also improved in note and timing accuracy within and across the training sessions, particularly in the second and third sessions. Importantly, all participants enjoyed the training and expressed a desire to continue piano lessons after the study (Villeneuve & Lamontagne, 2013).

Following these findings, Villeneuve et al. (2014) applied the same study protocol a larger sample, including 13 chronic stroke survivors, to assess the effects of home-based, self-managed MST piano training on manual dexterity, upper-limb functionality, and finger movement coordination. They also explored the relationship between the participants' clinical and demographic profiles, and motor gains. After 9 hours of training over three weeks, significant improvements were observed in all motor outcomes, both immediately after the intervention and at a three-week follow-up. Larger improvements in gross manual dexterity were seen in patients with mild paresis, while greater improvements in fine manual dexterity and upper-limb functionality were observed in those with moderate paresis. In a structured qualitative interview completed after the intervention, six participants reported that the training had a positive effect on their mood and motivation to engage in upper-limb exercises, eleven participants perceived changes in their upper-limb functions and motor performance in daily activities, and five participants expressed a desire to continue piano lessons after the study (Villeneuve et al., 2014).

In the same year, two exploratory studies tested MST with larger samples of chronic stroke patients (n = 20) and compared results to healthy controls (Amengual et al., 2013; Ripollés et al., 2015). Amengual et al. (2013) reported motor gains measured with TMS and 3D-movement analysis. After 10 hours of training over four weeks, participants showed increased excitability and sensorimotor cortical representation of the paretic hand, correlating with improved upper-limb motor function (Amengual et al., 2013). Ripollés et al. (2015) provided a more extensive evaluation, including behavioral and neurophysiological motor outcomes, as well as cognitive, mood, and QoL variables. Compared to healthy controls, who showed no changes between evaluation points, MST participants exhibited improved upper-limb motor function and gross manual dexterity, enhanced fMRI activity in auditory and motor regions, and increased functional connectivity between these regions. They also demonstrated better attention, processing speed, auditory verbal learning, depression symptoms, positive affect, and QoL related to family roles. During the MST sessions, participants also reported increased arousal (Ripollés et al., 2015).

Later, Grau-Sánchez et al., (2017) conducted an exploratory case study with a crossover design and higher training intensity to explore the progression of motor gains induced by MST. A man with chronic stroke completed a rehabilitation program with an ABAB reversal design, where MST was provided during periods B and no treatment during periods A. Each period lasted four weeks, with 18 hours of training per period. Motor skills were assessed weekly using behavioral tests measuring motor impairment, dexterity, grip strength, and motor performance in daily tasks, as well as 3D-movement analysis. In addition, his performance playing an octave with the keyboard was recorded after each session. The participant showed initial improvements in keyboard performance and speed tapping during the first MST period, with clinical gains observed by the end of the first treatment period in gross manual dexterity and daily task performance, indicating transfer to ADL. Improvements continued during the second MST period in upper-limb functionality, grip strength, and kinematic properties of a reaching task. Some gains were maintained after three months, suggesting long-term retention. During no-treatment periods, scores in gross manual dexterity and daily task performance remained stable, while upper-limb functionality improved, indicating that motor memories can become more robust in periods of no training (Grau-Sánchez et al., 2017).

More recently, Fujioka et al. (2018) tested the effectiveness of a modified MST protocol for chronic stroke compared to the conventional physical training Graded Repetitive Arm Supplementary Program (GRASP) (Harris et al., 2009). Modifications included changing the drum exercise scale from C to C’ (instead of G to G’), using drumsticks, brushes, and mallets to play the drums (instead of palm and fist), incorporating a djembe for timbre variations, and adding music-making exercises with a therapist. Twenty-eight participants were randomly assigned to MST or GRASP, both groups completing 30 hours of training over 10 weeks. Evaluations were conducted before, midway, and after the intervention, with a 3-month follow-up. Both groups showed no significant changes in upper-limb functionality or gross manual dexterity, but MST participants showed a tendency to improve in hand motor impairment and in the speed of completing the upper-limb functionality test. While neither group showed significant changes in verbal fluency, working memory, or executive functions, both completed executive function tests faster, with MST showing improvements at the midpoint, and GRASP at the end of the intervention. Importantly, both groups experienced reduced negative affect during the intervention, but only MST maintained this post-intervention. In stroke-related QoL, both groups showed trends toward increased positive emotion and self-perceived mobility post-intervention, with the latter being significant in the GRASP group. Both groups also improved significantly in self-perceived communication skills and participation, with the MST group achieving these improvements earlier (at the midpoint of the intervention) compared to the GRASP group (after the intervention). Regarding musical aptitudes, only MST participants improved in rhythm discrimination by the midpoint of the intervention, with no changes in melody discrimination (Fujioka et al., 2018).

1.4.3 Adapting Music-supported Therapy for chronic stroke

Despite the benefits that MST has shown in motor and cognitive functioning, emotional well-being, and QoL after stroke, two recent RCTs have found limited effects on enhancing upper-limb motor functions. In the trial conducted by Grau-Sánchez et al. (2018) with subacute stroke patients, the MST group outperformed the conventional physical therapy group in emotional well-being and QoL, but not in motor outcomes. Similarly, Fujioka et al. (2018) found non-significant improvements in upper-limb functionality among chronic stroke patients who completed either a slightly modified MST program or GRASP, with no differences between groups. Given the long-term needs of stroke survivors, modifying the original MST protocol by incorporating elements from motor learning theories could enhance its effectiveness.

It is crucial to note that access to rehabilitation programs drastically decreases in the chronic phase, as resources are primarily allocated to the subacute phase when recovery potential is highest (Chen et al., 2019). This represents a major concern for more than half of chronic stroke survivors who still experience residual upper-limb dysfunction (Ingram et al., 2021; Lin et al., 2021), affecting their autonomy in daily life (Moore & Barnett, 2012; Rafsten et al., 2019). However, factors such as lower income and transport inaccessibility may affect rehabilitation adherence for individuals who are prescribed more sessions during the chronic phase (Chen et al., 2019; McNamara & Dalton, 2024). Importantly, the primary goal of chronic stroke rehabilitation is to facilitate individuals' transitioning to home, autonomy, and reintegration into community life, which is hindered if they must continue rehabilitation at hospitals or clinics (Park & Lee, 2016). Considering than the original MST program provided in hospital settings may not be ideal for chronic stroke survivors, adapting it for home use could address physical and economic barriers while promoting community integration. Moreover, MST sessions are guided by a therapist, limiting individuals' self-regulated behaviors (Chan et al., 2009). Completing self-training MST sessions should thus increase individuals' autonomy, a key factor in motor learning (Wulf & Lewthwaite, 2016). In this context, the use of a technological device with Artificial Intelligence (AI) software that provides exercise instructions and tracks performance progress offers an optimal solution for home-based self-training MST sessions (Grau-Sánchez et al., 2020). However, maintaining motivation for home-based sessions is challenging. Despite the inherent enjoyment of music, the repetitive nature of rehabilitation exercises without supervision can become monotonous and reduce adherence (Tosto-Mancuso et al., 2022). Integrating gamification elements that provide positive feedback (e.g., points, trophies) and consequent intrinsic rewards could enhance motivation and engagement (Deterding et al., 2011), thereby improving task performance and motor learning (Wulf & Lewthwaite, 2016).

The WHO recommends rigorous evaluation of technological solutions from end-user, health, and societal perspectives to ensure its appropriate use for improving health (Jansen-Kosterink et al., 2022). Involving end-users in the development process helps capture the needs of the population that is going to benefit from the technological solution, which significantly improves its quality, usability, and social acceptance (Chávez et al., 2019; Laurisz et al., 2023; Wright & McCarthy, 2010). In this context, Agile Software Development (ASD) is well-suited for healthcare software because it emphasizes active end-user involvement to improve clinical outcomes, quality of healthcare delivery, healthcare management, and patient safety (Kokol, 2022). ASD involves multiple iterations of ideas, prototypes, and tests, allowing for continuous feedback and incremental adjustments until the final product is achieved (Grenier et al., 2021; Kokol, 2022; Tsangaris et al., 2022). Adapting MST for home and autonomous use through the creation of an app for electronic tablets using ASD involves several steps, as shown in Figure 1.7. First, an interdisciplinary team of technology developers and healthcare providers analyzes requirements for chronic stroke survivors, reviewing the theoretical framework and selecting the appropriate exercises and musical instruments (**step 1**). Next, the team designs the prototype software, addressing technological challenges like integrating musical exercises, instructions, gamification elements, and data tracking (**step 2**). Technology developers then code and develop the first version of the app by incorporating all the elements discussed in the previous step (**step 3**). Then, usability testing with end-users, including qualitative interviews and usability questionnaires, is essential to refine the app based on their needs and perspectives. Additionally, evaluating the health outcomes after completing the home-based eMST intervention using the novel app is crucial to assess its potential effectiveness for chronic stroke patients (**step 4**). Once the MST app is optimized, it can be deployed in a larger-scale clinical trial to test the effectiveness of home-based eMST in real-life settings for chronic stroke survivors (**step 5**). Finally, the last step involves reviewing the results and discussing potential improvements or commercialization options (**step 1**) (Chávez et al., 2019; Jansen-Kosterink et al., 2022; Kokol, 2022; Laurisz et al., 2023).

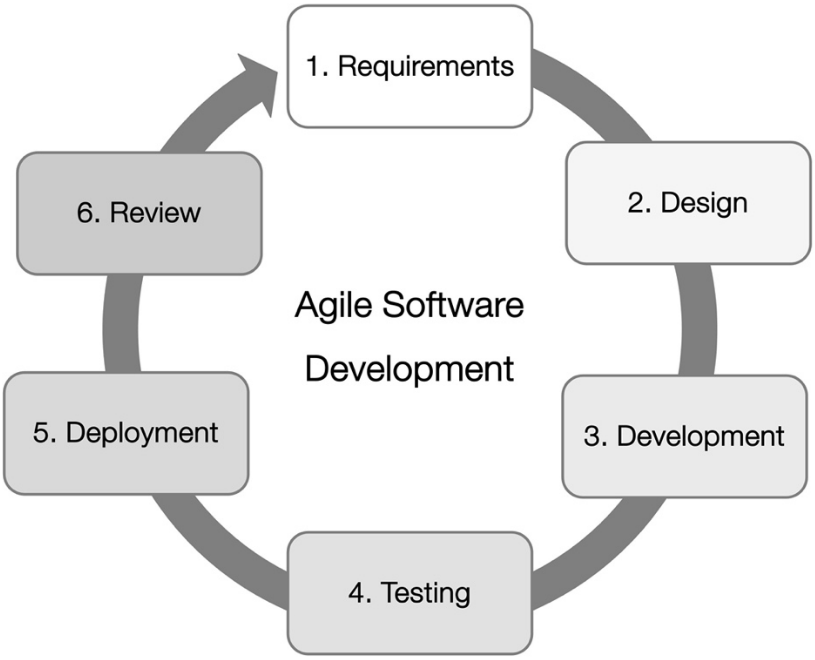


Figure 1.7. Agile Software Development scheme.
The Agile Software Development (ASD) process for developing software to provide health services involves the following steps: 1) Analyze product requirements based on end-user needs; 2) Design a prototype incorporating the appropriate elements to achieve the desired outcomes; 3) Develop and code the initial software version; 4) Test the software's usability and the feasibility of the intervention using it; 5) Deploy the lastest version of the app once critical issues are resolved to assess its effectiveness in achieving health outcomes; 6) Review the product's effectiveness and explore potential improvements and/or commercialization opportunities. Adapted from Grepon et al., 2021.

One of the main factors that could be affecting the limited effectiveness of MST in the chronic phase is training intensity and duration, which may need to be higher and longer to promote greater recovery (Kitago & Krakauer, 2013; Maier et al., 2019). Given that 30 hours of training over 10 weeks were insufficient to elicit significant motor changes in Fujioka et al. (2018), at least 10 additional hours of training may be needed (Feys et al., 2004). Another key factor in motor recovery is the range of movements trained, which is limited in the original MST program since it includes only two instruments. The range could be expanded by incorporating more diverse instruments and exercises that target upper-limb movements relevant for ADL. Additionally, adapting the program for home use makes the electronic drum set impractical due to its size. Using smaller percussion instruments and allowing participants to select the order in which they are played can enhance their autonomy and motivation during MST sessions, improving engagement and motor learning (Grau-Sánchez et al., 2020; Wulf & Lewthwaite, 2016).

Crucially, playing an instrument aids motor function recovery by engaging auditory-motor coupling, allowing the anticipation and adjustment of movements based on sound stimuli (Rodriguez-Fornells et al., 2012). In the original MST program, the piano and drum exercises are played without specific tempo cues. While they benefit from the auditory feedback provided by the instrument, incorporating temporal cues and rhythmic patterns of varying difficulty into the percussion exercises is crucial for facilitating movement anticipation and enhancing performance.

A major concern for individuals with chronic stroke is the common feeling of loneliness and social isolation, complicating their reintegration into the community (An et al., 2023). Given the importance of peer support in promoting stroke survivors' QoL, it is crucial to provide them with opportunities to engage in social activities (Chen et al., 2019; McNamara & Dalton, 2024; Shaik et al., 2024). Since MST sessions are typically conducted individually, incorporating group music therapy sessions guided by a music therapist could enhance social interaction and community reintegration (Chang et al., 2020). Additionally, setting a common goal for group sessions, such as learning to play a song to record or perform in a concert, could boost motivation to complete the entire intervention, thereby enhancing motor learning and MST effectiveness (Wulf & Lewthwaite, 2016).

1.5 Overview and gaps to address

With the rising prevalence of stroke (Katan & Luft, 2018), a leading cause of long-term disability worldwide (GBD 2019 Stroke Collaborators, 2021), it is essential to develop strategies that enhance survivors' physical and mental health and reduce the overall stroke burden. Major unmet needs among chronic stroke individuals include limited access to rehabilitation services, motor impairments, restricted leisure time, low mood, and social isolation (Chen et al., 2019; Hotter et al., 2018; Lin et al., 2021). Since motor impairment is the most common consequence of stroke (Langhorne et al., 2009; Siddique et al., 2009), many rehabilitation programs focus on improving motor function rather than promoting reintegration into community life (Borschmann & Hayward, 2020). However, restricted participation and the resulting social isolation have a detrimental impact on individuals' mental health (Aked et al., 2024; Bergström et al., 2017) and contribute to the decline of their motor and cognitive functions (Lo et al., 2022; Wondergem et al., 2017). Thus, it is essential to develop accessible, cost-effective, community-based rehabilitation programs that help chronic stroke survivors maintain or improve motor and cognitive functions while addressing their socio-emotional needs (Steultjens et al., 2003).

Instrumental music training is an intrinsically rewarding, task-specific, and goal-oriented activity that provides multisensory stimulation and fosters social bonding (Fancourt & Finn, 2019; Grau-Sánchez et al., 2020). It not only facilitates upper-limb motor recovery but also provides a meaningful experience that may help stroke survivors participate in the community and re-establish their occupational identity (Brunborg & Ytrehus, 2014; Dorstyn et al., 2014; Morris et al., 2015). Music-supported Therapy (MST) specifically targets upper-limb motor function through piano and percussion training (Schneider et al., 2007). MST has been shown to enhance motor recovery at both behavioral and neural levels, as well as improve cognitive functions, emotional well-being, and QoL in subacute and chronic stroke patients (Grau-Sánchez et al., 2020). However, MST has not demonstrated superior motor gains compared to conventional physical therapy (Fujioka et al., 2018; Grau-Sánchez et al., 2018). Given the needs of chronic stroke survivors, integrating socio-motivational and learning components into MST could enhance functional recovery and community reintegration.

Adapting the MST protocol for home-based self-training, and adding group music therapy sessions, could boost autonomy and social interaction, both vital for chronic stroke rehabilitation (Wulf & Lewthwaite, 2016). Increasing training intensity, movement variety, and incorporating rhythmic patterns to allow movement anticipation may further support functional recovery (Grau-Sánchez et al., 2020; Maier et al., 2019). Due to limited resources and mobility challenges faced by many stroke survivors (Chen et al., 2019; McNamara & Dalton, 2024), telerehabilitation (TR) is a promising solution to improve access to stroke care (Tamayo-Serrano et al., 2018). Developing an app that offers home-based self-training MST sessions could not only increase accessibility but foster patients' autonomy and reduce hospital or rehabilitation center visits, thereby aiding community reintegration. However, the effectiveness of music-based interventions in community settings and using TR remains understudied, and more interventions using this approach should be developed and tested.

Lastly, it is important to note that depression is the most common affective consequence following a stroke (Medeiros et al., 2020). Along with other common post-stroke psychological conditions, such as apathy and anhedonia, depression affects motivation and goal-directed behaviors, hindering engagement in rehabilitation and rewarding activities (Moore & Barnett, 2012). This, in turn, contributes to a decline in individuals' physical and mental health (Ramasubbu et al., 1998). Nevertheless, these mood disorders, and particularly anhedonia, are underdiagnosed and undertreated in the stroke population (Medeiros et al., 2020), and more research is needed to explore their prevalence, causes, impact, assessment, and treatment.

Research aims

2. Research aims

The main goal of this doctoral thesis is to test the effectiveness of an enriched version of Music-supported Therapy (eMST) that ingrates socio-motivational and learning components for chronic stroke survivors. Additionally, the thesis aims to explore the prevalence of anhedonia in the stroke population, an understudied condition that could diminish individuals' motivation to engage in rehabilitation programs and maintain an active lifestyle.

To achieve these goals, this thesis includes four studies, with specific objectives and hypotheses detailed in the following sections.

2.1 Study 1

The first study aimed to evaluate the usability of the MST app and the feasibility of the home-based eMST intervention for chronic stroke survivors. After developing the first version of the MST app, we conducted a pilot study to refine its technical features and optimize the rehabilitation program based on patients' feedback. Additionally, we assessed participants' motor gains during and after the intervention to examine its potential benefits for chronic stroke. The rationale for the study was to adapt the eMST intervention to the target population's needs and address potential implementation challenges when testing its effectiveness in a larger-scale clinical trial.

By involving chronic individuals with hemiparesis in the adjustment of the MST app and rehabilitation program (Kokol, 2022), we hypothesized that the refined version would achieve high usability scores. We also expected that the intervention would exhibit high adherence rates and no safety concerns, indicating its feasibility. Drawing on the effects of autonomy and intrinsic motivation on motor learning (Wulf & Lewthwaite, 2016), we further hypothesized that participants would achieve clinically relevant improvements in upper-limb motor functions after the intervention, and would enhance their piano performance over 30 sessions. This would highlight the feasibility and potential benefits of the home-based eMST program for motor skill reacquisition.

2.2 Study 2

The second study aimed to develop a clinical trial protocol to evaluate the effectiveness of enriched MST (eMST) for chronic stroke survivors using the latest version of the MST app and compared to a conventional home-based upper-limb motor rehabilitation program. We designed a pragmatic parallel-group randomized controlled trial (RCT) to assess the effectiveness of eMST under real-world circumstances. The primary outcome was upper-limb functionality, and secondary outcomes included other motor and cognitive functions, emotional well-being, QoL, self-regulation and self-efficacy. Both interventions were designed to provide 40 hours of training over 10 weeks, with masked evaluations conducted before and after the intervention, as well as at three-month follow-up to assess lasting effects. The main hypothesis of the designed trial was that eMST would outperform the conventional program in enhancing all outcomes due to the incorporation of socio-motivational and learning components aimed at fostering autonomy, intrinsic motivation, and social interaction (Wulf & Lewthwaite, 2016).

This study follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines, which provides essential items for accurately and consistently reporting RCT methods, including the detailed description of the intervention before testing its effectiveness. By adhering to CONSORT guidelines, we aimed to ensure the proper execution of a well-designed RCT and the reporting of clear, transparent, and reliable findings. In addition to testing the usability of the MST app and feasibility of the home-based program, this approach enhances the quality of clinical research, which is essential for improving clinical practice based on prior evidence (Hopewell et al., 2022).

2.3 Study 3

The third study aimed to test the effectiveness of enriched MST (eMST) in the rehabilitation of chronic stroke survivors compared to a conventional home-based upper-limb motor rehabilitation program. The primary goal was to improve upper-limb functionality, and secondary outcomes comprised other motor and cognitive functions, emotional well-being, QoL, self-regulation and self-efficacy. Additionally, the study aimed to explore the influence of stroke etiology, upper-limb motor deficit at baseline, intrinsic motivation, and sensitivity to music reward on motor improvement. We conducted a pragmatic parallel-group randomized controlled trial with follow-up assessment including chronic stroke survivors with hemiparesis and diverse clinical and sociodemographic profiles to demonstrate eMST's benefits in real-world conditions and in the long-term.

We hypothesized that eMST would lead to greater improvements in all motor outcomes, including upper-limb functionality, motor impairment, and performance in daily tasks, both immediately after the intervention and at follow-up when compared to the conventional program. Additionally, we expected the eMST group to show greater enhancements in cognitive functions, emotional well-being, QoL, self-regulation and self-efficacy after the intervention compared to the control group. Based on previous findings on MST (Grau-Sánchez et al., 2018) and motor learning theories (Wulf & Lewthwaite, 2016), we anticipated that participants with higher sensitivity to music reward and greater intrinsic motivation would exhibit greater motor gains. These results would highlight the benefits of promoting individuals' autonomy and social interaction in a MST intervention to enhance motor recovery and address the socio-emotional needs of chronic stroke survivors (Wulf & Lewthwaite, 2016).

2.4 Study 4

The last study aimed to assess for the first time the prevalence and severity of anhedonia in individuals with stroke and upper-limb motor dysfunction at both subacute and chronic phases of the disease. In addition, the study aimed to explore clinical, sociodemographic, and emotional factors potentially linked to anhedonia, including age, sex, education level, stroke etiology, affected hemisphere, lesion location, time since stroke, upper-limb functionality, global cognitive level, working memory, language memory, depression, non-anhedonic depression, apathy, and negative mood states such as anger, vigor, fatigue, tension, and confusion. Given anhedonia's potential negative impact, this study sought to better understand its onset and development after stroke, highlighting the importance of addressing it to improve individuals' emotional well-being and promote their adherence to rehabilitation and healthy active lifestyles.

We hypothesized that stroke survivors, whether in the subacute or chronic phase, would show a higher prevalence and severity of anhedonia compared to healthy individuals. The brain inflammatory response after a stroke causes an ongoing cell death in the injury site and penumbra, leading to a chronic low-grade inflammation that impairs the mesolimbic pathway over time (Pascotini et al., 2015; Shi et al., 2019; Stuckey et al., 2021). The disruption of this dopaminergic pathway results in abnormal reward processing and consequent development of anhedonia (Cooper et al., 2018; Der-Avakian & Markou, 2012). We therefore expected similar levels of anhedonia across stroke survivors, regardless of stroke etiology, affected hemisphere, lesion location, or time since stroke. Moreover, the disruption of this pathway not only impairs reward responses but also contributes to cognitive deficits, such as memory dysfunction (Isella et al., 2004). Therefore, we anticipated that stroke survivors would have lower global cognitive and memory functions compared to healthy controls. Considering anhedonia's role in reducing engagement in rewarding activities and its strong presence in depression (Verrienti et al., 2023), we also hypothesized that anhedonia would be strongly correlated with depression, apathy, and negative mood states such as anger, fatigue, and confusion. Lastly, we expected these associations to persist even after controlling for the influence of non-anhedonic depression, underscoring the individual role of anhedonia in diminishing emotional well-being after stroke.

Study 1

This study corresponds to:

Segura, E., Grau-Sánchez, J., Sanchez-Pinsach, D., Arcos, J. L., & Rodríguez-Fornells, A. (2021). Designing an app for home-based enriched Music-supported Therapy in the rehabilitation of patients with chronic stroke: a pilot and feasibility study. *Brain Injury*, *35*, 12-13.

3. Study 1

Designing an app for home-based enriched Music-supported Therapy in the rehabilitation of patients with chronic stroke: a pilot feasibility study

3.1 Introduction

Stroke is the leading cause of acquired long-term disability worldwide (Katan & Luft, 2018). Over fifty percent of stroke survivors have motor function impairments and require support, especially with instrumental activities of daily living (GBD 2010 Stroke Collaborators, 2014; Katan & Luft, 2018; Roger et al., 2012; White et al., 2007). The residual functional limitations in the upper limb cause difficulties with day-to-day physical and social activities affecting emotional well-being and quality of life (QoL) (Mayo et al., 2002; Salter et al., 2008). Therefore, engaging in rehabilitation programs based on promoting adaptive motor learning is critical for patients with stroke to restore motor functions as well as autonomy in daily life (Algurén et al., 2012; Hartman-Maeir et al., 2007; Langhorne et al., 2011; Mutai et al., 2016; Nys et al., 2007). Patients usually undergo formal rehabilitation programs during the first six months post stroke to take advantage of the increased plasticity period during the subacute phase (Dancause & Nudo, 2011; Krakauer et al., 2012; Langhorne et al., 2011; Stroemer et al., 1998; Carmichael et al., 2001), after this six-month rehabilitation period, most patients do not achieve full recovery of upper-limb motor function (Kwakkel et al., 2003). Moreover, patients with chronic stroke can suffer a decline in their motor functions due to the decrease in their physical activity after completing the rehabilitation program (Ashe et al., 2009; Billinger et al., 2014; Winstein et al., 2016). This may be related to the absence of an active routine previously provided by attending regular therapist-led sessions (Chan et al., 2009). Hence, the need to create more accessible rehabilitation programs has emerged in order to maintain or improve motor function in patients with chronic stroke (Sihvonen et al., 2017).

Musical training is increasingly recognized as a useful tool to enhance motor and cognitive functions as well as QoL in patients with stroke (Grau-Sánchez et al., 2020). Musical activities provide a multimodal experience that requires the simultaneous activation of different brain areas. These areas are involved in sensory-motor function, auditory processing, emotional processing, and cognitive functions such as memory and attention (Saarikallio, 2011; Särkämö, 2018). When playing a musical instrument, the immediate auditory feedback provided by the instrument is used to adjust future movements and reinforce motor learning (Rodriguez-Fornells et al., 2012; Roerdink et al., 2009; Rojo et al., 2011). Musical training can provide enjoyment, stress relief, and distraction from negative cognitive states and from physical effort (Dyrlund & Wininger, 2008; Saarikallio, 2011; Vuilleumier & Trost, 2015). Moreover, learning to play an instrument involves acquiring a new skill set enabling patients to gain a sense of competence (Rodriguez-Fornells et al., 2012). These effects can feed intrinsic motivation to adhere to motor exercises in which music is present (Wininger & Pargman, 2003).

Music-supported Therapy (MST) is one of the most investigated rehabilitation techniques based on musical training. It consists of playing musical instruments with the paretic upper extremity to improve both fine and gross motor functions post stroke (Schneider et al., 2007). This intervention is based on the principles of massive repetition of upper-limb movements, audio-motor coupling, shaping according to the individuals' progress, emotion-motivation effects, individualization of the program, and increase of exercise complexity (Grau-Sánchez et al., 2020; Rodriguez-Fornells et al., 2012; Schneider et al., 2007). MST sessions are usually provided by a therapist at the hospital or rehabilitation center, where patients play simple sequences with an electronic keyboard and/or rhythmic sequences with drum pads. MST has been shown to be effective in the rehabilitation of upper-limb motor function after stroke (Altenmüller et al., 2009; Amengual et al., 2013; Schneider et al., 2007) as well as in promoting cognitive and QoL improvements (Grau-Sánchez et al., 2018; Ripollés et al., 2016). In a pioneering study in 2007, Schneider et al. conducted a randomized controlled trial (RCT) about MST. In comparison to the control group, patients treated with MST demonstrated significant improvements in speed, motor control, precision and smoothness of their movements (Schneider et al., 2007). Recently, Grau-Sánchez et al. (2018) conducted a RCT where both MST and control groups demonstrated improvement in motor function but only the MST group showed significantly higher QoL. The motor function improvement was found to be associated with the ability to experience pleasure from musical activities (Grau-Sánchez et al., 2018).

One of the aims of stroke rehabilitation in the chronic phase is to develop and maintain maximum autonomy in order to facilitate participation and reintegration into community life (Park & Lee, 2016). Conducting home-based non-therapist-led sessions encourages patients to engage in self-regulated behaviors throughout the learning process, which can lead to a greater recovery according to motor learning theories (Deci & Ryan, 2000; Deterding et al., 2011; Malone, 1981; Wulf & Lewthwaite, 2016). This can help patients to develop autonomy by increasing participation in the chronic phase (Chan et al., 2009). In this line, telerehabilitation (TR) is an emerging modality of intervention and a promising option for patients with chronic stroke to conduct rehabilitation programs at home with greater independence (Knepley et al., 2021). Knepley et al. (2020) conducted a systematic review of 34 studies regarding stroke TR. They concluded that TR can be as effective as conventional hospital-based rehabilitation at improving motor and cognitive functions as well as QoL post stroke. They observed the following advantages: several application forms of therapy, ability to be delivered effectively in community settings, possible combination with hospital-based rehabilitation, increase of accessibility and decreased costs, and possibility of communicating and assessing patients' feelings (Knepley et al., 2021).

We designed an enriched MST (eMST) program to provide patients with chronic stroke with the opportunity of continuing rehabilitation at home. In this way, they could continue to improve motor functions once they have completed their formal rehabilitation program. We developed an app for electronic tablet to conduct the sessions at home together with a MIDI-piano and different percussion instruments (Sanchez-Pinsach et al., 2019). In order to achieve an active engagement from patients, the app incorporates the following features based upon previous MST programs: 1) continuous monitoring of therapy activities, 2) personalization of exercises adjusting the difficulty levels to patients' progress and needs, 3) incorporation of positive feedback and gamification strategies to enhance patient adherence and learning, and 4) empowerment of patients to self-regulate their training sessions (Sanchez-Pinsach et al., 2019). The main goal of the present study is to assess the feasibility of the home-based eMST program using the novel app. This was done before conducting a randomized RCT in order to avoid potential issues when testing the effectiveness of the eMST intervention. Firstly, we wanted to ensure the usability of the MST app through which the home-based intervention is provided. In order to obtain the maximum usability, we aimed to improve the first version of the app over the course of the study using patients' feedback and first-person experience. We also aimed to test the motor function gains, the intervention adherence and the safety to increase clinical experience and enhance the likelihood of success when applying the eMST intervention on a larger scale.

3.2 Methods

3.2.1 Participants

The recruitment was done by advertising the pilot study in a non-profit stroke patients' association in Barcelona (Spain) that has approximately 70 members. Four female patients and one male patient with chronic stroke contacted with us via telephone to participate in the study. After doing individual interviews at the hospital to assess whether they fulfilled the inclusion criteria, the five patients were subsequently accepted to participate (mean age 52.6 years ± 13.3; mean time since stroke 3 years and 8 months ± 36.38). The inclusion criteria was the following: 1) more than 6 months after stroke, 2) presence of mild-to-severe paresis of the upper extremity after stroke (having a score between 1 and 4 in the Medical Research Council Scale for Muscle Strength at the distal muscles of the upper extremity), 3) not doing rehabilitation at the time of recruitment, 4) no major cognitive deficits affecting comprehension (Mini-Mental State Examination > 24), 5) no neurological or psychiatric co-morbidity, with exception of post-stroke depression, and 6) no other musculoskeletal condition affecting upper-extremity motor function (e.g. fracture or arthritis).

A sample of 20 healthy participants (10 females, mean age = 63.5, SD = 8.77; 10 males, mean age = 65.3, SD = 6.85; with no significant difference in age between gender, $F = .262$, $p = .615$) were recruited as a control group to establish piano performance baseline values. They showed no neurological or psychiatric co-morbidity, nor any musculoskeletal condition affecting upper-extremity motor function. Patients' improvement could be checked by comparing their values with healthy controls performance values throughout the intervention.

The protocol of this study was approved by the Clinical Research Ethics Committee of the Bellvitge University Hospital (PR095/17; Barcelona, Spain) and the Hospitals del Mar i l'Esperança (Parc de Salut Mar, 2020/9523; Barcelona, Spain) and follows the Declaration of Helsinki to experiment with human beings. Participants signed an informed consent prior to participation explaining the feasibility objectives of the study and the absence of potential risks for completing the eMST intervention.

3.2.2 General procedure

Patients followed a 10-week eMST intervention using the novel app consisting of three sessions per week. They did 30 sessions of varying length as the number and time of percussion exercises were modified over the study to adjust the session length to one hour approximately. The first three recruited participants completed the first 15 sessions in the hospital with a music therapist, and the rest of the sessions at home alone. This was done to check that the first version of the app worked properly the first-time it was used by patients. In the first session, the music therapist showed the functionality of the electronic tablet and the app. In subsequent sessions at the hospital, she checked that patients were able to do the self-training sessions on their own and that the app did not have any technical glitches. During hospital-based sessions, the music therapist took notes of patients' feedback regarding some problems they may encounter (e.g., small font size, low volume, etc.). The other two participants completed the whole intervention at home alone, only doing the first session with the music therapist in order to learn how the tablet and the app work. The music therapist visited their homes to provide them with all the necessary materials for the intervention: an electronic tablet with charger, a MIDI-piano keyboard with a tablet connection cable, and a box with percussion instruments. Throughout the course of the home-based sessions, the music therapist remotely monitored patients' engagement and performance by weekly phone calls and checking the app inputs through the eMST website program.

3.2.3 App development

In order adapt the eMST program for home use, a multidisciplinary team of engineers and therapists worked together to create an app (Sanchez-Pinsach et al., 2019). Firstly, the therapists checked which of the musical exercises from the original MST program were the most appropriate for the eMST program. It was decided to introduce the original piano exercises and to add percussion exercises played with eight percussion instruments alongside the commonly used electronic drums. Each percussion exercise was designed considering the upper-limb movements currently performed in conventional interventions (without music) (Harris et al., 2009). Engineers and therapists collaborated on how to display the different exercises on the app whilst considering the technical constraints of doing so. Technical aspects encompassing the type of instructions, stimuli and feedback display, and inputs registered were also discussed. Video tutorials were recorded and added onto the app to display the instructions of how to play the percussion instruments. Gamification and telematic monitoring elements were also introduced to create an app based on reinforcing motor learning components (Sanchez-Pinsach et al., 2019). Throughout this study, the technical features of the first version of the app were changed according to patients' feedback obtained from the notes took by the music therapist in the hospital-based sessions and usability questionnaires answered post-intervention. For more details of the development and functions of the MST app, please see the study by Sanchez-Pinsach et al. (2019).

3.2.4 Intervention

The eMST intervention consisted of individual self-training sessions using an app on an electronic tablet. The app provided instructions on all the exercises, recorded patients' MIDI-piano performance, and gathered data regarding engagement and length of session. Each session was organized into two main parts: 1) playing percussion instruments to warm up the affected upper limb and train gross motor skills, and 2) playing the MIDI-piano to train fine motor skills. Below is the outline of both percussion and piano exercises.

The percussion exercises consisted of playing with the affected limb rhythmic patterns with four different percussion instruments in each session. Patients were asked to play each rhythmic pattern with a specific tempo depending on the exercise difficulty level (from 1 to 8), the instrument, the movement suggested to play it, and their level of motor impairment. Eight different percussion instruments were selected to play these exercises: tambourine, tambourine with beater, djembe, maracas, egg shaker, rainstick, castanets, and guiro. The app displayed the instructions on the tablet for the percussion exercises including the presentation of the instruments and movement tutorials (see Figure 3.1).

The piano exercises consisted of playing different note sequences with a MIDI-piano using different fingers or combination of fingers with the affected hand. The sequences were formed by white key notes and were classified into nine difficulty levels. To perform the piano exercises, instructions were displayed on the tablet including the presentation of the hand and finger/s that were to be used and the sequence of notes to be played (see Figure 3.1). When patients played an incorrect note, it was marked in red to make them aware of the mistake and allow for self-correction. More feedback was presented to motivate patients to play as best they could: a scoring system with numbers that increased as the participant followed the exercise; and a pie chart displayed at the end of each session with the proportion of correct and incorrect notes. To check piano performance progress, patients did two piano evaluation exercises after their daily exercise series over the 30 sessions. The evaluation exercises consisted of playing the simplest sequence of the two easiest levels of the piano exercises (see Table 3.1). Before finishing the session there was the option of playing a game called Simon, where a sequence of notes was progressively presented and should be repeated one by one.

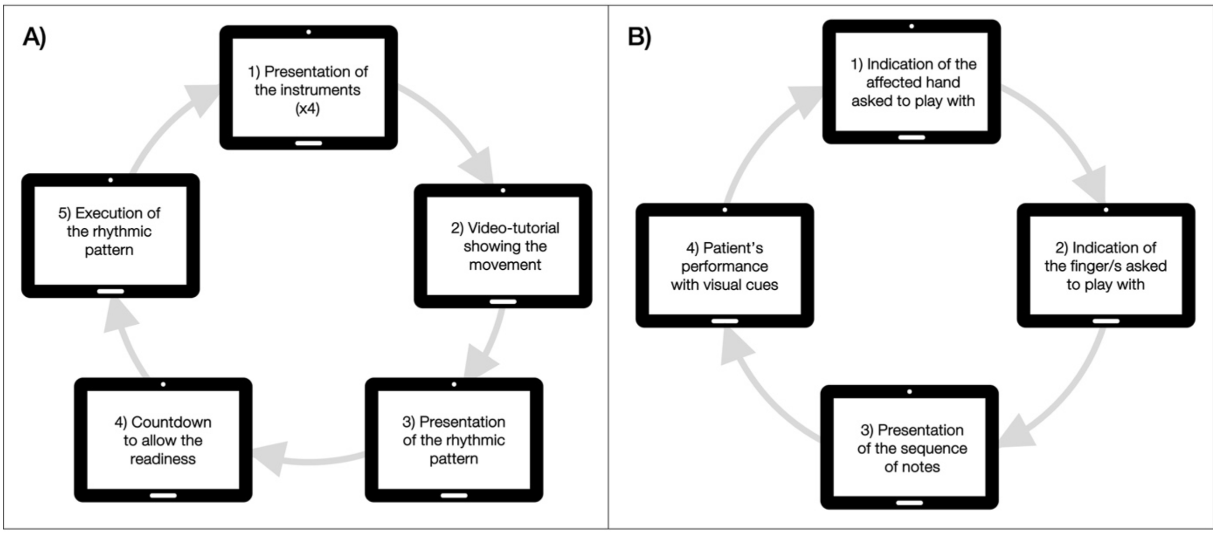


Figure 3.1. Exercises instruction for patients on the app.
Instructions presented on the app regarding the percussion exercises (A) and the MIDI-piano exercises (B). The sequence of the percussion instruction (A) is repeated for the four instruments required to play in each session.

Table 3.1. Piano evaluation exercises.
Musical characteristics of the piano evaluation exercises played daily by the chronic stroke patients. The exercises are upward series played with all the fingers and combination of fingers. The numbers in the arrangement represent the eight notes of the C major scale (being 1 = C, 2 = D, 3 = E, 4 = F, 5 = G, 6 = A, 7 = B, and 8 = C').

Evaluation exercise	Characteristic	Arrangement
1	Individual tones	1, 2, 3, 4, 5, 6, 7, 8
2	Interval of 2 tones	1 2, 1 3, 1 4, 1 5, 1 6, 1 7, 1 8

3.2.5 Main study objectives

The main study will be a RCT aiming to test the effectiveness of the home-based eMST intervention in improving upper-limb motor functions in patients with chronic stroke when compared to a validated conventional home-based rehabilitation program. Secondary objectives will be to assess cognitive functions, QoL, emotional well-being, as well as self-regulation and self-efficacy behaviors. We hypothesize that participants undergoing the eMST intervention will demonstrate greater motor and cognitive improvements, and enhanced QoL, emotional well-being, and self-regulated behaviors when compared to participants undergoing the conventional intervention.

3.2.6 Main study outcomes

The primary outcome of the main study is the functionality of the paretic upper extremity measured with the Action Research Arm Test (ARAT; Lyle, 1981). Secondary outcomes include other motor and cognitive functions, emotional well-being, and QoL measures as well as self-regulation and self-efficacy outcomes.

3.2.7 Feasibility and usability

The feasibility of the eMST intervention and the usability of the app were assessed using two questionnaires together with patients' feedback collected throughout the hospital-based sessions and telematic monitoring. The feasibility was measured using a structured interview at weeks 1, 5, and 10 of the intervention. The interview questions were focused on patients' opinion about different aspects of the rehabilitation program including total duration of the sessions, time per exercise, difficulty level of exercises and movements, comfort level using the app, comfort level using the instruments, and feeling of tiredness. In this structured interview some questions about the usability of the app were included. These questions were focused on patients' opinion about technical aspects of the app such as whether the volume, instructions and visual appearance were appropriate, and if the feedback was noted.

The usability was measured using The System Usability Scale (SUS) (Brooke, 1996). This questionnaire consists of 10 items with a 5-points score (from 1: Strongly disagree to 5: Strongly agree) regarding the convenience of using new devices and applications. Participants were asked to answer this questionnaire after the intervention to check whether they would use the app again and to which degree.

3.2.8 Clinical evaluation

To evaluate patients' motor function, the following motor outcomes were obtained pre- and post-intervention: 1) functional movements such as grasping, gripping and pinching were measured using the ARAT (Lyle, 1981), 2) motor impairment was measured using the upper-extremity subtest of the Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA-UE; Fugl-Meyer et al., 1975), 3) hand and finger dexterity were evaluated using the Box and Block Test (BBT; Mathiowetz et al., 1985) and the Nine Hole Pegboard Test (NHPT; Parker et al., 1986), and 4) motor performance in activities of daily living was assessed using the Chedoke Arm and Hand Activity Inventory (CAHAI; Barreca et al., 2004).

3.2.9 Piano performance

To evaluate patients' piano performance, the app was set to collect the information from the MIDI-piano which was connected to the electronic tablet as a MIDI-device. Patients' performance was assessed in every session by recording played notes, errors, inter-note time, key-pressure, and execution time for all the exercises. The percussion exercises could not be evaluated when they were performed at home because the app only collects data generated on a MIDI-device.

To analyze patients' piano performance, three variables related to speed and force tapping were selected: 1) execution time or total duration of each evaluation exercise measured in milliseconds, 2) inter-note time or time between notes played in each evaluation exercise measured in milliseconds, and 3) pressure applied on the keys in each exercise, codified as the velocity with which a key is pressed from 0 to 1.

To check the improvement in performance over the intervention, baseline values were established from control participants' piano performance. Patients' values were compared to baseline values to monitor whether and when they approached healthy controls performance.

3.2.10 Intervention adherence and safety

Patients' adherence to the eMST intervention was evaluated by comparing what was planned (completing 30 self-training sessions in 10 weeks) to what each patient did. Patients were asked to complete three sessions per week regardless at which day of the week and at what time were completed. To check the safety of conducting self-training eMST sessions at home alone, the therapist who monitored them remotely by phone calls asked them and took notes weekly about any adverse effects during the week (e.g., muscle pain, headache, joint pain, etc.).

3.2.11 Feasibility criteria

To evaluate the success of feasibility, we stated the following criteria: the usability questionnaires scores should be equal to or higher than 3 (and equal to or lower than 3 in the negative statements); the participants should complete all the sessions (a total of 30) in 10 weeks; the difference between the pre- and post-evaluation motor tests scores should achieve the Minimal Detectable Change (MDC) or the Minimally Clinically Important Difference (MCID); the speed and force tapping variables should achieve or be closer to the controls piano performance at some point over the whole intervention; the completion of the home-based intervention should not demonstrate potential risks for patients health.

3.2.12 Statistical analysis

To analyze the clinical motor test scores, we considered whether the difference between the pre- and post-evaluation scores achieved the MDC or the MCID. The MDC is defined as the smallest statistically relevant change that can be detected beyond the measurement error and represents a noticeable change in ability. The MCID establishes which changes in a clinical intervention are relevant for the patient or clinician.

To analyze the piano performance, statistical analysis was conducted using Excel (Windows 2010) and the Statistical Package for the Social Sciences (SPSS version 21, SPSS inc., Chicago, Illinois, USA). Each variable was analyzed by obtaining the mean and the standard error of the mean (SEM). Execution time was obtained by calculating the average time (in milliseconds) required to play each exercise with a specific finger or combination of fingers. The mean and SEM of all the exercises performed in each session was calculated. Inter-note time was obtained by first calculating the average time (in milliseconds) taken to play each note of an exercise with a specific finger or combination of fingers. The mean and SEM of all the exercises performed in each session were calculated. Key pressure was obtained by calculating the mean of the pressure (codified as the velocity with which a key is pressed from 0 to 1) taken to play each note of an exercise with a specific finger or combination of fingers. The mean and SEM of all the exercises performed in each session was then calculated. Key pressure values were converted into a scale of 0 to 100 to conduct analysis and create the graphics.

The variables of control participants' values were obtained by calculating the mean and SEM of the performance from all subjects. SPSS was used to check if there were significant differences between controls' age. Before comparing patients' performance with controls' performance, we made sure to have a homogeneous sample of control participants by calculating the coefficient of variation (CV) of each variable in each exercise.

The mean and SEM of patients and controls' piano performance values were visually reported in graphical representations. The controls' values were reported as the baseline, and patients' values were reported individually and on average in each session. This allowed us to observe the speed and force tapping progression of patients over the whole intervention, as well as checking whether their values achieved control values performance.

3.3 Results

3.3.1 Demographic and clinical data

The demographic and clinical characteristics of the five patients (P01, P02, P03, P04 and P05) are presented in Table 3.2. Four female patients and one male patient (mean age 52.6 years ± 13.3; mean time since stroke 3 years and 8 months ± 36.38) participated in the study and they all consented to participate. Three patients had an ischemic stroke, and two patients had a hemorrhagic stroke (three in the right hemisphere and two in the left hemisphere). The patient P05 had a moderate level of hemiparesis, while the other patients had a mild level of impairment. All were right-handed. Only patient P01 had prior musical training (4 years of non-professional piano experience before the age of 18). Patients P02 and P03 completed the first half of the intervention in the hospital with a therapist and the second half at home alone. Patients P04 and P05 completed all the intervention at home using the updated version of the app modified from the first three participants' feedback. Patient P01 completed the first 15 sessions in the hospital and only 10 sessions at home. This patient did not complete the whole intervention due to personal reasons.

Table 3.2. Demographic and clinical data.
This table provides the demographic and clinical information of the five patients engaged in the eMST program for the pilot study. The level of motor impairment is the Fugl-Meyer Assessment for Upper Extremity score pre-intervention.

Patient	Gender	Age	Lesioned hemisphere	Affected extremity	Type of stroke	Dominant hand	Time since stroke	Hemiparesis severity level
P01	Female	49y	Right	Left	Hemorrhagic	Right	3y 10m	64
P02	Female	33y	Left	Right	Hemorrhagic	Right	11m	61
P03	Female	51y	Right	Left	Ischemic	Right	8y 8m	59
P04	Female	65y	Left	Right	Ischemic	Right	3y 3m	66
P05	Male	65y	Right	Left	Ischemic	Right	1y 8m	41

3.3.2 Feasibility and usability questionnaires

According to patients' feasibility feedback they overall felt competent completing the whole intervention and comfortable playing all the instruments. Using the feasibility structured interview answers, the following aspects of the eMST program were adjusted: each percussion exercise was extended to one minute as patients felt thirty seconds was too short; the MIDI-piano keys' sensitivity was increased to avoid overstraining and ensure auditory feedback as patients P01 and P02 did not hear the notes when playing with minimum force in their first two sessions; a visual cue was added in percussion exercises to facilitate performance; three games called Piano Hero, Combo, and Impro were added to increase the number of optional activities outside of the musical learning program; the options to hear a voice message from the therapist at the beginning of each session and to record a voice message at the end of each session were added to establish a closer feeling of contact; and a 10-week intervention calendar was added so patients can check which sessions have been completed and which sessions remain.

Regarding the patients' feedback concerning technical aspects of the app, the following elements were changed to improve usability: the font size of the instructions was enlarged to a higher comfort of lecture; the scoring system was changed to a vertical score bar with stars that fills up as the exercise is being followed because patients did not understand the original system; and the option to connect speakers to the tablet was added as some patients could not clearly hear the audio instructions and piano performance.

Patients answered the usability questionnaire at the end of the intervention (see Table 3.3). The mean of patients' responses revealed that they considered the app as a useful and easy device to keep training their motor functions. More specifically, patients reported feeling confident using it during the intervention (mean = 5) and they would like to continue using it frequently (mean = 4). Patients found the app easy to use without help (mean = 4.5) and to learn how it works (mean = 3.5), considering all the functions to be well integrated (mean = 4.75). Patients provided low scores when they were asked about needing previous knowledge to use the app (mean = 2), or assistance (mean = 1.5), and whether it was unnecessarily complex (mean = 2.25), or with any awkward (mean = 1.25) or inconsistent (mean = 1.75) elements.

Table 3.3. System Usability Scale responses.
This table shows the answers of four patients to 10 statements regarding the usability of the MST app. The questionnaire was answered with a 5-point scale (From 1: Strongly disagree to 5: Strongly agree) at the end of the intervention. Patients' comments are also provided in the table.

System Usability Scale					
Items	P02	P03	P04	P05	Mean
1) I think that I would like to use this website frequently.	5	2	5	4	4
2) I found this website unnecessarily complex.	1	1	4 ("It can be difficult depending on the patient's condition")	2	2
3) I thought this website was easy to use.	5	5	5 ("It can be difficult depending on the patient's condition")	3	4.5
4) I think that I would need assistance to be able to use this app.	1	1	2 ("I would not need assistance to be able to use the app but the tablet")	2	1.5
5) I found the various functions in this website were well integrated.	5	5	5 ("Now better than the first week due to the fact that the app has been updated")	4	4.75
6) I thought there was too much inconsistency in this website.	1	2	1	3	1.75
7) I would imagine that most people would learn to use this system very quickly.	5	3 ("I would be necessary to conduct the first session with the therapist")	3 ("It can be difficult depending on the patient's condition")	3 ("It can be difficult depending on the patient's condition")	3.5
8) I found this website very cumbersome/awkward to use.	1	1	1	2	1.25
9) I felt very confident using the system.	5	5	5	5	5
10) I needed to learn a lot of things before I could get going with this website.	1	4	1 ("I have needed to learn how the tablet works")	3	2.25

3.3.3 Clinical evaluation

The clinical motor tests scores of patients P02, P03, and P05 evaluated pre- and post-intervention are shown in Table 3.4. Patients P01 and P04 were not evaluated post-intervention due to personal constraints.

In the ARAT, CAHAI, and FMA-UE, patients P02 and P03 obtained higher scores and patient P05 lower scores before the intervention. After completing the intervention, the three patients demonstrated an improvement in the three tests, reaching the MCID in the ARAT and the CAHAI. Patients P02 and P03 did not reach the MCID in the FMA-UE due to a ceiling effect: the initial high score did not allow for a 5.2-point difference from the maximum high score. Patient P05 showed greater improvements in the three tests and reached the MCID in the FMA-UE. In the BBT and NHPT none of the patients reached the MDC and only patient P02 showed an improvement post-intervention. Patient P05 did not complete the NHPT due to motor impairment.

Table 3.4. Clinical evaluation data.
This table provides the scores in all clinical motor tests of patients P02, P03 and P05. There is no maximum value in NHPT and BBT tests. The improvement in the NHPT is negative due to the fact that conducting the task in less time means a better performance. (ARAT: Action Research Arm Test; FMA-UE: Fugl-Meyer Assessment for Upper Extremity; BBT: Box and Block Test; NHPT: Nine Hole Pegboard Test; CAHAI: Chedoke Arm and Hand Activity Inventory; AE: Affected Extremity; NAE: Non-affected extremity).

Clinical test		ARAT	FMA-UE	BBT - AE	BBT - NAE	NHPT - AE	NHPT - NAE	CAHAI
Maximum value		57	66	Normative data	Normative data	Normative data	Normative data	91
MCD/MCID		5.7	5.2	5.5	5.5	-32.8’	-32.8’	6.3
P02	PRE	46	61	39	66	64’	17’	68
	POST	55	66	43	63	36’	19’	86
	Improvement	9	5	4	-3	-28’	2’	18
P03	PRE	51	59	40	58	41’	19’	74
	POST	57	61	42	58	39’	20’	85
	Improvement	6	2	2	0	-2’	1’	11
P05	PRE	36	41	27	53	-	20’	37
	POST	46	51	27	56	-	22’	45
	Improvement	10	10	0	3	-	2’	8

3.3.4 Piano performance

Three variables were chosen to analyze the evaluation exercises of patients’ piano performance: 1) execution time in milliseconds, 2) inter-note time in milliseconds, and 3) key-pressure from 0 to 100. Patient P01 did not complete the whole intervention and their values performance reached session 25. All the controls’ piano performance obtained a CV < 40% (see Table 3.5), considering this sample sufficiently homogeneous to be used as the baseline of people without motor impairments.

Table 3.5. Control participants' coefficient of variation.
This table provides the Coefficient of Variation (CV) in percentage of the total duration, inter-note time and key pressure scores obtained by controls' participants in the two piano evaluation exercises.

Evaluation exercise	Coefficient of Variation		
	Total duration	Inter-note time	Key pressure
1	23.7%	21.81%	9.48%
2	23.7%	23.85%	10.35%

3.3.4.1 Execution time

The execution time represents the tapping speed with which each piano exercise is played. The less time required by the patients to play the exercises, the quicker they are able to move their fingers, which means an improvement in fine mobility. Patients P02 and P05 required more time than other participants to complete the exercises and demonstrated a progressive improvement in Exercise 1 (see Figure 3.2). In Exercise 2, patient P02 demonstrated a higher performance improvement from session 4 and patient P05 remained consistent over baseline values with variability between sessions (see Figure 3.2). Patients P01, P03 and P04 remained constant and close to baseline values over the intervention, particularly patients P01 and P04 in Exercise 1, and patients P03 and P04 in Exercise 2. Patients' average execution time values demonstrated a tendency to reach controls' performance, particularly in Exercise 2.

3.3.4.2 Inter-note time

The inter-note time represents the tapping speed with which each note is played in a specific exercise. The lower the time patients require to press each key, the faster they are playing the piano, signifying an improvement in fine mobility. In Exercise 1, patients P02 and P05 performed slower than the other participants and demonstrated a progressive improvement with a slight tendency to reach controls' performance over the intervention (see **Figure 3.2**). Patients P01 and P04 played faster from the beginning and reached controls' performance at sessions 23 and 18, respectively. Patient P03 appeared to remain constant throughout the intervention with higher values than baseline and with variability between sessions. In Exercise 2, patients P01, P03, and P04 remained close to controls' performance over the intervention with a tendency to reach them, patient P04 being the only one who reached them in session 17 (see **Figure 3.2**). Patient P02 started with the slowest performance and demonstrated the highest improvement over the first four sessions, followed by a progressive tendency to reach controls' performance. Patient P05 showed a consistent performance with variability between sessions not reaching baseline values throughout the whole intervention. Patients' average inter-note time values showed the same pattern as in execution time: they demonstrated a tendency to reach controls' performance in both exercises, particularly in Exercise 2.

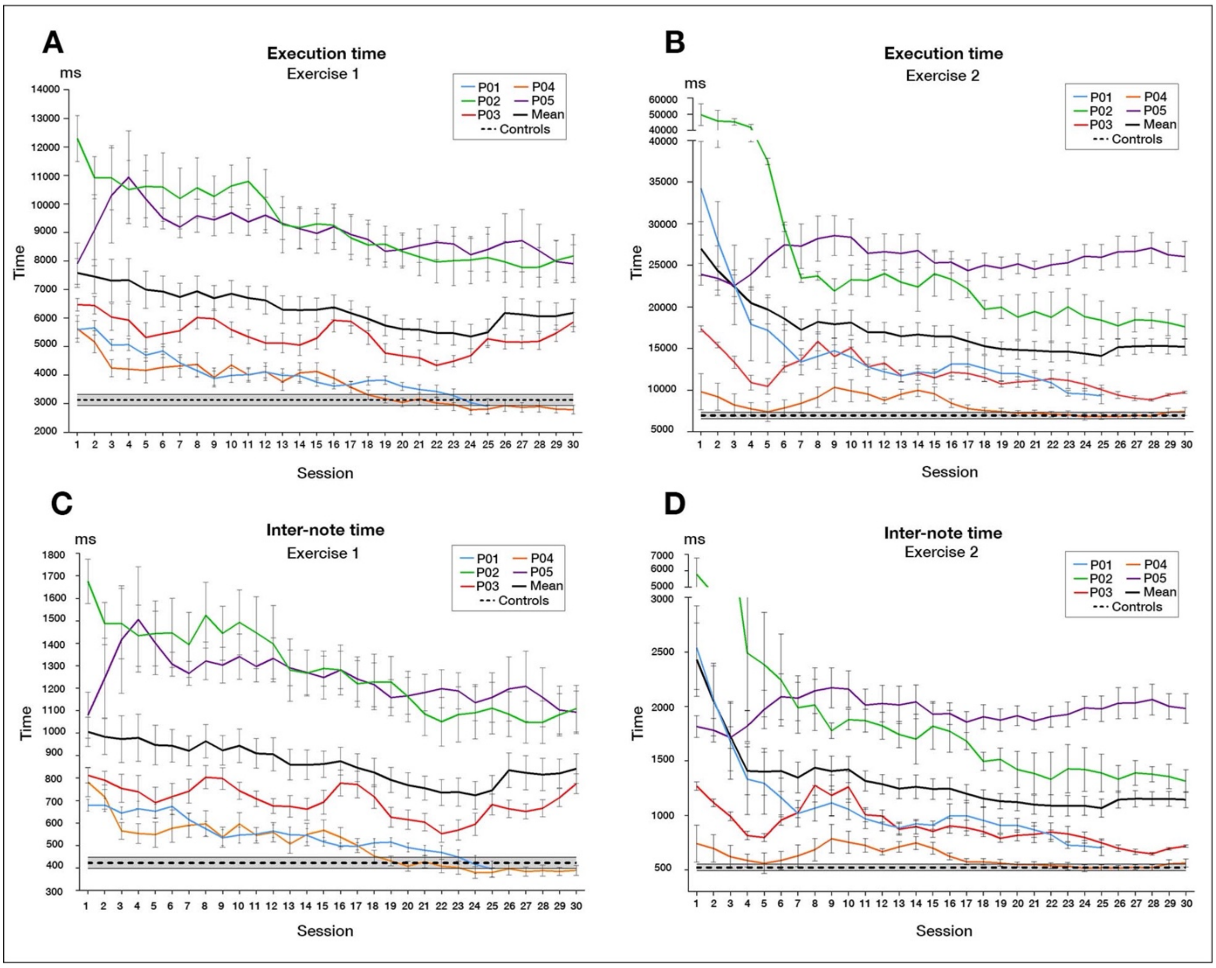


Figure 3.2. Patients' speed tapping.
This table is a graphical representation of patients P01, P02, P03, P04 and P05's performance while playing the piano evaluation Exercise 1 (A and C) and Exercise 2 (B and D) over 30 sessions (25 in the case of P01) regarding the two variables related to speed tapping: execution time (A and B) and inter-note time (C and D). The black line represents the patients' average performance. The dotted line represents the mean of controls' execution time values, and the grey bar represents the SEM of controls' execution time values.

3.3.4.3 Pressure

The pressure applied to the keys of the MIDI-piano represents the tapping force with which the notes are played. The more pressure patients apply on the keys, the stronger their fingers are, which in turn means an improvement in fine motor functions. In both exercises, patient P01 showed an increase in force tapping in the first three sessions reaching controls' performance (see Figure 3.3). Patient P04 demonstrated high pressure values similar to controls' performance throughout the intervention. Patients P02, P03, and P05 were not close to reaching controls' performance over the intervention in both exercises. Patients P02 and P03 showed high variability between sessions and patient P05's force tapping slightly decreased throughout the intervention. Patients' average pressure values did not reach controls' performance, showing a slight decrease in force tapping over the last five sessions.

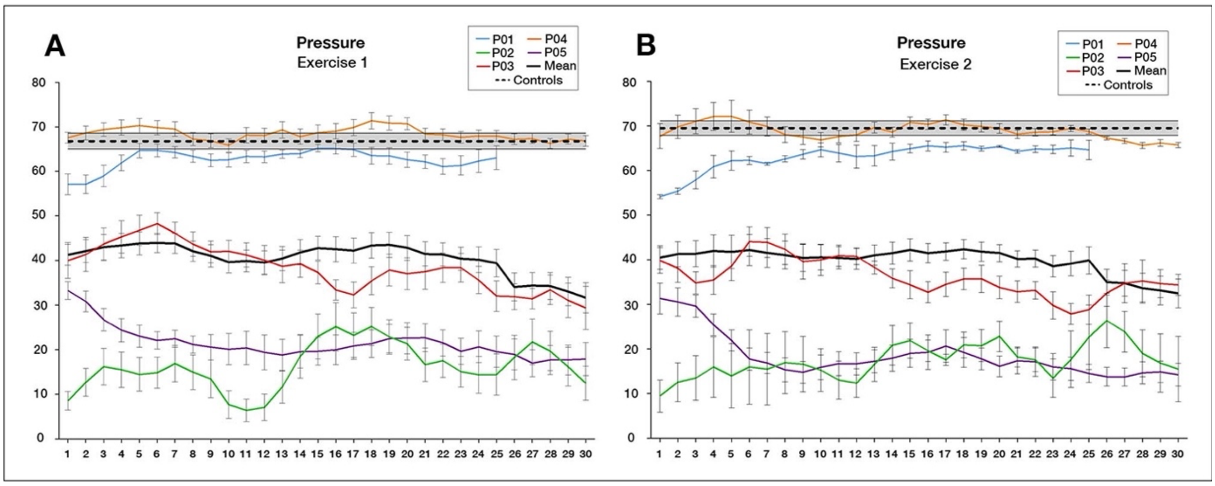


Figure 3.3. Patients' force tapping.
This table is a graphical representation of patients P01, P02, P03, P04 and P05's performance while playing the piano evaluation Exercises 1 (A) and Exercise 2 (B) over 30 sessions (25 in the case of P01) regarding the variable related to force tapping: pressure. The black line represents the patients' average performance. The dotted line represents the mean of controls' execution time values, and the grey bar represents the SEM of controls' execution time values.

3.3.5 Intervention adherence and safety

The intervention adherence of each patient during the study is presented in Table 3.6. The eMST rehabilitation program was designed to be completed in 10 weeks, doing three self-training sessions per week. With the exception of participant P01, who did not complete the whole intervention due to personal constraints, the rest of participants completed the 30 sessions. Only patient P05 did it in 10 weeks, while the rest of participants needed one or two weeks more, doing one or two sessions over a fortnight due to Summer Holidays, Eastern Holidays, or personal constraints. Regarding the time per session, the first three participants took less than one hour on average to complete each session (between 33 and 44 minutes). For this reason, we extended the time per percussion exercise. This modification was made before patients P04 and P05 started the intervention. They needed less than one hour and around one hour on average, respectively, to complete each session.

Table 3.6. Participants' intervention adherence.
This table provides the total number of sessions completed by each participant, the weeks they needed to complete the whole intervention, as well as the average of sessions per week and the mean and SD of the time needed to complete the sessions.

Patient	Sessions completed	Intervention duration (weeks)	Mean of sessions per week	Average session time (minutes)
P01	25	12	2.08	33 ± 8
P02	30	11	2.73	40 ± 7
P03	30	11	2.73	44 ± 8
P04	30	12	2.5	37 ± 9
P05	30	10	3	74 ± 10

We did not observe, and the participants did not report any serious or adverse safety concerns arising from completing the home-based eMST intervention at home. During the self-training sessions, in which the participants touched an electronic tablet and manipulated little percussion instruments, most of time sitting in a chair, no pain or uncomfortableness were notified.

3.4 Discussion

The present pilot study examined the feasibility of a novel eMST intervention designed to improve upper-limb motor function in patients with chronic stroke. This study allowed to evaluate and improve the feasibility of the eMST program by modifying some aspects of the intervention and technical features of the MST app according to patients' feedback. The importance of conducting pilot studies testing the feasibility and usability of novel interventions and devices should be underlined. This kind of study provides the opportunity to check if the implementation of a novel intervention could be effective before conducting a clinical trial (Craig et al., 2008). Importantly, this study demonstrated the feasibility of the eMST program by evaluating the usability of the eMST app, the motor function gains in the affected upper limb, the intervention adherence, and the safety of conducting this home-based intervention.

From the feasibility feedback regarding the eMST program and the usability questions about the eMST app, some aspects were modified. These changes increased the feasibility of the intervention and the usability of the home-based device. The app obtained usability ratings higher than 3 (and lower than 3 in the negative statements) at the end of the intervention, fulfilling the feasibility success criteria regarding the usability of the app. All patients reported the app as easy to use at home by themselves and they would recommend it and use it again. This conforms with previous research on TR programs which reported high usability and satisfaction ratings regardless of the type of therapy (Knepley et al., 2021). Previous studies have also highlighted several advantages such as easier accessibility and the opportunity to conduct sessions in patients' home, which has been linked to better recovery (Rawstorn et al., 2016). Patients overall were fully engaged in the home-based sessions. This suggests high levels of motivation possibly due to the perception of learning a new, enjoyable, and socially valued leisure activity (Villeneuve & Lamontagne, 2013).

Regarding the clinical assessment, patients demonstrated a decrease in upper-limb motor deficits after completing the eMST intervention. In line with previous studies, they showed clinically relevant improvements in functional movements such as grasping and pinching, which was reflected in a better performance in daily living activities (Altenmüller et al., 2009; Grau-Sánchez et al., 2017; Ripollés et al., 2016). However, hand and finger dexterity improvements were not observed. Previous research in patients with chronic stroke has not found relevant clinical improvements in finger dexterity using the NHPT after completing MST programs and has been argued that motor gains cannot be observed using this test (Amengual et al., 2013; Grau-Sánchez et al., 2017; Ripollés et al., 2016). The motor improvements were greater in patients P02 and P05, possibly due to the fact that had more severe hemiparesis and therefore a higher prospect for motor function recovery. These results indicate that the adaptation of the eMST program for home use promote the same motor improvements as the original MST program completed in the hospital (Grau-Sánchez et al., 2013; Knepley et al., 2020; Schneider et al., 2007; Tong et al., 2015; Villeneuve et al., 2014). This suggest that MST interventions can improve motor function after stroke regardless of completing a home-based or a hospital-based intervention.

Regarding piano performance, patients overall demonstrated the ability to play faster throughout the intervention with a tendency to reach healthy controls' performance. This is in consonance with previous research applying MST for subacute and chronic stroke where patients improved in finger tapping tasks, functional movements and daily activity performance (Grau-Sánchez et al., 2013, 2017; Ripollés et al., 2016; Schneider et al., 2007). In Exercise 2, the speed tapping improvement was greater during the first training sessions, similar to previous MST studies (Grau-Sánchez et al., 2017; Villeneuve & Lamontagne, 2013). This is in line with motor learning theories suggesting that a new motor skill develops more quickly at the beginning of training as the practice of a new motor task leads to initial memory acquisition and is consolidated at the end of training (Censor et al., 2012). In contrast, in Exercise 1 time performance values tended to decrease in a progressive way, possibly because this evaluation exercise was simpler and easier to memorize from the first session. Moreover, Exercise 2 appeared to be more sensitive to evaluate motor learning in speed tapping as patients' average values showed a higher tendency to reach controls' values than in Exercise 1. This may be due to the fact that patients applied more effort and concentration in Exercise 2. Regarding force tapping, patients overall maintained it constant and lower than controls throughout the intervention showing a slight decrease in the last week. Only one patient improved in force tapping following the typical trajectory of motor learning observed in previous studies (Grau-Sánchez et al., 2017; Villeneuve & Lamontagne, 2013). These results could be due to different factors: patients felt tired at the end of the intervention; patients realized that they could do the exercises faster if they applied less force onto the keys; or patients who completed the first half of the intervention at the hospital became distracted at home over the second half of the intervention. The only patient that demonstrated force and speed tapping similar to controls over the whole intervention was possibly because of having previous piano training. Although patients applied less force to play the piano evaluation exercises, they required less time to complete them throughout the intervention. This demonstrates that eMST involves task-specific training aimed to elicit similar processes that occur in motor skill learning (Willingham, 1998). These results can be reflected in the relevant clinical improvements observed in the functional hand movements assessed in the ARAT (grasping, gripping, and pinching), which could have been promoted by the speed tapping improvement observed in the piano performance.

Regarding the intervention adherence, only one participant completed the total 30 sessions in 10 weeks, bringing to light the potential difficulties we may have in recruiting patients in a 10-week period that may overlap the Summer and Easter Holidays. Thus, we will consider organizing the recruitment timing to avoid a decrease in the adherence rate. Regarding the time needed per session, the first three participants took less than one hour on average to complete each session. After extending the percussion exercises time, patient P05 needed around one hour to complete each session, but participant P04 took half an hour possibly due to the fact they had the lowest level of hemiparesis.

The motor improvements were observed in patients with different motor deficit levels, type of stroke, affected hemisphere, and time since stroke. This is one of the strengths of the current study as it provides the chance to examine the general effect of the eMST program on the chronic stroke population. The study also showed some limitations: the assessment was not blind, which might have biased motor outcomes; the intervention delivery form was heterogeneous between participants as not all of them completed the full eMST program at home, which might have biased expected results in a novel home-based rehabilitation program; the MIDI-piano keys' sensitivity was not increased until the third session completed by the first two participants, which could bias the piano performance results obtained from their first two sessions.

In conclusion, this pilot study demonstrates the feasibility of the eMST program for patients with chronic stroke. We tested the usability of the eMST app, the safety and adherence to the intervention, as well as examining the potential upper-limb motor function improvements in patients with different type of stroke, time since stroke, age and level of hemiparesis. In addition, we had the opportunity to examine the usefulness of the piano evaluation exercises. These findings give an insight into how to manage experimental resources as well as to analyze the results in future studies using the eMST program as a telerehabilitation tool.

Study 2

This study corresponds to:

Grau-Sánchez, J., Segura, E., Sánchez-Pinsach, D., Raghavan, P., Münte, T. M., Palumbo, A. M., Turry, A., Duarte, E., Särkämö, T., Arcos, J. L., & Rodríguez-Fornells, A. (2021). Enriched Music-Supported Therapy for Chronic Stroke Patients: a Study Protocol of a Randomised Controlled Trial. *BMC Neurology*, *21*(1), 1-16.

4. Study 2

Enriched Music-supported Therapy for chronic stroke: a study protocol of a randomized controlled trial

4.1 Introduction

Stroke is one of the leading causes of long-term disability worldwide (GBD 2016 DALYs and HALE Collaborators, 2017). The reduction of mortality rates, especially in developed countries, has resulted in more survivors living with disability and needing rehabilitation and long-term care and support (GBD 2013 Stroke Collaborators, 2015; Lackland et al., 2014). Many stroke patients experience unilateral paresis of the upper extremity, which affects the individual's autonomy in basic and instrumental activities of daily living, having a significant impact on participation and quality of life (QoL) (Chen & Winstein, 2009; Mayo et al., 2002; Wade, 2012).

Rehabilitation programs for stroke patients are usually delivered immediately following the stroke, when the potential for recovery is thought to be the greatest (Kitago & Krakauer, 2013; Verheyden et al., 2008). Rehabilitation aims to enable the individual to achieve the highest possible level of functioning in order to reintegrate the patient into community life (Albert & Kesselring, 2012). However, once acute rehabilitation ends, the individual affected by stroke faces multiple challenges during the chronic stage. More than one third of individuals live with some residual functional limitations in basic activities, 50% of chronic stroke patients need support with instrumental activities of daily living and 65% suffer restrictions in their reintegration into community life (Hankey et al., 2002; Mayo et al., 2002). These residual functional limitations correlate negatively with emotional well-being and life satisfaction, in particular with regard to vocational and leisure activities (Hartman-Maeir et al., 2007; Hildebrand et al., 2012; White et al., 2007). Despite the recommendations for maintaining an active lifestyle, stroke survivors show low levels of activity and they may even experience functional deterioration during the chronic phase (Ashe et al., 2009; Billinger et al., 2014; Gebruers et al., 2010; Meyer et al., 2015; Winstein et al., 2016). However, recovery has been shown to continue well into the chronic stage and depends on dose and intensity of the interventions provided (Daly et al., 2019). Several studies have demonstrated that home- and community-based interventions can increase functional independence, participation, and emotional well-being in chronic stroke patients (Bunketorp-Käll et al., 2017; García-Rudolph et al., 2019; Graven et al., 2011; Schönberger et al., 2010). In this vein, there is increasing interest in developing and validating interventions for chronic stroke patients aimed at enhancing physical and psychological well-being (Billinger et al., 2014).

One class of music-based intervention for stroke motor rehabilitation involve playing musical instruments with the affected upper extremity following the principles of motor learning and multimodal stimulation (Grau-Sánchez et al., 2020). These interventions are feasible to apply in the chronic phase (Aluru et al., 2014; Street et al., 2015). Among them, Music-Supported Therapy (MST) aims to enhance the motor function of the paretic upper limb by following a standardized program of keyboard and drum exercises (Schneider et al., 2007). MST includes necessary components for promoting motor learning such as mass repetition of movements, shaping, tailoring, task variability, instructional language and guidance by the therapist, modelling, and feedback (Grau-Sánchez et al., 2020). Of particular relevance in MST is audio-motor coupling since individuals receive auditory feedback from the musical instrument that may help detect errors and adjust future movements (Rodriguez-Fornells et al., 2012). Moreover, playing musical instruments is an activity that involves emotional and motivational aspects, which can boost motor learning and enhance emotional well-being (Raghavan et al., 2016; Salimpoor et al., 2013; Vuilleumier & Trost, 2015).

Two recent randomized controlled trials (RCT's) have shown that MST can lead to similar motor improvements as with standard rehabilitation (Fujioka et al., 2018; Grau-Sánchez et al., 2018). A previous study with 20 chronic stroke patients also found that brain plastic changes can occur after MST in the form of cortical motor map reorganization and enhanced functional coupling between motor and auditory regions (Ripollés et al., 2016). Furthermore, Grau-Sánchez et al. (2018) showed that subacute patients with higher sensitivity to music reward were the ones that showed greater motor improvements after MST, a finding that highlights the role of reward and motivation on learning during rehabilitation (Abe et al., 2011; Grau-Sánchez et al., 2018; O'Doherty, 2004).

Despite these promising findings, the training protocol of MST has some limitations that have precluded widespread application in the chronic stage. First, MST is often delivered in the hospital or in rehabilitation centers; however, this form of delivery may not be the most suitable option for chronic patients. One of the aims of rehabilitation in the chronic phase is reintegration into community life and transitioning to home- and community-based programs can assist with such reintegration (Park & Lee, 2016). Second, studies investigating MST usually provide between 15 and 20 sessions of 30 minutes during over three or four weeks. This training intensity is not sufficient in the chronic phase, as training protocols need to be of higher intensity and longer duration to effectively promote recovery (Daly et al., 2019; Kitago & Krakauer, 2013; Krakauer, 2006). Third, only two musical instruments have been used: a keyboard and an electronic drum set, which allows training fine finger movements and gross arm movements. The use of other instruments might improve MST by providing a wider range of movements. Fourth, sessions are provided individually, which does not promote social interaction with other patients and lack a key component of musical activity: social bonding (Clift et al., 2010; Freeman, 2000; Mithen et al., 2006). Especially in the chronic stage, patients with stroke often feel lonely and deprived of opportunities to engage in meaningful social activities (Hartman-Maeir et al., 2007; McKevitt et al., 2011). Peer support is particularly relevant in rehabilitation since it can increase patients' QoL (Levy et al., 2019). Finally, sessions are therapist-led, which in the chronic stage can diminish the patients' opportunities to engage in more self-regulated behaviours during their learning process (Chan et al., 2009). According to recent theories of motor learning (Wulf & Lewthwaite, 2016), optimization of learning is closely associated with social and intrinsic motivational factors. Therefore, interventions focused on strengthening motivational and self-control aspects could lead to greater recovery (Deci & Ryan, 2000; Deterding et al., 2011; Malone, 1981).

Considering the above constraints and taking into account previous experiences in adapting music interventions for home use (Friedman et al., 2011; Villeneuve & Lamontagne, 2013), we have designed a 10-week enriched MST (eMST) training program combining individual self-training sessions at home with online peer-group sessions. Compared to the standard MST program, eMST features i) increased training intensity and range of movements trained; ii) inclusion of peer-group sessions; iii) optimisation of learning through enhanced intrinsic motivational factors to promote more autonomy; and iv) adaptation of the program for home use.

The program comprises 40 one-hour sessions (40 hours in total) distributed evenly over 10 weeks (four sessions/week). We have also included additional percussion instruments to increase the range of movements that patients can train (Raghavan et al., 2016). Considering that participation in social music activities is one of the most important sources of reward derived from music (Mas-Herrero et al., 2014), we have included group sessions once a week to promote social interaction and group bonding (Mithen et al., 2006; Tarr et al., 2014). The self-training sessions are delivered at home using an electronic tablet, a keyboard, and a set of percussion instruments. We have designed an artificial intelligence (AI) platform taking into account recent theories of motor learning to optimize the learning process by boosting intrinsic motivational factors. In the sessions at home, patients are given opportunities to have more control of their behaviors during the training, which can have a significant impact on feelings of self-competence and autonomy. Moreover, the AI platform uses elements of gamification and continuously monitors the patient's performance and supports therapists in the design and personalization of training sessions by using prediction and prescription components (Sanchez-Pinsach et al., 2019). The adaptation of the program for home use may serve to increase motivation and reward derived from music, facilitate learning through self-controlled training and feedback, and enhance mood and QoL by improving self-esteem, competence, and autonomy.

This trial will test the effectiveness of eMST in improving upper-extremity motor function in chronic stroke patients. Secondary objectives include testing the effectiveness of this intervention in enhancing cognitive outcomes, emotional well-being, QoL, and self-regulation and efficacy, and compare the effects of this intervention to a conventional home-based program of upper-extremity exercises. We hypothesize that eMST will lead to larger motor and cognitive improvements, and enhanced emotional well-being and QoL compared with home-based physical exercises alone.

4.2 Methods

4.2.1 Study design

A parallel-group randomised controlled trial (RCT) will be conducted with participants being randomised to either eMST (eMST-group) or to a control treatment (CT-group), the latter receiving the Graded Repetitive Arm Supplementary Program (GRASP, Harris et al., 2009). The control treatment has already been validated and proven to be effective in enhancing the motor function of the upper extremity in chronic stroke patients (Connell et al., 2014; Fujioka et al., 2018; Harris et al., 2009).

Both interventions will comprise 40 one-hour sessions distributed over 10 weeks (four sessions per week, 40 hours in total). Before and after the treatment, both groups will undergo an evaluation of their motor and cognitive function, emotional well-being, and QoL. A follow-up assessment will be conducted at 3 months (see Figure 4.1).

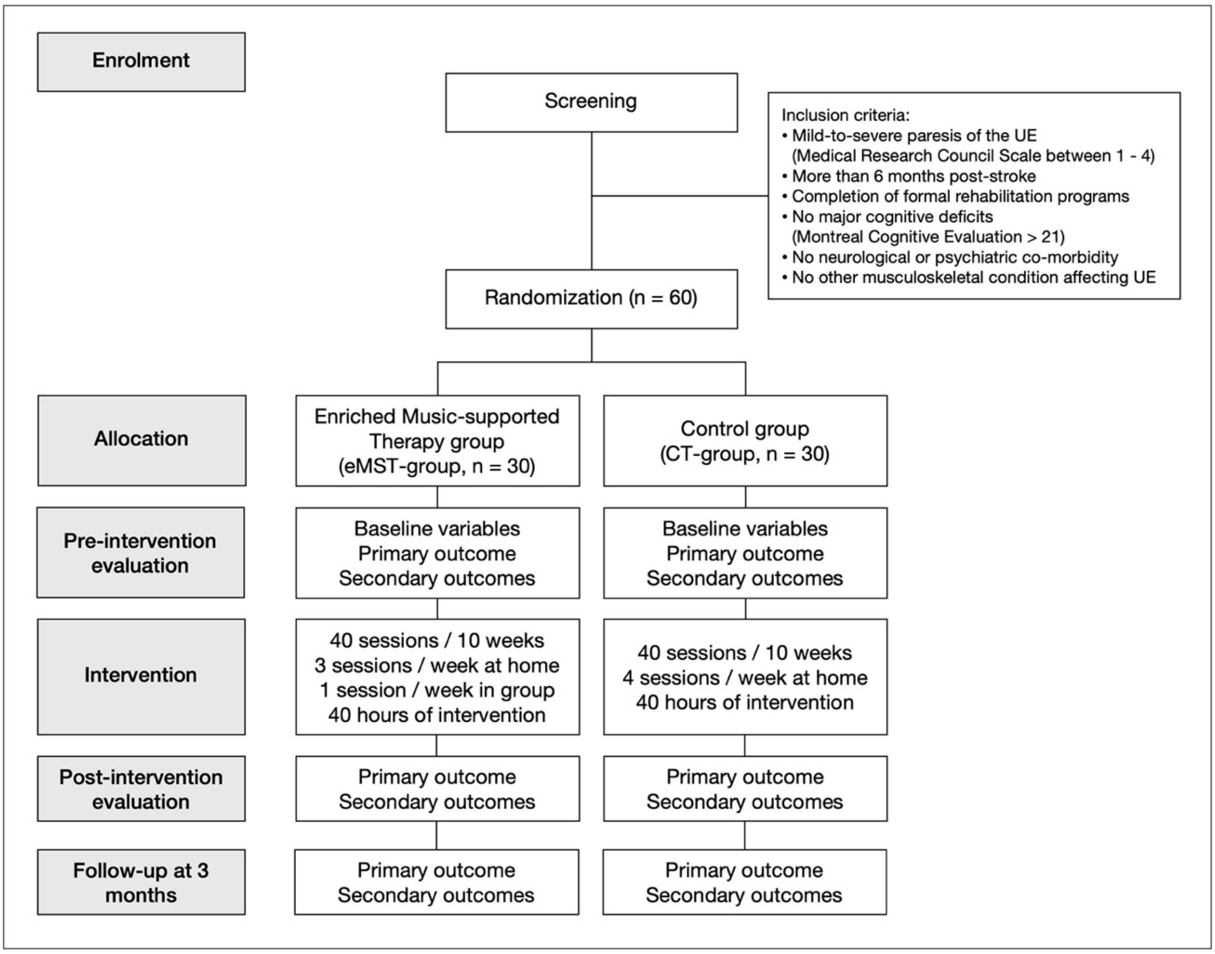


Figure 4.1. Study design.
This study is a parallel-randomized controlled trial with two treatment groups (enriched Music-supported Therapy group [eMST-group, n=30] and Control group [CT-group, n=30]). Participants will be evaluated before and after the intervention as well as in a 3-month follow-up.

4.2.2 Participants

Chronic stroke patients will be recruited from two tertiary hospitals of the Barcelona metropolitan area (Hospitals del Mar i l'Esperança and Bellvitge University Hospital). These hospitals have stroke units and specialized inpatient and outpatient neurological rehabilitation departments.

Patients diagnosed with ischemic or hemorrhagic stroke will be eligible as participants if they fulfil the following criteria: presence of mild-to-severe paresis of the upper extremity after a stroke defined as having a score between 1 and 4 in the Medical Research Council Scale for Muscle Strength at the distal upper-limb muscles; more than 6 months after stroke; completion of formal rehabilitation programs; no major language or cognitive deficits affecting comprehension (Montreal Cognitive Evaluation, MoCA > 21); no neurological or psychiatric co-morbidity; and no other musculoskeletal condition affecting upper-extremity motor function (e.g. fracture or arthritis).

Two clinical researchers will review medical records of stroke patients who had been treated in the rehabilitation departments of the recruiting hospitals. Phone contacts will be made to screen for potential participants followed by an appointment to evaluate if the patient fulfils the inclusion criteria. Patients will receive a detailed explanation of the procedures of the study and will provide written informed consent prior to participation.

4.2.3 Experimental treatment: Enriched Music-supported Therapy program

Participants in the eMST-group will follow a 10-week intervention that will consist of four weekly one-hour sessions (total program duration: 40 hours). The training program comprises three individual home-based self-training sessions and one group session per week.

4.2.3.1 Individual home-based self-training sessions

The individual sessions at home are delivered using an app on electronic tablets, which provides instructions and cues for patients, records the patient's performance, and gathers data about exercises and compliance. At the beginning of the intervention program, a therapist visits the patient's home to provide the materials for treatment and instructions on the app for home use. The participant is provided with percussion musical instruments (see Table 4.1), an electronic keyboard, and an electronic tablet. In each session, the participant is asked to play four percussion instruments and the electronic keyboard to train gross and fine mobility, respectively. Table 4.1 describes the different movements that can be trained with each instrument. Each individual session has the same fixed structure (described in

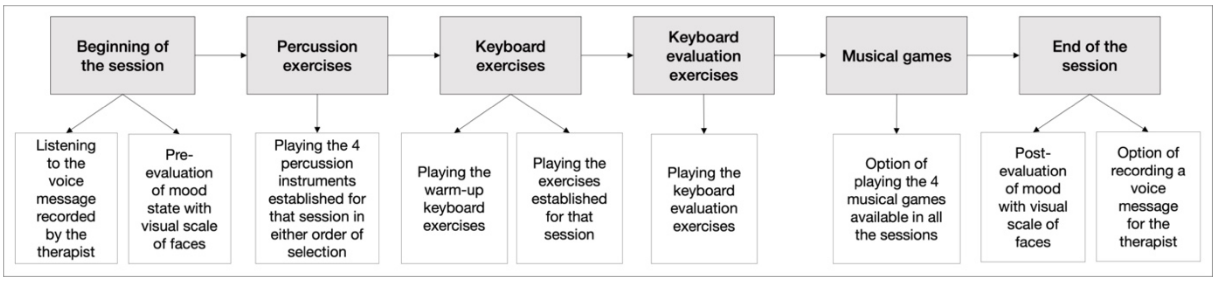


Figure 4.2), starting with percussion exercises as a warm-up and as a form of gross mobility training (20 min), followed by keyboard exercises to train fine movements (20 min), and finally, play musical games (15 min). Motor performance and mood are evaluated at the end of each session (5 min).

Table 4.1. Manual for therapists enriched Music-Supported Therapy: Instruments and movements.
This table provides information about the different movements that can be trained with each instrument. For sitting exercises, the patient must be seated in a chair without armrests in a comfortable position with both knees and hip at 90°. For standing exercises, the patient must be standing up having the chair at their back and with feet slightly separated.

Instrument	Type of movement	Body position	Movement description
Tambourine with beater	Shoulder flexion/extension (shoulder at 90° and elbow at 0°)	Sitting/ Standing	**Position**: Hold the tambourine with the unaffected extremity and the beater with the affected extremity. Both shoulders should be at 90° with the elbows at 0°. **Movement**: Hit the tambourine with the beater trying to keep the elbow at 0° to produce movements of shoulder flexion and extension.
	Shoulder internal/external rotation and elbow flexion/extension (elbow at 90°)	Sitting/ Standing	**Position**: Hold the tambourine with the unaffected extremity and the beater with the affected extremity. **Movement**: Hit the tambourine with the beater to produce movements of elbow flexion and extension.
	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	Sitting/ Standing	**Position**: Hold the tambourine with the unaffected extremity and the beater with the affected extremity. **Movement**: Hit the tambourine with the beater trying to keep the elbow at 90° to produce movements of wrist flexion and extension.
Tambourine	Shoulder abduction/adduction (elbow at 0°)	Standing	**Position**: Hold the tambourine with the affected extremity. Standing up, extremities should drop on either side of the body. **Movement**: Hit the tambourine in the side of your leg trying to keep the elbow at 0° to produce movements of shoulder abduction/adduction.
	Shoulder abduction/adduction (elbow at 0°)	Standing	**Position**: Hold the tambourine with the affected extremity. Standing up, extremities should drop on either side of the boy. **Movement**: Hit the tambourine in the front of your leg trying to keep the elbow at 0° to produce movements of shoulder abduction/adduction.
	Wrist flexion/extension (shoulder at 0° and elbow at 0°)	Standing	**Position**: Hold the tambourine with the affected extremity. Standing up, extremities should drop on either side of the body. **Movement**: Hit the tambourine in the side of your leg trying to keep the elbow at 0° to produce movements of wrist flexion/extension.
	Forearm supination/pronation (shoulder at 0° and elbow at 90°)	Sitting/ Standing	**Position**: Hold the tambourine with the affected extremity. The shoulder should be at 0° and elbow at 90°. **Movement**: Turn your forearm up and down trying to keep the elbow at 90°.
	Forearm supination/pronation (shoulder at 90° and elbow at 0°)	Sitting/ Standing	**Position**: Hold the tambourine with the affected extremity. The shoulder should be at 90° and elbow at 0°. **Movement**: Turn your forearm up and down trying to keep the elbow at 0°.
Maracas	Elbow flexion/extension (shoulder at 0°)	Sitting/ Standing	**Position**: Hold a maraca with the affected extremity. **Movement**: Starting with the elbow at 90°, shake the maraca to produce movements of elbow flexion and extension.
	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	Sitting/ Standing	**Position**: Hold a maraca with the affected extremity. **Movement**: Shake the maraca to produce movements of wrist flexion and extension trying to keep the elbow at 90°.

Instrument	Type of movement	Body position	Movement description
Guiro	Elbow flexion/extension (no gravity)	Sitting	**Position**: Hold the guiro with the unaffected extremity and the stick with the affected extremity. The guiro can rest over the knees and both elbows should be at 0° of flexion. **Movement**: Rub the sick along the notches of the guiro.
Rain stick	Forearm supination/pronation (shoulder at 90° and elbow at 0°)	Sitting/ Standing	**Position**: Hold the rain stick with the affected extremity. The shoulder should be at 90° with the elbow at 0°. **Movement**: Turn your forearm up and down.
Egg Shaker	Elbow flexion/extension (shoulder at 0°)	Sitting/ Standing	**Position**: Hold the egg shaker with the affected extremity. The shoulder should be at 0° and the elbow at 90°. **Movement**: Starting with the elbow at 90°, shake the egg to produce movements of elbow flexion and extension.
	Elbow flexion/extension (no gravity)	Sitting/ Standing	**Position**: Hold the egg shaker with the affected extremity. **Movement**: Shake the egg side to side.
	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	Sitting/ Standing	**Position**: Hold the egg shaker with the affected extremity. The shoulder should be at 0° and the elbow at 90°. **Movement**: Shake the egg up and down trying to keep the elbow at 90° to produce movements of wrist flexion and extension.
Castanets	Fingers mass flexion/extension (shoulder at 0° and elbow at 90°)	Sitting	**Position**: Hold a castanet with the affected extremity, leaving the castanet resting on the palm. The elbow should be at 90° of flexion and shoulder at 0° of flexion. **Movement**: Press the castanet with the fingers to produce movements of finger mass flexion and extension.
Djembe	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	Sitting	**Position**: Hold the djembe with the nonaffected extremity and lean it between your knees. The shoulder should be at 0° and the elbow at 90°. **Movement**: Hit the djembe with the affected hand trying to keep the elbow at 90° to produce movements of wrist flexion and extension.
	Elbow flexion/extension (shoulder at 0° and elbow at 90°)	Sitting	**Position**: Hold the djembe with the nonaffected extremity and lean it between your knees. The shoulder should be at 0° and the elbow at 90°. **Movement**: Hit the djembe with the affected hand trying to shoulder at 0° to produce movements of elbow flexion and extension.

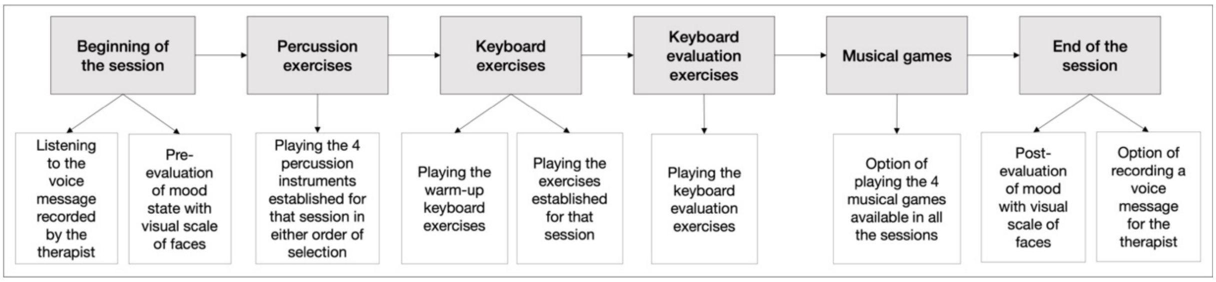
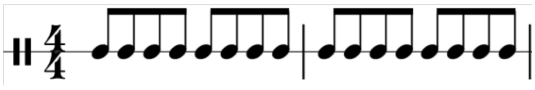
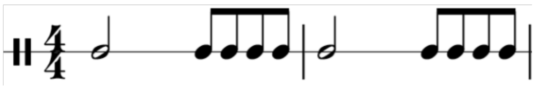
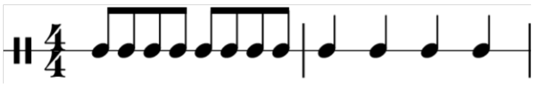


Figure 4.2. Structure of individual sessions.
The individual sessions comprise both percussion and keyboard exercises and include a mood assessment at the beginning and a keyboard assessment at the end of each session.

Percussion exercises. In each session, the participant is presented with an image of four different percussion instruments and has to select the order in which she / he would like to play them. For each exercise, the app first displays a short video demonstrating how to play the particular instrument and provides instructions to avoid compensatory movements (see Figure 4.3). Then, the participant is instructed to play the instrument in a rhythmic pattern as shown on the tablet. The patient is asked to listen to the rhythmic pattern for later imitation. A visual cue provides a countdown to ensure the readiness of the patient. Then, the patient is asked to reproduce the pattern following auditory and visual cues. Table 4.2 describes the rhythmic patterns of the percussion exercises, which are graded by difficulty.

Table 4.2. Rhythmic patterns.
This table provides the different rhythmic patterns that are asked to play in the home-based eMST sessions with different percussion instruments*. They are divided by level of difficulty, which was checked with the pilot participants. It should be noted that not all the rhythmic patterns are played with all the percussion instruments since some rhythmic patterns are unworkable to play with instruments that require some specific movements. Moreover, the tempo with which the rhythmic pattern is presented and asked to play is also adapted to each instrument** and movement, which was checked with the pilot participants. The tempos can be 30, 40, 50, 60, and 70bpm (beats per minute). However, they can be adapted during the intervention according to the participants' difficulties.
* It is not used any rhythmic pattern with the rain stick.
**It is not used any tempo with the rain stick.

Rhythmic patterns	
Level 1	
Level 2	
Level 3	

Level 4	
Level 5	
Level 6	
Level 7	
Level 8	

Keyboard exercises. For the exercises with the keyboard, participants are asked to play simple sequences that gradually increase in difficulty (see Figure 4.3). The app provides visual instructions as well as cues to prompt finger movements and records the performance of the patient with the keyboard. Exercises with the keyboard increase in difficulty depending on the patient’s progress. During each exercise, different types of feedback encourage the participant to play as well as they can. A vertical score bar on the right side of the screen with a star on the top fills up as the participants play the notes correctly. At the end of the session, participants receive a number of stars, up to a maximum of four if they achieve an 80% success rate, and a chart with the proportion of correct and incorrect notes played. In addition, playing an incorrect note causes the keys to turn red so that the participants can realize their mistake and play the correct note. Furthermore, a message to encourage participants is presented at the end of each keyboard exercise, along with a curiosity or inspirational quote at the beginning of each session.

Games. Participants have the possibility to play musical games, an optional part of the treatment they can skip if they are tired or not in the mood to play. They can choose between four different games: 1) Simon says, comprising the participant is asked to repeat a sequence that is presented, which becomes progressively longer and more complex as she/he succeeds; 2) Piano Hero, notes scroll on-screen to the different keys and participants have to play in time to score points; 3) Combo, the participants plays along songs that are rehearsed during the group sessions by accompanying the melody with the keyboard and/or using the percussion instruments; and 4) Impro, the participant improvises freely on the keyboard.

Monitoring. The keyboard is connected to the electronic tablet as a MIDI-device, which allows recording the played notes, any errors made, key-pressure, and the execution time for each exercise. The AI platform is based on three main components (visualization, prediction, and prescription). All the information is processed to visually summarize the performance of the patient. To tailor the intervention to the individual needs of the patient, the therapist can virtually prescribe exercises and instruments to be used for each session. The prediction component computes an initial performance estimation based on baseline assessments. The prescription component recommends appropriate exercises to the therapist by taking into account the performance of the patient and adjusting them for difficulty. Since the percussion instruments have no sensors, the AI platform only gathers data related to the interaction with the app (watching the video, listening to the rhythm, and starting the exercise).

Daily evaluation. At the end of the home-based sessions the motor performance and the mood of the participants are evaluated. Five keyboard exercises of 3-5 minutes duration are applied ranging in difficulty from playing simple sequences with one finger to playing complex sequences with five fingers. Moreover, participants are asked to rate their mood on a visual scale of emotional faces (from 1 = I am feeling very bad to 5 = I am feeling very good). Participants can also record a voice message for the therapist. The therapist's response is shown at the beginning of the following session.

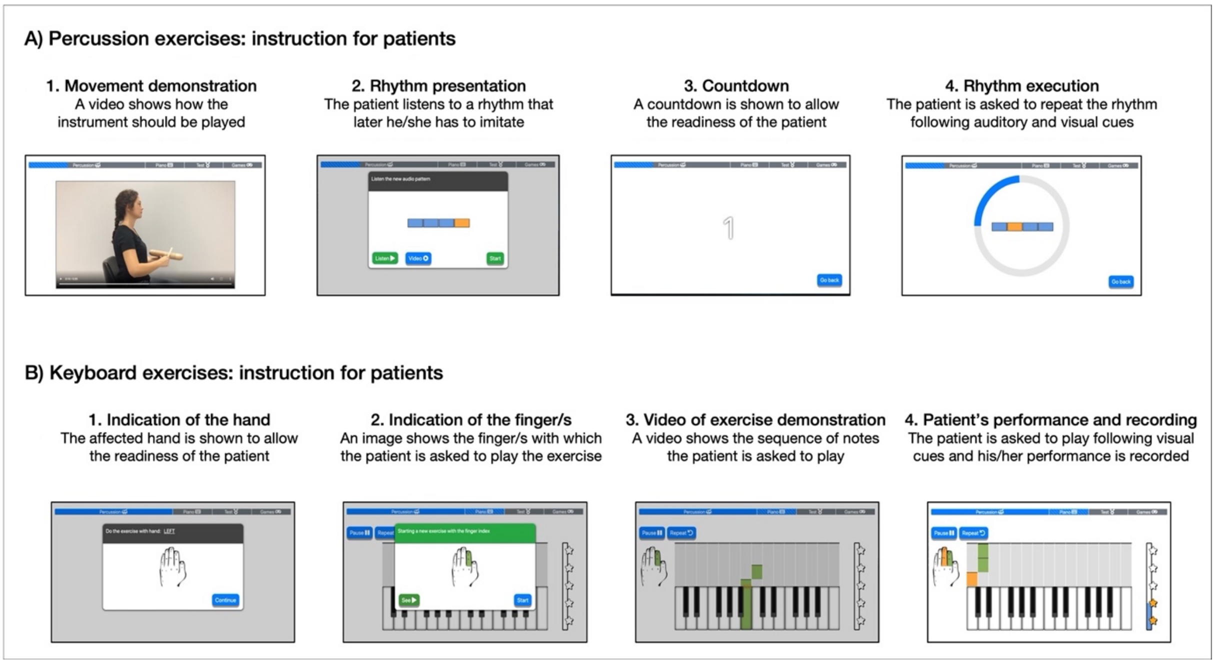


Figure 4.3. Percussion and keyboard exercises: instructions for patients.
A) Percussion exercises: instructions for patients. First, there is a video to instruct how the instrument should be played (1) followed by the presentation of the rhythmic pattern (2). After a visual countdown (3), the patient has to reproduce the rhythm with the instrument (4). B) Piano exercises: instructions for patients. A drawing of the affected hand is shown (1) followed by a cue that indicates the finger/s that should be used in the exercise (2). After a short clip showing the sequence of notes to be played (3) the patient has to play the keyboard following visual cues (4).

4.2.3.2 Group sessions

Once per week a one-hour virtual group session of music therapy will be conducted using a video communication platform that is installed in the electronic tablet provided to participants. Participants will be split into groups of three to four people for the group sessions. A music therapist and an occupational therapist will conduct the group sessions, providing instructions for the music therapy exercises. The sessions involve active and passive music therapy exercises structured into three parts: 1) Beginning, featuring warming-up exercises; 2) Core, comprising musical improvisation and playing of favorite songs; and 3) Ending, featuring relaxation exercises. All the exercises will be accompanied by live music with the music therapist playing along on the piano or guitar. Participants will be asked to play musical instruments during the sessions to train gross and fine motor skills, but they can select the musical instruments they wish to play from many different percussion instruments. Table 4.3 describes the instruments used in the group sessions. Participants will be encouraged to play with the affected extremity to showcase what they have learned during their individual sessions. At the beginning and the end of the session, therapists will facilitate a discussion where patients can share their progress, difficulties, and worries. The selection of songs for the group sessions is done with the participants, taking into account their musical preferences. For this reason, a semi-structured interview will be conducted at the beginning of the intervention to understand cultural preferences, professional and leisure activities, musical knowledge, and previous musical experience and preferences.

Table 4.3. Percussion exercises.
This table provides the musical information about the percussion exercises conducted in the home-based eMST sessions. On one hand, it shows the rhythmic patterns that are played with each instrument and movement since some specific rhythmic patterns are unworkable to play with some instruments and movements. On the other hand, it shows at what tempo in bpm (beats per minute) the rhythmic pattern is asked to be played according to the movement and instrument, which was checked with the pilot participants. The boxes with 2 tempos are referred to those rhythmic patterns that are played with both tempos: the first one in the early part of the intervention, and the second one in the final part of the intervention. Moreover, the tempo can be adapted during the intervention according to the participants' difficulties.
*It is not used any rhythmic pattern with the rain stick.

Instrument	Movement	Rhythmic patterns	Tempo
Tambourine with beater	Shoulder flexion/extension (shoulder at 90° and elbow at 0°)	1, 2, 3	30
	Shoulder internal/external rotation and elbow flexion/extension (elbow at 90°)	1, 2, 3, 4, 7, 8	40
	Wrist flexion/extension (shoulder at 0° and elbow at 0°)	1, 2, 3, 4, 5, 6, 7, 8	60
Tambourine	Shoulder abduction/adduction (elbow at 0°)	1, 2, 3	30
	Shoulder abduction/adduction (elbow at 0°)	1, 2, 3	30
	Wrist flexion/extension (shoulder at 0° and elbow at 0°)	1, 2, 3, 4, 5, 6, 7, 8	60
	Forearm supination/pronation (shoulder at 0° and elbow at 90°)	1, 2, 3, 4, 5, 6, 7, 8	60
	Forearm supination/pronation (shoulder at 90° and elbow at 0°)	1, 2, 3, 4, 5, 6, 7, 8	60
Maracas	Elbow flexion/extension (shoulder at 0°)	1, 2, 3, 4, 6, 8	50

Instrument	Movement	Rhythmic patterns	Tempo
	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	1, 2, 3, 4, 5, 6, 7, 8	60
Guiro	Elbow flexion/extension (no gravity)	1, 2, 3, 4, 5, 6, 7, 8	60
Rain stick*	Forearm supination/pronation (shoulder at 90° and elbow at 0°)	-	-
Egg Shaker	Elbow flexion/extension (shoulder at 0°)	1, 2, 3, 4, 6, 8	50
	Elbow flexion/extension (no gravity)	1, 2, 3, 4, 5, 6, 7, 8	60
	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	1, 2, 3, 4, 5, 6, 7, 8	60
Castanets	Fingers mass flexion/extension (shoulder at 0° and elbow at 90°)	1, 2, 3, 4, 5, 7, 8	60, 70
Djembe	Wrist flexion/extension (shoulder at 0° and elbow at 90°)	1, 2, 3, 4, 5, 6, 7, 8	60, 70
	Elbow flexion/extension (shoulder at 0° and elbow at 90°)	1, 2, 3, 4, 5, 6, 7, 8	50

Daily evaluation. At the end of the group session, each participant will be asked to answer the Participant Post-Session Questionnaire, consisting of four short questions about the feelings of connection to music and the people in the group on a 4-point Likert scale. Moreover, the therapists will evaluate the overall performance of each patient as well as their engagement in music making using the 9-point Music Engagement Scale adapted from the Music Therapy Communication and Social Interaction scale (MTCSI; Bell et al., 2014). Each participant is also asked to rate the social connectedness with others following the Inclusion of Other in the Self Scale (Aron et al., 1992), and participants have to rate their mood using a visual scale of emotional faces (from 1 = I am feeling very bad to 5 = I am feeling very good).

4.2.4 Control treatment: GRASP

Participants in the control intervention group will follow the Graded Repetitive Arm Supplementary Program (GRASP, Harris et al., 2009). This program consists of self-directed arm and hand exercises for stroke patients and it is validated to be performed by patients on their own at home. GRASP seeks to promote hand and arm motor function recovery through mass repetition of movements and task-specific exercises, encouraging the use of the affected extremity in everyday activities. Participants will be asked to complete four weekly one-hour sessions for 10 weeks (total program duration: 40 hours).

A booklet describing the exercises and the equipment needed will be provided to participants. Exercises involve arm and hand strengthening, coordination, and manual skills using everyday objects (e.g., toothpicks, Lego bricks, clothespins, or paper clips). The participant will be asked to perform the exercises sitting in a chair or next to a table in sets of 5 or 10 repetitions. The number of sets and the exercises prescription will be adjusted to the patient's needs and endurance.

At the beginning of the intervention, the therapist will visit the participant's home to provide instructions and equipment to follow the program. Patients will be asked to register the type and number of exercises for each session on a record sheet. Moreover, after each session, participants will be asked to rate their mood using a visual scale of emotional faces (from 1 = I am feeling very bad to 5 = I am feeling very good). The therapist will contact the participant by phone once a week to monitor her/his progress and difficulties.

4.2.5 Treatment compliance and withdrawal

Completion of protocol would require the patient to perform ≥ 80% of the sessions.

4.2.6 Evaluation

An initial baseline evaluation will include the collection of demographical and clinical variables. In addition, primary and secondary motor, cognitive and emotional well-being and QoL outcomes will be evaluated before and after the intervention as well as at 3-month follow-up. Table 4.4 summarizes the instruments used in the study. Considering the current health crisis due to the COVID-19 pandemic, the evaluation will be carried out at the participant's home in order to avoid unnecessary visits to the hospital.

Table 4.4. Variables and outcomes of the study.
This table summarizes the evaluation instruments used in each evaluation point.

Instrument	Reference	Baseline	Post-intervention	Follow-up
Demographic and clinical variables				
Montreal Cognitive Assessment	Nasreddine et al., 2005	•		
Digit span subtest	Wechsler, 2008	•		
Boston Naming Test, short form	Mack et al., 1992	•		
Vocabulary subtest	Wechsler, 2008	•		
Scale and rhythm subtests Montreal Battery of Evaluation of Amusia	Peretz et al., 2003	•		
Barcelona Music Reward Questionnaire	Mas-Herrero et al., 2013	•		
Grit scale	Duckworth et al., 2007	•		
Multidimensional Scale of Perceived Social Support	Zimet et al., 1988	•		
Primary outcome				
Action Research Arm Test	Lyle, 1981	•	•	•
Secondary motor outcomes				
Fugl-Meyer Assessment of Motor Recovery after Stroke	Fugl-Meyer et al., 1975	•	•	•
Grip strength	Mathiowetz et al., 1984	•	•	•
Box and Block Test	Mathiowetz et al., 1985	•	•	•
Nine Hole Pegboard Test	Parker et al., 1986	•	•	•

Instrument	Reference	Baseline	Post-intervention	Follow-up
Chedoke Arm and Hand Activity Inventory	Barreca et al., 2004	•	•	•
Secondary cognitive outcomes				
Behaviour Rating Inventory of Executive Function	Roth et al., 2005	•	•	•
Sustained Attention to Response Task	Robertson et al., 1997	•	•	•
Figural memory subtest	Wechsler, 2013	•	•	•
Rey Auditory Verbal Learning Test	Rey, 1964	•	•	•
Fluency test	Thurstone, 1938	•	•	•
Secondary emotional well-being and quality of life outcomes				
Beck Depression Inventory-II	Beck et al., 1996	•	•	•
Apathy Evaluation Scale	Marin et al., 1991	•	•	•
Profile of Mood States	McNair et al., 1971	•	•	•
Stroke Impact Scale	Mulder & Mijland, 2016	•	•	•
Self-regulation and self-efficacy outcomes during intervention				
Treatment Self-regulation questionnaire	Richard & Connell, 1989	•		
Treatment Questionnaire Concerning Continued Program	Richard & Connell, 1989	•		
Intrinsic Motivation Inventory	Ryan, 1982		•	
Strategies Used to Promote Health Questionnaire	Lev & Owen, 1996	•	•	•

4.2.6.1 Baseline demographic and clinical variables

Demographic and clinical variables such as age, gender, level of education, living situation, previous musical training, stroke etiology and location, and lesion laterality will be collected from medical records as well as during a first interview with the participant.

In order to characterize individual differences that can have a mediating effect on treatment success, we will evaluate cognitive functions, differences in the processing and integration of music, music reward, perseverance and social support at the beginning of the intervention. Therefore, the baseline evaluation will include the Montreal Cognitive Assessment (Nasreddine et al., 2005) to assess global cognitive function, the digit span (included in the Wechsler Adult Intelligence Scale, WAIS-IV, (Wechsler, 2013) to assess working memory, a short version of the Boston Naming Test (Mack et al., 1992) to assess language production, and the vocabulary subtest of the WAIS-IV. In addition, the scale and rhythm subtests from the shortened version of the Montreal Battery of Evaluation of Amusia (Peretz et al., 2003) will be used to screen for amusia at baseline. Participants will complete the Barcelona Music Reward Questionnaire (Mas-Herrero et al., 2013) on the first evaluation to assess individual differences in pleasure derived from musical experiences. Finally, individual differences in perseverance and passion for long-term goals will be assessed with the Grit Scale (Duckworth & Quinn, 2009), and social support will be assessed using the Multidimensional Scale of Perceived Social Support (Zimet et al., 1990).

4.2.6.2 Primary outcome

The primary outcome will be upper-extremity function measured with the Action Research Arm Test (ARAT, Lyle, 1981). The ARAT is recommended for use in chronic stroke and outpatient rehabilitation by the StrokeEDGE Task Force Group (Sullivan et al., 2013) and has excellent test-retest and inter/intra-rater reliability (Van Der Lee et al., 2001; Platz et al., 2005). The measure is a 19-item test divided into four subtests (grasp, grip, pinch, and gross movement). For each item, the patient is asked to perform a simple task that involves a functional movement of the affected upper limb. Each task is rated using a 4-point ordinal scale. The maximum possible score is 57 and the minimally clinically important difference (MCID) is 5.7 points (Van Der Lee et al., 2001).

4.2.6.3 Secondary outcomes

Motor outcomes

The upper-extremity subtest of the Fugl-Meyer Assessment of Motor Recovery after Stroke (FMA-UE; Fugl-Meyer et al., 1975) will be used to evaluate motor impairment; grip strength will be assessed with a dynamometer, and functional movements and dexterity will be assessed with the Box and Block Test (BBT; Mathiowetz et al., 1985) and the Nine Hole Pegboard Test (NHPT; Parker et al., 1986). The Chedoke Arm and Hand Activity Inventory will be used to evaluate the patients' motor performance in everyday tasks (CAHAI; Barreca et al., 2004).

The FMA-UE comprises 33 items that evaluate motor impairment in the affected upper limb. The test is divided into four sections (shoulder, forearm and elbow, wrist, hand, and coordination) assessing reflexes, flexor and extensor synergies, range of motion, and overall coordination and speed of the upper extremity. Each item is graded using an ordinal scale from 0 to 2. The maximum possible score is 66 and the MCID for chronic stroke patients is 5.2 points (Page et al., 2012).

The grip strength will be measured for both hands as the mean of three consecutive trials (Mathiowetz et al., 1984).

The Box and Block Test assesses gross manual dexterity by using a setup consisting of a box with two compartments and wood cubes. The participant is asked to grasp cubes and transport them from one compartment to the other. The number of cubes successfully transported within one minute is scored for the affected and the unaffected extremity. The minimal detectable change (MDC) for the Box and Block Test is 5.5 cubes (Chen & Winstein, 2009).

The Nine Hole Pegboard Test evaluates fine dexterity by asking the patient to pick up nine pegs and place them into holes on a board and then remove them. The patient is asked to complete this task as fast as possible, and the time needed is scored for the affected and the unaffected hand. The MCD for this test is 32.8 seconds (Chen & Winstein, 2009).

The Chedoke Arm and Hand Activity Inventory is a performance test that measures the patient's ability to perform everyday tasks with both extremities. The test is composed of 13 different tasks (e.g., open a jar of coffee, make a phone call, clean a pair of eyeglasses) and each task is graded using an ordinal scale from 1 to 7. The scores are given based on the involvement of the affected extremity in the task, ranging from less than 25% of involvement in the task needing total assistance to complete independence in the task (adequate time and safety). The MCID is 6.3 points (Barreca et al., 2004).

Cognitive outcomes

The neuropsychological evaluation will focus on assessing executive function, attention, visuospatial memory, and verbal learning and fluency. Executive function will be evaluated using the Behaviour Rating Inventory of Executive Function (BRIEF; Roth et al., 2005). The Sustained Attention to Response Task (Robertson et al., 1997) will be used to assess sustained attention whereas the Figural Memory subtest from the Wechsler Memory Scale-Revised (Wechsler, 2013; adapted to Spanish by Pearson Clinical & Talent Assessment) will evaluate visuospatial memory. Verbal learning will be evaluated using the Rey Auditory Verbal Learning Test (Marqués et al., 2013), and a fluency test (Peña-Casanova et al., 2009) will be used to examine verbal fluency.

The adult version of the BRIEF is a self-report questionnaire that evaluates executive functioning in everyday life situations. The questionnaire includes a self and informant reports. Both versions comprise 75 items describing various behaviors, and the participant is asked to report if the behavior is never a problem, sometimes a problem, or often a problem. The BRIEF provides two broad indexes (behavioral regulation and metacognition) as well as an overall score. It includes nine scales which assess the ability to inhibit, self-monitor, plan/organize, shift, initiate, task monitor, emotional control, working memory, and organization of materials.

The Sustained Attention to Response Task is a computerized test that evaluates sustained attention by presenting the participant with one number at a time and asking him or her to respond as fast as possible when a target number appears. This test provides measures of reaction times and changes on this variable over the task, as well as inhibition errors.

The Figural Memory subtest from the Wechsler Memory Scale-Revised (Wechsler, 2013) measures visuospatial recall and recognition memory. The participant is presented with abstracts designs that later he or she has to identify from an array.

The Rey Auditory Verbal Learning Test evaluates verbal learning by asking the patient to recall a list of 15 words. The list is presented 5 times and after each trial, the patient is asked to repeat as many words as he/she recalls. Then, a second list of words is presented as interference. The number of words recalled from the original list after the interference and after a break of 20 minutes is determined. A recognition test with distractors is also performed at the end of the test.

The verbal fluency test comprises two tasks: category and letter fluency. The participant is asked to produce as many words as possible for a minute of the same semantic category (i.e. animals) or words that start with the same letter (i.e. words starting with 'p'). The number of unique words produced is counted as the score for each task.

Emotional well-being and Quality of life outcomes

The emotional well-being evaluation will assess depression with the Beck Depression Inventory-II (Beck et al., 1996), apathy with the Apathy Evaluation Scale (Marin, 1991) and mood with the Profile of Mood States (McNair et al., 1971). Health-related QoL will be measured with the Stroke Impact Scale (Mulder & Nijland, 2016).

The Beck Depression Inventory-II is a self-report measure that comprises 21 multiple-choice questions that are scored on a scale from 0 to 3. The participant is asked about feelings, thoughts and behaviors of the past week. Higher scores indicate depression severity and the maximum possible score of the measure is 63.

The Apathy Evaluation Scale evaluates behavioral, cognitive, and emotional indicators of apathy. The scale comprises a self and informant reports both consisting of 18 items that are scored on a 4-point Likert scale, where higher scores indicate more apathy.

The Profile of Mood States evaluates different dimensions of mood by asking the participant to rate feelings or emotion felt during the past week. The measure includes 65 items that are scored on a 5-point Likert scale (ranging from 0: not at all, to 4: extremely).

The Stroke Impact Scale is a 59-item self-report questionnaire that assesses muscle strength, hand function, basic and instrumental activities of daily living, global mobility, communication, emotion, memory and thinking, and participation.

Self-regulation and self-efficacy outcomes

Domain-specific individual differences in motivation and self-regulation for joining, participating in and engagement during the rehabilitation program will be assessed with the Treatment Self-Regulation Questionnaire (adapted from: Ryan & Connell, 1989), the Treatment Questionnaire Concerning

Continued Program Participation (adapted from: Ryan & Connell, 1989), and the Intrinsic Motivation Inventory (Ryan, 1982), respectively. Self-efficacy will be measured with the Strategies Used by People to Promote Health questionnaire (Lev & Owen, 1996).

The Treatment Self-Regulation Questionnaire is an adaptation of the standard version called Academic Self-Regulation Questionnaire (SRQ-A) (Ryan & Connell, 1989) created for the study. It evaluates the type of self-regulation (external, interjected, identified, or intrinsic) or motivation (external or intrinsic) of the participants to engage with the rehabilitation program. It is a 15-item self-report questionnaire scored on a 7-point scale (1: not all true; 4: somewhat true; 7: very true). The items are questions about the reasons why the participants enrolled in the current study. Thus, the participants will be asked to answer it only at the beginning of the intervention.

The Treatment Questionnaire Concerning Continued Program Participation is a version of the TSRQ to evaluate the type of self-regulation or motivation of the participants for continuing to participate in the rehabilitation program to which they have been assigned. It is a 15-item self-report questionnaire scored on a 7-point scale (1: not all true; 4: somewhat true; 7: very true). The items are questions about why the participants continue to engage with the rehabilitation program. Hence, the participants will be asked to complete it only in the middle of the intervention (the 5th week).

The Intrinsic Motivation Inventory is a multidimensional measure which assesses the content and level of motivation during an intervention. Therefore, participants will be asked to answer it only on completion of the rehabilitation program. The measure was adapted for the current study and consists of 24 self-report questions divided into six different psychological constructs reflecting positive or negative predictors of intrinsic motivation: 1) interest/enjoyment; 2) perceived competence; 3) effort/importance; 4) pressure/tension; 5) perceived choice; and 6) value/usefulness. It is scored on a 7-point scale (1: not all true; 4: somewhat true; 7: very true). The MST-group will complete 4 additional items on the psychological construct of relatedness in order to evaluate the effect of the group sessions on motivation levels.

The Strategies Used by People to Promote Health is a 29-item self-report questionnaire that evaluates the degree of self-care and self-efficacy through four factors consistent with the underlying self-efficacy theory upon which the scale is based: 1) coping, 2) stress reduction, 3) making decisions, and 4) enjoying life. It is scored on a 5-point scale (from 1: very little confidence to 5: quite a lot of confidence) and the participants will be asked to answer it in both pre- and post-intervention evaluations.

4.2.7 Blinding

A clinical researcher with expertise in stroke rehabilitation will perform the evaluations and will be blinded to participants' group allocation.

4.2.8 Randomization

Participants will be randomized to one of the groups following a block randomization procedure. As the eMST program requires three participants for the group sessions, randomization will consider clusters of three participants. The randomization sequence will be computer-generated and only accessible to a research assistant who will not be involved in the recruitment, treatment, or evaluation of participants.

4.2.9 Ethical considerations and data management

The protocol of this study has been approved by the ethics committee of the Hospitals del Mar i l'Esperança (Barcelona, Spain) and follows the Declaration of Helsinki to experiment with human beings. As mentioned previously, participants will be informed about study procedures and will sign an informed consent form prior to participation. Each participant will be identified with a code when collecting demographic and clinical variables and outcomes. All the information will be stored on an internal secure server from the Artificial Intelligence Research Centre, which is maintained by the IT team following institutional security standards. Additionally, patients are de-identified using the generated code. Connections between the tablet and server use a secure credential in an API Rest through a HTTPS protocol.

4.2.10 Sample size

The sample size calculation is based on a clinically relevant difference between treatment groups with 80% power and a 5% significance level. Considering that the MCID of the ARAT (primary outcome) is 5.7 points and that an acceptable difference between groups of 15% is defined to be clinically meaningful (Schönberger et al., 2010; Street et al., 2018), a sample size of 26 participants will be required in each group. From experience gathered in previous studies (Grau-Sánchez et al., 2018; Schneider et al., 2007), the dropout rate in this type of interventions is relatively low (15%). Taking this rate into consideration, a final estimation of 60 participants is needed in the study, 30 per group.

4.2.11 Data analysis

Statistical analysis will be performed using R (R Core Team, 2019) and the Statistical Package for the Social Sciences (SPSS version 21, SPSS inc., Chicago, Illinois, USA). For descriptive analyses, quantitative data will be analyzed using mean and standard deviation if the data is normally distributed and median and interquartile range will be used for variables that are not normally distributed. Qualitative variables will be presented using frequency distributions and percentages.

An intention-to-treat analysis will be performed for all outcome variables including all patients that were assigned to a group and for whom the primary outcome was collected at baseline. In the case of participants that withdraw from the study, the score at baseline will be assigned for all the evaluation points and reasons for withdrawal will be reported.

The effect of the intervention on the primary outcome, the ARAT, will be assessed using the chi-square test. Taking into account the MCID of this test (5.7 points), data will be dichotomized into two categories: clinically improved or unchanged / deteriorated. An analysis of covariance (ANCOVA) will be carried out for all secondary outcomes to determine differences between groups across time using demographical and clinical baseline variables as covariates. The level of significance will be set at $p < 0.05$ for all statistical tests and corrected for multiple comparisons when necessary.

4.2.12 Trial registration

The trial has been registered at ClinicalTrials.gov and identified as NCT04507542.

4.3 Discussion

Chronic stroke patients with residual motor deficits experience limitations in activities of daily living and restrictions in participation in community life (Hankey et al., 2002). The impact of these residual motor deficits on function coupled with low levels of physical activity can lead to poor emotional well-being, life satisfaction, and QoL (Billinger et al., 2014; Hildebrand et al., 2012). There is increasing interest in developing home- and community-based interventions for chronic stroke patients to address their needs and improve their autonomy, participation and overall well-being (Bunketorp-Käll et al., 2017; Graven et al., 2011).

MST aims at improving motor and cognitive functions, emotional well-being and quality of life in stroke patients and could be a feasible intervention to apply in the chronic phase (Grau-Sánchez et al., 2018; Ripollés et al., 2016; Street et al., 2018). We have adapted the original MST program for home use, and we have increased training intensity and variability, incorporated group sessions, and modified the protocol to boost learning by enhancing motivation and promoting autonomy. The incorporation of these changes and the adaptation of the program take into account the Medical Research Council Framework for Developing and Evaluating Complex Interventions. In order to further develop MST we identified relevant evidence in the literature and developed a theoretical understanding of the processes of change (Grau-Sánchez et al., 2020). Moreover, we have modelled the intervention process and outcomes and assessed feasibility with a pilot study.

The study has been designed following the CONSORT guidelines for conducting clinical trials. The evaluation protocol includes baseline variables such as social support, perseverance or musical reward to take into account individual differences that may modulate the treatment effect. The outcomes of the study address various dimensions of functioning, with instruments that evaluate body functions, activity, and participation. In addition, we have included measures of self-regulation and self-efficacy. Considering that the intervention is home- and community-based, these factors may have a crucial role in treatment adherence and success.

We expect that patients treated with eMST will show larger functional improvements than patients treated with the control therapy regimen. On the basis that MST improves several dimensions of functionality beyond the motor function, we expect that patients will improve their mood and emotional well-being after MST.

Study 3

This study corresponds to:

Segura, E., Grau-Sánchez, J., Cerda-Company, X., Porto, M.F., De la Cruz-Puebla, M., Sanchez-Pinsach, D., Cerquides, J., Duarte, E., Palumbo, A., Turry, A., Raghavan, P., Särkämö, T., Münte, T.F., Lluis Arcos, J., Rodríguez-Fornells, A. (2024). Enriched Music-supported Therapy for Individuals with Chronic Stroke: A Randomized Controlled Trial. *Journal of Neurology*, *271*, 6606-6617.

5. Study 3

Enriched Music-supported Therapy for individuals with chronic stroke: a randomized controlled trial

5.1 Introduction

Stroke is a leading cause of long-term adult disability worldwide (GBD 2016 Stroke Collaborators, 2019; Katan & Luft, 2018). Motor impairment ranks among the most common neurological deficit, with approximately 50% of survivors experiencing impaired upper-limb movements six months after stroke (Ingram et al., 2021; Lee et al., 2015). Access to chronic-phase rehabilitation services is limited (Cieza et al., 2020), and the absence of a post-rehabilitation training routine can even worsen motor functions (Ashe et al., 2009). Long-lasting physical deficits reduce autonomy in daily activities and hamper participation in family, work, and social contexts (Hartman-Maeir et al., 2007). These consequences have a negative impact on emotional well-being (Salter et al., 2008) and quality of life (QoL) (Northcott et al., 2016).

The rising stroke incidence and its substantial economic burden (GBD 2016 Stroke Collaborators, 2019) emphasize the urgency of developing new cost-effective community-based rehabilitation programs (Ding et al., 2022). Music-based interventions are increasingly used in neurorehabilitation to recover motor functions because they elicit motor actions in an enjoyable learning context (Jäncke, 2008). Additionally, music can promote individuals' engagement and motivation during rehabilitation sessions (Wininger & Pargman, 2003). Music-supported Therapy (MST) is a structured training program with keyboard and electronic drum exercises aimed to enhance upper-limb motor function after stroke (Schneider et al., 2007). This intervention has shown to improve upper-limb mobility, cognitive functions, QoL, and emotional well-being in subacute and chronic stroke participants (Altenmüller et al., 2009; Amengual et al., 2013; Fujioka et al., 2018; Grau-Sánchez et al., 2018; Ripollés et al., 2016; Rojo et al., 2011; Schneider et al., 2007; Van Vugt et al., 2016; Villeneuve et al., 2014). Studies evaluating MST-induced plasticity with neuroimaging and neurophysiological techniques reported an increase in the excitability and reorganization of the lesioned sensorimotor cortex in subacute and chronic stroke survivors (Amengual et al., 2013; Grau-Sánchez et al., 2013). Despite these positive results, two recent randomized controlled trials (RCTs) (Fujioka et al., 2018; Grau-Sánchez et al., 2018) showed no superiority of MST in motor recovery over a conventional motor exercise-based program. We therefore designed an enriched version of MST (eMST) by integrating socio-motivational and learning components aimed at boosting functional recovery. For this purpose, we applied the following modifications to the original MST program: 1) we adapted it for home-use by developing a tablet-based app (Sanchez-Pinsach et al., 2019) that provides exercise instructions with positive feedback and gamification strategies to enhance learning and autonomy (Deterding et al., 2011; Wulf & Lewthwaite, 2016), 2) we introduced guided music therapy group sessions to foster social interaction and community participation (Chang et al., 2020); 3) we increased training intensity and incorporated a wider range of percussion instruments to reinforce and diversify movement training and boost intrinsic motivation (Raghavan et al., 2016a); and 4) we added a temporal cue in the percussion exercises along with a series of rhythmic patterns with different difficulty levels to boost auditory-motor coupling and movement anticipation (Rodriguez-Fornells et al., 2012).

In this RCT, we aimed to test eMST's effectiveness in improving functional abilities and QoL in chronic stroke survivors compared to a conventional home-based motor program, the Graded Repetitive Arm Supplementary Program (GRASP; Harris et al., 2009). The GRASP has demonstrated to be effective in improving upper-limb function and QoL (Klempel et al., 2023), and it is strongly endorsed by the Canadian Stroke Best Practice Recommendations for the Upper Extremity (Hebert et al., 2016). The methodology of the study was pre-registered and published (Grau-Sánchez et al., 2021) after evaluating its feasibility using the MST app (Segura et al., 2021). We evaluated upper-limb motor function improvement, and secondary objectives included assessing changes in cognitive functions, emotional well-being, QoL, self-regulation, and self-efficacy. Grounded in prior MST trials, we expected eMST participants to exhibit superior motor and cognitive improvements, along with enhanced emotional well-being and QoL compared to GRASP participants. Based on the results of a previous trial (Grau-Sánchez et al., 2018), we predicted that eMST participants with higher levels of the sensorimotor component of musical hedonia, defined as the capacity to derive pleasure from music (Mas-Herrero et al., 2013), would show greater motor improvements.

5.2 Methods

5.2.1 Research design

We conducted a pragmatic two-arm parallel-group RCT comparing the effectiveness of eMST with GRASP (Harris et al., 2009). Enrollment began October 2020 and ended March 2023, with the last follow-up in June 2023. Data were analyzed from June to September 2023.

The study was approved by the Clinical Research Ethics Committee of the Bellvitge University Hospital (PR095/17; Barcelona) and the Hospital del Mar (Parc de Salut Mar, 2020/9523; Barcelona). Participants provided informed consent, and the study followed CONSORT reporting guidelines. The study protocol, including all details on the interventions, evaluation, outcomes, and sample size calculation, was published in January 2021 (Grau-Sánchez et al., 2021).

5.2.2 Setting and participants

The recruitment process entailed contacting stroke survivors previously treated at the Hospital del Marc, Centre l'Esperança (Barcelona), and advertising the non-profit stroke survivors' association Superar l'Ictus Barcelona (Barcelona). Inclusion criteria comprised individuals with ischemic and hemorrhagic stroke who: 1) had slight-to-severe upper-limb paresis (Medical Research Council Scale for Muscle Strength at the distal upper-extremity muscles: 1 - 4+); 2) were more than 6 months after stroke; 3) had previously completed a formal rehabilitation program; 4) exhibited no major language or cognitive deficits affecting comprehension (Montreal Cognitive Evaluation, MoCA > 21); 5) had no neurological or psychiatric co-morbidity, except for post-stroke depression; and 6) had no other musculoskeletal condition affecting upper-limb mobility (e.g., fracture or arthritis). Participants suffering from spasticity were injected with botulinum toxin prior to the intervention to enhance their upper-limb function and potential recovery (Hara et al., 2019).

5.2.3 Interventions

The eMST intervention involved a 10-week program of musical training doing three weekly individual self-training sessions using the MST app (Sanchez-Pinsach et al., 2019; Segura et al., 2021), and one weekly group music therapy session led by a music therapist on Zoom. Both self-training and group eMST sessions consisted of playing the keyboard and various percussion instruments while performing different upper-limb movements (Grau-Sánchez et al., 2021). The GRASP intervention involved a 10-week conventional motor program doing four individual self-training sessions per week. The GRASP sessions consisted of completing upper-limb motor exercises using everyday objects, and encouraging patients to use their upper limb during daily activities (Harris et al., 2009). Both interventions comprised a total of 40 hours of training and were completed at home. A therapist provided telemonitoring to both groups of participants by doing weekly phone calls, and participants were allowed to call the therapist any weekday they needed to address any questions or concerns.

After the baseline evaluation and the first session of the intervention, the therapist adjusted the training to each participant considering their motor limitations by applying the following changes: i) removing those exercises involving movements that the patient was unable to complete or that were leading to compensatory movements; ii) removing or adapting those objects that patients were unable to hold or with high difficulty (percussion instruments in eMST, and everyday objects in GRASP); iii) only in the eMST intervention, adjusting the tempo of the rhythmic exercises to the patients' motor abilities.

Throughout the weekly monitoring, the number of repetitions per exercise, the exercises' difficulty level, and the tempo of the eMST rhythmic exercises were also adjusted, if necessary, considering the time patients required to complete the sessions and their fatigue level at the end of the session.

To track compliance with the eMST intervention, we used the MST app website to monitor session timing and duration. For the GRASP intervention, participants were provided with a tracking sheet to record the times and duration of the sessions and discussed it with the therapist during the weekly monitoring phone calls.

5.2.4 Evaluation

Assessments were performed pre- and post-intervention, and at 3-month follow-up at the Hospital del Mar, Centre l'Esperança (Barcelona) by a neurologist and a neuropsychologist, both masked to group assignments in all evaluations.

5.2.5 Outcomes and other measures

Demographic, clinical, and personal traits variables including social support (Multidimensional Scale of Perceived Social Support, MSPSS), musical hedonia (Barcelona Music Reward Questionnaire - extended version, eBMRQ), musical melodic and rhythmic perception skills (Montreal Battery of Evaluation of Amusia, MBEA), and perseverance (Grit Scale) were collected at baseline from medical records and a structured interview.

The primary outcome was upper-limb motor function measured with the Action Research Arm Test (ARAT). Secondary outcomes included motor impairment (Fugl-Meyer Assessment for Upper Extremity, FMA-UE), daily life motor performance (Chedoke Arm and Hand Activity Inventory, CAHAI), hand dexterity (Box and Block Test and Nine Hole Pegboard Test), grip strength measured with a dynamometer, executive function (Behaviour Rating Inventory of Executive Function), sustained attention (Sustained Attention to Response Task), visuospatial memory (Figural Memory subtest from the Wechsler Memory Scale-Revised), verbal learning (Rey Auditory Verbal Learning Test), verbal fluency (fluency test in Spanish), depression (Beck Depression Inventory-II), apathy (self- and informant-version of Apathy Evaluation Scale, AES), mood (Profile of Mood States, POMS), stroke-related QoL (Stroke Impact Scale, SIS), motivation (Treatment Self-Regulation Questionnaire, TSRQ, administered pre-intervention and in the 5th week of intervention; and Intrinsic Motivation Inventory, IMI, administered post-intervention), and self-care strategies (Strategies Used by People to Promote Health). Throughout the weekly telemonitoring calls, a qualitative assessment of adverse effects was conducted by querying participants regarding potential harms (e.g., pain, fatigue, stress, frustration, overload, etc.).

5.2.6 Sample size calculation

In our study protocol, the sample size calculation estimated 60 participants (30 per group) (Grau-Sánchez et al., 2021) to find clinically relevant differences in the primary outcome with 80% power and a 5% significance level.

5.2.7 Randomization

Following a computer-generated sequence, participants were randomly assigned to one of the intervention groups in a 1:3 ratio, until each group reached the required sample size (n = 30). This allocation was established considering that the eMST intervention required three participants per group session. A research assistant informed the group allocation to the therapist after baseline evaluation.

5.2.8 Statistical analysis

Intention-to-treat (ITT) and per-protocol (PP) analyses (Armijo-Olivo et al., 2009) were performed to assess the effectiveness of eMST compared to GRASP. The ITT analysis set involved all randomized participants with available pre-evaluation data, including those who were not able to complete the entire intervention. The PP set included participants who completed > 95% of the sessions within 10 to 16 weeks and had both pre- and post-evaluation data. Descriptive information for all randomized participants in each group was calculated with means (SDs) or medians (IQRs) for parametric and nonparametric continuous variables, and absolute frequencies and percentages for categorical variables. Descriptive variables were compared between participants who completed the intervention and those who did not.

The intervention's effect on upper-limb motor function (primary outcome: ARAT) and motor impairment (secondary outcome: FMA-UE) was examined with both ITT and PP analysis sets. First, data was dichotomized into clinically improved or unchanged/deteriorated categories considering the minimally clinically important difference (MCID) of ARAT (5.7 points) (Van Der Lee et al., 2001) and the MCID of FMA-UE (5.25 points) (Page et al., 2012), which is similar to the minimal detectable change (MDC) of FMA-UE (5.2 points) (Wagner et al., 2008), based on the population used to establish these thresholds (i.e., chronic stroke). The proportion of individuals who achieved a clinically relevant change for both intervention groups was measured using the chi-square test and the combination of chi-square tests in the PP and ITT analyses, respectively. Second, t-tests for the PP set and combination of t-tests for the ITT set were used to compare ARAT and FMA-UE improvement distributions between groups at post-intervention (post- minus baseline scores) and follow-up (follow-up minus baseline scores) evaluations.

Linear models were fitted with the PP dataset to check the effects of stroke etiology, motor deficit at baseline, musical hedonia, and intrinsic motivation on upper-limb motor improvement and long-term improvement. Both ARAT and FMA-UE score changes post-intervention and at follow-up were established as response variables, and stroke etiology, FMA-UE baseline score, eBMRQ total and sensorimotor component scores, TSRQ scores before and during the intervention, and IMI scores post-intervention were established as predictor factors. The intervention group was established as a main effect predictor in all models, except in the models measuring the influence of musical hedonia and intrinsic motivation, where it was established as an interaction. Linear models were chosen over ANCOVA, as specified in the protocol (Grau-Sánchez et al., 2021), due to their ability to handle both categorical and continuous predictors with non-parametric distribution (Bolker, 2015). The linear models were run with the PP dataset because it has been shown that regression models on imputed data can lead to unstable results (Twisk et al., 2013).

Before conducting the ITT analysis, a multiple imputation procedure was performed with chained equations algorithm to replace missing values using baseline variables as predictors (van Buuren & Groothuis-Oudshoorn, 2011). Ten imputation datasets, each with ten inferences, were generated to ensure accurate estimation by including variables with a missing rate threshold of 30% (Austin et al., 2021). Multiple imputation procedures were preferred over using baseline scores for all evaluation points, as specified in the protocol (Grau-Sánchez et al., 2021), due to their robustness in handling moderate drop-out rates (Armijo-Olivo et al., 2009).

Secondary analysis involved comparing improvements in additional motor and cognitive functions, emotional well-being, QoL, self-regulation, and self-efficacy between groups using the PP dataset.

Statistical analyses were performed using R (version 4.2.2) and RStudio (version 2023.06.2+561) with specific packages including mice (van Buuren & Groothuis-Oudshoorn, 2011) and lme4 (Bates et al., 2015). Statistical significance was based on a two-sided p-value < 0.05. The Statistical Package for the Social Sciences (SPSS; version 21) was used to compute self-report questionnaires scores, and both RStudio and GraphPad (version 9.0.1) were used to create the graphs.

5.3 Results

5.3.1 Participant flow and sample characteristics

One hundred eighteen chronic stroke survivors were assessed for eligibility, of whom 52 did not fulfil the inclusion criteria and eight declined to participate. Fifty-eight participants were evaluated, randomly allocated to one of the intervention groups (eMST-group or CT-group) and included in the ITT analysis. Six participants from the eMST-group and 12 participants from the CT-group discontinued the intervention. Forty participants completed the whole intervention and post-evaluation and were thus included in the PP analysis. Two participants from the eMST-group and one participant from the CT-group did not complete the 3-month follow-up evaluation. Participant flow and reasons of discontinuation are reported in Figure 5.1. Of those participants who dropped out, a greater proportion from the CT-group did it in the first half of the intervention (91.67%) compared to the eMST-group (66.67%), without significant differences between groups (F(0.003, 4.883) = .203; p = .245).

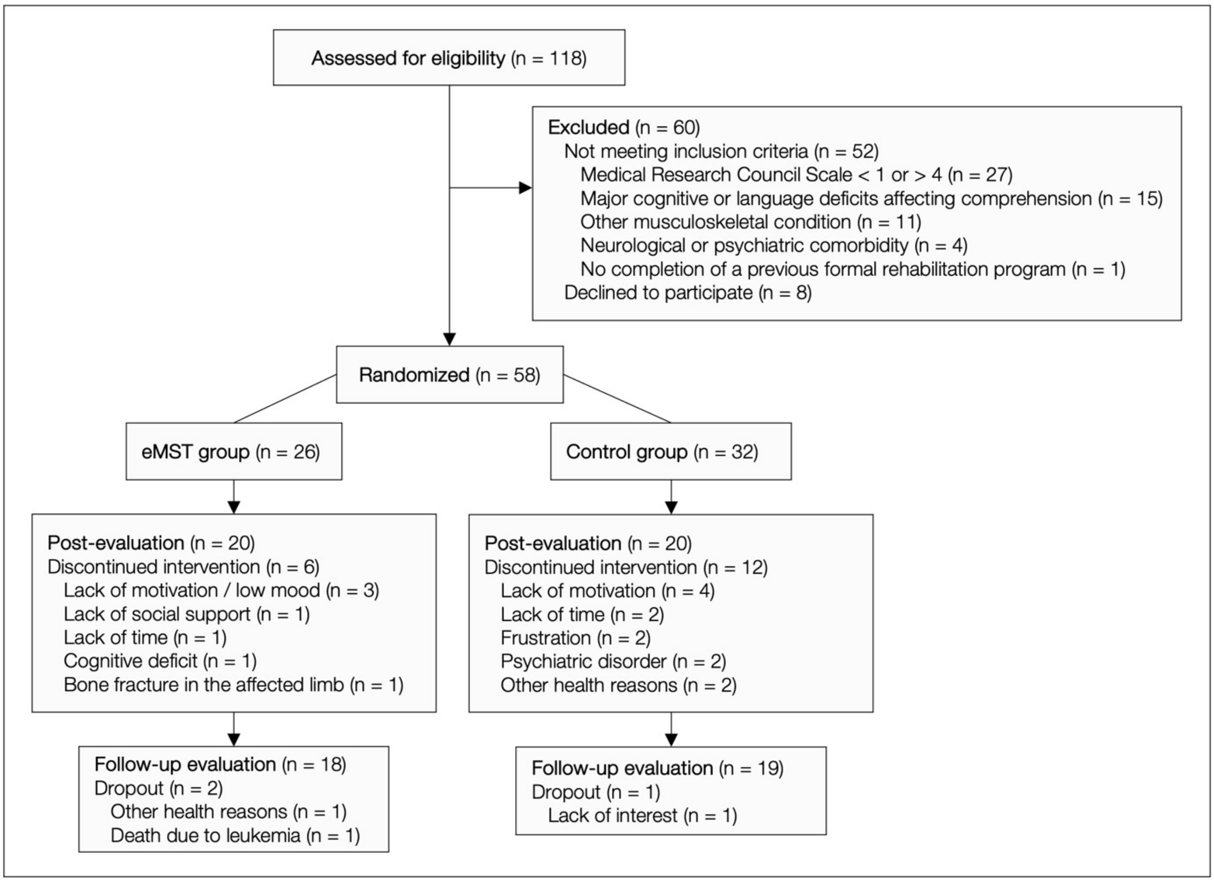


Figure 5.1. Flow diagram of participants.
CONSORT flow diagram of recruitment and evaluation among eMST-group and CT-group participants.

Baseline characteristics of randomized participants are provided in Table 5.1. In both groups, ischemic stroke (eMST-group: 61.5%; CT-group: 71.9%) and subcortical lesions (eMST-group: 57.7%; CT-group: 43.3%) were the most prevalent. The eMST-group presented a trend towards a greater baseline upper-limb motor impairment and musical hedonia than the CT-group, but both were not statistically significant. Sociodemographic, clinical, motor, cognitive, musical, and personal situation variables were similar for both groups (see Table 5.1). Participants who completed the entire intervention showed no significant differences in any sociodemographic, clinical, emotional, or personality characteristics at baseline between groups (see Supplementary Table 1 in Appendix). One participant in the eMST-group and one in the CT-group received botulinum injections prior to the start of the intervention, and the latter dropped out of the study in the first half of the intervention.

Table 5.1. Baseline characteristics.
This table shos the sociodemographic, clinical, functional and personal baseline characteristics of randomized participants to both eMST and control groups.

Characteristic	eMST group (n=26)	Control group (n=32)	p-v
Sociodemographic variables			
Age, mean (SD), y	64.2 (12.5)	62.2 (12)	.540
Females, No. (%)	6 (23.1)	8 (25)	.999
Education, mean (SD), y	19.7 (3.9)	17.5 (4.6)	.055
Clinical variables			
Ischemic stroke, No. (%)	16 (61.5)	23 (71.9)	.580
Lesion location, No. (%)			.084
Cortical	0 (0)	5 (15.6)	
Cortico-subcortical	5 (19.2)	6 (18.8)	
Subcortical	15 (57.7)	14 (43.8)	
Brainstem	2 (7.7)	6 (18.8)	
Cerebellum	4 (15.4)	1 (3.1)	
Time since stroke, median [IQR], y	2.8 [2.9]	1.8 [6.2]	.679
Upper-extremity motor function			
Affected dominant hand, No. (%)	12 (46.2)	17 (53.1)	.792
Medical Research Council Scale, median [IQR]	3 [1.8]	3 [1]	.095
Fugl-Meyer Assessment baseline, median [IQR]	47.5 [19.8]	55 [18]	.138
Cognitive functions			
Montreal Cognitive Assessment, mean (SD)	25.2 (2.5)	25.2 (2.6)	.997
Mild cognitive impairment level, No. (%)	14 (53.8)	14 (43.8)	.598
Digit span (Wechsler Adult Intelligence Scale - IV), mean (SD)	12 (2.6)	11.8 (3.3)	.844
Vocabulary (Wechsler Adult Intelligence Scale - IV), mean (SD)	12.4 (3.2)	12.4 (3.3)	.969
Boston Naming Test, median [IQR]	13 [2]	14 [1.3]	.681
Musical reward and skills			
Barcelona Music Reward Questionnaire (extended), mean (SD)	84.1 (14.2)	74.6 (22.3)	.069
Montreal Battery of Evaluation of Amusia (Scale), mean (SD)	24.1 (5.6)	22 (4.7)	.178
Montreal Battery of Evaluation of Amusia (Rhythm), mean (SD)	25.4 (3.7)	24.5 (4)	.421
Perseverance and social support			
Grit Scale, mean (SD)	3.8 (0.6)	3.8 (0.5)	.836
Social Support questionnaire, median [IQR]	6 [0.9]	5.7 [1.2]	.635

Participants who completed the intervention reported significantly higher levels of social support, and lower levels of anger, confusion, and depression than those who dropped out (see Supplementary Table 2 in Appendix). The remaining characteristics were similar among all participants, but completers also tended to higher levels of executive function and QoL-related positive emotion than non-completers.

Regarding the adverse effects, participants in both groups reported experiencing fatigue in some sessions, leading to periodically adjustments in training intensity and tempo of the percussion exercises for each individual (e.g., decreasing the tempo from 50bpm to 40bpm and removing one percussion and one piano exercise per session in the following week). Dropouts due to bone fracture, non-stroke health reasons, and death (see Figure 5.1) were not related to the participation in the study and the completion of the interventions.

5.3.2 Primary outcome

Minimally Clinically Importance Difference. In both ITT and PP analyses, no significant differences were found between groups in the proportion of participants achieving MCID post-intervention (ITT: OR = 1.6 (95% CI, 0.6 to 4.6), $F(1, 5721.18) = 0.403$, $p = .526$; PP: OR = 1.5 (95% CI, 0.4 to 5.2), $\chi^2(1) = 0.1$, $p = .752$), with 53.5% (ITT) and 55% (PP) of participants reaching it in the eMST-group and 41.6% (ITT) and 45% (PP) in the CT-group. At 3-month follow-up, a significantly greater proportion of eMST participants (ITT: 61.5%; PP: 66.7%) reached the MCID when compared to CT participants (ITT: 30%, PP: 26.3%) in both analyses (ITT: OR = 3.7 (95% CI, 1.3 to 11.1), $F(1, 27654.69) = 4.790$, $p = .029$; PP: OR = 4.5 (95% CI, 1.2 to 17.4), $\chi^2(1) = 4.545$, $p = .033$) (see Figure 5.2 and see Supplementary Table 3 in Appendix).

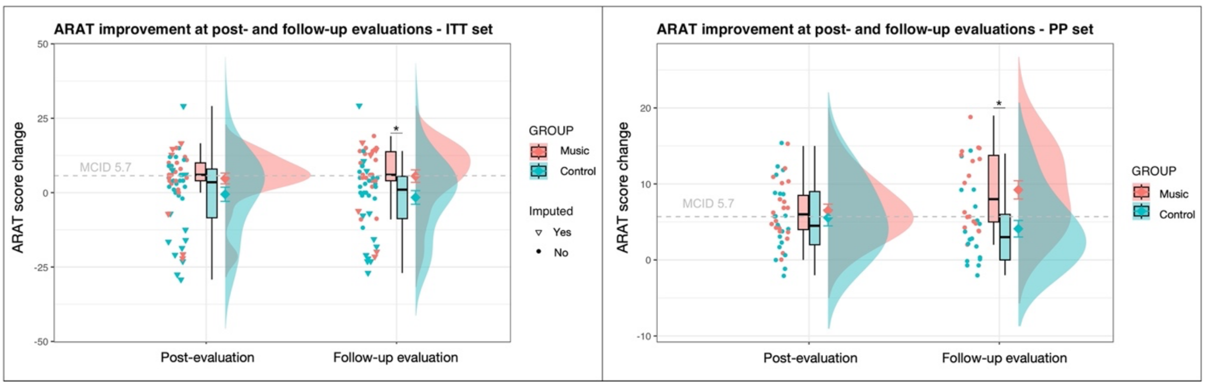


Figure 5.2. Distribution of ARAT improvements.
These graphs show the distribution of ARAT improvement at post- and follow-up evaluations for both groups with the A) Intention-to-treat set, and B) Per-protocol set.

Distribution of improvements. No differences were observed in ARAT improvement distributions between groups post-intervention in both ITT (group difference = 2 (95% CI, 0.8 to 3.1), $F(1,245.5) = 0.930$, $p = .336$) and PP analyses (group difference = 0.9 (95% CI, -1.8 to 3.7), $t(36) = 0.702$, $p = .487$). At follow-up, the eMST-group showed a significantly greater score change compared to the CT-group in both analyses (ITT: group difference = 6 (95% CI, 5.5 to 6.5), $F(1, 25888.2) = 5.669$, $p = .017$; PP: group difference = 5.1 (95% CI, 1.8 to 8.4), $t(34.5) = 3.156$, $p = .003$; See Supplementary Table 4 and Supplementary Figure 1 in Appendix).

Factors associated to recovery. In both groups, stroke etiology, baseline motor deficit, musical hedonia (global and sensorimotor component scores), and intrinsic motivation (SR and IMI scores) did not predict ARAT improvement post-intervention and at follow-up.

5.3.3 Secondary outcomes

Motor outcomes. The eMST-group showed a significantly greater number of participants reaching the MCID and MDC in FMA-UE compared to the CT-group at post- and follow-up evaluations in ITT and PP analyses (see Figure 5.3 and Supplementary Table 5 in Appendix), with a significantly higher FMA-UE improvement in both evaluations (see Supplementary Table 6 and Supplementary Figure 2 in Appendix). Regarding the performance in daily activities, the eMST-group showed a significantly higher long-term improvement in CAHAI compared to the CT-group, with no significant differences in the remaining motor outcomes (see Supplementary Table 7 in Appendix). Both groups showed no significant associations between FMA-UE improvement (post-intervention and at follow-up) and stroke etiology, baseline motor deficit, musical hedonia, and intrinsic motivation.

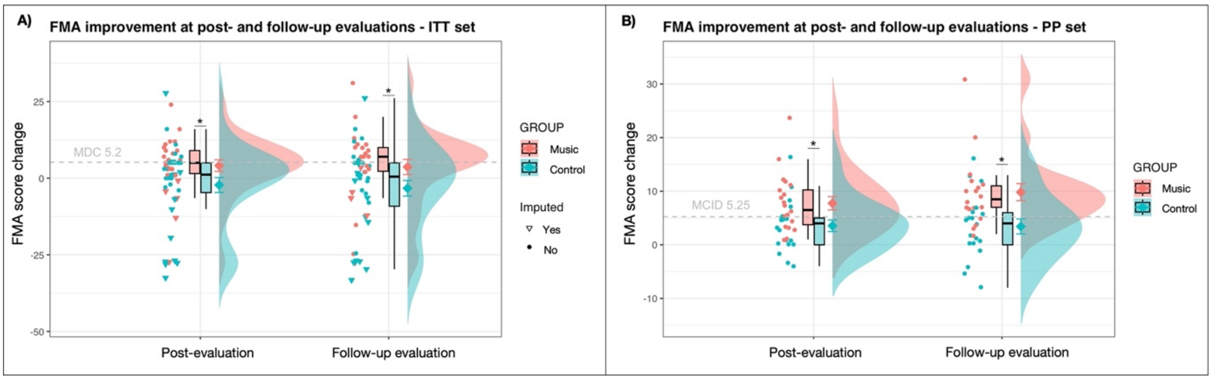


Figure 5.3. Distribution of FMA-UE improvements.
These graphs show the distribution of FMA-UE improvements at post- and follow-up evaluations for both groups with the A) Intention-to-treat set; B) Per-protocol set.

Cognitive outcomes. Groups did not differ significantly in cognitive functions score changes (see Supplementary Table 8 in Appendix).

Emotional well-being and quality of life outcomes. The eMST-group reported a significant decrease in apathy (AES, informant-version) and anger (POMS), and a significant increase in positive emotion and participation (SIS) post-intervention compared to the CT-group (see Figure 5.4 and **Supplementary Table 9** in Appendix).

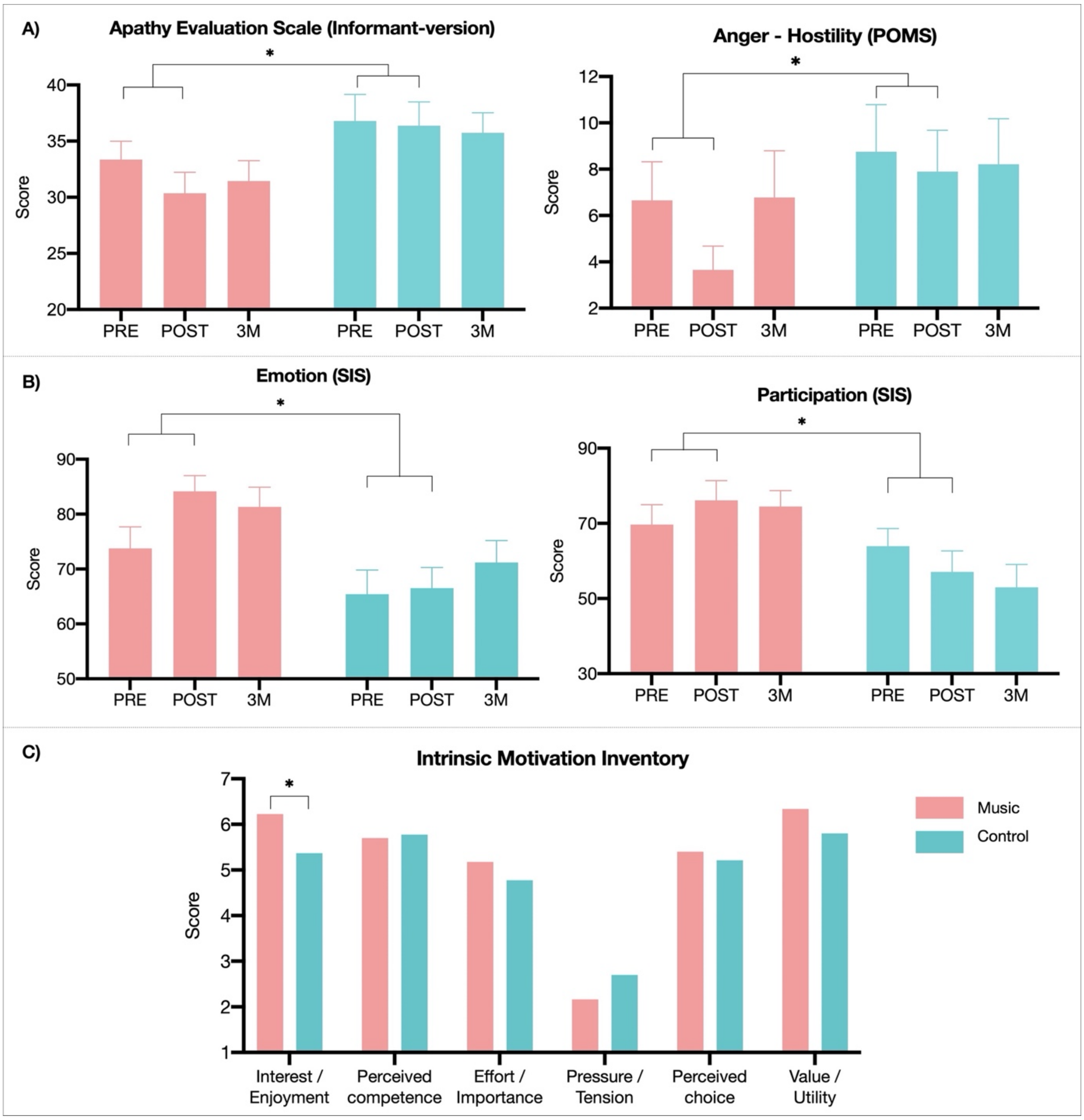


Figure 5.4. Mean scores of emotional, QoL and self-regulation variables.
These graphs show A) emotional, B) QoL and C) self-regulation outcomes that differed significantly between groups for each evaluation point.

Self-regulation and self-efficacy outcomes. Groups did not differ significantly in the motivation type score change between the first and fifth weeks of the intervention. After the intervention, eMST participants reported having experienced a significantly higher level of enjoyment (IMI subscale) during the sessions compared to the CT-group (see Supplementary Table 10 in Appendix). No significant changes were observed between groups in self-efficacy score change (see Supplementary Table 11 in Appendix).

5.4 Discussion

We conducted a pragmatic RCT to evaluate eMST's effectiveness in enhancing functional abilities and QoL in chronic stroke survivors compared to a conventional rehabilitation program (GRASP, Harris et al., 2009). The eMST exhibited notably superior effects in reducing upper-limb motor impairment (measured with the FMA-UE) post-intervention and after three months. Participants undergoing eMST also displayed improved upper-limb function and everyday task performance (measured with the ARAT and CAHAI, respectively) at follow-up compared to GRASP participants. Both PP and ITT analyses supported these findings, reinforcing the potential benefits of eMST for chronic stroke rehabilitation (Hollis & Campbell, 1999). These results must be highlighted considering the clinically relevant effects that GRASP has previously demonstrated in enhancing upper-limb mobility in chronic stroke (Klempel et al., 2023). Notably, both groups showed greater improvements in FMA-UE than in ARAT at both evaluation points. Improvement in FMA-UE requires gains in shoulder, elbow, wrist, and hand functions, which could subsequently be reflected in improved upper-limb function and activity measured with the ARAT. In addition, it has been suggested that the FMA-UE is more responsive than the ARAT to a motor intervention, and that it is a good predictor of ARAT improvement after stroke (Chen et al., 2022).

Previous studies applying the original MST protocol for subacute and chronic stroke rehabilitation failed to demonstrate greater motor improvements than conventional physical programs (Fujioka et al., 2018; Grau-Sánchez et al., 2018). Noteworthy, the present trial is the first to show that eMST can lead to superior upper-limb function gains over GRASP (Fujioka et al., 2018), a previously validated conventional program that has been shown to be effective in chronic stroke (Klempel et al., 2023). This finding underlines the relevance of the elements incorporated in eMST (Grau-Sánchez et al., 2021). Increasing training intensity and diversifying upper-limb training movements could be the main factors driving this advantage (Kitago & Krakauer, 2013; Zeiler & Krakauer, 2013). In addition, the incorporation of a temporal cue to follow rhythmic patterns in percussion exercises might have enhanced the synchronization of auditory and motor cortices, facilitating the immediate adjustment and coordination of upper-limb movements (Rodriguez-Fornells et al., 2012). Adapting the program for home-use and incorporating group sessions to promote individuals' autonomy and social interaction might have also contributed to participant engagement and adherence (Szeto et al., 2023; Wulf & Lewthwaite, 2016). Importantly, the level of motor deficit at the onset of the intervention demonstrated no influences on motor improvement. However, the eMST group showed a slightly higher motor deficit at baseline, which might affect the motor progression, leading to greater changes (Alawieh et al., 2018).

In line with previous MST trials (Fujioka et al., 2018; Grau-Sánchez et al., 2018; Ripollés et al., 2016), eMST improved emotional well-being and QoL (Altenmüller et al., 2009; Amengual et al., 2013; Fujioka et al., 2018; Grau-Sánchez et al., 2018; Ripollés et al., 2016; Rojo et al., 2011; Schneider et al., 2007; Van Vugt et al., 2016; Villeneuve et al., 2014), reducing anger, and increasing self-perceived positive emotion and community participation compared to the control group. Furthermore, eMST participants reported higher enjoyment during the sessions, which might have reinforced their emotional well-being and intrinsic motivation for eMST adherence. Crucially, more individuals in the control group discontinued their participation despite not differing at baseline characteristics. The overall attrition rate was related to the lack of social support from the participants' environment, along with feelings of anger, confusion, and depression (see Supplementary Table 2 in Appendix). This result is consistent with a recent review on GRASP underscoring the pivotal role of social support in facilitating the successful completion of this intervention (Klempel et al., 2023), and with previous research suggesting a strong link between emotional well-being and stroke motor recovery. In this sense, higher levels of positive emotion could be enhancing motor performance expectations and driving behaviors associated with successful recovery (Ostir et al., 2008; Wulf & Lewthwaite, 2016).

In the current study, group sessions were designed to enhance emotional well-being and QoL. However, it is noteworthy that social interaction has also been identified as a key factor in promoting motor recovery in patients with ischemic stroke (Chang et al., 2020). Considering the lack of group sessions in GRASP and that previous MST trials showed no superior effects to control interventions, the social component of eMST could also drive motor improvement. Nevertheless, previous studies applying a group music-making intervention for stroke survivors reported improvements in QoL, with increased self-perceived activity and community participation in SIS, but found no significant motor function improvements compared to a home-based motor intervention (Palumbo et al., 2023; Raghavan et al., 2016a). Another study applying a home-based task-specific intervention using non-immersive reality technology showed QoL and motor improvements in stroke survivors, but without outperforming a home-based intervention involving one-to-one recreational activities (Saposnik et al., 2016). Adding a social element to the non-immersive reality technology intervention might have further enhanced its effectiveness (Venna et al., 2014).

In contrast to a previous MST trial for subacute stroke (Grau-Sánchez et al., 2018), we observed no association between musical hedonia or its sensorimotor component and motor progress in eMST participants. Here, learning a new skill could have a more substantial impact (Wulf & Lewthwaite, 2016). Compared to the control group using everyday objects for upper-limb training, eMST participants embarked on acquiring new skills, potentially motivating hand use. Conversely, participants undergoing GRASP might have faced frustration when attempting daily tasks that became challenging after stroke. This suggests that developing new skills during eMST might have contributed to long-term motor improvement by increasing awareness of their paretic upper-limb functionality (Ellis-Hill et al., 2000). In fact, eMST participants showed greater motor changes at follow-up than post-intervention, similarly to previous findings on MST benefits for subacute stroke (Grau-Sánchez et al., 2018). Long-term improvements in upper-limb motor function and motor impairment have also been observed in other studies on stroke rehabilitation, suggesting the influence of younger age, higher initial functional scores, and motor gains during the intervention that provided the basis for training further activities during the follow-up period (Feys et al., 2004; Kuptniratsaikul et al., 2017). Lastly, incorporating a variety of percussion instruments, catering to diverse musical preferences, along with introducing a social component in eMST, might have heightened participants' enjoyment and engagement, irrespective of their ability to derive pleasure from music.

The pragmatic design of this trial, including individuals with diverse sociodemographic profiles, varying motor impairment levels, and maintaining their activity or rehabilitation routines, highlights eMST's real-world benefits (Ford & Norrie, 2016). Furthermore, individuals with both ischemic and hemorrhagic stroke showed similar motor improvement, indicating the benefits regardless of stroke etiology.

Community-based programs like eMST are crucial in eliminating hospital costs and distance-related barriers, facilitating continued rehabilitation irrespective of resource limitations in specialized hospitals or centers (Broeren et al., 2006). While eMST group sessions require the guidance of a music therapist or rehabilitation clinician experienced in music performance, the self-training sessions can be telemonitored by any rehabilitation clinician familiar with the eMST app. This makes eMST an accessible intervention with the potential to reduce physical disability and enhance QoL of stroke survivors.

5.5 Strengths and limitations

This study provides a pragmatic estimate of eMST's real-world benefits and its potential when implemented as intended (Hollis & Campbell, 1999). However, it has some limitations. First, imputations required for ITT analysis were applied with a 30% missing data rate, diminishing result reliability (Pedersen et al., 2017). Second, the lack of group sessions in the control intervention might have benefited eMST for better outcomes. Future research should test the effectiveness of eMST compared to GRASP including group sessions to disentangle the beneficial effects of eMST on both emotional and physical states. However, we provided the original GRASP protocol as a control intervention because it was previously validated (Harris et al., 2009) and allows for comparison of results across studies that also used GRASP as a control treatment (Fujioka et al., 2018). Lastly, conducting the trial immediately after the COVID-19 pandemic posed recruitment challenges in a health-risk population, resulting in a smaller-than-planned sample size.

5.6 Conclusion

This pragmatic RCT demonstrated the effectiveness of eMST in improving upper-limb functions and QoL in chronic stroke survivors. Participants in eMST reported greater enjoyment, community participation, and intrinsic motivation, potentially boosting treatment adherence and leading to improved outcomes. Unlike previous MST studies, eMST yielded significantly greater motor changes compared to a conventional motor intervention, underscoring the importance of the integrated socio-motivational elements. Therefore, eMST is an efficient and cost-effective tool for chronic stroke individuals to pursue home-based rehabilitation while fostering community integration.

Study 4

This study corresponds to:

Segura, E., Vilà-Ballo, A., Mallorquí, A., Porto, M.F., Duarte, E., Grau-Sánchez, J., & Rodríguez-Fornells, A. (2024). The presence of anhedonia in individuals with subacute and chronic stroke: an exploratory cohort study. *Frontiers in Aging Neuroscience*, *16*, 1-14.

6. Study 4

The presence of anhedonia in subacute and chronic stroke

6.1 Introduction

Anhedonia is defined as the diminished capacity to experience pleasure. The concept was rarely used before the 1980s and was officialized in the DSM-III, becoming a necessary symptom for depression diagnosis (Der-Avakian & Markou, 2012). In 2008, the American Psychiatric Association developed the Research Domain Criteria framework to integrate transdiagnostic neurobehavioral evidence in the study of mental disorders, where anhedonia was considered a behavioral correlate of the negative valence human systems domain (Cuthbert, 2021). Anhedonia has also been addressed as a residual symptom of schizophrenia (Der-Avakian & Markou, 2012), but most recently, it was included in the DSM-V as a crucial symptom for diagnosing the major depression melancholic subtype and differentiating it from other mental disorders (American Psychiatric Association, 2013).

Besides the medical symptom approach, anhedonia has been described as an enduring and stable behavioral trait that characterizes individual's personality (Der-Avakian & Markou, 2012). The manifestation of anhedonia has been associated with deficits in the reward processing system, specifically in the dopaminergic projections between the midbrain dopaminergic nucleus, striatum, amygdala, hippocampus, and prefrontal cortex, requested for modulating behavioral responses to rewards (Camara et al., 2009; Der-Avakian and Markou, 2012). Previous studies have suggested the genetic influence of developing anhedonia by demonstrating genetic polymorphisms of dopamine synthesis, metabolism, and regulator proteins that impair functional activity of brain regions belonging to the reward system (Ren et al., 2018). Accordingly, it has been proposed the potential endophenotype role of anhedonia as a vulnerability marker present before the onset of depression that might increase the severity and prolong the course of this mood disorder (Gong et al., 2017). Furthermore, suffering depression with severe symptoms of anhedonia has also been associated with an elevated risk of suicide (Bonanni et al., 2019). Individuals with high anhedonia-trait levels could thus be more likely to develop depression in a particular context (Pizzagalli et al., 2005; Auerbach et al., 2019). For example, anhedonia has been associated with increased levels of depression at hospital discharge in stroke patients (Sibon et al., 2012). In this regard, the disruption of dopaminergic networks after a stroke could trigger the onset of mood disorders and cognitive deficits including memory dysfunction, leading to the development of anhedonia (Isella et al., 2004).

In addition to mental health disorders, anhedonia has been found in other health conditions involving chronic pain and inflammatory processes (Carpinelli et al., 2019; Lucido et al., 2021). For instance, a control-case study reported higher anhedonia levels in chronic pain sufferers when compared to healthy controls, with 25% of patients obtaining scores over the standard cutoff point (Garland et al., 2020). Interestingly, this result was not entirely motivated by a comorbid depression diagnosis, pointing out a more nuanced perspective of the psychological consequences of some health conditions. Furthermore, a recent review on endometriosis, a gynecological chronic systemic inflammatory disease characterized by the presence of chronic pelvic pain, presented anhedonia as a severe symptom which is not assessed in the usual clinical treatment despite the deleterious consequences in patients' mental health and quality of life (QoL) (Mallorqui et al., 2022).

Stroke is the most prevalent neurological disease and a leading cause of acquired long-term disability worldwide (GBD 2016 Stroke Collaborators, 2019; Katan & Luft, 2018). Motor, cognitive, and language deficits are common post-stroke consequences that limit the accomplishment of daily activities and restrict participation in familiar, social, work, and community life (Hartman-Maeir et al., 2007; Tang et al., 2020). The reduction of the functional autonomy of stroke survivors has negative effects on their emotional well-being and QoL, leading to mood disorders such as depression and anxiety (Diamond et al., 2023; Marcheschi et al., 2018). Importantly, most patients still present or even increase motor deficits in the chronic phase of the disease (Kwakkel et al., 2003). Once patients complete formal rehabilitation programs, a decrease in physical activity, mostly attributed to a lack of a rehabilitation routine and/or therapist presence, can provoke a decline in motor functions (Ashe et al., 2009). This underscores the importance of intrinsic motivation in sustaining a healthy and active lifestyle (Chan et al., 2009).

Stroke survivors pass through challenging periods in which they need to adapt their lives to their new condition. Between 25% and 79% of stroke patients suffer post-stroke depression (PSD), whose cause is associated with the physical and psychological adversities they must cope with (Whyte & Mulsant, 2002). Previous research have demonstrated the negative impact of PSD on motor and cognitive recovery, becoming an additional disabling factor responsible for 15% of increased disability (Paolucci et al., 2019). This detrimental consequence has been associated with deficits in regulating motivated-related behaviors (Gainotti et al., 2001). Many studies have focused on exploring the negative impact of apathy on stroke rehabilitation (Marin, 1991; Sibon et al., 2012), but motivational mechanisms and goal-directed behaviors are also disrupted by anhedonia, an understudied condition in the stroke population. Despite the substantial overlap between apathy and anhedonia, the former is associated with an impairment in selecting future behaviors based on emotional signals, while anhedonia is characterized by diminishing sensitivity to everyday pleasures and positive mood, crucial aspects for goal-directed engagement in rewarding activities (Verrienti et al., 2023). Considering the role of anhedonia in motivational aspects crucial for stroke survivors' recovery, a recent study by Ashaie et al. (2023) explored the association between three dimensions of PSD somatic symptoms, negative affect, and anhedonia. They found that anhedonia predicted subsequent increases in somatic symptoms during the first year after rehabilitation discharge, indicating its impact on physical distress rather than stroke itself. In this regard, the authors emphasized the importance of examining specific dimensions of PSD, such as anhedonia, to understand their development and etiology and thus be able to guide clinicians in implementing targeted treatments and improving therapeutic outcomes (Ashaie et al., 2023). Currently, no previous study has examined the presence of anhedonia in patients with both ischemic and hemorrhagic stroke and over a wide range of time after stroke.

In the present exploratory cohort study, we aimed to determine the prevalence and levels of anhedonia in subacute and chronic stroke survivors with upper-limb motor deficits, and to explore the factors associated with this condition in the stroke population. We hypothesized that two groups of subacute and chronic stroke patients would show a higher prevalence and level of anhedonia than a group of healthy individuals, and that anhedonia would be related to negative mood states. A better understanding of the onset of post-stroke anhedonia and its related factors would help design more effective and evidence-based interventions aimed to improve patients' emotional well-being and promote adherence to rehabilitation and healthy active lifestyles.

6.2 Methods

6.2.1 Participants

Two groups of patients, one with subacute stroke (SS) (n = 54; females = 24; age = 61.44 ± 8.72 years; time since stroke = 2 ± 1.5 months) and another with chronic stroke (CS) (n = 71; females = 17; age = 62.27 ± 11.40; time since stroke = 20.75 ± 48.63 months), were included in the present study. All patients were recruited from the Physical Medicine and Rehabilitation Department of Hospital del Mar, Centre l'Esperança (Barcelona, Spain) to participate in experimental studies or randomized controlled trials that aimed to test the effectiveness of music-based interventions in the improvement of upper-limb motor functions. As part of these studies, patients underwent a basal evaluation that included motor, cognitive, emotional well-being, and QoL assessment (Grau-Sánchez et al., 2018, 2021; Ripollés et al., 2016).

The studies were conducted by a group of research assistants that included psychologists and occupational therapists with training in clinical research. The recruitment process was conducted at the Hospital del Mar, Centre l'Esperança and the inclusion criteria for both samples of stroke patients were: 1) slight-to-severe paresis of the upper extremity after a first-ever stroke; 2) no major cognitive deficits affecting comprehension; 3) no neurological or psychiatric co-morbidity, except for PSD; 4) no other musculoskeletal condition affecting upper-extremity motor function (e.g., fracture or arthritis); 5) ability to speak Spanish and/or Catalan. The specific inclusion criteria for the subacute sample were 1) less than 6 months after the stroke and 2) being involved in a program of outpatient rehabilitation at the Department of Physical Medicine and Rehabilitation at the Hospital del Mar, Centre l'Esperança. The specific inclusion criteria for chronic sample were 1) more than 6 months after stroke, and 2) have previously completed a 6-month formal rehabilitation program.

A group of healthy participants (HC) (n = 70; females = 31; age = 59.31 ± 13.81 years) who never suffered a stroke was recruited as a control group. The inclusion criteria were: 1) no presence of paresis or any musculoskeletal condition affecting upper-limb motor function; 2) no major cognitive deficits affecting comprehension; 3) no neurological or psychiatric co-morbidity; 4) ability to speak Spanish and/or Catalan. When recruiting the control sample, we considered their age, sex, and level of education to obtain similar groups in terms of demographic characteristics. They were recruited through the dissemination of the study in social networks, among relatives of research assistants, and from a residential service of temporary stays for elderly people called Respir in Barcelona.

6.2.2 Assessment

Demographic and clinical variables such as age, sex, stroke etiology, affected hemisphere, lesion location, and time since stroke were collected from medical records. A structured interview was conducted at the hospital to assess patients' upper-limb paresis and global cognitive function and check if they fulfilled the inclusion criteria. Paresis level was measured using the Medical Research Council Scale at the distal muscles of the upper extremity. Global cognitive function was measured using the Spanish version of the Mini-Mental State Examination (MMSE, Folstein & Folstein, 1975; Lobo, 1999) in subacute stroke patients, chronic stroke patients recruited by Ripollés et al. (2016), and healthy control participants; and the Spanish version of Montreal Cognitive Assessment (MoCA, Lozano-Gallego et al., 2009; Nasreddine et al., 2005) in chronic stroke patients recruited by Grau-Sánchez et al. (2021). The presence of mild cognitive impairment (MCI) was defined following the cutoffs used in Pendlebury et al. (2012), indicating MCI when scoring lower than 27 in MMSE; and the cutoffs established by Pereiro et al. (2017), indicating the presence of MCI when scoring lower than 26 in MoCA.

Those patients who fulfilled the inclusion criteria were invited to attend another day at the hospital to complete the baseline evaluation. It consisted of a one-hour session of motor and cognitive functions assessments and was conducted by research members blinded to the intervention group.

Furthermore, self-report emotional and QoL questionnaires were given to patients to complete at home (Grau-Sánchez et al., 2018, 2021; Ripollés et al., 2016). The motor, cognitive, and emotional evaluation of healthy controls participants was performed entirely in person at their home or remotely via the Zoom platform depending on their preference.

6.2.2.1 Motor evaluation

Upper-limb functional movements were evaluated using the Action Research Arm Test (ARAT, Lyle, 1981). The ARAT has excellent test-retest and inter/intra-rater reliability (Van Der Lee et al., 2001; Platz et al., 2005) and it is recommended for use in chronic stroke and outpatient rehabilitation by the StrokeEDGE Task Force Group (Sullivan et al., 2013). The test consists of 19 items divided into four subtests: grasp, grip, pinch, and gross movement. For each item, the patient is asked to perform a simple task involving a functional movement of the affected upper limb. Each task is rated with a 4-point ordinal scale (from 0: not possible to perform the task, to 3: performing the task normally). The minimum score is 0 and the maximum is 57, with higher scores indicating a higher level of upper-limb functionality.

6.2.2.2 Cognitive evaluation

Working memory and attention were assessed using the Digit Span (forward and backward) subtest from the Wechsler Adult Intelligence Scale III (WAIS-IV, Wechsler, 2013). It consists of two parts: Digit Span Forward, in which participants are asked to repeat aloud a series of digits in the same order that gradually increases until the individual is unable to repeat the sequence; and Digit Span Backward, with the same procedure but the digits must be repeated in the reverse order. Scores are based on the longest length of sequence repeated correctly for each part. The minimum score is 0 and the maximum scores are 16 and 14 in the Forward and Backward parts respectively. Raw scores were transformed into normative data considering individuals' age according to Wechsler (2013), with higher scores indicating a higher capacity of attention and working memory.

Verbal learning and memory abilities were measured using the Spanish Version of the Rey Auditory Verbal Learning Test (RAVLT, Marqués et al., 2013). In this test, participants are asked to listen and memorize a list of 15 unrelated words and immediately recall them for a total of five trials. Then, an interference list of 15 different unrelated words is presented and participants are asked to recall as many words as possible. After a 20-minute delay, participants are asked to recall as many words as possible from the first list, and to complete a recognition task on both lists with distractors. For each task, the minimum score is 0 and the maximum is 15. The total sum words of the first five trials (0-75 score) were transformed into normative data considering individuals' age according to Stricker et al. (2021), with higher scores indicating a higher capacity of verbal memory.

6.2.2.3 Emotional and mood evaluation

Depression was assessed using the Spanish version of the Beck Depression Inventory-II (BDI-II, Beck et al., 1996; Sanz et al., 2003), a self-report measure comprised of 21 multiple-choice questions scored from 0 to 3 about patients' feelings, thoughts, and behaviours over the past week. The minimum score is 0 and the maximum is 63, with higher scores indicating depression severity. The level of depression was defined following the cutoffs established by Beck and Beamesderfer (1974) for the stroke population: no depression (0-9 scores), mild depression (10-18 scores), moderate depression (19-29 scores), and severe depression (30-63 scores).

Anhedonia was assessed by calculating the total sum score of four items from the BDI-II that describe the symptoms of this behavioural trait according to Pizzagalli et al., (2005): loss of pleasure (item 4), loss of interest (item 12), loss of energy (item 15), and loss of interest in sex (item 21). The minimum score is 0 and the maximum is 12, with higher scores indicating higher anhedonia. Participants were classified into higher or lower levels of anhedonia following the cutoff obtained from calculating the 95% distribution value of the anhedonia BDI-II subscale score in HC, which was 4. Participants who obtained an anhedonia score greater than 4 were classified as higher anhedonic (HAnh), while those who obtained a score equal to or lower than 4 were classified as lower anhedonic (LAnh).

A non-anhedonic component of depression was calculated by subtracting the anhedonia BDI-II subscale score from the BDI-II total score, in order to explore the relationship between anhedonia and the non-anhedonic component of depression. The minimum score is 0 and the maximum 51, with higher scores indicating higher non-anhedonic depression. Individuals were classified into two levels of non-anhedonic depression following the cutoff obtained from calculating the 95% distribution value of the non-anhedonic depression BDI-II subscale score in HC, which was 16.65. Participants who obtained a non-anhedonic depression score greater than 16.65 were classified as higher non-anhedonic depressed (HDep), while those who obtained a score equal to or lower than 16.65 were classified as lower non-anhedonic depressed (LDep).

Apathy was evaluated using the Self-Rated Version of the Apathy Evaluation Scale (AES-S) and the Informant Version of the Apathy Evaluation Scale (AES-I), both translated into Spanish (Marin, 1991). The AES-S and AES-I consist of 18 items scored on a 4-point Likert scale (from 1: a lot, to 4: nothing) about behavioral, cognitive, and emotional aspects of patients' apathy over the past four weeks. The minimum score is 18 and the maximum 72, with higher scores indicating more apathy. The presence of apathy was defined following the cutoffs established by Andersson et al. (1999), indicating the presence of apathy in the stroke population when scoring equal or higher than 34 in both the self and informant versions of the apathy scale (AES-S and AES-I).

Different dimensions of mood such as anger, vigor, fatigue, confusion, tension, and depression levels were assessed with the Profile of Mood States (POMS) by asking the participant to rate feelings or emotions felt over the past week (McNair et al., 1971). This measure includes 65 items scored on a 5-point Likert scale (from 0: not at all, to 4: extremely) and classified into the six subscales. The minimum score is 0 in all subscales, and the maximum scores are 48 in Anger-Hostility, 32 in Vigor-Activity and Tension-Anxiety, 28 in Fatigue-Inertia, 24 in Confusion-Bewilderment, and 60 in Depression-Dejection. Higher scores indicate higher levels of each mood dimension.

6.2.3 Statistical analysis

6.2.3.1 Descriptive analysis

Absolute frequencies and percentages were calculated for the categorical variables: sex, stroke etiology, affected hemisphere, lesion location, global cognitive function level (MCI < 27 in MMSE; MCI < 26 in MoCA), depression level (none: 0-9 scores; mild: 10-18 scores; moderate: 19-29 scores; severe: 30-63 scores), anhedonia level (HAnh > 4; LAnh ≤ 4), non-anhedonic depression level (HDep > 16.65; LDep ≤ 16.65), and presence of apathy (scoring ≥ 34 in AES-S and AES-I). The mean and standard deviation (SD) were calculated for the quantitative variables with a parametric distribution: age, Digit Span, RAVLT, and Vigor-POMS score. The median and the interquartile range (IQR) were calculated for the quantitative variables with a nonparametric distribution: years of education, months after stroke, and the scores on ARAT, MMSE, MoCA, anhedonia BDI-II subscale, AES-S, AES-I, BDI-II, non-anhedonic depression BDI-II subscale, and all POMS subscales. Regarding the level of global cognitive function, we combined MMSE and MoCA scores due to their strong correlation ($r = 0.79$) in subacute stroke patients (Toglia et al., 2011).

The differences between the three groups (SS, CS, and HC) were evaluated with two-way ANOVA test and Kruskall-Wallis test for independent samples for quantitative variables with parametric and nonparametric distribution, respectively, and Fisher's exact test for categorical variables. Post-hoc analysis was conducted using Tukey's and Dunn's tests for continuous variables with parametric and nonparametric distribution, respectively, applying Bonferroni correction for multiple comparisons. We used Fisher's exact test for pairwise comparisons of categorical variables between groups.

Considering that anhedonia level did not differ between subacute and chronic samples (see Table 6.4), a secondary analysis was performed to explore the contribution of anhedonia to different factors in the stroke population. Thus, demographic, clinical, and emotional outcomes were compared between stroke patients classified as HAnh (scoring > 4 in anhedonia BDI-II subscale) and LAnh (scoring ≤ 4 in anhedonia BDI-II subscale).

6.2.3.2 Correlation analysis

The anhedonia score was correlated with continuous demographic, clinical, and emotional variables to further explore which factors were related to anhedonia levels in both groups of patients (SS and CS). We used Spearman's test to check correlations since anhedonia scores showed a nonparametric distribution.

Due to the strong correlation between anhedonia and non-anhedonic depression, partial correlation analyses were applied to explore the relationship between the anhedonia and the continuous demographic, clinical, and emotional variables while controlling for the influence of the non-anhedonic depression BDI-II subscale in subacute and chronic stroke patients, as well as in the whole sample of patients. Based on the strong correlation between anhedonia and the other emotional variables in both SS and CS groups (see Table 6.3 and Supplementary Table 13 in Appendix), an additional analysis was performed comparing anhedonia level between stroke patients and the HC group while controlling for the confounding effects of total BDI-II score, non-anhedonic BDI-II subscale score, AES-S and AES-I scores, and all POMS subscales scores.

The descriptive and correlation statistical analyses were conducted using the R (version 4.2.2) and RStudio (version 2022.12.0+353), and the level of significance was set at 0.05.

6.3 Results

6.3.1 Descriptive analysis

There were no significant differences in age, years of education, stroke etiology, and affected hemisphere between groups (see Table 6.1). The SS showed a major distribution of stroke lesions in cortico-subcortical regions compared to the CS, which showed a major distribution in subcortical areas. Post-hoc analysis (see Table 6.2) revealed significant differences in sex between the CS and the other two groups, but all showed a greater percentage of men. The HC showed higher levels of motor and global cognitive functions when compared to SS and CS, who showed no differences between them. The HC showed 11.43% of individuals with MCI (MCI < 27 in MMSE; MCI < 26 in MoCA), compared to 40.74% and 36.62% in SS and CS, respectively. Finally, SS demonstrated lower scores in Digit Span than CS and HC.

Table 6.1. Descriptive analysis of demographic and clinical variables.
Absolute frequencies and percentages are shown for the variables sex, stroke etiology, affected hemisphere, lesion location, and cognitive level. The mean and the standard deviation (SD) or the median and interquartile ranges [IQR] are shown for the quantitative variables with parametric and nonparametric distribution respectively. $p < 0.05$. (ARAT: Action Research Arm Test; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; Mild impairment < 27 in MMSE and < 26 in MoCA).

	Subacute group N = 54	Chronic group N = 71	Healthy group N = 70	p-value
Demographic variables				
Age	61.44 (8.72)	62.27 (11.40)	59.31 (13.81)	.379
Sex				
Females	24 (44.44 %)	17 (23.94 %)	31 (44.29 %)	.016*
Males	30 (55.56 %)	54 (76.06 %)	39 (55.71 %)	
Education level				
Years of education	18 [5.25]	18 [10]	18 [13]	.266
Clinical variables				
Stroke etiology				
Ischemic	42 (77.78 %)	46 (64.79 %)		.117
Hemorrhagic	12 (22.22 %)	25 (35.21 %)		
Affected hemisphere				
Right	24 (44.44 %)	37 (52.11 %)		.471
Left	30 (55.56 %)	34 (47.89 %)		
Lesion location				
Cortical	2 (3.70 %)	10 (14.08 %)		< .001*
Cortico-subcortical	34 (62.96 %)	16 (22.54 %)		
Subcortical	13 (24.07 %)	34 (47.89 %)		
Brainstem	2 (3.70 %)	7 (9.86 %)		
Cerebellum	3 (5.56 %)	4 (5.63 %)		
Time since stroke				
Months after stroke	2 [1.50]	20.75 [48.63]		< .001*
Motor ability				
ARAT	41.50 [21.75]	42 [15]	57 [0]	< .001*
Cognitive level				
MoCA/MMSE score	27 [3]	27 [4.50]	30 [1.75]	< .001*
No impairment (%)	32 (59.25 %)	45 (63.38 %)	62 (88.57 %)	< .001*
Mild impairment (%)	22 (40.74 %)	26 (36.62 %)	8 (11.43 %)	
Memory				
Digit Span (normative) score	10.02 (2.86)	11.77 (2.90)	12.27 (2.60)	< .001*
RAVLT (normative) score	114.11 (30.13)	126.65 (40.5)	127.99 (44.10)	.076

Table 6.2. Post-hoc analysis of demographic and clinical variables.
P-values of pairwise comparisons are shown for those variables that differed significantly between groups in Table 6.1. $p < 0.05$. (ARAT: Action Research Arm Test; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment).

Demographic and clinical variables		p-values of group comparisons				
		Sex	ARAT score	MMSE/ MoCA score	Cognitive impairment	Digit Span score
Subacute group	Chronic group	< .021*	> .999	< .550	< .710	< .002*
Healthy group	Subacute group	> .999	< .001*	< .001*	< .001*	< .001*
	Chronic group	< .021*	< .001*	< .001*	< .001*	< .540

There were significant differences between groups in all emotional variables, except for the classification of non-anhedonic depression level (HDep > 16.65 in non-anhedonic depression BDI-II subscale) and for the POMS, where groups only differed in Vigor-Activity subscale (see Table 6.3). Post-hoc analysis revealed that all significant differences were between HC and both groups of patients, who did not differ between them (see Table 6.4). The SS and CS groups showed a significantly higher anhedonia score than HC (see Figure 6.1). Compared to 4.29% of HC exhibiting HAnh (scoring > 4 in anhedonia BDI-II subscale), 18.52% of SS and 19.72% of CS patients showed a clear presence of anhedonia. The SS and CS also obtained a significantly higher score in apathy scales (AES-S and AES-I), BDI-II, and non-anhedonic depression BDI-II subscale. A greater percentage of patients reached the cutoff point for apathy presence (scoring ≥ 34 in AES-S and AES-I) (SS: 52.83% in self- and informant-versions; CS: 61.97% in self-version and 56.34% in informant-version) compared to HC (30% in self-version and 23.08% in informant-version) (see Figure 6.2). A greater percentage of patients also showed moderate (19-29 scores in BDI-II) or severe (30-63 scores in BDI-II) level of depression (SS: 18.51%; CS: 19.72%) compared to HC (5.72%) (see Figure 6.2). Finally, the HC scored significantly higher on the Vigor-Activity POMS compared to both SS and CS.

Table 6.3. Descriptive analysis of emotional variables.
Absolute frequencies and percentages are shown for the level of anhedonia, presence of apathy, and level of depression. The mean and the standard deviation (SD) or the median and interquartile ranges [IQR] are shown for the quantitative variables with parametric and nonparametric distribution respectively. $p < 0.05$. (BDI-II: Beck Depression Inventory-II; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; POMS: Profile of Mood States; None depression: 0-9 scores in BDI-II; Mild depression: 10-18 scores in BDI-II; Moderate depression: 19-29 scores in BDI-II; Severe depression: 30-63 scores in BDI-II; Lower anhedonia ≤ 4 in anhedonia BDI-II subscale; Higher anhedonia > 4 in anhedonia BDI-II subscale; Lower non-anhedonic depression ≤ 16.65 in non-anhedonic depression BDI-II subscale; Higher non-anhedonic depression > 16.65 in non-anhedonic depression BDI-II subscale; Presence of apathy ≥ 34 in AES-S and AES-I).

	Subacute group N = 54	**Chronic group N = 71**	**Healthy group N = 70**	**p-value**
Emotional variables				
Anhedonia				
Anhedonia score	2 [3]	3 [3]	1 [2]	< .001*
Lower anhedonia	44 (81.48 %)	57 (80.28 %)	67 (95.71 %)	.009*
Higher anhedonia	10 (18.52 %)	14 (19.72 %)	3 (4.29 %)	
Depression				
BDI-II score	9 [9.75]	11 [10.50]	4 [4.75]	< .001*
None	28 (51.85 %)	30 (42.25 %)	59 (84.29 %)	< .001*
Mild	16 (29.63 %)	27 (38.03 %)	7 (10 %)	
Moderate	8 (14.81 %)	8 (11.27 %)	3 (4.29 %)	
Severe	2 (3.7 %)	6 (8.45 %)	1 (1.43 %)	
Non-anhedonic BDI-II score	7 [7.5]	10 [8]	3 [3]	< .001*
Lower non-anhedonic depression	45 (83.33 %)	59 (83.10 %)	66 (94.29 %)	.074
Higher non-anhedonic depression	9 (16.67 %)	12 (16.90 %)	4 (5.71 %)	
Apathy informed by patient				
AES-S score	34 [8]	36 [10.5]	31 [8]	< .001*
Presence	28 (52.83 %)	44 (61.97 %)	21 (30 %)	< .001*
No presence	25 (47.17 %)	27 (38.03 %)	49 (70 %)	
Apathy informed by caregiver				
AES-I score	34 [11.75]	35 [14.50]	28 [8]	< .001*
Presence	28 (52.83 %)	40 (56.34 %)	15 (23.08 %)	< .001*
No presence	25 (47.17 %)	31 (43.66 %)	50 (76.92 %)	
POMS				
Anger-Hostility score	6 [8]	6 [11]	6 [7.75]	.853
Vigor-Activity score	14.64 (5.14)	13.41 (5.39)	17.04 (4.97)	< .001*
Fatigue-Inertia score	6 [10]	5 [8]	6 [8]	.691
Tension-Anxiety score	7 [10]	6 [8.50]	7.50 [9]	.756
Confusion-Bewilderment score	3 [7]	3 [10]	2 [7]	.916
Depression-Dejection score	8 [12]	9 [16.50]	6 [8.75]	.174

Note: All participants completed the whole evaluation, except for one SS participant who did not respond the AES-S and POMS; and one SS and five HC participants who did not provide the AES-I. Spouses mainly answered the AES-I, followed by siblings, children, and caregiver.

Table 6.4. Post-hoc analysis of emotional variables.
P-values of pairwise comparisons are shown for those variables that differed significantly between groups in Table 6.3. $p < 0.05$. (BDI-II: Beck Depression Inventory-II; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; POMS: Profile of Mood States).

Emotional variables		p-values of group comparisons				
		Anhedonia score	Higher anhedonia presence	BDI-II score	Non-anhedonic BDI-II score	Depression level
Subacute group	Chronic group	< .293	> .999	< .774	> .989	< .474
Healthy group	Subacute group	< .001*	< .016*	< .001*	< .001*	< .001*
	Chronic group	< .001*	< .008*	< .001*	< .001*	< .001*
		AES-S score	Apathy presence by patient	AES-I score	Apathy presence by caregiver	Vigor (POMS) score
Subacute group	Chronic group	< .129	< .359	< .456	< .854	< .389
Healthy group	Subacute group	< .029*	< .015*	< .001*	< .002*	< .031*
	Chronic group	< .001*	< .001*	< .001*	< .001*	< .001*

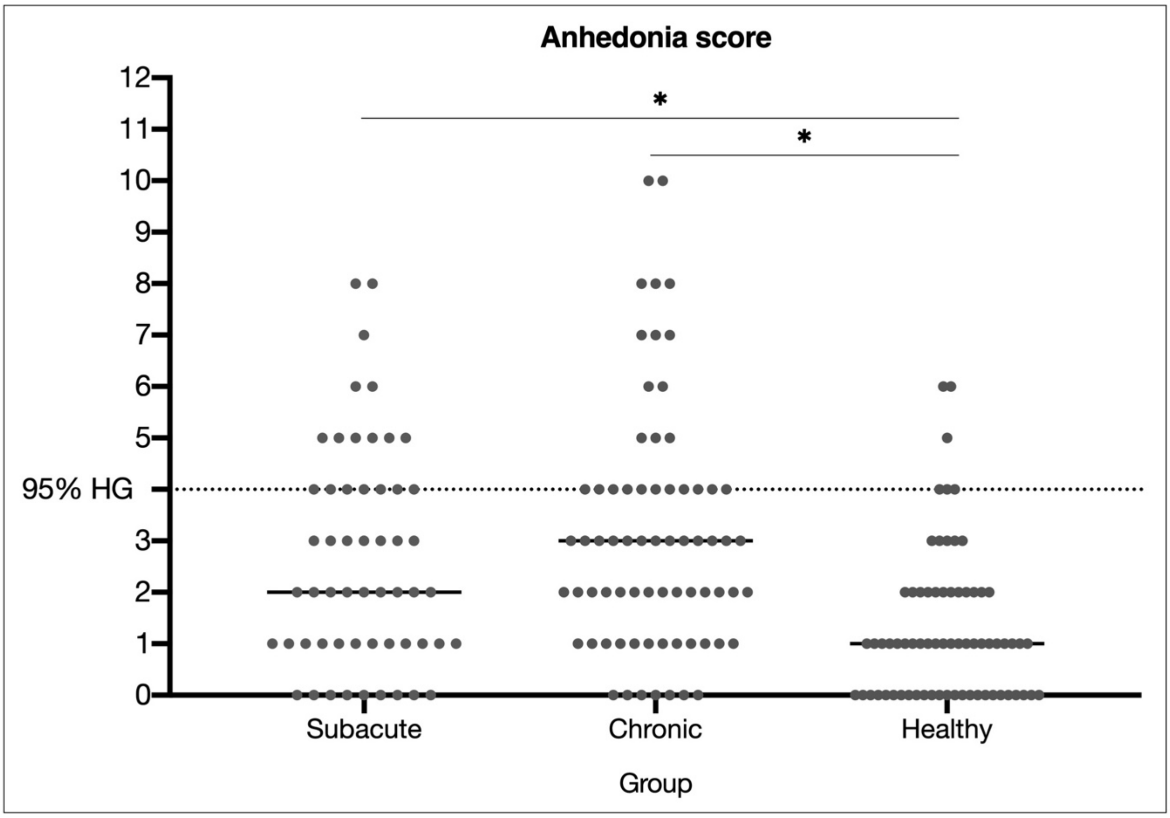


Figure 6.1. Anhedonia distribution between groups.
Anhedonia score is shown for all individuals of each group: subacute stroke, chronic stroke, and healthy controls.

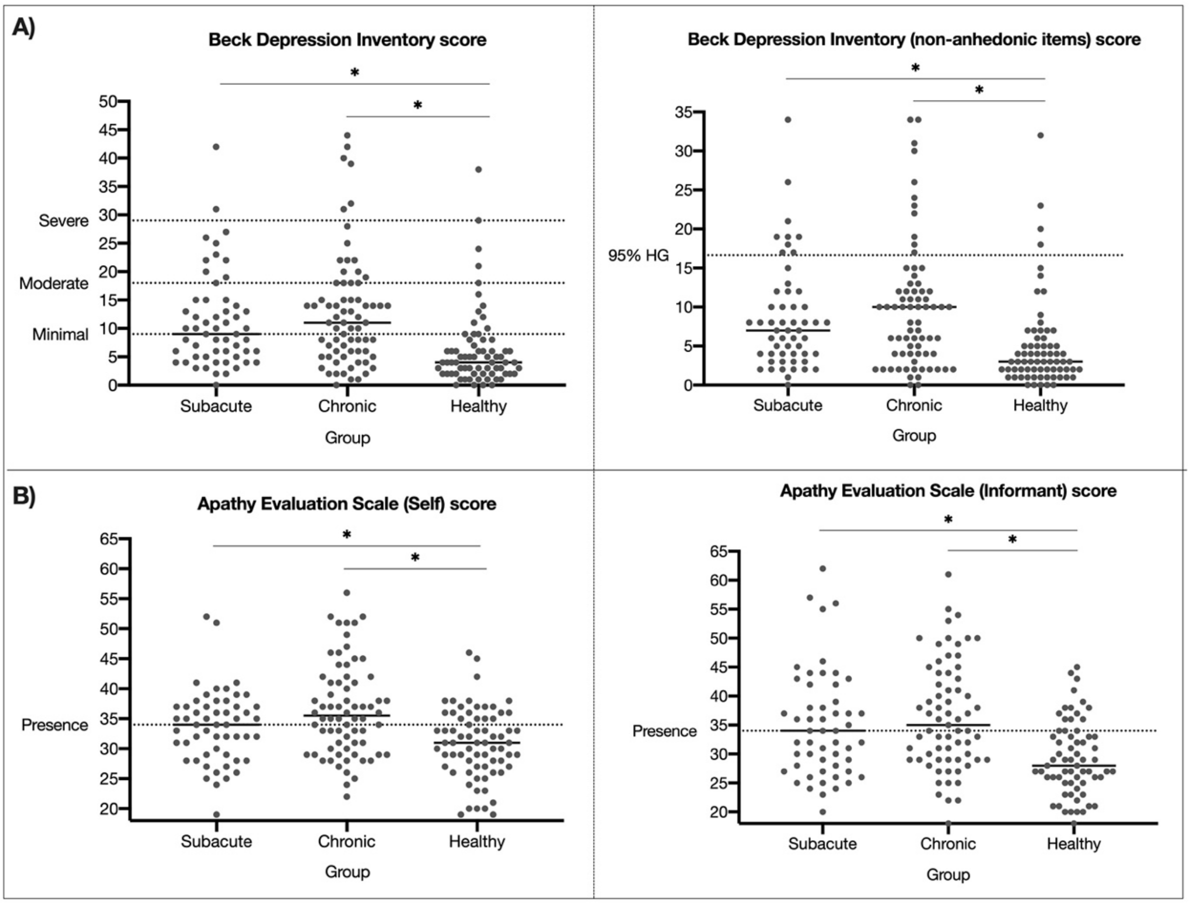


Figure 6.2. Apathy and depression distribution between groups.
A) Depression scores with all the items and without the anhedonia items are shown for all individuals from each group; B) Apathy scores of both self- and informant-versions are shown for all individuals from each group.

When comparing demographic variables between stroke patients with different anhedonia level, HAhn patients (scoring > 4 in anhedonia BDI-II subscale) showed significantly lower years of education than LAhn patients, while no differences were found on any clinical variable. At the emotional level, HAhn patients reported significantly higher levels of depression, apathy (AES-S and AES-I), Anger-Hostility, Fatigue-Inertia, Tension-Anxiety, and Confusion-Bewilderment, and significantly lower levels of Vigor-Activity compared to LAhn patients. While 70.83% of HAhn patients showed moderate and severe levels of depression, 93.07% of LAhn patients demonstrated no or mild depression, with none of them reaching the severe level. A significantly larger percentage of relatives reported presence of apathy of HAhn patients (79.17%) compared to LAhn patients (49.50%). Interestingly, no differences were found in the proportion of patients classified as HDep (scoring > 16.65 in non-anhedonic depression BDI-II subscale) and LDep between groups (see Supplementary Table 12 in Appendix).

6.3.2 Correlation analysis

Correlation analyses were applied to explore the association between anhedonia and the continuous demographic, clinical, and emotional variables in SS and CS patients (see Figure 6.3 and Supplementary Table 13 in Appendix). In both groups, anhedonia correlated positively with non-anhedonic depression BDI-II subscale and apathy scales (AES-S and AES-I), being AES-S more strongly correlated in CS than in SS patients (see Supplementary Figure 3 in Appendix). Moreover, anhedonia correlated with most POMS subscales, except for Vigor-Activity, which correlated negatively only in CS patients (see Figure 6.3 and Supplementary Figure 4 in Appendix). The variable that correlated most strongly with the anhedonia in both groups was the non-anhedonic depression BDI-II subscale, followed by Fatigue-Inertia, Depression-Dejection, and Anger-Hostility of POMS. In CS patients, anhedonia correlated positively higher with AES-S compared to SS patients.

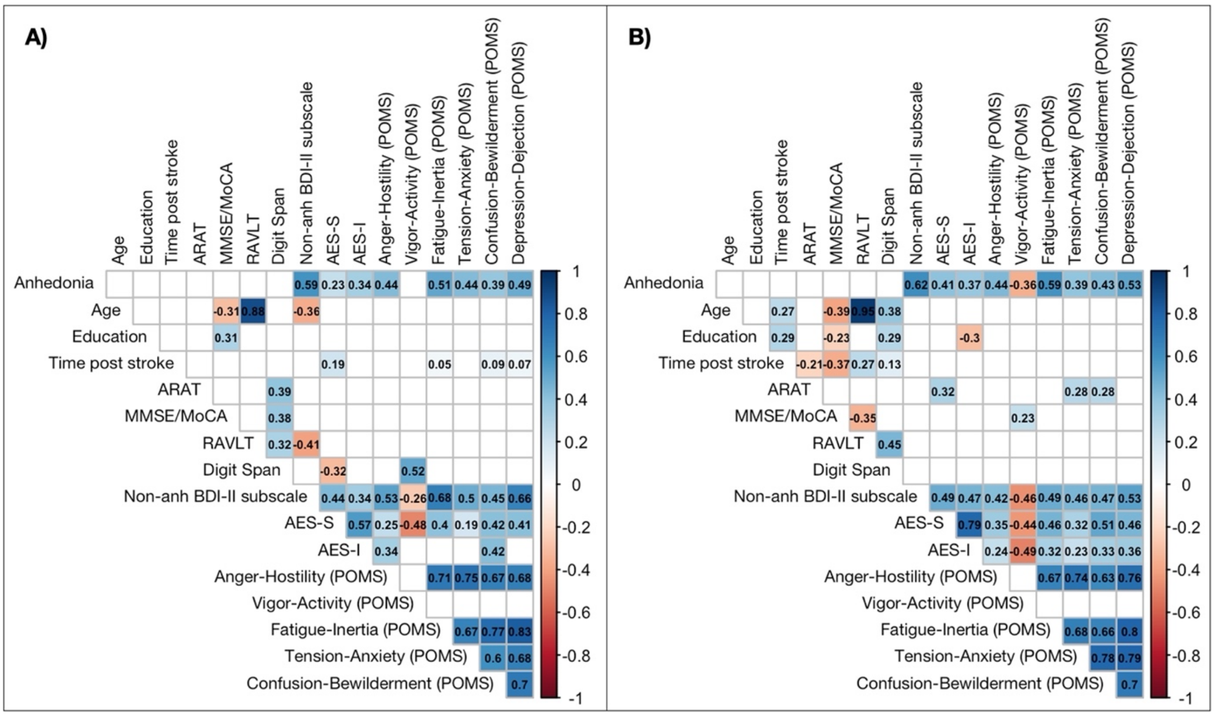


Figure 6.3. Correlations between demographic, clinical, and emotional variables.
Significant correlation coefficients are shown for A) subacute stroke patients, and B) chronic stroke patients. $p < 0.05$. (ARAT: Action Research Arm Test; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; BDI-II: Beck Depression Inventory-II; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; POMS: Profile of Mood States; POMS subscales: Anger-Hostility; Vigor-Activity; Fatigue-Inertia; Tension-Anxiety; Confusion-Bewilderment; Depression-Dejection).

Partial correlation analyses were applied to explore the relationship between the anhedonia and the continuous demographic, clinical, and emotional variables while controlling for the influence of the non-anhedonic depression BDI-II subscale in subacute and chronic stroke patients, and in the whole sample of patients (see Figure 6.4 and Supplementary Table 14 in Appendix). In SS patients, the anhedonia score correlated positively with time since stroke (measured in days). By contrast, in CS patients, anhedonia positively correlated with patients' age and three subscales of POMS: Anger-Hostility, Fatigue-Inertia, and Depression-Dejection. When looking at the whole sample of stroke patients, anhedonia correlated positively with age and four subscales of POMS: Anger-Hostility, Fatigue-Inertia, Confusion-Bewilderment, and Depression-Dejection.

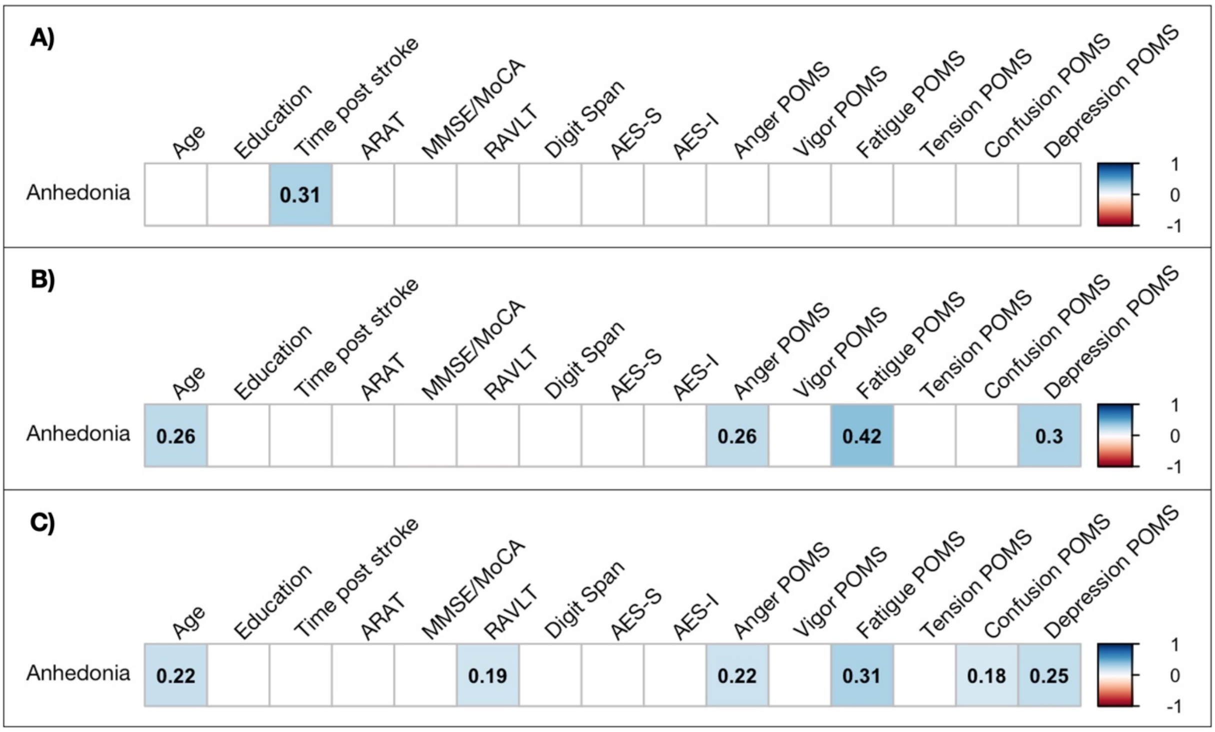


Figure 6.4. Partial correlations of anhedonia with demographic, clinical, and emotional variables.
Significant correlation coefficients are shown for A) subacute stroke, B) chronic stroke, and C) all stroke patients. $p < 0.05$. (ARAT: Action Research Arm Test; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; POMS: Profile of Mood States; POMS subscales: Anger-Hostility; Vigor-Activity; Fatigue-Inertia; Tension-Anxiety; Confusion-Bewilderment; Depression-Dejection).

After comparing anhedonia level between stroke patients and HC while controlling for the confounding effects of the other emotional outcomes, we observed significant differences between stroke and healthy samples ($t(189.72) = 5.95$; $p < .001$; anhedonia mean score in stroke patients = 2.9 ± 2.3; anhedonia mean score in healthy controls = 1.3 ± 1.4).

6.4 Discussion

Anhedonia is an enduring behavioral trait characterized by a lack of reactivity to pleasurable stimuli (Der-Avakian & Markou, 2012). Although anhedonia has been associated with high levels of depression at hospital discharge after stroke, no previous studies have explored its prevalence in subacute and chronic stroke patients with both ischemic and hemorrhagic etiologies (Sibon et al., 2012). We conducted an exploratory cohort study to investigate the prevalence and level of anhedonia in stroke survivors with upper-limb motor deficits in the subacute and chronic phases of the disease covering a wide range of time since stroke, from 1 month to 17 years after stroke. We examined demographic, clinical, cognitive, motor, and emotional factors that could be related to post-stroke anhedonia. The exploratory nature of the study aimed to check the usefulness and importance of assessing anhedonia and related factors in the stroke population at both early and late stages of the disease (Hallingberg et al., 2018).

Our results clearly showed that people who had suffered a stroke were significantly more anhedonic than people who never suffered a stroke with similar age and years of education. In both subacute and chronic stroke patients, nearly 18-20% of individuals showed a higher level of anhedonia, whereas only 4.3% of healthy controls. Importantly, studies on chronic pain and other inflammatory conditions have observed similar results (Lucido et al., 2021). For example, Garland et al. (2020) reported that nearly 25% of chronic pain patients exhibited higher anhedonia levels, which is in line with previous research demonstrating higher anhedonia levels in women suffering endometric chronic pelvic pain (Mallorqui et al., 2022). Additionally, a recent review revealed the relationship of acute and chronic stress with increased peripheral and central inflammation and consequent dysregulation of the reward system, leading to the onset or development of anhedonia (Boyle et al., 2023).

Patients with both subacute and chronic stroke showed similar levels of anhedonia regardless of stroke etiology, time since stroke, affected hemisphere, lesion location, and levels of motor and cognitive functions. In contrast to previous studies that found a correlation between stroke in the left frontal cortex or left basal ganglia and the risk for PSD (Starkstein & Robinson, 1989), the present results are in line with other studies that did not support the influence of the affected hemisphere and the exact lesion location on the development of emotional and mood disorders (Carson et al., 2000; Colita et al., 2024). Our findings align with a neurophysiological explanation based on the inflammatory effect on brain functioning, which has been increasingly recognized as a key factor in the onset or development of several psychiatric disorders, including depression (Hassamal, 2023). When an ischemic or hemorrhagic stroke occurs, it results in neuronal cell death and the release of cytokines that elicit localized inflammation in the damaged brain region, among other neurochemical events (Brouns & De Deyn, 2009; Fann et al., 2013). At six months after stroke, in the chronic phase of the disease, inflammatory cytokines levels have been found to decrease in the infarct zone and increase in more distal ipsilateral and contralateral brain areas (Hou et al., 2021; Pascotini et al., 2015; Stuckey et al., 2021). Notably, neuroinflammatory cytokines provoke a decrease in dopamine and an increase in glutamate concentrations, reducing the functional connectivity between the ventral striatum and prefrontal cortex (Felger et al., 2016). The altered neurotransmission in the reward system would result in abnormal reward valuation, abnormal calculation of required effort, and deficits in decision-making for optimal reward-based actions, thus affecting hedonic capacity (Cooper et al., 2018; Der-Avakian & Markou, 2012).

Although the state of neuroinflammation after several years after stroke remains unknow, previous studies on ischemic stroke demonstrated that inflammatory cytokines released in the acute phase can lead to damage tissue and continued cell death in the injury site and penumbra (Pascotini et al., 2015; Tobin et al., 2014). This process has been associated with a more severe, prolonged, and treatment-resistant course of this mood disorder (Hassamal, 2023). Hence, the chronic low-grade endogenous inflammation could continuously shape the pathology following stroke, promoting the ongoing impairment of the mesolimbic pathway in the long term regardless of lesion location, stroke etiology, and time since stroke (Shi et al., 2019; Stuckey et al., 2021). Additionally, these impairments in top-down cognitive-behavioral processes could alienate patients from natural and previously acquired resources of pleasure and positive experiences, potentially contributing to anhedonia development even years after stroke (Mallorqui et al., 2022).

Individuals with anhedonia are characterized by enjoying less of things in life by themselves and with others, which triggers a lack of interest in engaging in rewarding activities and participating in community life in the long term (Kusec et al., 2019). In the stroke population, this could affect the desire and motivation to initiate and complete interventions at various steps of the neurorehabilitation process, thus decreasing the likelihood of potential recovery. Engaging in rehabilitation programs has been strongly associated with improving motor, neurocognitive, psychological, biological, and socio-environmental outcomes (Maclean & Pound, 2000; Siegert & Taylor, 2004). In this vein, a negative loop could be installed in which high levels of anhedonia impede recovery, leading to a decrease in patients' autonomy and emotional well-being, which in turn could increase anhedonia levels. In our results, stroke patients demonstrated significantly lower motor and cognitive functions than healthy controls, while no differences were found between subacute and chronic groups. Based on prior evidence suggesting a correlation between moderate or severe depression and poor functional outcomes in both subacute and chronic stroke phases (Pohjasvaara et al., 2001), we expected to find a correlation between anhedonia and functional impairments. However, no associations were observed between any functional outcome and the level of anhedonia and non-anhedonic depression in both groups of patients (see Supplementary Table 12 and Supplementary Table 13 in Appendix). While improved mood has been correlated with a greater cognitive enhancement in depressed patients (Murata et al., 2000), the influence of PSD on motor recovery is not clear. Some studies found no difference in motor improvement between depressed and non-depressed patients (Nannetti et al., 2005), while others suggested a poor motor recovery in non-treated depressed stroke patients (Gainotti et al., 1997). In this vein, larger-scale longitudinal studies testing the score change in functional outcomes would be needed to explore the influence of post-stroke anhedonia on functional outcomes recovery.

Most stroke survivors must cope with a sudden reduction of their autonomy and QoL, a context that can trigger the onset or development of mood disorders such as depression, often manifesting with symptoms such as anhedonia (Der-Avakian and Markou, 2012; Feigin et al., 2017; Marcheschi et al., 2018). As expected, anhedonia after stroke was associated with a lack of motivation and negative mood states. Both groups of patients were significantly more apathetic than healthy controls. Moreover, apathy was more strongly correlated with anhedonia in chronic patients. Importantly, the decrease in affection, enthusiasm, and interest caused by apathy has been associated with delayed rehabilitation, reduced social interaction, and increased caregiver burden, affecting the QoL of patients and their relatives (Åström et al., 1992; Hama et al., 2007). Anhedonia was also strongly related to negative mood states such as fatigue-inertia, and to a lesser extent, anger-hostility, depression-dejection, tension-anxiety, and confusion-bewilderment in both groups of patients. Only the chronic group showed a decreased sense of vigor-activity related to anhedonia, suggesting the long-term negative impact of anhedonia on engaging in a healthy active lifestyle. These results are in line with a recent previous study suggesting the role of anhedonia as a predictor of somatic symptoms of depression, such as fatigue, over the first year after discharge from rehabilitation (Ashaie et al., 2023). Our findings also underlines the likely role of anhedonia in generating a deteriorating looping effect at a behavioral level (Mallorqui et al., 2022). Additionally, older patients in the chronic group exhibited higher levels of anhedonia, consistent with previous research suggesting that the ageing brain is more sensitive to neurodegeneration mechanisms (Stuckey et al., 2021). Consequently, older patients with stroke would be at a higher risk of suffering from anhedonia in the long term, not only due to the greater likelihood of social isolation (Yeh & Lo, 2004), but also because of the detrimental neurophysiological effects provoked by the brain injury. Crucially, anhedonia was significantly higher in stroke patients compared to healthy controls when controlling for the confounding effects of depression, apathy, fatigue, anger, vigor, tension, and confusion despite its strong correlation with them. This suggests the individual role of anhedonia as an emotional condition that can appear or increase in individuals after suffering a stroke.

The present study has some limitations. First, the results cannot be extrapolated to all stroke patients, as the sample was selected for its recovery potential to participate in intensive post-stroke rehabilitation programs. Therefore, the data we explored belong to a group of patients with a higher motivation and activity level than the entire stroke population. Moreover, due to the exploratory nature of this study, our sample of stroke patients was small and limited to those with upper-limb motor deficits. Considering that stroke patients also experience other neurological and cognitive impairments such as aphasia, execution dysfunction, or memory disorders (Cramer et al., 2023; Grönberg et al., 2022), our inclusion criteria made the results not representative of the entire stroke population. However, motor impairment remains one of the most prevalent consequences after stroke, with approximately half of survivors experiencing impaired upper-limb movements in the chronic phase of the disease (Ingram et al., 2021; Lee et al., 2015). Additionally, the clinical characterization of lesion location was overly broad, constraining the extent to which meaningful conclusions can be drawn regarding the impact of this variable on the development of anhedonia. Lastly, due to the difficulty of recruiting patients with identical demographic and clinical characteristics, the stroke groups were unbalanced in terms of sex and lesion location, which could affect the association of these factors with anhedonia.

6.5 Conclusion

This exploratory cohort study provides valuable insights about the prevalence, level, and factors related to anhedonia in the stroke population. The results reveal an important increase in anhedonia among individuals with ischemic and hemorrhagic stroke and at both subacute and chronic stages compared to a sample of healthy individuals. Crucially, patients exhibited similar levels of anhedonia regardless of stroke etiology, time since stroke, affected hemisphere, lesion location, and levels of motor and cognitive functions. Furthermore, anhedonia was associated with a lack of motivation and higher levels of negative mood states such as fatigue and anger, thereby reducing emotional well-being and QoL, and presumably leading to a potential decrease in engagement with rehabilitation programs. Importantly, anhedonia levels were significantly superior in stroke patients compared to healthy controls when controlling for the confounding effects of depression, non-anhedonic depression, apathy, fatigue, anger, vigor, confusion, and tension, suggesting its individual role in the stroke population. Anhedonia has been identified as a stable trait over time with poor remission despite pharmacological, psychological or neurostimulation treatments (Pizzagalli, 2022; Shankman et al., 2010). For this reason, more research is needed to explore the presence of anhedonia in large-scale cohort and longitudinal studies, including stroke patients with other functional consequences, to test its influence on long-term functional and emotional recovery. Lastly, studying the prevalence of anhedonia in patients with other neurological and inflammatory diseases would contribute to a better understanding of the etiology of this condition and help develop more effective behavioral interventions to incorporate its treatment into stroke rehabilitation programs.

General Discussion

7. General Discussion

Nowadays, around 1 in 50 people worldwide live with stroke (Institute for Health Metrics and Evaluation, 2021). Of concern, many of these individuals experience chronic upper-limb dysfunction, severely limiting their ability to perform daily activities (Ingram et al., 2021; Rafsten et al., 2019). This loss of autonomy restricts participation in family, work, and social contexts (Aked et al., 2024; Palstam et al., 2019), affecting activities that hold personal significance (Boop et al., 2020). Consequently, stroke survivors often experience social isolation and a disruption of their occupational identity, affecting their mental health and self-identity (An et al., 2023; Boop et al., 2020). Notably, research suggests that stroke survivors prioritize community belonging over functional independence (Palstam et al., 2019; Van Der Zee et al., 2013; Vargus-Adams & Majnemer, 2014). Thus, the primary goal of stroke rehabilitation in the chronic phase is to enhance autonomy and community participation rather than solely improve motor functions (Borschmann & Hayward, 2020). The increasing burden caused by this non-communicable disabling disease requires substantial personnel, infrastructure, and financial resources (Katan & Luft, 2018). Given the benefits of MST in enhancing motor function, autonomy, emotional well-being, and QoL, this thesis aimed to evaluate the effectiveness of an enriched version of MST (eMST) designed to address unmet needs of chronic stroke patients. This version incorporates motivational components, fosters peer interaction, and improves accessibility, potentially making it more cost-effective. We also aimed to explore the prevalence of anhedonia, an understudied condition that might be preventing stroke patients from engaging in rehabilitation programs (Verrienti et al., 2023).

The thesis comprises four studies addressing these clinical goals. In Study 1, we assessed the usability of the MST app for providing home-based self-training sessions, and the feasibility of the home-based eMST rehabilitation program. Feedback from five chronic stroke participants led to optimizations of both the app and rehabilitation protocol. The revised app received high usability ratings post-intervention, with all participants demonstrating clinically relevant improvements in upper-limb functionality and motor performance in daily tasks. Additionally, piano performance improved, adherence rates were high, and no safety concerns were reported, confirming the feasibility and potential benefits of home-based eMST. Study 2 involved developing a clinical trial protocol to evaluate the effectiveness of eMST compared to a conventional home-based physical program for chronic stroke. We designed a pragmatic parallel-group RCT with 40 hours of either eMST or control therapy over 10 weeks. The eMST intervention included three self-training sessions and one group-led session weekly, while the control group had four self-training sessions per week. We established a necessary sample size of 30 participants per group, with evaluations conducted pre- and post-intervention, and at three-month follow-up. The primary outcome was upper-limb functionality, and secondary outcomes included other motor and cognitive functions, emotional well-being, QoL, self-regulation, and self-efficacy. In this study, we also provided all the details regarding the musical exercises of the eMST program. In Study 3, the pragmatic RCT was conducted to compare the effectiveness of eMST to the conventional program. Both intention-to-treat and per-protocol analyses revealed that more eMST participants achieved clinically relevant improvement in upper-limb motor impairment, functionality, and performance than those in the control group. Notably, eMST participants experienced reductions in anger and apathy, increased positive emotions and community participation post-intervention, and reported having more fun during the sessions. No specific factors were associated with motor gains, and no changes were observed in other outcomes. Finally, Study 4 explored for the first time the prevalence and severity of anhedonia, as well as its clinical, demographic, and emotional correlates, among subacute and chronic stroke survivors with hemiparesis. Results indicated a higher prevalence (20%) and severity of anhedonia in stroke patients compared to healthy controls (4%), irrespective of stroke phase and the rest of clinical variables. Anhedonia was significantly associated with older age, anger, and fatigue in chronic stroke survivors when controlling for confounding effects of non-anhedonic depression, highlighting its distinct role in long-term emotional well-being after stroke.

Below, I address the findings from the four studies. First, I discuss eMST's effectiveness in reducing motor impairment and enhancing autonomy, participation, emotional well-being, and QoL. Second, I talk about the mechanisms underlying its benefits. Third, I highlight the importance of addressing affective and social needs of chronic stroke survivors, including the reconstruction of their occupational identity. Lastly, I address the strengths and limitations of this work and suggest future research directions.

7.1 Benefits of enriched Music-supported Therapy in chronic stroke

7.1.1 Upper-limb impairment, functionality, and everyday use

The primary finding of this thesis is that, for the first time, a Music-supported Therapy (MST) program outperformed conventional therapy in improving upper-limb motor functions and autonomy after stroke (Fujioka et al., 2018; Grau-Sánchez et al., 2018). In Study 3, participants with chronic stroke who underwent the enriched version of MST (eMST) showed significant reductions in upper-limb motor impairment after 40 hours of training over 10 weeks, with improvements maintained after three months. They also exhibited greater enhancements in paretic upper-limb functionality at follow-up compared to those in the control group. The assessment of motor impairment involved specific joint movements, such as elbow flexion and extension, or shoulder abduction and adduction (Fugl-Meyer et al., 1975). The improvements in these movements likely facilitated more complex motor functions, such as grasping and pinching, after three months. Indeed, prior evidence suggested that motor impairment measured with FMA-UE is a reliable predictor of upper-limb functionality measured with ARAT following stroke (Chen et al., 2022). Additionally, Study 3 found that eMST participants demonstrated better motor performance in everyday tasks three months post-intervention, showing that motor skills acquired with eMST can be generalized to daily tasks unrelated to the musical activity (Reinkensmeyer et al., 2016). Importantly, these motor gains can promote sense of competence, autonomy, and community participation (Aked et al., 2024; Palstam et al., 2019; Wulf & Lewthwaite, 2016). This is particularly crucial since reduced autonomy in daily life has been documented between two- and fifteen-years after stroke (Hartman-Maeir et al., 2007; Teasdale & Engberg, 2005), and residual motor deficits are the strongest predictors of autonomy in chronic stroke (Moore & Barnett, 2012).

The results in Study 3 were anticipated based on findings from the pilot Study 1, where participants exhibited clinically relevant improvements in upper-limb functionality, motor performance in daily tasks, and motor impairment after completing only 30 hours of self-training MST sessions using the initial version of the app. The benefits observed in Study 3 were thus likely influenced by the patient-centered approach applied in Study 1, where we optimized both the app and the rehabilitation program based on end-users' feedback (Laurisz et al., 2023). This underscores the value of conducting pilot studies to assess the feasibility and usability of novel interventions prior to clinical trials (Craig et al., 2008).

Previous MST studies have also demonstrated clinically relevant improvements in upper-limb functionality and motor impairment using the same tests employed here (ARAT and FMA-UE) in both subacute (Altenmüller et al., 2009; Grau-Sánchez et al., 2013, 2018; Schneider et al., 2007; Tong et al., 2015) and chronic stroke (Amengual et al., 2013; Grau-Sánchez et al., 2017; Ripollés et al., 2015; Rojo et al., 2011). Some studies reported significant long-term improvements in motor performance tasks, using the same assessment we applied (CAHAI) for subacute and chronic patients (Grau-Sánchez et al., 2017, 2018). However, none of the studies comparing MST with conventional therapies (PT, OT, or GRASP) reported superior outcomes for MST in subacute and chronic stroke survivors (Fujioka et al., 2018; Grau-Sánchez et al., 2018), highlighting the benefits of elements incorporated in eMST (Study 2).

In this thesis (Studies 1 and 3), the home-based eMST intervention showed a slight trend toward improving fine and gross manual dexterity and grip strength (measured with the NHPT, BBT and a dynamometer, respectively), but was not enough to outperform the control intervention. Prior MST trials have demonstrated significant improvements in gross manual dexterity and grip strength in both subacute (Altenmüller et al., 2009; Grau-Sánchez et al., 2013, 2018; Schneider et al., 2007; Van Vugt et al., 2014, 2016) and chronic patients (Grau-Sánchez et al., 2017; Ripollés et al., 2015). However, only two studies focused on home-based MST piano sessions with chronic stroke reported significant improvements in finger dexterity using the NHPT (Villeneuve et al., 2014; Villeneuve & Lamontagne, 2013). This raises the possibility that motor gains may be difficult to observe with this test after stroke (Grau-Sánchez et al., 2017; Ripollés et al., 2015), or that more intense training may be required (Wittenberg et al., 2003). However, the lack of improvements in this test did not impede enhancements in upper-limb functionality and motor performance in daily tasks.

When exploring the piano performance progression throughout 30 one-hour self-training eMST sessions over 10 weeks (Study 1), we observed a tendency for improved speed tapping during the first few weeks of training. According to motor learning theories, the development of this skill progressed rapidly at the onset of training, with practice facilitating motor memory consolidation by the end (Censor et al., 2012). The substantial clinical improvements in functional hand movements observed at the end of the intervention may have been supported by the acquisition of speed tapping skills. However, we did not observe a similar trend in force tapping, which could explain the lack of significant gains in grip strength in Study 3. In this case, participants may have found that using less force on the keys allowed for faster playing. Although we assessed clinical motor improvements only after the intervention, these results align with those reported by Grau-Sánchez et al. (2017), where initial improvements in speed tapping occurred during the first MST period, while clinical gains in gross manual dexterity, upper-limb functionality, motor performance in daily tasks, grip strength, and kinematic properties were noted during the subsequent MST period (Grau-Sánchez et al., 2017).

The eMST's benefits observed in Study 3 are highlighted by three factors. First, the conventional treatment used as a control intervention was GRASP, which has shown to be effective in several prior trials for motor rehabilitation in chronic stroke survivors (Klempel et al., 2023). Second, all motor gains were evident both in the group of participants who completed the entire intervention as planned and in all randomized participants (including those who withdrew before the end of the intervention). This reflects effectiveness in real-world circumstances despite patient discontinuation rates (Hollis & Campbell, 1999). Third, the gains in upper-limb functionality and motor impairment were not influenced by participants' stroke etiology or baseline motor deficits, musical hedonia, or intrinsic motivation before and during the intervention. However, in Study 1 motor improvements were more pronounced in patients with severe hemiparesis, and in Study 3, the eMST group exhibited slightly higher baseline motor deficits than the control group, which indicate a greater potential for motor function recovery and consequent improvements (Alawieh et al., 2018). Notably, previous MST studies typically included only participants with mild to moderate paresis, while Study 3 encompassed a broader range of motor deficits, from slight to severe. This underscores eMST's potential benefits for a wider range of patients regardless of clinical and personal factors.

7.1.2 Emotional well-being and reintegration into community

Beyond improving upper-limb functionality, a primary goal of eMST is to enhance the overall QoL for chronic stroke survivors by promoting their autonomy and reintegration into community life. In Study 3, patients undergoing eMST reported significantly greater increases in self-perceived positive emotion and community participation post-intervention compared to the control group. These results are particularly important given that unmet needs related to socialization and community involvement have a substantial impact on the QoL of chronic stroke survivors (Chen et al., 2019; McNamara & Dalton, 2024; Shaik et al., 2024). Furthermore, participants in the eMST program experienced reduced feelings of anger, and their relatives perceived them as less apathetic compared to those in the control group. This finding is critical considering that in Study 4 we observed a high prevalence of apathy among stroke survivors (53% in the subacute and 62% in the chronic phases compared to 30% in healthy controls). In this context, eMST could promote motivational behaviors to enhance rehabilitation engagement, crucial for maintaining or improving physical and mental health after stroke (Moore & Barnett, 2012; Ramasubbu et al., 1998). Notably, the adherence rate was higher in the eMST group than in the GRASP group, despite participants not differing in baseline characteristics. In addition, those who dropped out exhibited higher levels of anger, fatigue, confusion, tension, and depression, highlighting the need for interventions focused on improving mood and emotional well-being.

Although emotional outcomes were not assessed in Study 1, prior MST trials consistently showed significant improvements in emotional well-being, including reductions in depression, anxiety, and fatigue, alongside increases in mood, positive affect, and QoL in subacute and chronic patients (Grau-Sánchez et al., 2018; Ripollés et al., 2015; Van Vugt et al., 2014, 2016). The most recent trial comparing MST to GRASP in chronic stroke patients also found increased self-perceived positive emotion and community participation, but the improvements were similar between groups (Fujioka et al., 2018). In contrast, our findings indicate that eMST outperformed GRASP in enhancing these aspects, suggesting that the group sessions integrated into eMST (Study 2) could foster feelings of connectedness, social inclusion, and life satisfaction, consistent with outcomes from other community-based stroke programs (Zeng et al., 2023).

Another notable finding is that participants in eMST reported having more fun during sessions than those in GRASP. This enjoyment likely contributed to increase positive affect and intrinsic motivation to complete the intervention (Gentsch & Synofzik, 2014; Wulf & Lewthwaite, 2016). Similar findings were reported by Ripollés et al. (2015), indicating higher arousal levels during MST sessions.

Furthermore, Van Vugt et al. (2014) noted that patients in paired MST sessions perceived their partners as more sympathetic when playing in turns rather than simultaneously. In eMST group sessions, participants often played instruments in turns due to technical constraints of conducting sessions remotely via Zoom, which could enhance their positive affect despite the physical distance.

The emotional and social benefits of eMST highlight the value of adapting the program for home use and incorporating group sessions, which increased access to rehabilitation and supported the reintegration of patients into community life (Cott et al., 2007; Magwood et al., 2020; Zeng et al., 2023). This emphasizes the need to evaluate the level of functioning within the IFC framework years after stroke, considering not only body functions but also activity levels and participation, both of which significantly contribute to QoL (ICF, World Health Organization, 2001; Vargus-Adams & Majnemer, 2014).

7.1.3 Mechanisms underlying the effectiveness of enriched Music-supported Therapy

The motor benefits observed with MST stem from key rehabilitation principles: massive repetition of upper-limb movements, immediate auditory feedback reinforcing actions, adaptive complexity and difficulty of exercises based on individual progress, and emotional and motivational aspects associated with music-making and learning a new skill (Schneider et al., 2007; Rodriguez-Fornells et al., 2012). These principles facilitate a learning process that allows for lasting neural and behavioral changes (Moore & Barnett, 2012; Nudo, 2007). In motor learning, enduring reorganization of sensorimotor areas and improved motor functions arise from dopaminergic projections linking brain regions involved in reward, attention, and memory consolidation (Dayan & Cohen, 2011; Draganski & May, 2008). Thus, inherent rewards and attentional processing are crucial for optimizing motor learning and reestablishing motor functions after stroke (Wulf & Lewthwaite, 2016).

The MST protocol offers a music training program that is enjoyable, task-specific, and goal-oriented (i.e., playing an instrument). The intrinsic reward of music fosters engagement in musical activities (Mas-Herrero et al., 2013; Zatorre & Salimpoor, 2013), while having a meaningful rehabilitation goal unrelated to health outcomes can increase patients' motivation and focus on the actions required to achieve it (Chun & Turk-Browne, 2007; Dorstyn et al., 2014; Moore & Barnett, 2012). On one hand, intrinsic motivation drives behaviors that yield inherent rewards, stimulating dopamine release and enhancing motor learning (Swanson & Whittinghill, 2015; Verrienti et al., 2023; Wulf & Lewthwaite, 2016). On the other hand, attentional processing guides the brain in prioritizing relevant information for task performance, also optimizing learning (Fishman et al., 2021; Kitago & Krakauer, 2013; Posner et al., 2014). Particularly, an external focus to the task goal (i.e., playing an instrument correctly) promotes unconscious movements that enhance motor performance (Marchant et al., 2009; Pascua et al., 2015), thereby increasing competence and motivation (Wulf & Lewthwaite, 2016). Furthermore, auditory feedback from instruments allows for movement adjustments, improving performance and optimizing learning (Rodriguez-Fornells et al., 2012; Wulf & Lewthwaite, 2016).

Despite these beneficial elements, MST has not previously outperformed conventional rehabilitation programs. In contrast, eMST is the first to show superior gains compared to a conventional program, suggesting that its socio-motivational and learning components (detailed in Study 2) enhanced its effectiveness, leading to improved motor and emotional outcomes for individuals with chronic stroke (Study 3). First, we increased training intensity. Prior studies on MST for chronic stroke provided between 10 and 30 hours of training delivered over a period of 4 to 10 weeks. By extending this to 40 hours over 10 weeks, eMST likely facilitated greater motor improvements, as higher intensity and longer duration are essential for effective recovery in chronic stroke patients (Kitago & Krakauer, 2013). However, since the training intensity of the GRASP intervention was the same, other elements in eMST must have enhanced its effectiveness in improving motor function. Second, we adapted the MST program for home-based self-training by developing an app for electronic tablets (Study 1). In eMST, patients were responsible for independently scheduling their interventions, enabling them to complete the program entirely at home and avoid hospital visits. This approach likely enhanced participants' feelings of autonomy and facilitated their reintegration into community life (Study 3). Importantly, autonomy is a basic psychological need that allows humans to achieve optimal functioning. The fulfillment of this basic need during motor training can enhance dopamine release, intrinsic motivation, and long-term retention of motor skills (Dayan & Cohen, 2011; Draganski & May, 2008; Wulf & Lewthwaite, 2016). Third, the MST app integrates gamification strategies to boost intrinsic motivation. Notably, eMST participants in Study 3 reported greater enjoyment during the sessions and had lower dropout rates, suggesting that they were more intrinsically motivated throughout the intervention. The sentence flows well and is appropriate for a PhD thesis. It clearly conveys the relationship between enjoyment, dropout rates, and intrinsic motivation. In this vein, consistent positive feedback should enhance motor performance expectations and positive affect, both critical for successful performance and optimized learning (Ostir et al., 2008; Wulf & Lewthwaite, 2016). Fourth, incorporating percussion instruments with varied movements expanded the range of joint motions, including wrist flexion and extension, shoulder internal and external rotation, forearm supination and pronation, and fingers mass flexion and extension (as detailed in Study 2). The training of these movements in Study 3 resulted in significant improvements in upper-limb motor impairment post-intervention, as well as long-term enhancements in complex motor tasks such as grasping and griping, leading to greater engagement of the paretic upper limb in daily activities (Moore & Barnett, 2012). Additionally, the inclusion of eight different percussion instruments catered to a wider range of musical tastes, potentially boosting intrinsic motivation among participants (Wulf & Lewthwaite, 2016). Patients were also given the autonomy to choose the order in which they played the instruments during sessions, further enhancing their sense of control and promoting motor learning (Wulf & Lewthwaite, 2016). Fifth, the inclusion of temporal cues and progressively challenging rhythmic patterns in the percussion exercises allowed participants to anticipate and plan movements effectively (Rodriguez-Fornells et al., 2012). This feedforward loop, coupled with auditory feedback, contributes to reacquiring motor skills. Moreover, we tailored the difficulty of percussion exercises to individual deficits, which likely enhanced self-efficacy, performance expectations, and a sense of competence, all intrinsic rewards that stimulate dopamine release, maximizing motor learning and functional recovery after stroke (Wulf & Lewthwaite, 2016).

Lastly, we included guided group music therapy sessions to foster social interaction, strengthen social bonds, and facilitate reintegration into community life. Considering that individuals with chronic stroke tend to feel alone and socially isolated (An et al., 2023), providing the opportunity to socialize in an enriched context is crucial to improve patients' QoL (Levy et al., 2019). Noteworthy, the sense of relatedness (i.e., having relationships where one feels respected and cared) is also a basic psychological need. In this vein, fulfilling this need with group sessions can provoke an intrinsic reward that enhance motivation to complete the whole training (Chang et al., 2020; Verrienti et al., 2023; Wulf & Lewthwaite, 2016). Furthermore, the collaborative goal of recording favorite songs during the group sessions in Study 3 may have further boosted motivation and engagement, thereby enhancing eMST effectiveness (Wulf & Lewthwaite, 2016). Finally, therapist involvement during group sessions could enhance treatment effectiveness by providing feedback, reinforcement, and confidence-building (Moore & Barnett, 2012).

Interestingly, improvements in upper-limb motor functions in Study 3 were not influenced by participants' ability to derive pleasure from music, contrary to the findings from Grau-Sánchez et al. (2018) on MST for subacute stroke patients. In eMST, the opportunity for socialization in a community setting likely played a more significant role in motivation, regardless of musical anhedonia. The remote nature of group sessions and technical limitations often led to participants playing in turns, which could reduce frustration and enhance learning through observation (Van Vugt et al., 2014). In Study 1, participants exhibited clinically relevant motor improvements despite not completing group sessions. In this case, their involvement in designing the app and rehabilitation program could have enhanced their feelings of competence and autonomy, thereby optimizing their motor learning during the intervention (Wulf & Lewthwaite, 2016).

7.2 The role of socio-motivational aspects for stroke recovery

7.2.1 Addressing anhedonia after stroke

In Study 4, we found that approximately 20% of stroke survivors exhibited higher levels of anhedonia, with no significant differences between 1 month and 17 years after stroke, compared to about 4% of healthy individuals of similar age and education. This suggests that stroke survivors are more likely to experience a diminished capacity to enjoy everyday pleasures, significantly reducing their interest in rewarding activities and community participation over the long term (Kusec et al., 2019). Such psychological conditions can negatively impact stroke survivors' motivation to engage in rehabilitation programs, decreasing their likelihood of recovery and potentially exacerbating anhedonia (Maclean & Pound, 2000; Siegert & Taylor, 2004).

While anhedonia is often associated with depression, present in approximately 55% of stroke survivors (Medeiros et al., 2020; Sibon et al., 2012), Study 4 demonstrated that its presence after stroke is independent of levels of depression, non-anhedonic depression, apathy, and various negative mood states, including fatigue, anger, vigor, tension, and confusion, despite its strong correlation with them. When we controlled for non-anhedonic depression, which is closely linked to anhedonia, we observed distinct affective patterns across stroke phases. In subacute stroke survivors, anhedonia was primarily related to the time since the stroke, which could indicate its onset or development after the stroke's impact on neural and behavioral levels (Mohr et al., 1997; Moore & Barnett, 2012; Pessoa, 2008). In contrast, chronic stroke individuals with higher levels of anhedonia tended to be older, angrier, and more fatigued. This correlation with negative mood states in the chronic phase highlights anhedonia's potential role in creating a detrimental feedback loop that adversely affects stroke survivors years after onset (Mallorqui et al., 2022). Indeed, chronic stroke patients with higher levels of anhedonia exhibited increased apathy, along with decreased vigor and activity levels, emphasizing its long-term negative impact on maintaining an active and healthy lifestyle.

Interestingly, the presence of anhedonia was not influenced by patients' motor and cognitive functioning, stroke etiology, affected hemisphere, lesion location, or time since the stroke. Consistent with studies on other inflammatory conditions (e.g., chronic pain and endometriosis) that report an anhedonia prevalence of around 25% (Garland et al., 2020; Lucido et al., 2021; Mallorqui et al., 2022), post-stroke anhedonia may be linked to inflammatory responses that disrupt the reward system (Boyle et al., 2023; Felger et al., 2016). Indeed, this link is supported by prior research on various psychiatric disorders, including depression (Hassamal, 2023). Physiological alterations in the reward system can lead to abnormal reward valuation, effort calculations, and decision-making deficits, all crucial for engaging in rewarding activities (Cooper et al., 2018; Der-Avakian and Markou, 2012). The enduring tissue damage and ongoing cell death following a stroke (Pascotini et al., 2015; Tobin et al., 2014) can result in chronic low-grade inflammation, contributing to a more severe, prolonged, and treatment-resistant course of anhedonia, regardless of stroke-related clinical factors (Hassamal, 2023; Shi et al., 2019; Stuckey et al., 2021). However, we noted an age-related influence in the chronic group, where older stroke patients demonstrated higher levels of anhedonia, likely due to the aging brain's sensitivity to neurodegenerative mechanisms (Stuckey et al., 2021). This underscores the importance of addressing anhedonia several years after a stroke to mitigate its negative neurophysiological effects, especially in older patients.

Importantly, in **Study 3** we found that eMST significantly reduced feelings of anger and apathy, two variables closely associated with anhedonia in chronic stroke survivors in **Study 4**. Although we did not observe significant changes in anhedonia levels post-intervention, participants undergoing eMST showed a trend toward reduced anhedonia three months later compared to the control group. The greater enjoyment reported in eMST sessions suggests its potential to activate the reward system, helping to diminish anhedonia and increase engagement in rehabilitation programs perceived as more rewarding than conventional treatments (Ostir et al., 2008; Wulf & Lewthwaite, 2016). Indeed, interventions addressing psychosocial factors have been previously shown to decrease post-stroke depression and apathy (Medeiros et al., 2020), both of which are prevalent mood disorders that hinder engagement in various activities (Moore & Barnett, 2012; Ramasubbu et al., 1998).

Additionally, participants in **Study 3** who dropped out of both intervention groups exhibited significantly higher baseline levels of anger, fatigue, confusion, tension, and depression compared to those who completed the whole intervention. Prior research has suggested that depression not only leads to lack of motivation but also fatigue after stroke (Moore & Barnett, 2012), which can hinder community participation (Van Der Zee et al., 2013). Our findings emphasize the necessity of developing rehabilitation programs that address the socio-emotional needs of chronic stroke survivors, as well as assessing and treating anhedonia, which may be may preventing patients from maintaining optimal mental and physical health (Medeiros et al., 2020).

7.2.2 The importance of social support and interaction

As a social species, maintaining relationships within our social networks is crucial for our health and well-being (Mellor et al., 2008). In a qualitative study examining factors that promote well-being 10 years after stroke, patients highlighted spouses, family, and friends as the most significant contributors to their well-being, emphasizing the importance of social networks (Brunborg & Ytrehus, 2014). It is therefore not surprising that, in **Study 3**, participants who dropped out of the intervention reported significantly less social support compared to those who completed it. These participants also experienced higher levels of anger, fatigue, confusion, tension, and depression at baseline. Among these negative mood states, depression is strongly associated with a lack of social support, which increases the risk of developing more severe depression (Medeiros et al., 2020). Social support is also a critical predictor of community participation after stroke, offering protective benefits through emotional support, motivation for treatment, and assistance with daily activities (Medeiros et al., 2020; Van Der Zee et al., 2013).

Although we found no significant differences in dropout reasons between the intervention groups, 12 participants in the control group abandoned the program compared to only six in the eMST group, despite similar baseline characteristics (**Study 3**). Group music therapy sessions led by a therapist could have improved treatment adherence by enhancing participants' sense of relatedness. Music is known to foster social bonding, supporting the evolutionary hypothesis that human musicality developed to promote social connections. This idea is reinforced by prior research showing that music-making facilitates social bonding regardless of group size (Savage et al., 2021). The biological mechanisms underlying this benefit are based on the release of neurochemicals during synchronized human activities, especially musical interactions. These chemicals include endorphins (linked to pleasure and pain relief), oxytocin (promoting trust and empathy), serotonin (involved in mood regulation and stress reduction), and dopamine (key in motivation and reward processes) (Chanda & Levitin, 2013; Fancourt & Finn, 2019; Moraes et al., 2018; Savage et al., 2021; Tarr et al., 2014). It has been demonstrated that synchronized music-making, such as drumming, engages brain regions involved in movement and social cognition, enhancing positive affect and motor performance more effectively than music listening (Launay et al., 2016). During the group music therapy sessions conducted in **Study 3**, participants often played instruments in turns due to sound constraints during Zoom sessions. However, the warm-up exercises involved simultaneous body percussion to patient-selected songs, allowing participants to see their synchronized movements and potentially boosting positive affect and feelings of belonging.

Additionally, motor behavior in humans is socially contextual, with stereotypes tied to expected performances based on age and gender. The presence of more individuals may either provide reassurance or create pressure to perform better. In rehabilitation settings, group training with peers and a healthcare professional has been shown to positively influence motor performance (Wulf & Lewthwaite, 2016). Therapeutic relationships fosters group cohesion, a construct that includes individual attraction to the group, integration around tasks, and social bonding (Pohl et al., 2018). Peer support is particularly beneficial for stroke survivors' QoL, since it allows them to share common fears and advice with those who have similar experiences (Levy et al., 2019). Indeed, prior evidence has suggested that shared moods and a sense of community in a musical context fosters positive emotion (Stige, 2012). In this context, group sessions in **Study 3** should have played a vital role in enhancing individuals' self-perceived positive emotion and community participation after the intervention. Previous evidence suggests that being part of a community and feeling accepted, without being disadvantaged due to disability, is essential for enhancing the QoL of stroke survivors (Cott et al., 2007). Given the high likelihood of isolation among the chronic stroke population, it is crucial offering opportunities for peer socialization (An et al., 2023; Levy et al., 2019).

7.2.3 Reconstruction of the occupational identity

The impact of a stroke on an individual's life varies widely, shaped by numerous clinical, personal, and environmental factors. These variables influences the recovery process from motor function improvements to the reconstruction of self-identity (Martin-Saez & James, 2021). Indeed, a common concern for many stroke survivors, even years after the event, is a disrupted sense of identity (Shaik et al., 2024). Approximately 72% of stroke survivors report a lack of meaningful activities that once formed part of their occupational identity (Bergström et al., 2017; Boop et al., 2020; Mayo et al., 2002). Since occupational identity is integral to self-identity and mental health, its disruption often leads to feelings of emptiness, diminished self-worth, and even a sense of uselessness (Palstam et al., 2019; Van Der Zee et al., 2013; Vargus-Adams & Majnemer, 2014). Therefore, finding new ways of living after stroke is critical for maintaining individuals' mental health and QoL (Palstam et al., 2019).

Several factors contribute to the disruption of occupational identity after a stroke, including physical impairments, reduced autonomy, and altered social interactions, all of which limit participation in meaningful activities (Hartman-Maeir et al., 2007). Additionally, acceptance of their new reality plays a role in how individuals engage with their communities, influencing their ability to pursue significant activities (Palstam et al., 2019). While some stroke survivors find new activities or ways to reinvent their occupational selves, others struggle with self-confidence, leading to avoidance of both old and new tasks for fear of failure and frustration. This maladaptive response further exacerbates the disruption of occupational identity (Martin-Saez & James, 2021).

In this context, leisure activities have been shown to enhance engagement and participation in life, reducing social isolation and boredom while improving well-being and QoL (An et al., 2023; Hartman-Maeir et al., 2007; O'Sullivan & Chard, 2010; Teasdale & Engberg, 2005). Through leisure, stroke survivors can find new meaningful activities that help rebuild their occupational identity, fostering a more active lifestyle with physical and mental health benefits (Brunborg & Ytrehus, 2014; Dorstyn et al., 2014; Morris et al., 2015; Teasdale & Engberg, 2005). In this line, musical training offers a leisure activity for individuals with chronic conditions to adapt or replace valued activities they can no longer pursue. Given the benefits of eMST in improving upper-limb functions, positive emotion, and perceived community participation in chronic stroke survivors (**Study 3**), this music-based rehabilitation program not only can help patients mitigate physical disability but also offers a meaningful activity that can contribute to occupational identity. By improving upper-limb functionality, eMST can also enhance individuals' awareness of their motor skills (Ellis-Hill et al., 2000). This could foster self-confidence and motivation to try activities they previously avoided, thereby reestablishing aspects of their pre-stroke lifestyle (An et al., 2023; Boop et al., 2020).

Nowadays, hospitals offer limited opportunities for meaningful occupational participation. Given the significant impact that occupational identity disruption has on mental health (Palstam et al., 2019; Van Der Zee et al., 2013; Vargus-Adams & Majnemer, 2014), there is a pressing need for more occupation-focused community-based rehabilitation programs, such as eMST. These programs can offer stroke survivors opportunities to engage in valued occupations, allowing them to either reinvent their occupational self or pursue their desired identity (Martin-Saez & James, 2021).

7.3 Strengths and limitations of the present work

This doctoral thesis proposes an effective and accessible musical training program for the rehabilitation of individuals with chronic stroke, contributing into the growing field of music-based interventions for this population. In addition, it provides new evidence on the affective and motivational factors that can hinder individuals in maintaining optimal physical and mental health after stroke.

A key strength of this work is its patient-centered and pragmatic approach, which allowed us to optimize a rehabilitation treatment and demonstrate its real-world benefits. In Study 1, involving end-users in the development of both the MST app and the rehabilitation program enabled us to address the needs of chronic stroke survivors, thereby enhancing the intervention's effectiveness (Chávez et al., 2019; Laurisz et al., 2023; Wright & McCarthy, 2010). Additionally, the collaboration between healthcare and software development professionals within a transdisciplinary team resulted in a more successful digital health solution, potentially having a greater impact on global healthcare (Kokol, 2022). However, due to the pilot nature of the study, we included only five participants, but a larger sample size would have allowed for better refinement of the MST app and rehabilitation protocol. Despite the diversity in sociodemographic and clinical characteristics, including varying levels of hemiparesis, this limited number of participants did not adequately represent the stroke population with upper-limb dysfunction.

A major strength in Study 3 is the demonstration of eMST's real-world benefits for chronic stroke rehabilitation. The pragmatic design of this study included chronic stroke patients with diverse sociodemographic and clinical profiles, ranging from severe to slight paresis, with varying lesion locations, stroke etiology, and time since stroke (from 6 months to 14 years). Participants were also allowed to maintain their usual routines while engaging in the study, reflecting real-life circumstances. Furthermore, we assessed the effectiveness of the intervention through per-protocol (i.e., including only those participants who completed the interventions as planned) and intention-to-treat analyses (i.e., including all randomized participants, even those who dropped out), which provided insights into the intervention's real-world applicability (Hollis & Campbell, 1999). However, the multiple imputations required for the intention-to-treat analysis were applied with a 30% missing data rate from participants who dropped out, which diminishes the reliability of the reported motor gains (Pedersen et al., 2017). Notably, we found no effect of stroke-related clinical variables on motor improvements. Nevertheless, a limitation of both Studies 3 and 4 is the broad classification of lesion locations, which hampers the robustness of our findings regarding eMST's effectiveness on recovery among patients with varying clinical profiles and those experiencing anhedonia after stroke.

We also established that eMST is effective compared to the Graded Repetitive Arm Supplementary Program (GRASP; Harris et al., 2009), a validated home-based conventional motor program that has proven effective in enhancing motor functions among chronic stroke survivors (Klempel et al., 2023). Noteworthy, this program is highly endorsed by the Canadian Stroke Best Practice Recommendations for the Upper Extremity (Hebert et al., 2016), suggesting the potential for eMST's future implementation in public health services. However, it is important to note the absence of group sessions in the control intervention, which may have contributed to eMST's superior outcomes in both motor and emotional domains. Further research is thus needed to disentangle the socio-motivational and learning components that may account for eMST's effectiveness. In addition, although we measured the long-term effects of the interventions after three months, future longitudinal assessments incorporating qualitative structured interventions are essential for evaluating eMST's impact on physical and mental health over the years and its influence on patients' occupational identity. Furthermore, although the modification of the intervention for home use aimed to reduce economic expenditure for patients, we did not assess the cost-effectiveness of the intervention, a gap that future research should address.

Regarding the MST app (Studies 1 and 3), there are limitations that future research should consider. First, the app currently gathers data only on piano exercises, as the MIDI-piano is connected to the electronic tablet. However, the motor performance parameters for percussion exercises during self-training sessions are not recorded. While in Study 3 the therapist played a crucial role in monitoring compensatory movements during group sessions, movement sensors would have provided more accurate monitoring of motor performance. Additionally, exercises were prescribed manually by therapists based on participants' baseline motor deficits and progression, but future research should develop AI software to automate exercise prescriptions based on data collected during sessions (e.g., accuracy of notes played, rhythms followed, and time taken to complete exercises).

Another limitation is the recruitment of participants from a single hospital in Barcelona for **Studies 1** and **3**, and from two hospitals in the same city for **Study 4**. In clinical research, multicentric trials provide several benefits over unicentric trials, since they enhance reliability and generalizability by including a larger sample with varied clinical and sociodemographic profiles, allowing for a broader application of findings (Chung et al., 2010). Despite the local nature of our studies, the preparation and publication of the RCT protocol in **Study 2**, which outlines the new elements of eMST and provides detailed explanations of the musical exercises, are crucial for ensuring replicability. Replication is essential for validating innovative rehabilitation programs across different countries, assessing their impact on stroke survivors with diverse clinical and sociodemographic profiles, and evaluating their effects on various health systems worldwide (Van Stan et al., 2019). In addition, both the RCT protocol (**Study 2**) and the RCT (**Study 3**) followed CONSORT guidelines in reporting methods and results, ensuring transparency, reliability, and internal and external validity. This consistency minimizes biases, confounding factors, and errors, while also enabling the real-world application of the findings and their inclusion in systematic reviews. Thus, the methodological development of eMST, including the co-design and usability evaluation of the MST app, the feasibility assessment of the home-based program, protocol publication, and reporting of its benefits in accordance with CONSORT guidelines, meets all standards for improving evidence-based clinical practice (Hopewell et al., 2022).

Additionally, **Studies 1**, **3**, and **4** have inherent biases due to participant selection, as stroke survivors who agree to participate are generally more motivated. Moreover, our exclusion criteria eliminated individuals with lower global cognitive levels or conditions affecting comprehension or language, therefore diminishing the generalizability of eMST's effectiveness and the extrapolation of anhedonia prevalence to the entire stroke population (Cramer et al., 2023; Grönberg et al., 2022). Future research should explore these gaps in the stroke population, particularly among those with functional and affective deficits. Nevertheless, motor impairment remains the most prevalent consequence of stroke in both subacute and chronic phases, with approximately half of survivors experiencing upper-limb movement decifits in the chronic phase (Ingram et al., 2021; Lee et al., 2015). Furthermore, **Study 4** stands out for including a broad range of time since stroke, with participants ranging from 1 month to 17 years after stroke, which enhanced the generalizability of our results.

7.4 Future directions

7.4.1 Adapting enriched Music-supported Therapy according to individual needs

As we detailed throughout this work, eMST incorporates various socio-motivational elements that enhance its effectiveness. This program promotes patient autonomy by offering home-based self-training sessions that enable individuals to manage aspects of their rehabilitation while encouraging socialization in peer-group sessions. We also incorporated motivational features, such as gamification elements in the MST app and the use of different percussion instruments to train upper-limb motor functions. While we have demonstrated eMST's effectiveness in improving motor functions, emotional well-being, QoL, and self-regulation outcomes, further research is needed to disentangle the effects of each component. A more detailed evaluation of patients' profiles should consider stroke-related clinical variables, sociodemographic factors, functional and affective states, self-regulation and self-efficacy behaviors, personality traits, contextual factors, unmet needs, technological competence, prior musical experience, and dimensions of musical hedonia.

By obtaining a comprehensive profile of each patient, we could adapt and personalize eMST beyond just their level of motor deficit, addressing their unique features and needs. For instance, individuals with lower global cognitive function, diminished self-efficacy, or lack of social support may struggle to use the MST app effectively on their own. In such cases, prescribing more group sessions than self-training sessions or involving a therapist during home-based sessions until patients become accustomed to the technology could be more appropriate and avoid feelings of frustration. Conversely, some individuals may not enjoy social interaction as much as others, or they may not feel the need for additional socialization beyond their daily activities. These patients might prefer to focus on enhancing their fine manual dexterity and could benefit from more hours of self-training with piano exercises rather than percussion exercises. By personalizing the program in this way, we can provide an effective rehabilitation program tailored to individual needs, thereby optimizing the rehabilitation process and enhancing their QoL. Additionally, this approach could expand the program's applicability to patients with various neurological conditions, including traumatic brain injury, cerebral palsy, multiple sclerosis, and neurodegenerative diseases.

7.4.2 Implementation of the enriched Music-supported Therapy program

The WHO states that music-based interventions lead to significant improvements in well-being and QoL, encouraging engagement in musical activities to promote healthy lifestyles (Fancourt & Finn, 2019; McCrary et al., 2022). Given the lack of access to rehabilitation during the chronic phase of stroke (Chen et al., 2019), which represents a major unmet need for many chronic stroke survivors experiencing residual upper-limb dysfunction (Ingram et al., 2021; Lin et al., 2021; Moore & Barnett, 2012), the implementation of accessible, cost-effective, and community-based musical training rehabilitation programs could have significant medical and social benefits. Such programs may reduce the burden of stroke while promoting healthy lifestyles among individuals with enduring physical impairments. The eMST’s effectiveness in enhancing upper-limb motor functions, emotional well-being, QoL, and self-regulation makes the commercialization of the MST app a promising telerehabilitation solution. This approach would provide ongoing access to rehabilitation from home, particularly benefiting individuals in rural areas or those with lower incomes (Tamayo-Serrano et al., 2018).

The commercialization process should involve various stakeholders, including stroke survivors, caregivers, healthcare professionals, institutions, and policymakers, to refine the MST app before its launch. Their feedback on the current prototype would guide necessary modifications. Proposed enhancements may include integrating movement sensors to track upper-limb movements during percussion exercises, and developing AI software for automated exercise prescriptions based on collected data regarding motor performance and training intensity. Additionally, allowing users to select their own songs for both percussion and piano exercises can boost intrinsic motivation and enhance motor recovery (Sihvonen et al., 2017; Wulf & Lewthwaite, 2016). We should also strive to simplify the device and its technological elements to increase usability for a broader audience. Furthermore, it is crucial to minimize the risk of injury by avoiding extreme movements, such as rapid motions or poor posture. Therefore, the motor sensors should be designed to detect these potentially harmful movements and alert both the patient and therapist (Tamayo-Serrano et al., 2018).

Once the refinement process is complete, obtaining the necessary regulatory approvals and certifications for the app would be essential to ensure compliance with data privacy and medical device regulations. Following this, we should test its feasibility, viability, effectiveness, and cost-effectiveness in real-world scenarios. If successful, we could establish a sustainable business model for market entry, where healthcare institutions and rehabilitation organizations play a critical role in integrating the MST app into existing care pathways and recommending it to suitable patients. In this context, the MST app would serve as a new therapeutic solution that optimizes healthcare management processes and reduces overall burdens on the system (Laurisz et al., 2023).

7.4.3 Exploring the long-term effects of motivational factors after stroke

In Study 4, we found a high and persistent prevalence of anhedonia among stroke survivors, irrespective of stroke etiology or time since stroke. Importantly, anhedonia levels in these patients were higher compared to healthy controls, even after accounting for other common affective disorders following stroke, such as apathy and depression. This suggests that anhedonia may have a distinct onset and progression after brain injury. Furthermore, negative mood states, including fatigue and anger, were notably linked to anhedonia, particularly during the chronic phase of the disease. Therefore, it is essential to conduct a larger-scale study to assess the prevalence of anhedonia in patients with varying functional and affective impairments.

Additionally, the evidence regarding the influence of mood disorders, particularly depression, on functional recovery is inconsistent. Some studies report no difference in motor improvement between depressed and non-depressed patients (Nannetti et al., 2005), while others indicate that untreated depression correlates with poorer motor recovery in stroke patients (Gainotti et al., 1997). Given that anhedonia can hinder engagement in rewarding activities, it may significantly impact functional recovery. To address this gap, a longitudinal study is warranted to explore the long-term effects of anhedonia on maintaining optimal physical and mental health in stroke survivors. For the analyses, employing linear mixed models could help investigate the potential causes and consequences of anhedonia following a stroke. New insights into this condition may lead to the development of rehabilitation strategies tailored to meet the socio-emotional needs of chronic stroke survivors (Medeiros et al., 2020). Such strategies could enhance training adherence and promote active lifestyles, ultimately contributing to improved QoL for individuals several years after stroke.

Conclusions

8. Conclusions

This doctoral thesis evaluated the effectiveness of the enriched version of Music-supported Therapy (eMST), an instrumental training program designed to enhance the rehabilitation of chronic stroke survivors through the integration of socio-motivational and learning components. The eMST intervention was adapted for home use and combines both self-training and group music therapy sessions to foster autonomy and social interaction, respectively. We also increased training intensity and introduced new instruments, upper-limb movements, and rhythmic patterns to aid the reacquisition of motor skills. To facilitate home-based intervention, we developed a tablet-based application that provides instructions for musical exericses and incorporates gamifications strategies to boost engagement.

The first version of the MST app was refined based on feedback from chronic stroke survivors, resulting in a user-friendly application that proved feasible for home use, achieving high adherence rates and posing no safety concerns. A 10-weeks intervention consisting of 30 hours of home-based self-training eMST sessions demonstrated to promote clinically relevant changes in upper-limb functionality and motor performance in daily tasks, as well as improvements in the speed of piano performance, particularly during the initial weeks.

The 10-week eMST program, which included 30 hours of self-training and 10 hours of group music therapy sessions, yielded greater improvements in motor and emotional outcomes compared to a conventional home-based physical program of equivalent intensity. The music-based intervention led to more substantial gains in upper-limb motor impairment after the intervention, which were maintained after three months, as well as in upper-limb functionally and motor performance in daily tasks at follow-up. Notably, motor improvements were observed among both participants who adhered to the intervention plan and those who dropped out before completing the entire program, underscoring its real-world benefits. Furthermore, motor gains were not linked to clinical, sociodemographic, or personal variables. The absence of a correlation between individuals' levels of musical hedonia and motor improvements suggests that factors such as social interaction may play a more significant role in motor recovery. Crucially, eMST also resulted in a greater reduction in anger and apathy, along with an increase in positive emotion and community participation after the intervention. Moreover, the eMST sessions were perceived as more fun and enjoyable than the control intervention. The elements incorporated into the eMST may have enhanced autonomy, socialization, and intrinsic motivation, which are vital for promoting both motor learning and emotional well-being.

Finally, this work underscores the high and enduring prevalence of anhedonia among stroke survivors, affecting 20% of participants compared to only 4% in a healthy control group. Crucially, these differences were observed when controlling for the influence of other negative emotions, indicating the distinct role and development of anhedonia following a stroke. The prevalence of anhedonia was consistent across stroke survivors, regardless of stroke etiology, lesion location, affected hemisphere, or time since stroke, suggesting a potential effect of low-grade chronic inflammation that disrupts the mesolimbic pathway. Furthermore, anhedonia was associated with older age, anger, and fatigue in chronic stroke survivors when controlling for the confounding effects of non-anhedonic depression, highlighting its individual impact in the chronic phase of stroke. This condition, marked by diminished sensitivity to everyday pleasures, may hinder patients from engaging in rewarding activities, potentially reducing their adherence to rehabilitation programs. Further research is needed to explore the etiology and long-term consequences of anhedonia and address its treatment in the stroke population.

[CAT] Conclusions

Aquesta tesi doctoral ha avaluat l’efectivitat de la versió enriquida de la Teràpia amb suport Musical (eMST), un programa d'entrenament instrumental dissenyat per millorar la rehabilitació de supervivents d'ictus crònic mitjançant la integració de components socio-motivacionals i d'aprenentatge. La intervenció eMST va ser adaptada per a ús domiciliari i combina sessions d’autoentrenament amb sessions de musicoteràpia grupal per fomentar l'autonomia i la interacció social, respectivament. També vam augmentar la intensitat de l'entrenament i vam introduir nous instruments, moviments de l'extremitat superior, i patrons rítmics per ajudar a la recuperació de les habilitats motores. Per facilitar la intervenció domiciliària, vam desenvolupar una aplicació per tauleta electrònica que proporciona instruccions per als exercicis musicals i incorpora estratègies de gamificació per augmentar l’adherència.

La primera versió de l'aplicació MST va ser refinada en funció de les opinions i suggeriments de supervivents d'ictus crònic, resultant en una aplicació fàcil d’utilitzar i viable per a l'ús domiciliari, aconseguint elevades taxes d'adherència i sense comportar problemes de seguretat. Una intervenció de 10 setmanes, amb un total de 30 hores d'autoentrenament domiciliari amb MST, va demostrar promoure canvis clínicament rellevants en la funcionalitat de l'extremitat superior i el rendiment motor en les tasques de la vida diària, així com millores en la velocitat d'execució al piano, especialment durant les primeres setmanes.

El programa eMST de 10 setmanes, que incloïa 30 hores d'autoentrenament i 10 hores de sessions de musicoteràpia grupal, va generar millores més grans en els resultats motors i emocionals en comparació amb un programa de rehabilitació motora convencional domiciliari d'intensitat equivalent. La intervenció basada en la música va conduir a guanys més substancials en la reducció de la discapacitat motora de l'extremitat superior després de la intervenció, que es van mantenir després de tres mesos, així com en la funcionalitat de l'extremitat superior i el rendiment motor en les tasques diàries en el seguiment a llarg termini. Cal remarcar que les millores motores es van observar tant en els participants que van seguir el pla d'intervenció com en aquells que es van retirar abans de completar tot el programa, ressaltant els seus beneficis en circumstàncies reals. A més, els guanys motors no es van correlacionar amb variables clíniques, sociodemogràfiques, o personals. L'absència de correlació entre els nivells d'hedonia musical dels individus i les millores motores suggereix que factors com la interacció social poden jugar un paper més significatiu en la recuperació motora. És important destacar que l'eMST també va donar lloc a una major reducció de la ira i l'apatia, juntament amb un major augment d'emocions positives i participació comunitària després de la intervenció. A més, les sessions d'eMST van ser percebudes com més divertides i agradables que la intervenció de control. Els elements incorporats a l'eMST poden haver potenciat l'autonomia, la socialització, i la motivació intrínseca, aspectes fonamentals per promoure tant l'aprenentatge motor com el benestar emocional.

Finalment, aquest treball emfatitza l'alta i persistent prevalença de l'anhedonia entre els supervivents d'ictus, afectant el 20% dels individus en comparació amb només el 4% d'un grup d'individus controls sans. Crucialment, aquestes diferències es van observar controlant la influència d'altres emocions negatives, indicant el paper i el desenvolupament únic de l'anhedonia després d'un ictus. La prevalença de l'anhedonia va ser consistent entre els supervivents d'ictus, independentment de l'etiologia de l'ictus, la localització de la lesió, l'hemisferi afectat, o el temps des de l'ictus, suggerint un possible efecte d'una inflamació crònica de baix grau que altera la via mesolímbica. A més, l'anhedonia es va associar amb l'edat avançada, la ira i la fatiga en supervivents d'ictus crònic quan es van controlar els efectes de la depressió no anhedònica, destacant el seu impacte individual en la fase crònica de l'ictus. Aquesta condició, marcada per una disminució de la sensibilitat als plaers quotidians, pot dificultar que els pacients participin en activitats gratificants, reduint potencialment la seva adherència als programes de rehabilitació. Així doncs, futura investigació és necessària per explorar l'etiologia i les conseqüències a llarg termini de l'anhedonia, i abordar el seu tractament en la població d'ictus.

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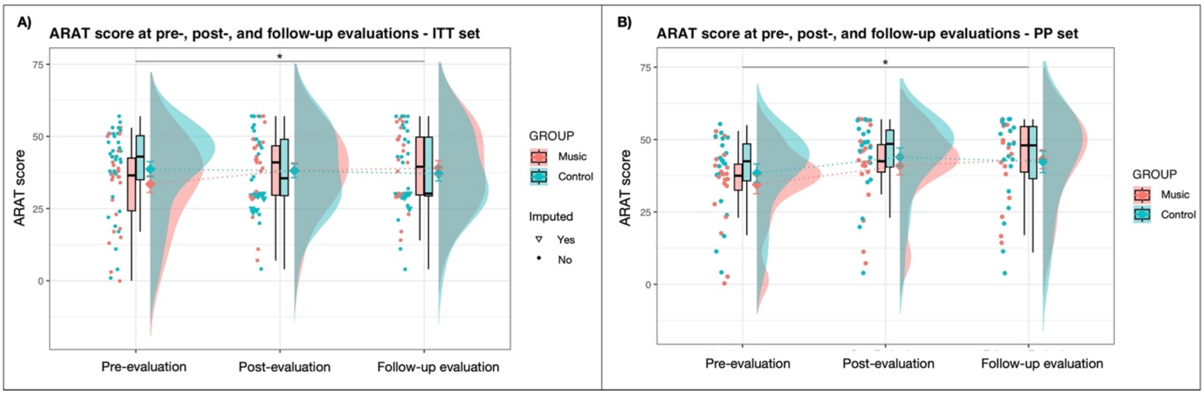
Appendix

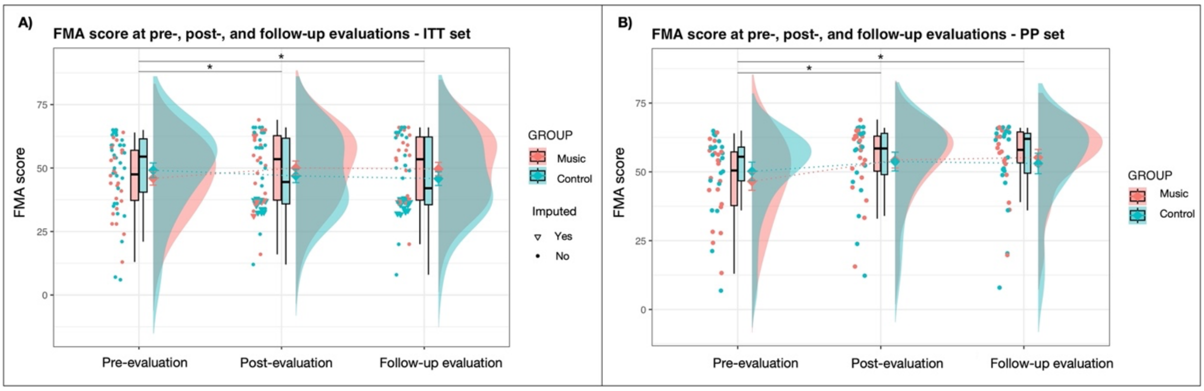
Appendix

Supplementary Figures

Study 3

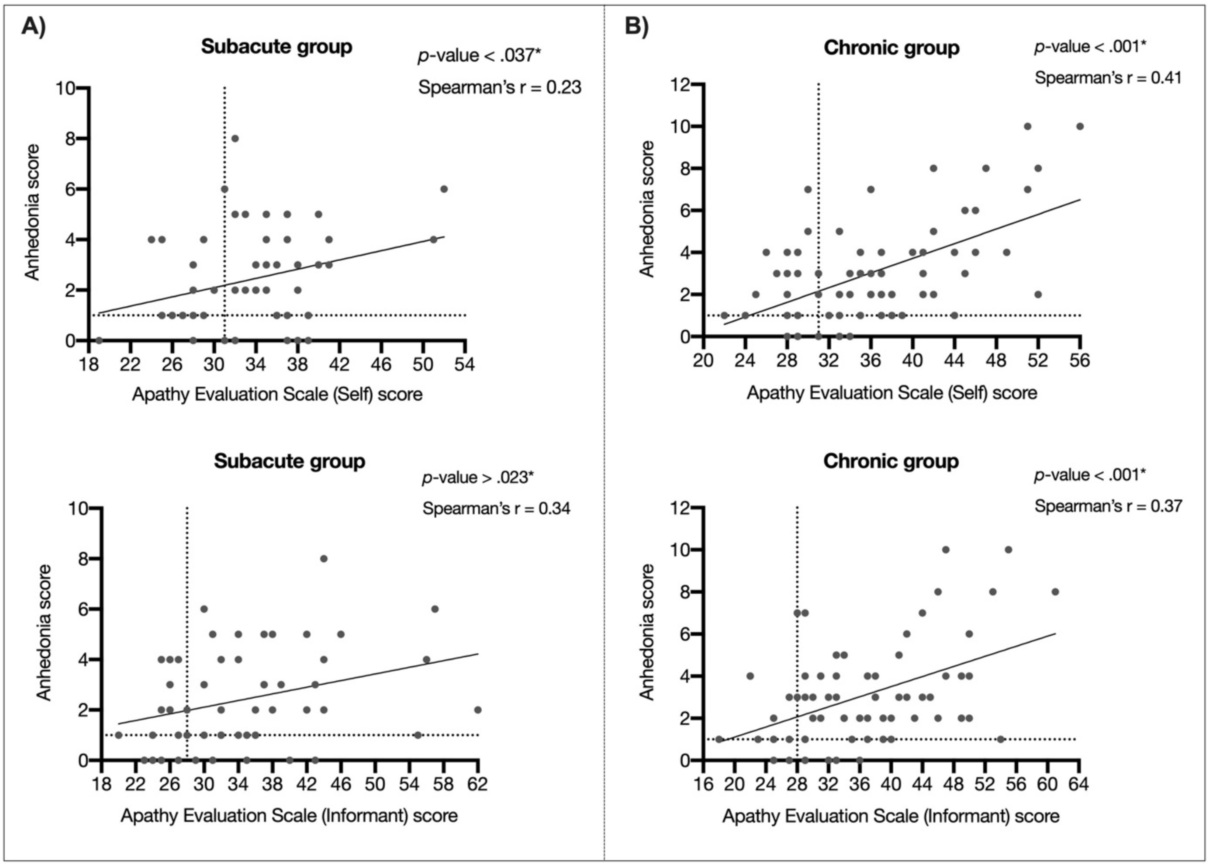


Supplementary Figure 1. Distribution of ARAT scores.
These graphs show the distribution of ARAT scores at each evaluation point for both groups with the A) Intention-to-treat set, and B) Per-protocol set.

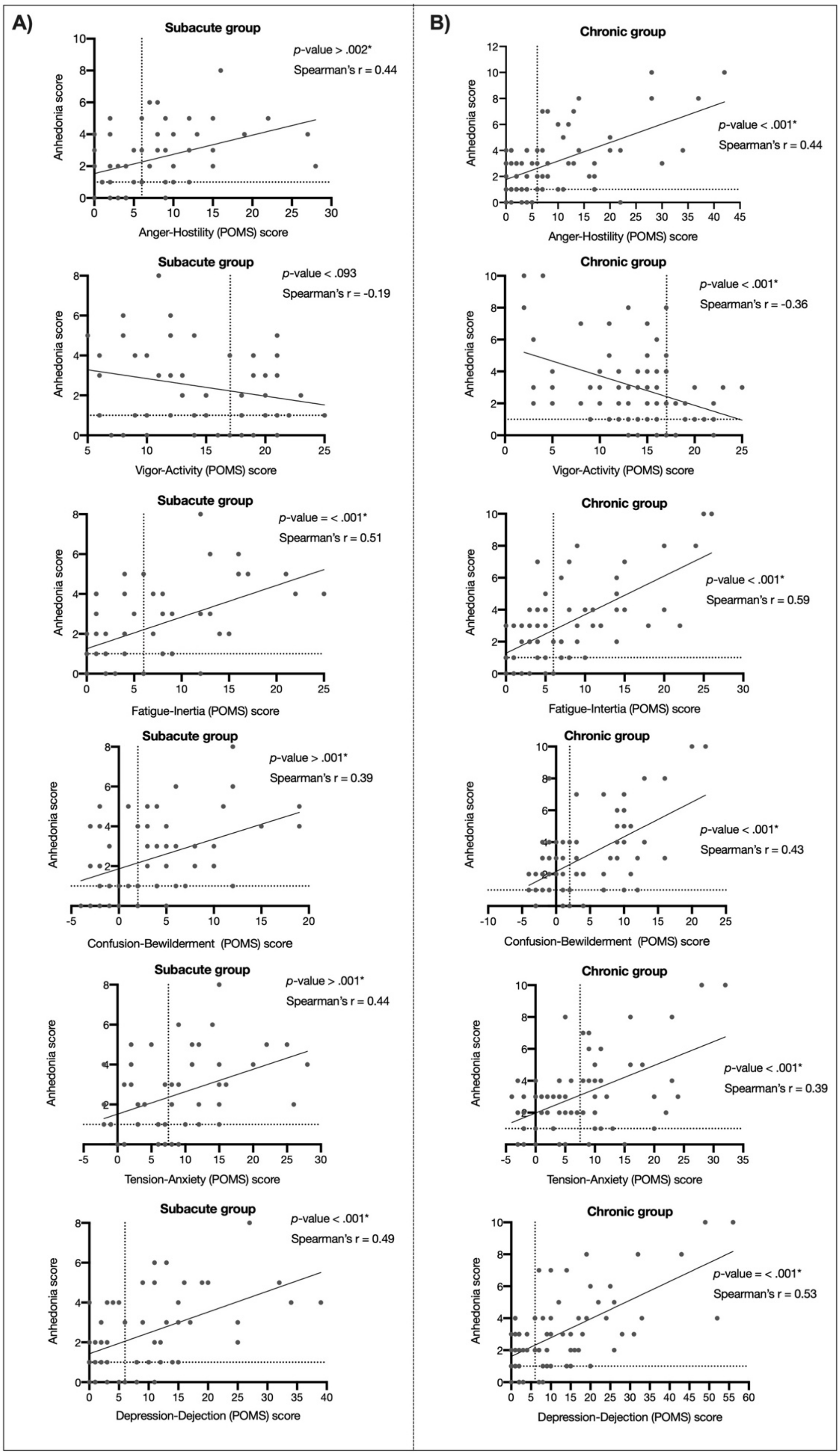


Supplementary Figure 2. Distribution of FMA-UE scores.
These graphs show the distribution of FMA-UE scores at each evaluation point for both groups with the A) Intention-to-treat set, and B) Per-protocol set.

Study 4



Supplementary Figure 3. Correlations plots of anhedonia with apathy scales.
These graphics show the correlation between the anhedonia score and self- and informant-versions of apathy scores for A) subacute stroke, and B) chronic stroke.



Supplementary Figure 4. Correlations plots of anhedonia with POMS.
These graphics show the correlation between anhedonia scores and all POMS subscales scores for A) subacute stroke, and B) chronic stroke. (POMS: Profile of Mood States).

Supplementary Tables

Study 3

Supplementary Table 1. Baseline characteristics of completers for both groups.
Baseline characteristics among eMST and control group participants who completed the intervention and whose data were included in the PP analysis.

Characteristic	eMST group (n=20)	Control group (n=20)	p-v
Socio demographic variables			
Age, mean (SD), y	64.05 (10.52)	64.95 (12.14)	.804
Females, No. (%)	4 (20)	5 (25)	.999
Education, mean (SD), y	19.1 (4.2)	17 (4.8)	.151
Clinical variables			
Ischemic stroke, No. (%)	12 (60)	13 (65)	.999
Lesion location, No. (%)			.091
Cortical	0 (0)	1 (5)	
Cortico-subcortical	2 (10)	5 (25)	
Subcortical	14 (70)	8 (40)	
Brainstem	1 (5)	5 (25)	
Cerebellum	3 (15)	1 (5)	
Time since stroke, median [IQR], y	2.6 [2.6]	2 [7.7]	.570
Upper extremity motor function			
Affected dominant hand (%)	11 (55)	11 (55)	.999
MRCS (range), median [IQR]	3.5 [1]	4 [1]	.171
Fugl-Meyer Assessment baseline, median [IQR]	50.5 [19.5]	55.5 [12.3]	.316
Cognitive functions			
MoCA, mean (SD)	25.1 (2.3)	24.6 (2.5)	.510
Mild cognitive impairment level, No. (%)	10 (50)	13 (65)	.523
Digit span (WAIS), median [IQR]	12.5 [2.5]	11 [2.5]	.595
Vocabulary (WAIS), mean (SD)	12.42 (3.17)	12 (3.27)	.689
Boston Naming Test, median [IQR]	13 [2.3]	13.5 [1]	.989
Musical reward and skills			
Barcelona Music Reward Questionnaire (extended), mean (SD)	82.8 (14.4)	74.3 (21.8)	.167
MBEA scale, mean (SD)	24.9 (5.4)	21.8 (4.7)	.060
MBEA rhythm, mean (SD)	25.8 (3.5)	24.1 (3.9)	.150
Perseverance and social support			
Grit, mean (SD)	3.8 (0.6)	3.8 (0.5)	.826
Social Support, median [IQR]	6 [0.9]	5.7 [1.2]	.635
Emotional state			
Beck Depression Inventory – II, median [IQR]	8 [7]	10.5 [8.3]	.175
Anhedonia (Beck Depression Inventory – II subscale), median [IQR]	2 [2.3]	3 [2]	.321
Apathy Evaluation Scale (Self-version), mean (SD)	33 (6)	35.7 (6.9)	.193
Apathy Evaluation Scale (Informant-version), mean (SD)	33.4 (7.3)	36.8 (10.6)	.250
Anger-Hostility (Profile of Mood State), median [IQR]	6 [6.3]	5.5 [9.8]	.356
Vigor-Activity (Profile of Mood State), mean (SD)	14.5 (4.6)	13.9 (5.7)	.716
Fatigue-Inertia (Profile of Mood State), mean (SD)	5.6 (5.5)	8.3 (5.2)	.117
Confusion-Bewilderment (Profile of Mood State), median [IQR]	2 [2]	1 [4.5]	.900
Tension-Anxiety (Profile of Mood State), median [IQR]	3 [6]	4.5 [6.3]	.370
Depression-Dejection (Profile of Mood State), median [IQR]	4 [8.3]	11 [11.3]	.074
Strength (Stroke Impact Scale), mean (SD)	40.3 (21.1)	45.9 (12.7)	.315
Memory (Stroke Impact Scale), mean (SD)	79.8 (17)	73 (22.3)	.285
Emotion (Stroke Impact Scale), mean (SD)	73.7 (17.6)	65.4 (19.7)	.166
Communication (Stroke Impact Scale), median [IQR]	96.4 [19.8]	89.3 [22.3]	.490
Activity (Stroke Impact Scale), mean (SD)	61.6 (25)	64.4 (24)	.725
Mobility (Stroke Impact Scale), median [IQR]	75 [34]	72.2 [45.1]	.892
Hand function (Stroke Impact Scale), mean (SD)	40.8 (32.3)	43 (26.3)	.811

Characteristic	eMST group (n=20)	Control group (n=20)	p-v
Participation (Stroke Impact Scale), mean (SD)	69.7 (23.8)	63.9 (21)	.423
Recovery (Stroke Impact Scale), median [IQR]	55 [22.5]	60 [30]	.912

Supplementary Table 2. Baseline characteristics: completers vs. non-completers.
Baseline characteristics of participants who completed the intervention versus those who did not.

Characteristic	Included (n = 40)	Excluded (n = 18)	p-v
Socio demographic variables			
Age, mean (SD), y	64.5 (11.2)	59.8 (13.8)	.218
Females, No. (%)	9 (22.5)	5 (27.8)	.744
Education, mean (SD), y	18.1 (4.6)	19.3 (3.9)	.230
Clinical variables			
Ischaemic stroke, No. (%)	25 (62.5)	14 (77.8)	.367
Time since stroke, median [IQR], y	2.3 [3.8]	1.7 [3.8]	.391
Upper extremity motor function			
Affected dominant hand, No. (%)	22 (55)	7 (38.9)	.395
Fugl-Meyer Assessment baseline, median [IQR]	54 [17.3]	48 [29]	.951
Action Research Arm Test baseline, median [IQR]	39.5 [12.3]	41 [31]	.749
Global cognitive function			
Montreal Cognitive Assessment, mean (SD)	28.9 (2.4)	25.8 (2.9)	.214
Global Executive Composite (Self)	59 (12.6)	65.5 (11.5)	.078
Global Executive Composite (Informant)	54.5 (10.5)	65.2 (16.2)	.059
Perseverance and social support			
Grit Scale, mean (SD)	3.8 (0.5)	3.5 (0.6)	.170
Social Support, median [IQR]	6 [1]	4.8 [2.6]	.019*
Emotional state			
Beck Depression Inventory – II, median [IQR]	8 [9]	13 [11.5]	.070
Anhedonia (Beck Depression Inventory – II subscale), median [IQR]	3 [3]	3 [2]	.166
Apathy Evaluation Scale (Self-version), mean (SD)	34.4 (6.5)	38.7 (7.3)	.056
Apathy Evaluation Scale (Informant-version), mean (SD)	35 (9)	36.8 (10)	.569
Anger-Hostility (Profile of Mood State), median [IQR]	6 [8.5]	10 [14]	.018*
Vigor-Activity (Profile of Mood State), median [IQR]	14 [5]	15 [5.5]	.791
Fatigue-Inertia (Profile of Mood State), median [IQR]	5 [7]	14 [14.5]	.037*
Confusion-Bewilderment (Profile of Mood State), median [IQR]	2 [2.3]	8 [9.5]	.005*
Tension-Anxiety (Profile of Mood State), median [IQR]	4 [6]	10 [19.5]	.038*
Depression-Dejection (Profile of Mood State), median [IQR]	7.5 [12.3]	20 [24]	.004*
Strength (Stroke Impact Scale), median [IQR]	43.1 (17.4)	38.4 (20.3)	.447
Memory (Stroke Impact Scale), median [IQR]	82.1 [28.6]	75 [37.1]	.685
Emotion - Stroke Impact Scale, mean (SD)	69.6 (18.9)	59.3 (15.8)	.057
Communication (Stroke Impact Scale), median [IQR]	94.6 [22.3]	94.6 [22.3]	.936
Activity - Stroke Impact Scale, mean (SD)	63 (24.3)	56.5 (23.9)	.396
Mobility (Stroke Impact Scale), median [IQR]	73.6 [41.7]	56.9 [40.3]	.343
Hand function (Stroke Impact Scale), median [IQR]	40 [46.3]	22.5 [47.5]	.247
Participation - Stroke Impact Scale, mean (SD)	66.8 (22.3)	56.4 (31)	.266
Perceived recovery - Stroke Impact Scale, median [IQR]	60 [30]	50 [37.5]	.764

Supplementary Table 3. Proportion of participants reaching a relevant change in ARAT.
Proportion of participants who reached the MCID in Action Research Arm Test (ARAT) at post- and follow-up evaluations for both groups and analysis sets.

Set	Group	Post-evaluation				Follow-up evaluation			
		N (%)	OR (95% CI)	Statistic	p-v	N (%)	OR (95% CI)	Statistic	p-v
ITT	eMST (n = 26)	13.9 (53.5)	1.6 (0.6 to 4.6)	F = 0.403	.526	16 (61.5)	3.7 (1.3 to 11.1)	F = 4.790	.029*
	GRASP (n = 32)	13.3 (41.6)				9.6 (30)			
PP	eMST (n = 20)	11 (55)	1.5 (0.4 to 5.2)	$X^2 = 0.100$	.752	12 (66.7)	4.5 (1.2 to 17.4)	$X^2 = 4.545$	.033*
	GRASP (n = 20)	9 (45)				5 (26.3)			

Supplementary Table 4. Improvements in ARAT.
Mean improvement in Action Research Arm Test (ARAT) at post- and follow-up evaluations for both groups and analysis sets.

Set	Group	Post-evaluation				Follow-up evaluation			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
ITT	eMST (n = 26)	6 [6]	2 (0.8 to 3.1)	F = 0.930	.336	1 [14.2]	6 (5.5 to 6.5)	F = 5.669	.017*
	GRASP (n = 32)	3.5 [16.4]				6 [9.8]			
PP	eMST (n = 20)	6.5 (3.7)	0.9 (-1.8 to 3.7)	t = 0.702	.487	9.2 (5.1)	5.1 (1.8 to 8.4)	t = 3.156	.003*
	GRASP (n = 20)	5.6 (4.8)				4.1 (4.7)			

Supplementary Table 5. Proportion of participants reaching a relevant change in FMA-UE.
Proportion of participants who reached the MCID in Fugl-Meyer Assessment – Upper Extremity (FMA-UE) at post- and follow-up evaluations for both groups and analysis sets.

Set	Group	Post-evaluation				Follow-up evaluation			
		N (%)	OR (95% CI)	Statistic	p-v	N (%)	OR (95% CI)	Statistic	p-v
ITT	eMST (n = 26)	14.3 (55)	4.5 (1.4 – 14)	F = 5.470	.019*	17 (65.4)	4.7 (1.5 – 14.3)	F = 5.924	.029*
	GRASP (n = 32)	6.9 (21.6)				9.2 (28.8)			
PP	eMST (n = 20)	12 (60)	6 (1.5 – 24.7)	$X^2 = 5.104$	.024*	14 (77.8)	5.4 (1.4 – 21.1)	$X^2 = 6.192$	.013*
	GRASP (n = 20)	4 (20)				6 (31.6)			

Supplementary Table 6. Improvements in FMA-UE.

Mean improvement in Fugl-Meyer Assessment – Upper Extremity (FMA-UE) at post- and follow-up evaluations for both groups and analysis sets.

Set	Group	Post-evaluation				Follow-up evaluation			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
ITT	eMST (n = 26)	5 [7.5]	6 (5.5 to 6.5)	F = 5.620	.018*	7 [7.7]	6.5 (4.4 to 8.6)	F = 5.669	.023*
	GRASP (n = 32)	1.2 [9.5]				0.5 [14.2]			
PP	eMST (n = 20)	7.8 (5.5)	4.2 (0.9 to 7.5)	t = 2.565	.014*	9.8 (6.7)	6.4 (2.1 to 10.7)	X^2 = 3.156	.005*
	GRASP (n = 20)	3.6 (4.8)				3.4 (6.1)			

Supplementary Table 7. Improvements in secondary motor outcomes.
Mean improvement in secondary motor outcomes at post- and follow-up evaluations for both groups in the per-protocol analysis set.

Outcome	Group	Post-evaluation				Follow-up evaluation			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
Chedoke Arm and Hand Activity Inventory	eMST	7 [4.8]	2 (-2 to 4)	W = 221	.578	10.9 (7.1)	5.6 (0.8 to 10.5)	t = 2.353	.024*
	GRASP	5 [5.3]				5.3 (7.5)			
Box and Blocks Test	eMST	1.5 (3.9)	-0.5 (-3.1 to 2.2)	t = -0.350	.729	1.8 (3.2)	-0.3 (-3.5 to 2.9)	t = -0.176	.862
	GRASP	2 (4.3)				2.1 (6)			
Nine Hole Pegboard Test	eMST	-3 [12]	-1 (-12 to 5)	W = 120.5	.588	2 [11.5]	5 (-3 to 11)	W = 160	.226
	GRASP	-2 [8]				-3 [6]			
Grip Strength (mean of three scores)	eMST	1.8 [4]	-0.2 (-2 to 2.2)	W = 194.5	.892	1.6 [2.8]	0.2 (-1.6 to 2)	W = 177	.650
	GRASP	2 [3]				1.4 [3.8]			
Grip Strength (maximum of three scores)	eMST	1.5 [2.5]	-1.3 (-3 to 1.5)	W = 158	.261	1 [2.9]	-0.8 (-2.2 to 1.5)	W = 156	.862
	GRASP	2.8 [3.7]				1.8 [3.6]			

Supplementary Table 8. Improvements in secondary cognitive outcomes.
Mean improvement in secondary cognitive outcomes at post- and follow-up evaluations for both groups in the per-protocol analysis set.

Outcome	Group	Post-evaluation				Follow-up evaluation			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
Behavioural Regulation Index (Self-version)	eMST	-4.5 [6.8]	- 0.5 (-3 to 6)	W = 210	.582	-5.5 [6.3]	- 1.5 (-9 to 8)	W = 156.5	.670
	GRASP	-4 [6.5]				-4 [20]			
Metacognition Index (Self-version)	eMST	-4 [6.8]	0 (-4 to 6)	W =210.5	.786	-5 [8.3]	-2 (-10 to 1)	W =122.5	.144
	GRASP	-4 [9]				-3 [12]			
Global Executive Composite (Self-version)	eMST	-4.3 (9.5)	0.8 (-4.7 to 6.3)	t = 0.298	.769	-6.2 (8.4)	-3 (-9.2 to 3.1)	t = -0.993	.328
	GRASP	-5.1 (7.3)				-3.2 (10)			
Behavioural Regulation Index (Informant-version)	eMST	-3.8 (5.6)	-3.2 (-8.5 to 2)	t = -1.261	.218	-2.3 (8.4)	0.1 (-5.2 to 5.5)	t = 0.054	.957
	GRASP	-0.6 (9.9)				-2.4 (7.6)			
Metacognition Index (Informant -version)	eMST	-2.5 [6.3]	-0.5 (-5 to 4)	W = 176.5	.714	-0.5 [4.5]	2.5 (-1 to 8)	W = 220	.140
	GRASP	-2 [6.5]				-3 [7]			
Global Executive Composite (Informant -version)	eMST	-2.5 [5]	-1.5 (-6 to 5)	W =171.5	.612	-0.5 [4.5]	2.5 (-0.7 to -3.6)	t = 1.201	.238
	GRASP	-1 [9.5]				-3 [7]			
Sustained Attention to Response Task (% correct answers)	eMST	0.4 [5.8]	0.2 (-2.5 to 4.1)	W =212	.758	0.9 [4.8]	0.2 (-4.7 to 2.5)	W = 156	.663
	GRASP	0.2 [4.2]				0.7 [6.8]			
Sustained Attention to Response Task (reaction time, milliseconds)	eMST	-23.6 (91.3)	-22.1 (-71.2 to 27)	t = -0.918	.366	-17.2 (113.3)	-19.9 (-82.2 to 42.4)	t = -0.657	.517
	GRASP	-1.5 (57.3)				2.7 (62.4)			
Figural Memory WMS-III: Recall score	eMST	1.3 (2.9)	0.5 (-1.7 to 2.6)	t = 0.415	.673	1.6 (2.8)	-0.6 (-2.4 to 1.3)	t = -0.597	.554
	GRASP	0.8 (3.7)				2.2 (2.8)			
Figural Memory WMS-III: Retention rate	eMST	1 (2.9)	-0.2 (-2.1 to 1.7)	t = -0.208	.836	1.7 (3.3)	0.5 (-1.5 to 2.6)	t = 0.506	.617
	GRASP	1.2 (3.1)				1.2 (2.8)			
Figural Memory WMS-III: Copy score	eMST	2.2 (3.3)	2.2 (-0.2 to 4.5)	t = 1.866	.070	1 [3]	1 (-1 to 5)	W = 198	.251
	GRASP	0 (4)				0 [7]			
Figural Memory WMS-III: Recognition score	eMST	1.1 (2.6)	1.3 (-0.1 to 2.7)	t = 1.853	.073	2 (3.9)	0.4 (-0.9 to 3.7)	t = 1.300	.212
	GRASP	-0.2 (1.8)				0.6 (2.7)			
Rey Auditory Verbal Learning Test: Sum of short-term recall	eMST	0.7 (8.1)	0.1 (-4.8 to 5)	t = 0.041	.968	5.6 (10.1)	-0.4 (-6.8 to 6)	t = -0.123	.903
	GRASP	0.6 (7.3)				6 (9)			

Outcome	Group	Post-evaluation Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Follow-up evaluation Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
Rey Auditory Verbal Learning Test: Long-term retention	eMST	0.5 (7.2)	1 (-4.5 to 6.4)	t = 0.352	.727	2.4 (6.9)	1.3 (-3.4 to 5.9)	t = 0.560	.579
	GRASP	-0.5 (9.6)				1.1 (7.1)			
Rey Auditory Verbal Learning Test: Recognition score	eMST	1.4 (20.3)	0.8 (-10.6 to 12.2)	t = 0.143	.887	3.6 (20.6)	0.2 (-11.2 to 11.5)	t = 0.024	.981
	GRASP	0.6 (14.7)				3.4 (11.4)			
Verbal Fluency Task: Phonetic	eMST	1 (2.6)	-0.7 (-2.4 to 0.9)	t = -0.923	.352	-0.1 (3)	-1 (-2.6 to 0.6)	t = -1.311	.203
	GRASP	1.7 (2.5)				0.9 (1.3)			
Verbal Fluency Task: Semantic	eMST	0 [3]	0 (-2 to 1)	W = 183.5	.657	4.5 [3.8]	0.5 (-1 to 3)	W =201.5	.358
	GRASP	0 [4]				4 [3.5]			

Supplementary Table 9. Improvements in emotional and QoL outcomes.
Mean improvement in emotional and quality of life (QoL) outcomes at post- and follow-up evaluations for both groups in the per-protocol analysis set.

Outcome	Group	Post-evaluation Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Follow-up evaluation Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
Beck Depression Inventory – II	eMST	-2.5 (3.9)	-0.3 (-3.2 to 2.6)	t = -0.204	.840	-1.9 (3)	0.9 (-1.6 to 3.4)	t = 0.724	.475
	GRASP	-2.2 (4.9)				-2.8 (4.4)			
Anhedonia (Beck Depression Inventory – II subscale)	eMST	-0.5 [2]	-0.5 (-2 to 0)	W = 136.5	.117	-1 [2]	-1 (-2 to 0)	W = 113	.069
	GRASP	0 [1]				0 [0.5]			
Apathy Evaluation Scale (Self-version)	eMST	-1.9 (6)	-8 (-4.3 to 2.8)	t = -0.428	.672	-1.5 (3.6)	-0.8 (-3.8 to 2.1)	t = -0.562	.578
	GRASP	-1.1 (4.8)				-0.7 (5.2)			
Apathy Evaluation Scale (Informant-version)	eMST	-3 (4.2)	-2.8 (-5.2 to 0)	t = -2.029	.050*	-1.5 (3.6)	-0.8 (-4.2 to 3.7)	t = -0.144	.886
	GRASP	-0.2 (3.7)				-0.7 (5.2)			
Anger-Hostility (Profile of Mood State)	eMST	-3 (5.3)	-3.6 (-7 to -0.3)	t = -2.207	.034*	0 [7]	0 (-4 to 2)	W = 158.5	.713
	GRASP	0.6 (5)				0 [4.5]			
Vigor-Activity (Profile of Mood State)	eMST	0.6 (2.9)	2 (-0.3 to 4.1)	t = 1.755	.088	0.2 (3.5)	-2.3 (-5.5 to 1)	t = -1.404	.171
	GRASP	-1.4 (3.8)				2.5 (6)			
Fatigue-Inertia (Profile of Mood State)	eMST	-1 [4.3]	1 (-2 to 2)	W = 193	.944	0.2 [3.5]	-2.3 (-2 to 3)	W = 176	.890
	GRASP	-2 [3]				2.5 [6]			

Outcome	Group	Post-evaluation Mean (SD) / Median [IQR]	Post-evaluation Difference (95% CI)	Post-evaluation Statistic	Post-evaluation p-v	Follow-up evaluation Mean (SD) / Median [IQR]	Follow-up evaluation Difference (95% CI)	Follow-up evaluation Statistic	Follow-up evaluation p-v
Confusion-Bewilderment (Profile of Mood State)	eMST	0 [2]	0 (-2 to -1)	W = 169.5	.568	0.5 [1]	0.5 (-2 to 2)	W =168.5	.951
	GRASP	0 [3]				0 [3]			
Tension-Anxiety (Profile of Mood State)	eMST	-1.7 (3.2)	-2.4 (-5.2 to 0.4)	t = -1.746	.091	0.5 (4.1)	-1.4 (-4.7 to 1.8)	t = -0.905	.372
	GRASP	0.7 (5.1)				1.9 (5.6)			
Depression-Dejection (Profile of Mood State)	eMST	-0.5 [5.3]	1.5 (-4 to 4)	W = 202	.746	0.5 [1]	0.5 (-4 to 4)	W = 167	.915
	GRASP	-2 [7]				0 [3]			
Strength (Stroke Impact Scale)	eMST	0 [25]	-6.3 (-6.2 to 12.5)	W =2 03.5	.706	6.3 [23.4]	6.3 (-6.2 to 12.5)	W = 196.5	.441
	GRASP	6.3 [18.8]				0 [25]			
Memory (Stroke Impact Scale)	eMST	3.9 (16.1)	1.2 (-7.9 to 10.4)	t = 0.283	.779	7.3 (10.3)	5.6 (-2.1 to 13.3)	t = 1.486	.147
	GRASP	2.7 (11.9)				1.7 (12.7)			
Emotion (Stroke Impact Scale)	eMST	10.4 (15.9)	11.1 (0.8 to 21.5)	t = 2.174	.036*	5.6 (14.1)	1.7 (-9.2 to 12.4)	t = 0.303	.764
	GRASP	-0.7 (16.1)				3.9 (18)			
Communication (Stroke Impact Scale)	eMST	0 [7.1]	0 (-7.1 to 7.1)	W = 182	.832	5.6 [14.1]	1.7 (-7.2 to 3.6)	W = 139.5	.338
	GRASP	0 [0.7]				3.9 [18]			
Activity (Stroke Impact Scale)	eMST	5 [17.5]	2.5 (-7.5 to 13.6)	W = 212.5	.536	1.3 [6.9]	1.3 (-5 to 17.5)	W = 204	.321
	GRASP	2.5 [17.5]				0 [23.8]			
Mobility (Stroke Impact Scale)	eMST	2.8 [14.6]	0 (-8.3 to 8.3)	W = 190	< .999	5.6 [12.5]	5.6 (-8.9 to 8.3)	W = 171	< .999
	GRASP	2.8 [13.9]				0 [13.9]			
Hand function (Stroke Impact Scale)	eMST	10.5 (16.9)	2.6 (-9 to 14.2)	t = 0.456	.651	0 [18.8]	-5 (-20 to 10)	W = 157.5	.692
	GRASP	7.9 (18.7)				5 [32.5]			
Participation (Stroke Impact Scale)	eMST	6.5 (17.6)	10.3 (0.6 to 25.9)	t = 2.126	.041*	2.6 (22.7)	13.5 (-2.6 to 29.6)	t = 1.701	.098
	GRASP	-6.8 (21.1)				-10.9 (25.5)			
Recovery (Stroke Impact Scale)	eMST	10 [10]	0 (-10 to 10)	W = 201	.756	10 [10]	0 (-4.7 to 10)	W = 189.5	.566
	GRASP	10 [10]				10 [10]			

Supplementary Table 10. Improvements in sef-regulation outcomes.
Mean improvement in self-regulation outcomes during and post-intervention for both groups in the per-protocol analysis set.

Treatment Self-regulation Questionnaire	Group	Score change between the first and the fifth week of intervention			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
External motivation	eMST	0.1 [1.1]	0 (-0.5 to 0.8)	W = 221.5	.568
	GRASP	0 [0.7]			
Introjected motivation	eMST	0.1 [1.5]	-0.2 (-1.2 to 0.5)	W = 173	.470
	GRASP	0.3 [1.3]			
Identified motivation	eMST	0 [0.6]	0 (-0.5 to 0.7)	W = 204	.924
	GRASP	0 [1.3]			
Internal motivation	eMST	0.3 [1]	0.5 (0 to 1.3)	W = 261	.100
	GRASP	-0.2 [1.4]			
Intrinsic Motivation Inventory	Group	Score post-intervention			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
Interest – Enjoyment	eMST	6.5 [1.1]	1 (0.3 to 1.5)	W = 279	.012*
	GRASP	5.5 [1.9]			
Perceived competence	eMST	5.5 [1.3]	-0.5 (-0.8 to 0.3)	W = 161	.420
	GRASP	6 [1]			
Effort - Importance	eMST	5.2 (1)	0.8 (-0.2 to 1)	t = 1.263	.214
	GRASP	4.8 (1)			
Pressure - Tension	eMST	1.9 [1.8]	-0.1 (-1.3 to 0.3)	W = 152.5	.289
	GRASP	2 [2.5]			
Perceived choice	eMST	5.5 [0.5]	0 (-0.2 to 0.5)	W = 224	.336
	GRASP	5.5 [0.8]			
Value - Utility	eMST	6.6 [1]	0.6 (0 to 1)	W = 239.5	.162
	GRASP	6 [1.5]			

Supplementary Table 11. Improvements in self-efficacy outcomes.
Mean improvement in self-efficacy outcomes at post- and follow-up evaluations for both groups in the per-protocol analysis set.

Strategies Used by People to promote Health	Group	Post-evaluation				Follow-up evaluation			
		Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v	Mean (SD) / Median [IQR]	Difference (95% CI)	Statistic	p-v
Coping	eMST	0 [0.9]	-0.1 (-0.3 to 0.6)	W = 197.5	.844	0.2 [0.8]	0.2 (-0.3 to 0.7)	W = 193	.513
	GRASP	0.1 [0.4]				0 [0.9]			
Stress reduction	eMST	0.4 (1.1)	0.2 (-0.4 to 0.9)	t = 0.786	.437	0.3 (1)	0 (-0.8 to 0.9)	t = 0.128	.899
	GRASP	0.2 (0.9)				0.3 (1.5)			
Decision making	eMST	0 [0.3]	0 (-0.3 to 0.3)	W = 172.5	.623	0 [0.6]	0 (-0.7 to 0.3)	W = 144	.410
	GRASP	0 [0.7]				0 [0.7]			
Enjoyment of life	eMST	0 [0.4]	0 (-0.3 to 0.3)	W = 182	.829	0.2 [0.9]	0.2 (-0.3 to 0.7)	W = 203	.334
	GRASP	0 [0.7]				0 [1.2]			
Positive attitude	eMST	0.1 [0.7]	0 (-0.2 to 0.5)	W = 209.5	.593	0.1 [0.7]	0.1 (-0.2 to 0.6)	W = 194.5	.484
	GRASP	0.2 [0.4]				0 [0.7]			

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Supplementary Table 12. Descriptive analysis: higher vs lower anhedonia.
Absolute frequencies and percentages are shown for sex, rehabilitation phase, stroke etiology, affected hemisphere, lesion location, cognitive level, depression level, non-anhedonic depression level, and presence of apathy. The mean and the standard deviation (SD) or the median and interquartile ranges [IQR] are shown for the quantitative variables with parametric and nonparametric distribution respectively. $p < 0.05$. (HAnh: Higher Anhedonia; LAnh: Lower Anhedonia; HDep: Higher non-anhedonic Depression; LDep: Lower non-anhedonic Depression; ARAT: Action Research Arm Test; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; BDI-II: Beck Depression Inventory-II; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; POMS: Profile of Mood States; Mild impairment < 27 in MMSE and < 26 in MoCA; None depression: 0-9 scores in BDI-II; Mild depression: 10-18 scores in BDI-II; Moderate depression: 19-29 scores in BDI-II; Severe depression: 30-63 scores in BDI-II; Presence of apathy ≥ 34 in AES-S and AES-I; Higher anhedonia > 4 in anhedonia BDI-II subscale; Lower anhedonia ≤ 4 in anhedonia BDI-II subscale; Higher non-anhedonic depression > 16.65 in non-anhedonic depression BDI-II subscale; Lower non-anhedonic depression ≤ 16.65 in non-anhedonic depression BDI-II subscale).

	HAnh (n = 40)	LAhn (n = 101)	p-value
Demographic variables			
Age	60.2 (11.05)	62.3 (10.13)	.369
Sex			
Female	10 (41.67 %)	31 (30.70 %)	.338
Male	14 (58.33 %)	70 (69.30 %)	
Education level			
Years of education	15.5 [4.75]	18 [7]	.023*
Clinical variables			
Rehabilitation phase			
Subacute	10 (41.67 %)	44 (43.56 %)	>. 999
Chronic	14 (58.33 %)	57 (56.43 %)	
Stroke etiology			
Ischemic	15 (62.50 %)	73 (72.28 %)	.317
Hemorrhagic	9 (37.50 %)	28 (27.72 %)	
Affective hemisphere			
Right	11 (45.83 %)	50 (49.50 %)	.822
Left	13 (54.17 %)	51 (50.50 %)	
Lesion location			
Cortical	2 (8.33 %)	10 (9.90 %)	>. 999
Cortico-subcortical	11 (45.83 %)	39 (38.61 %)	
Subcortical	9 (37.50 %)	38 (37.62 %)	
Brainstem	1 (4.17 %)	8 (7.92 %)	
Cerebellum	1 (4.17 %)	6 (5.94 %)	
Time since stroke			
Months post stroke	7.5 [18.75]	9.5 [23.50]	.745
Motor ability			
ARAT	42 [20.50]	42 [17]	.940
Cognitive level	69.6 (18.9)	59.3 (15.8)	.057
MoCA/MMSE	27 [5]	27 [4]	.762
No impairment (%)	15 (62.50 %)	62 (61.39 %)	>. 999
Mild impairment (%)	9 (37.50 %)	39 (38.61 %)	
Memory			
Digit span (normative)	10.17 (3.27)	11.22 (2.91)	.123
RAVLT (normative)	34.25 (9.06)	37.67 (11.35)	.172
Emotional variables			
Anhedonia			
Anhedonia score	6 [3]	2 [2]	< .001*
Depression			
BDI-II score	23.5 [13.25]	8 [8]	< .001*
None	0 (0 %)	58 (57.43 %)	< .001*
Mild	7 (29.17 %)	36 (35.64 %)	

Moderate	9 (37.50 %)	7 (6.93 %)	
Severe	8 (33.33 %)	0 (0 %)	
Non-anhedonic depression			
Non-anhedonic BDI-II score	7 [9]	8 [8]	.676
Lower non-anhedonic depression	19 (79.17 %)	86 (85.14 %)	.536
Higher non-anhedonic depression	5 (20.83 %)	15 (14.85 %)	
Apathy informed by patient			
AES-S score	40 [16]	34 [9]	< .001*
Presence	16 (69.57 %)	56 (55.45 %)	.249
No presence	7 (30.43 %)	45 (44.55 %)	
Apathy informed by caregiver			
AES-I score	43 [13.75]	33 [11]	< .001*
Presence	19 (79.17 %)	50 (49.50 %)	.011*
No presence	5 (20.83 %)	51 (50.50 %)	
POMS			
Anger-Hostility score	12 [9.5]	5 [7]	< .001*
Vigor-Activity score	10.52 (5.28)	14.71 (5.01)	< .001*
Fatigue-Inertia score	14 [10]	4 [7]	< .001*
Tension-Anxiety score	12 [8.5]	5 [9]	< .001*
Confusion-Bewilderment score	10 [7]	2 [7]	< .001*
Depression-Dejection score	20 [14]	6 [11]	< .001*

Note: All participants completed the whole evaluation, except for one participant in the subacute group who did not respond the AES-S and POMS and did not provide SS the AES-I. Spouses mainly answered the AES-I, followed by siblings, children, and caregiver.

Supplementary Table 13. Correlations of anhedonia with baseline variables.
This table shows the Spearman's rho and p-value of the correlations between the anhedonia score and the demographic, clinical, and emotional continuous variables score. $p < 0.05$. (ARAT: Action Research Arm Test; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; BDI-II: Beck Depression Inventory-II; POMS: Profile of Mood States).

	Subacute stroke		Chronic stroke	
	Spearman's rho	p-value	Spearman's rho	p-value
Demographic variables				
Age	-0.08	< .552	0.09	< .439
Education	-0.26	< .057	-0.06	> .609
Clinical variables				
Time post stroke	0.27	> .051	0.11	> .358
Motor function				
ARAT	0.02	> .869	-0.02	> .868
Cognitive functions				
MMSE/MoCA	-0.02	< .885	-0.19	< .122
RAVLT	-0.10	< .491	0.10	< .419
Digit Span	-0.13	> .367	0.06	> .600
Emotional variables				
Non-anhedonic BDI-II subscale	0.59	< .001*	0.62	< .001*
AES-S	0.23	< .037*	0.41	< .001*
AES-I	0.34	> .023*	0.37	< .001*
Anger-Hostility (POMS)	0.44	> .002*	0.44	< .001*
Vigor-Activity (POMS)	-0.23	< .093	-0.36	< .001*
Fatigue-Intertia (POMS)	0.51	< .001*	0.59	< .001*

Tension-Anxiety (POMS)	0.44	> .001*	0.39	< .001*
Confusion-Bewilderment (POMS)	0.39	> .001*	0.43	< .001*
Depression-Dejection (POMS)	0.49	< .001*	0.53	< .001*

Supplementary Table 14. Partial correlations of anhedonia with baseline variables.
Spearman's rho and p-value correlations between anhedonia score and the continuous demographic, clinical, and emotional variables score while controlling for the influence of the non-anhedonic depression BDI-II subscale are shown for both groups of stroke patients and all patients together. $p < 0.05$. (ARAT: Action Research Arm Test; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; AES-S: Self-Rated Version of the Apathy Evaluation Scale; AES-I: Informant Version of the Apathy Evaluation Scale; BDI-II: Beck Depression Inventory-II; POMS: Profile of Mood States).

	Subacute stroke		Chronic stroke		All patients	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
Demographic variables						
Age	0.21	< .126	0.26	< .031*	0.22	< .014*
Education	-0.20	< .161	0.06	< .643	-0.05	> .565
Clinical variables						
Time post stroke	0.31	< .025*	0.07	< .560	0.16	< .079
Motor function						
ARAT	0.11	< .451	-0.09	> .450	0.02	< .832
Cognitive functions						
MMSE/MoCA	0.19	< .188	-0.21	> .078	-0.09	> .327
RAVLT	0.20	> .152	0.21	> .080	0.19	< .033*
Digit Span	0.04	< .765	0.08	< .502	0.07	< .436
Emotional variables						
AES-S	-0.04	< .775	0.15	< .210	0.08	> .354
AES-I	0.18	< .210	0.13	> .302	0.15	< .111
Anger-Hostility (POMS)	0.18	< .211	0.26	< .033*	0.22	> .015*
Vigor-Activity (POMS)	-0.05	< .706	-0.11	> .372	-0.10	< .273
Fatigue-Intertia (POMS)	0.19	< .182	0.42	< .001*	0.31	< .001*
Tension-Anxiety (POMS)	0.20	> .153	0.16	> .190	0.15	< .091
Confusion-Bewilderment (POMS)	0.17	< .240	0.21	> .085	0.18	< .048*
Depression-Dejection (POMS)	0.17	< .240	0.30	> .012*	0.25	< .006*

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