TESIS DOCTORAL

The neuropsychiatric spectrum: Multidomain evaluation and treatment in post-stroke aphasia

Autora:
Lisa Marie Edelkraut

Directores:
Dr. Marcelo L. Berthier Torres
Dra. Guadalupe Dávila Arias

UNIVERSIDAD DE MÁLAGA

PROGRAMA DE DOCTORADO EN PSICOLOGÍA
FACULTAD DE PSICOLOGÍA Y LOGOPEDIA
UNIVERSIDAD DE MÁLAGA
2023

Tesis doctoral por compendio de publicaciones

The neuropsychiatric spectrum: Multidomain evaluation and treatment in post-stroke aphasia

Autora:
Lisa Marie Edelkraut

Directores:
Dr. Marcelo L. Berthier Torres
Dra. Guadalupe Dávila Arias

Programa de Doctorado en Psicología
Facultad de Psicología y Logopedia
Universidad de Málaga
2023

AUTORA: Lisa Marie Edelkraut

https://orcid.org/0000-0001-7444-2686

EDITA: Publicaciones y Divulgación Científica. Universidad de Málaga

DECLARACIÓN DE AUTORÍA Y ORIGINALIDAD DE LA TESIS PRESENTADA PARA OBTENER EL TÍTULO DE DOCTOR

Dña. LISA MARIE EDELKRAUT

Estudiante del programa de doctorado PSICOLOGÍA de la Universidad de Málaga, autora de la tesis, presentada para la obtención del título de doctor por la Universidad de Málaga, titulada: THE NEUROPSYCHIATRIC SPECTRUM: MULTIDOMAIN EVALUATION AND TREATMENT IN POST-STROKE APHASIA

Realizada bajo la tutorización de GUADALUPE DÁVILA ARIAS y dirección de MARCELO LUIS BERTHIER TORRES & GUADALUPE DÁVILA ARIAS

Declaro que:
La tesis presentada es una obra original que no infringe los derechos de propiedad intelectual ni los derechos de propiedad industrial u otros, conforme al ordenamiento jurídico vigente (real Decreto Legislativo 1/1996, de 12 de abril, por el que se aprueba el texto refundido de la Ley de Propiedad Intelectual, regularizando, aclarando y armonizando las disposiciones legales vigentes sobre la materia), modificado por la Ley 2/2019, de 1 de marzo.

Igualmente asumo, ante la Universidad de Málaga y ante cualquier otra instancia, la responsabilidad que pudiera derivarse en caso de plagio de contenidos en la tesis presentada, conforme al ordenamiento jurídico vigente.

En Málaga, a 14 de septiembre, de 2023

Fdo.: LISA MARIE EDELKRAUT Doctoranda	Fdo.: GUADALUPE DÁVILA ARIAS Tutora
Fdo.: MARCELO L. BERTHIER TORRES & GUADALUPE DÁVILA ARIAS Directores de Tesis	

Edificio Pabellón de Gobierno. Campus El Ejido
29071
Tel.: 952 13 10 28/ 952 13 14 61/ 952 13 71 10
E-Mail: doctorado@uma.es

UNIVERSIDAD DE MÁLAGA

FACULTAD DE PSICOLOGÍA Y LOGOPEDIA
Universidad de Málaga

D. Marcelo Luis Berthier Torres, Profesor Catedrático de Neurología Clínica del Departamento de Medicina y Dermatología de la Facultad de Medicina de la Universidad de Málaga y D.ª Guadalupe Dávila Arías, Profesora Titular de Fundamentos de Psicobiología II del Departamento de Psicobiología y Metodología de las Ciencias del Comportamiento de la Facultad de Psicología de la Universidad de Málaga certifican que D.ª Lisa Marie Edelkraut ha efectuado bajo su dirección la tesis doctoral titulada: The neuropsychiatric spectrum: Multidomain evaluation and treatment in post-stroke aphasia.

La investigación responde a los requisitos de una Tesis Doctoral y la metodología adoptada es apropiada a los fines de investigación. Por tanto, entienden que reúne los requisitos para optar al Grado de Doctora según la legislación vigente y, en consecuencia, autorizan su depósito y posterior presentación y defensa ante el tribunal designado para tal fin.

En Málaga a 14 de septiembre del 2023

Fdo.: Marcelo L. Berthier Torres & Guadalupe Dávila Arías

Directores de Tesis

Edificio Pabellón de Gobierno. Campus El Ejido
29071
Tel.: 952 13 10 28/ 952 13 14 61/ 952 13 71 10
E-Mail: doctorado@uma.es

INFORME DE IDONEIDAD DE LA PRESENTACIÓN POR COMPENDIO DE ARTÍCULOS

El Dr. Marcelo Luis Berthier Torres Profesor Catedrático del Departamento de Medicina y Dermatología de la Universidad de Málaga, como director de la tesis doctoral, junto a la Dra. Guadalupe Dávila Arias, Profesora Titular del Departamento de Psicobiología y Metodología de las Ciencias del Comportamiento de la Universidad de Málaga, como tutora y directora de la tesis doctoral titulada: The neuropsychiatric spectrum: Multidomain evaluation and treatment in post-stroke aphasia presentada por la doctoranda Lisa Marie Edelkraut, informan de la idoneidad de la presentación de la tesis por compendio de artículos, dado que cumple con todos los criterios establecidos para ello por la Universidad de Málaga. Asimismo certifican que que las publicaciones que avalan la tesis doctoral no han sido utilizadas en tesis anteriores.
Los trabajos que componen la tesis doctoral son los siguientes:

- Edelkraut, L., López-Barroso, D., Torres-Prioris, M. J., Starkstein, S. E., Jorge, R. E., Aloisi, J., Berthier, M. L., & Dávila, G. (2022). Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia. *World Journal of Psychiatry,* 12(3): 450-469. https://doi.org/10.5498/wjp.v12.i3.450
- Berthier, M. L., Edelkraut, L., Mohr, B., Pulvermüller, F., Starkstein, S. E., Green-Heredia, C., & Dávila, G. (2022). Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study. *Neuropsychological Rehabilitation*, 32(1): 148–163. https://doi.org/10.1080/09602011.2020.1809463.
- Berthier, M. L., Edelkraut, L., López-González, F. J., López-Barroso, D., Pulvermuelller, F., Starkstein, S. E., Jorge, R. E., Torres-Prioris M. J., & Dávila, G. (2023). Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study. *Brain and Language,* 236: *1-9.* https://doi.org/10.1016/j.bandl.2022.105205

En Málaga a 14 de septiembre del 2023

Fdo. Marcelo L. Berthier Torres

Fdo. Guadalupe Dávila Arias

Edificio Pabellón de Gobierno. Campus El Ejido
29071
Tel.: 952 13 10 28/ 952 13 14 61/ 952 13 71 10
E-Mail: doctorado@uma.es

Dissertation Author

Lisa Marie Edelkraut
ORCID: 0000-0001-7444-2686

Dissertation Supervisors

Dr. Marcelo L. Berthier Torres
ORCID: 0000-0002-6393-3487

Dr. Guadalupe Dávila Arias
ORCID: 0000-0002-3297-4243

“What does one person give to another? He gives of himself, of the most precious he has, he gives of his life. This does not necessarily mean that he sacrifices his life for the other—but that he gives him of that which is alive in him; he gives him of his joy, of his interest, of his understanding, of his knowledge, of his humor, of his sadness—of all expressions and manifestations of that which is alive in him. In thus giving of his life, he enriches the other person, he enhances the other's sense of aliveness by enhancing his own sense of aliveness. He does not give in order to receive; giving is in itself exquisite joy. But in giving he cannot help bringing something to life in the other person, and this which is brought to life reflects back to him.”

Erich Fromm, *The Art of Loving*

Für meine Familie

A mi Familia

Acknowledgements

Deseo expresar mi más profundo agradecimiento a todas las personas cuya colaboración y apoyo han hecho posible la culminación de esta tesis doctoral. Para comenzar, me gustaría agradecer de corazón a ti, Marcelo, por tu entusiasmo, pasión y energía que has transmitido en el día a día en la UNCA; Por todas las palabras de apoyo y gestos de ayuda. Por los "*bien hecho, Lisa*" que tanto se agradecen en este camino tan largo y lleno de incertidumbre. Por las tardes en la oficina corrigiendo mis textos y animándome a seguir aprendiendo y a seguir creciendo como persona y como profesional… Muchas gracias a ti, Lupe, por cambiar literalmente el rumbo de mi vida con una simple pregunta: "¿Por qué no solicitas una beca de investigación y haces la tesis con nosotros?" Gracias a esa pregunta, comenzó una vida llena de lecturas, debates, coloquios, risas, aprendizajes, frustraciones, amistades y mucho más. Tu apoyo constante y tu dedicación al leer y perfeccionar mis trabajos han sido invaluables. Además, agradezco tu paciencia al explicarme en múltiples ocasiones el funcionamiento de la Universidad para que no me perdiera por el camino. Gracias también por tu inquebrantable perseverancia, que inspira a todos los compañeros de la UNCA. Gracias a ambos por haber sido mis supervisores de tesis.

En segundo lugar, me gustaría agradecer a mis compañeros de la UNCA. A María José por toda tu ayuda y paciencia a lo largo de estos años, por analizar y corregir mis análisis estadísticos y por ser mi compañera mayor de FPU que todo me lo explicaba. A Diana por socorrerme en momentos de duda y por contribuir a las publicaciones con tus increíbles diseños gráficos. Gracias a ambas por regalarme libros y juegos de mesa, por animarme a correr en el grupo de la UMA y, a través de ello, ganar confianza, fuerza y nuevos amigos. A Javier y Flor por nuestras comidas y charlas que muchas veces acababan ahogadas en risas. A Karl por tu humor, tus ganas de hacer cosas nuevas y explorar el mundo a tu manera, por tantas horas de conversaciones y noches enteras de juegos de mesa, con huidas rápidas a tu casa para que no te multasen durante el toque de queda de la Pandemia. También quiero agradecer a los nuevos doctorandos, Ariane, África, Ana, Jorge y Sergio que han traído conversaciones, risas y, sobre todo, buen rollo a la UNCA. Seréis los próximos en escribir los agradecimientos.

Después quisiera agradecer la asistencia de varios compañeros de la Facultad de Psicología. A Estela Castilla por compartir conmigo los años de docencia y, con ello, aventuras inesperadas. Gracias por convertirte rápidamente en un pilar de mi carrera profesional, por apoyarme en innumerables ocasiones y por incluirme en proyectos profesionales tan fascinantes. Gracias a Carmen Pedraza, por tu ayuda constante tanto en cuestiones de la docencia como de la tesis. Finalmente también quisiera dar las gracias a todos los compañeros del Departamento de Psicobiología que han hecho que estos años en la UMA resultaran ser los más especiales de mi vida.

A Anne Weigand por recibirme con los brazos abiertos en tu grupo de investigación en Berlín y por confiar en mí para tantos proyectos profesionales. Me hace mucha ilusión que sigamos colaborando juntas.

A mis compañeras y a mis docentes (los tres Albertos y Gabriel) del *Centro Soluciones* que me han apoyado en toda mi formación paralela como psicoterapeuta. Compaginar una tesis doctoral con la formación en psicoterapia no ha sido tarea fácil y vuestra ayuda constante ha sido una aportación valiosísima. Termino esta etapa con una sensación de competencia y orgullo profesional que sin vosotros no hubiese adquirido. Gracias también por ofrecerme nuevos proyectos profesionales, me siento muy honrada.

A Miguel Ángel por invitarme a colaborar como profesional en el Servicio de Atención Psicológica de la UMA y por dejarme participar en tus grupos de supervisión, he aprendido muchísimo de ti. Desde aquí también un abrazo a mi primera “alumna en prácticas” Cecilia, que has compartido sesiones de terapia conmigo y me has transmitido tu energía e ilusión. Me has hecho sentir toda una profesional.

Todos estos años también habrían sido muy difíciles de sobrellevar si no hubiese sido por mis amigos. Gracias a Fátima, Mercedes, Estela, Laura y Rocío (de Marbella). Gracias a Luis y a María Eugenia (de la carrera), a Thomas (de Colonia), a Jutta (de Berlín), a Dani y Juan (de “nuestra casa”), a Mar, Guille, Irene, Leo y los demás (del ZenDerismo), y a tanta gente que enriquece de forma maravillosa mi vida.

Gracias a ti, Manuel, por caminar juntos una década de nuestras vidas. Han sido años llenos de viajes, risas y conversaciones. Gracias por haberme apoyado en tantas facetas de mi vida. Una parte de ti siempre se vendrá conmigo. Gracias a Puri y Manolo por vuestro amor incondicional. Y a ti Alejandra, por tu juventud madura e ilusionante, por cantar juntas en el coche, por hablar de todo y por sacar mi lado más bobo.

A ti Juanmi, por estar en mi vida. Por haberme obligado a crecer y convertirme en una persona más feliz, más segura y confiada en la belleza de la vida. Por los libros que me has hecho leer, por todos los que me harás leer. Por los "*va a salir bien piojillo, ya verás*". Por los cafés, los miedos y las ilusiones compartidas. Por las aventuras que ya hemos vivido y las que nos quedan por vivir. Por abrazarme con fuerza y apoyarme en absolutamente todo. Gracias. También un abrazo a Sergio y a Sonsoles, simplemente por ser geniales.

A ti, mamá, por ser la persona más increíble que conozco. Por tu sonrisa infatigable, por las aventuras que vivimos sobre nuestras bicicletas, atravesando países, montañas, ciénagas, playas, bosques... Por los cafés que me traes a la tienda de campaña mientras cantas a pleno pulmón durante una mañana nebulosa. Por tu imparable energía y ganas de vivir con intensidad. Por tu afán de nunca rendirte. Por ser un modelo a seguir en tantas cosas: el entusiasmo vital, la alegría, la confianza en el mundo y las personas que hay en ella. Por ser una madre maravillosa.

A Sascha, por ser la persona más fuerte que conozco, emocional y físicamente. Por ser un espíritu libre que se ha forjado su felicidad a base de hacer las cosas de forma diferente. Por ser mi hermano mayor con quien puedo compartirlo todo, a pesar de la distancia, y quien me entiende porque somos iguales a pesar de ser tan diferentes. Por tu valentía, tu bondad y todos tus malditos talentos que te hacen ser tan especial. A Janina por ser mi hermana mayor maravillosa, sonriente, feliz y vividora. Por defender ideales tan bonitos, por regalarme dos sobrinos maravillosos. Tus mensajes de audio de 18 minutos me alegran el día y la vida.

A Opa, por ser el más grande de todos, el abuelo de la familia, el oso Edelkraut. Por tu canto profundo que retumba por toda la casa cuando te afeitas por la mañana. Por tu risa profunda y auténtica. Por transmitir amor y orgullo incondicional. Por tus brazos enormes que me aprietan con fuerza, por ser "tu niña" y por darme un hogar. A Rosy, por hacer que dicho hogar esté siempre lleno de flores y de vida, con olor a pan o bizcocho recién horneado. Por estar siempre al tanto de mis avances. Por hacer feliz a mi abuelo y mantener unida a la familia. Por ser los dos un super equipo después de treinta años de matrimonio. A mis dos abuelas, Doris y Hilde, que solo supieron dar amor, y a mi padre por haber sembrado recuerdos tan bonitos durante mi infancia.

A Arno, por ser el último en entrar en la familia y dejar una huella tan profunda. Por tratarme como tu hija y apoyarme en absolutamente todo. Por saber todo de mí ya que nada se te olvida. Por ser el único (que yo sepa) que ha intentado leer mis publicaciones

para hablar de mí con más orgullo aún. Por los viajes increíbles, las horas interminables de juegos de mesa y, también, por hacerme sentir en casa. Por ser de la familia, para siempre. Al resto de la familia Edelkraut, Darmstädter, Opfer, Kempf y Clemens. Gracias a todos por apoyarme y acompañarme en este hermoso camino de la vida.

(*Auf Deutsch für meine Familie)*

An dich, Mama, weil du der unglaublichste Mensch bist, den ich kenne. Für dein unermüdliches Lächeln, für die Abenteuer, die wir auf unseren Fahrrädern erleben, während wir durch Länder, Berge, Sümpfe, Strände und Wälder radeln. Für die Kaffees, die du mir ins Zelt bringst, während du an einem nebligen Morgen aus voller Kehle singst. Für deine unaufhaltsame Energie und dein Verlangen, mit Intensität zu leben. Für deinen Eifer, niemals aufzugeben. Dafür, dass du in so vielerlei Hinsicht ein Vorbild bist: in deiner Lebensfreude, deinem Vertrauen in die Welt und die Menschen darin. Dafür, dass du eine wunderbare Mutter bist.

Sascha, weil du der stärkste Mensch bist, den ich kenne, emotional und körperlich. Dafür, dass du ein Freigeist bist, der sein Glück dadurch aufgebaut hat, dass du Dinge anders machst. Dafür, dass du mein großer Bruder bist, mit dem ich alles teilen kann, trotz der Entfernung, und der mich versteht, weil wir gleich sind, obwohl doch so unterschiedlich. Für deinen Mut, deine Freundlichkeit und all deine verdammten Talente, die dich so besonders machen. An Janina, weil du meine wunderbare, lächelnde, fröhliche und lebhafte große Schwester bist. Dafür, dass du so schöne Ideale vertrittst und mich zur glücklichsten Tante gemacht hast. Deine 18-minütigen Audionotizen machen meinen Tag und mein Leben heller.

An Opa, der der Größte von allen ist, der Großvater der Familie, der Edelkrautbär. Für deinen tiefen Gesang, der durch das Haus schallt, wenn du dich morgens rasierst. Für dein tiefes und echtes Lachen. Für deine bedingungslose Liebe und deinen Stolz. Für deine riesigen Arme, mit denen du mich fest umarmst, dafür, dass ich "dein Mädchen" bin und dass du mir ein Zuhause gibst. An Rosy, dafür, dass dieses Zuhause immer voller Blumen und Leben ist, mit dem Geruch von frisch gebackenem Brot oder Kuchen. Dafür, dass du immer über meine Fortschritte informiert bist. Dass du meinen Großvater glücklich gemacht und die Familie zusammengehalten hast. Dafür, dass ihr nach dreißig Jahren Ehe ein super Team seid. An meine beiden Großmütter Doris und Hilde, die nur Liebe zu geben wussten, und an meinem Vater, der mir so schöne Kindheitserinnerungen beschert hat.

An Arno, weil du als letzter in die Familie kamst und mein Herz so sehr geprägt hat. Dafür, dass du mich wie deine Tochter behandelst und mich in allem unterstützt. Dass du alles über mich weißt, und nie etwas vergisst. Dafür, dass du der Einzige bist, der versucht hat, meine Veröffentlichungen zu lesen, um mit noch mehr Stolz über mich zu sprechen, wenn das überhaupt möglich ist. Für die großartigen Reisen, die endlosen Stunden mit Brettspielen und auch dafür, dass ich mich wie zu Hause fühle. Dafür, dass wir eine Familie sind, für immer. An den Rest der Familien Edelkraut, Darmstädter, Opfer, Kempf und Clemens. Danke, dass ihr mich auf dem schönen Weg des Lebens unterstützt und begleitet.

Declaration

This work, presented to obtain the PhD degree from the University of Málaga, has been developed during the years 2018 - 2023. The studies presented here have been funded by the predoctoral contract *Formación de Profesorado Universitario* (FPU17/04136) from the Spanish *Ministerio de Universidades*. This thesis is presented as a compendium of publications and consists of the following three original articles.

Study 1 **Edelkraut, L.**, López-Barroso, D., Torres-Prioris, M. J., Starkstein, S. E., Jorge, R. E., Aloisi, J., Berthier, M. L., & Dávila, G. (2022). Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia. *World Journal of Psychiatry,* 12(3): 450-469. https://doi.org/10.5498/wjp.v12.i3.450.

Study 2 Berthier, M. L., **Edelkraut, L.**, Mohr, B., Pulvermüller, F., Starkstein, S. E., Green-Heredia, C., & Dávila, G. (2022). Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study. *Neuropsychological Rehabilitation*, 32(1): 148–163. https://doi.org/10.1080/09602011.2020.1809463.

Study 3 Berthier, M. L., **Edelkraut, L.**, López-González, F. J., López-Barroso, D., Pulvermuelller, F., Starkstein, S. E., Jorge, R. E., Torres-Prioris M. J., & Dávila, G. (2023). Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study. *Brain and Language,* 236: *1-9.* https://doi.org/10.1016/j.bandl.2022.105205

Thesis abstract

Each year, 13 million individuals experience strokes worldwide, a substantial proportion of whom survive due to advancements in medical treatment. Consequently, stroke stands as the predominant contributor to global disability, resulting in neuropsychiatric sequelae that exert adverse impacts on the rehabilitation progress, engagement in daily tasks, functional self-sufficiency, and personal autonomy. Among the most prevalent neuropsychiatric manifestations following a stroke are depression, anxiety, and apathy. Pharmacological interventions and psychotherapeutic approaches are recognized as the primary modalities for delivering therapeutic support to post-stroke patients.

Post-stroke aphasia (PSA) is an acquired language disorder caused by a stroke that induces the loss or impairment of some or all language dimensions: spontaneous speech, comprehension, repetition, reading, writing, and everyday communication. Approximately one-third of all stroke survivors cope with PSA. The classification of aphasia subtypes conventionally relies on the evaluation of distinctive symptomatology encompassing verbal expression characteristics (namely, the distinction between fluent and non-fluent speech), comprehension capabilities, and the individual's capacity for repetition. In addition, the time since stroke onset needs to be taken into consideration for aphasia classification, specifically, the duration elapsed since the onset of the cerebrovascular event translates into the classification of aphasic conditions. Typically, aphasic impairments following a stroke exhibit maximal severity during the acute phase (occurring within the initial month), with the most pronounced recuperative gains manifesting within the subsequent 3 to 6 months, referred to as the subacute phase. Thereafter, recovery trajectories tend to decelerate, entering a chronic phase that extends beyond 6 months.

Effective communication plays a pivotal role in numerous facets of human existence; thus, the emergence of PSA can precipitate and significantly exacerbate NPS. The extant body of research dedicated to the investigation of NPS in individuals with aphasia is notably limited, primarily owing to the prevalent exclusion of afflicted individuals from studies on account of the formidable language and communication impediments characteristic of this population. Recent advances have been made in the validation of depression questionnaires for the aphasic patient. However, even when adequately assessed and diagnosed, people with aphasia (PWA) do not benefit from standard psychotherapeutic interventions, as they are primarily language-based. Massed-practised

language therapies, such as *Intensive Language-Action Therapy* (ILAT), consist of intensive intervention sessions (minimum of 2 to 3 hours of training per day) in a short period (generally two weeks) within a group format of conversational turn-taking. ILAT has effectively improved the severity of aphasia and has also proven preliminary positive results for low mood in chronic non-fluent aphasia. Strengthening this therapy's socio-communicative actions and interactional schemes is believed to be a central pillar for improving depression. However, little is known about the impact of ILAT on chronic fluent aphasia and NPS.

Pharmacotherapy effectively treats PSA, particularly drugs targeting the neurotransmitter acetylcholine (e.g., Donepezil). It is still unknown whether this cognitive-enhancing agent also improves NPS in PSA, but studies of dementia and non-aphasic stroke provide promising results for apathy and depression. Currently, multimodal therapy approaches, with combined behavioural and pharmacological interventions, are expanding rapidly, as the benefits of combined therapies exceed the individual gains of each administered separately. That raises the possibility that neuropsychiatric sequelae would also be amenable to improvement by enhancing language and communication functions with combined therapy approaches (ILAT and pharmacotherapy) in PWA. Finally, decades of psychiatric imaging have revealed structural and functional changes in the brain impacted by stroke. However, there is scarce neuroimaging information tailored to the neuropsychiatric sequelae in PSA. The aims of the current thesis were thus the following:

Study 1 — (A) This study aims to conduct a comprehensive review of the scientific literature regarding the spectrum of NPS in PSA. It will summarize data on prevalence, risk factors, assessment tools, pathophysiology, and available treatment options. Additionally, (B) the feasibility of assessing a broader range of NPS in 20 individuals with chronic PWA will be explored. This will involve examining the frequency, nature, and comorbidity of the neuropsychiatric symptoms using a combination of proxy-based and direct evaluation instruments.

Study 2 — This study will focus on analyzing the effects of two weeks of Intensive Language-Action Therapy (ILAT) on individuals with chronic fluent aphasia. Specifically, changes in aphasia severity and depression scores following the ILAT intervention will be assessed.

Study 3 (A) The primary objective of this study is to evaluate the outcomes of monotherapy with Donepezil and combined therapy with Donepezil-ILAT in individuals with PWA. We will assess changes in aphasia severity, as well as depression and apathy scores. (B) Furthermore, this study will investigate the functional and structural changes in the brain that may occur as a result of these interventions.

Study 1 consists of a two-part investigation including a narrative literature review and an observational study of NPS in 20 participants with chronic aphasia. For the literature review, keywords for post-stroke aphasia and NPS were cross-referenced in several scientific databases that covered prevalence, risk factors, assessment tools, pathophysiology, and treatment approaches from inception to the year 2021. For the observational study, primary outcome measures were the Western Aphasia Battery-Aphasia Quotient (WAB-AQ) and the Barthel Index, for aphasia severity and functional independence respectively. Furthermore, neuropsychiatric outcomes were measured with the Neuropsychiatric Inventory (NPI), the Stroke Aphasia Depression Questionnaire-10 (SADQ-10), the Starkstein Apathy Scale (SAS), and the Hospital Anxiety and Depression Scale (HADS). The latter was administered directly to the PWA, while all other NPS scales were proxy-administered to a caregiver. In the literature review, most of the selected articles focused on depression, anxiety, and quality of life, covering the assessment/diagnosis and behavioural and pharmacological intervention approaches for these conditions. Few articles examined prevalence data for other NPS in PWA, risk factors, or pathophysiological mechanisms. Sources also show that NPS in PSA is rarely routinely evaluated, let alone treated, except in some studies of depression. On the other hand, the observational study provides evidence that PWA in the chronic stage present mild to moderate symptoms of depression, irritability, agitation, anxiety, and apathy. These symptoms were present in more than half of the participants evaluated. Overall, the median number of NPS were five in the evaluated sample.

In **Study 2** a proof-of-concept case–controlled-study is presented, evaluating language and depression outcomes amongst people with fluent PSA. Thirteen participants were included for these purposes. Five participants entered the intervention group receiving ILAT for two consecutive weeks with 30 hours of training, while eight participants entered a waiting list without treatment arm. Primary outcome measures were the Western Aphasia Battery-Aphasia Quotient (WAB-AQ) and the Stroke Aphasic Depression

Questionnaire-21 (SADQ-21). The main findings were that participants in the active treatment arm significantly improved in aphasia severity and depression scores, while no significant changes were found in the control group for either variable. Therefore, the implementation of ILAT shows to be beneficial in improving clinical language deficits in people with chronic fluent aphasia while also significantly contributing to the improvement of depressive symptoms after therapy.

In **Study 3** a 10-week open-label intervention trial was conducted in ten PWA administering Donepezil alone (10 mg/day) for 8 weeks, and then Donepezil combined with ILAT (Donepezil-ILAT) for additional 2 weeks. The primary outcome measures were the WAB-AQ and the SADQ-21. Neuroimaging measures included structural magnetic resonance imaging (MRI) and functional ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET). Data were acquired at baseline (T1), after Donepezil (T2, week 8), and Donepezil-ILAT (T3, week 10). Treatment with Donepezil alone and in combination with ILAT significantly improved aphasia severity, while the symptoms of apathy and depression improved significantly with combined Donepezil-ILAT treatment. Exploratory neuroimaging data show that combined therapy with Donepezil-ILAT induced structural changes associated with improved depression in the insular and cingulate cortices - intrinsic Salience Network (SN) components. On the other hand, Donepezil-ILAT increased metabolic activity in structurally spared nodes of the Salience and Default Mode Networks (DMN), which correlated with a reduction in apathy scores. The altered connection pattern of the SN with other white matter networks, such es the DMN, has been consistently associated with endogenous NPS symptoms. Therefore, study 3 provides exploratory data that combining pharmacological therapy with behavioral interventions induces brain changes in networks involved in the regulation of motivation and mood.

The results of the three studies presented in this doctoral dissertation suggest that neuropsychiatric disturbances are feasible to assess in PWA, depending on the selection of appropriate psychometric instruments and the provision of specialist training. NPS are prevalent and functionally limiting even in the chronic stage of stroke evolution. The severity of aphasia and depressive symptomatology improves significantly with ILAT in chronic fluent PWA. In contrast, apathy and depression improve significantly with the combined treatment Donepezil-ILAT, leading to preliminary structural and functional changes in the brain of the participants. In general, combined intervention approaches seem to be a major predictor of neuropsychiatric improvement in PWA. However, most neuropsychiatric studies still exclude PWA based on communication difficulties, leading to an underestimation of the findings and a lack of available services for the particular needs of this cohort. In the future, inclusive NPS research in PSA should be pursued, broadening the general understanding of these conditions on short and long-term quality of life in PWA and supporting pertinent holistic treatment approaches. This dissertation's findings and clinical suggestions will contribute to understanding and caring for neuropsychiatric disorders in PWA.

Abbreviations

ACC	Anterior Cingulate Cortex
AI	Anterior Insula
BI	Barthel Index
CEN	Central Executive Network
dACC	dorsal Anterior Cingulate Cortex
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
***DP**	**Donepezil**
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
HADS	Hospital Anxiety and Depression Scale
ICF	International Classification of Functioning, Disability, and Health
ILAT	**Intensive Language-Action Therapy**
LAG	Language Action Game
MRI	Magnetic Resonance Imaging
NPI	Neuropsychiatric Inventory
NPS	**Neuropsychiatric Symptoms**
OFC	Orbitofrontal Cortex
PCC	Posterior Cingulate Cortex
^{18}FDG-PET	18fluorodeoxyglucose Positron Emission Tomography
PWA	**People with Aphasia**
PSA	**Post-Stroke Aphasia**
PSD	Post-Stroke Depression
SADQ	**Stroke Aphasia Depression Questionnaire**
SAS	Starkstein Apathy Scale
SLT	Speech Language Therapy
SN	Salience Network
SSRI	Selective Serotonin Reuptake Inhibitors
VBM	Voxel Based Morphometry
vmPFC	ventromedial Prefrontal Cortex
WAB	**Western Aphasia Battery**
WAB-AQ	Western Aphasia Battery-Aphasia Quotient

*Highlighted acronyms appear frequently in the text.

Table of content

Chapter 1: Introduction

Stroke and post-stroke aphasia

Stroke due to infarction or haemorrhage is a clinical syndrome of sudden onset that entails neural cell damage in the brain with the subsequent deficits of neurological functions (Hankey, 2017; Intercollegiate Stroke Working Party, 2016). Stroke currently accounts for the second leading cause of disability and mortality worldwide (Feigin et al., 2017; Katan & Luft, 2018). Twenty to thirty-five per cent of stroke patients die within the first month, and up to one-third of survivors lose their functional independence (Jones et al., 2020). As the global population is aging and stroke is becoming more common in developing countries, the incidence is expected to increase steadily over the next decades (GBD Stroke Collaborators, 2019). Furthermore, the impact of stroke extends well beyond the initial brain injury and, depending on the location, severity, and extent of brain damage, commonly induces a wide range of disorders, including post-stroke aphasia (PSA), post-stroke depression (PSD), and other neuropsychiatric symptoms (NPS) (Bullier et al., 2020; Code et al., 1999; Hilari et al., 2010).

PSA is considered the most devastating outcome of stroke (Breitenstein et al., 2017; Saxena & Hillis, 2017), and it is associated with more severe stroke syndromes, and more extended hospital stays, in addition to a two-to three-fold higher mortality rate compared to patients with non-aphasic strokes (Lazar & Boehme, 2017). Aphasia is defined as the total or partial loss of different language modalities, including expression (fluent or non-fluent expression), comprehension, repetition, naming, reading, writing, and gesturing (Berthier & Pulvermüller, 2011; Berthier, 2005; Brady et al., 2012). PSA is often the result of an occlusion or rupture of the left middle cerebral artery that irrigates the left perisylvian area and its underlying nuclei and white matter tracts (Fridriksson et al., 2018; O'Sullivan et al., 2019). Lesions or disconnection of these structures can result in classic aphasias (Broca, Wernicke, conduction, and global aphasia) (Berthier, 2005), whereas infarcts in the frontal or caudal territories of the vascular "borderzone" can occur in other, less frequent, types of aphasia (transcortical and anomic aphasias) (Berthier et al., 2011; 2014). Typically, aphasic disorders are most severe in the acute phase (0-1 month), with the greatest recovery taking place during the first 3-6 months, the subacute phase, while decelerating in the chronic phase (over 6 months) (Sheppard & Sebastian, 2021). In addition, PSA is often accompanied by cognitive impairments that involve attention, short and long-term memory, executive and non-verbal functions, resulting in a multidomain cognitive disorder that affects approximately 20-40% of all people experiencing a stroke

(Cahana-Amitay & Albert, 2015; Flowers et al., 2016; Laska et al., 2001; Mcneil & Pratt, 2001).

PSA can cause severe sadness and distress. However, even though NPS, and in particular PSD, have been extensively studied in the non-aphasic stroke population (Angelelli et al., 2004; Ferro et al., 2016; Hackett et al., 2014; Nemani & Gurin, 2021), they have not received the same clinical attention in PWA regarding its assessment, pathophysiology, and clinical management (Brady et al., 2013; Cruice et al., 2010; Hilari et al., 2003; Santo Pietro et al., 2019; Townend et al., 2007). Importantly, an estimated 2.5 million Europeans will require professional attention due to stroke during the next two decades, many of whom will present PSA (Flowers et al., 2016). Stroke will have a global cost of more than 60 billion euros and health care will account for 45% of the expenditure (Luengo-Fernandez et al., 2020; Wafa et al., 2020). An essential portion of these costs will be budgeted toward treating secondary stroke impairments: cognitive deficits (aphasia), depression, and other NPS (Huffman & Stern, 2003; Miyoshi et al., 2010). In adittion, it is known that stroke survivors have six times the chance of suffering from another cerebrovascular accident when coping with poststroke mental illness (Whyte et al., 2004). Such relevant consequences require a better understanding of the brain pathology underlying NPS in PSA and effective interventions based on neuroscientific evidence (Breitenstein et al., 2017; Lazar & Boehme, 2017). But first, a brief excursus on the scientific field of neuropsychiatry.

Neuropsychiatry

Neuropsychiatry is a theoretical and clinical discipline, understood as an interwoven area of knowledge that combines psychiatry, neurology, and neuropsychology and whose objective is to discern the neurobiological basis of behaviour, as well as to improve the care and treatment of patients with neurological diseases and associated NPS (Arzy & Danziger, 2014). Neuropsychiatry has been heterogeneously defined at different historical points (Trimble, 2021), but is based on the foundational assumption that mental disorders are caused by structural and functional brain changes (Berrios & Markova, 2002). Nowadays, the science of neuropsychiatry centres on the diagnosis and treatment of organically caused mental disorders (e.g., depression) behind which identifiable neural mechanisms (e.g., stroke) are hidden (Aybek & Bogousslavsky, 2007; Fornaro et al., 2017; Ojagbemi et al., 2021; Popkin & Tucker, 1992). Several publications highlight the high prevalence of post-stroke NPS due to the renewed interest in psychiatric conditions after brain damage. In a hospital-based cross-sectional study, 518 patients with stroke were evaluated with a widely employed semi-structured clinical interview entitled Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) three to six months after hospital admission. The results showed that more than half of the evaluated patients had one or more NPS (Wong et al., 2016). The most frequent symptom cluster was *mood disturbance* (including depression, apathy, anxiety, sleep disturbances, and appetite disturbances), followed by *behavioural disorders* (disinhibition, agitation, irritability, and motor disturbances), psychosis and euphoria. Gupta et al. (2013) found an even higher prevalence of NPS in post-stroke patients. After three months of hospital admission, 89% of all participants (n = 60) manifested one or more NPS. Angelleli et al. (2004) obtained similar results when evaluating 124 stroke patients. His research team started neuropsychiatric assessment at stroke-onset up until 12 months of stroke evolution. Depression was prevalent in 61% of the patients, irritability and eating disorders in 33%, agitation in 28%, apathy in 27%, and anxiety in 23% of all patients (Angelelli et al., 2004). Depression peaked at 6 months and irritability at 1 year, yet both remained significantly present during the entire evaluation.

Several expert reviews have been published for NPS after stroke (Carota et al., 2002; Ferro et al., 2016; Ferro & Santos, 2019; Nemani & Gurin, 2021; Stolwyk et al., 2018; Tsarkov & Petlovanyi, 2019; Ueki et al., 1999; Wijenberg et al., 2019; Wong et al., 2016). These works highlight that neuropsychiatric disorders are frequent and have profound adverse effects on daily independence, social functioning, and quality of life in stroke patients, while also affecting recovery of motor and cognitive functioning (Campbell Burton et al., 2013; Paranthaman & Baldwin, 2006; Stein et al., 2018; Van Rijsbergen et al., 2019). In fact, NPS reduce patient autonomy and increase caregiver burden (Carota et al., 2002), becoming an important cause of stress and exhaustion for caregivers and often accelerating the patient's re-institutionalization (Hackett et al., 2014). Even early NPS can increase the risk of mortality and recurrence in patients with stroke (Cai et al., 2019). Although physical and cognitive impairments associated with stroke are typically appreciated and treated, the management and therapy of most NPS after stroke are not satisfactory (Zhang et al., 2020). That is because affective and emotional sequelae can be less discernible and more difficult for clinicians to detect and thus treat (Stolwyk et al., 2018). Additionally, the obstacles in detecting and treating NPS increase considerably when stroke patients suffer from PSA.

In general, very little attention has been paid to NPS after PSA, even when the few articles published on this topic indicate that they appear to be considerably prevalent and play a negative impact in functional recovery (Cahana-Amitay & Albert, 2015; Frey et al., 2011; Wong et al., 2016). Many psychometric instruments that measure neuropsychiatric disturbances after stroke are not validated for PWA (Rose et al., 2022; Townend et al., 2007; Wallace et al., 2020), and important limitations of patient-informed neuropsychiatric evaluations are common. Thus most PWA are excluded from epidemiological and intervention studies (Baker et al., 2018; Townend et al., 2007). Only depression has been investigated to some extent in the aphasic population, showing a severely negative impact on language, cognitive rehabilitation, and overall quality of life (Worrall et al., 2016, 2011).

The effects of aphasia go far beyond the reduction of speech and the ability to communicate (Doogan et al., 2018). Self-concept, family, and professional status are threatened. About 80% of those affected by aphasia fall permanently out of employment, leading to material deprivation and social dependence (Doogan et al., 2018). To further highlight the critical limitations imposed by PSA, a scientific study surveyed the relationship between 75 diseases or conditions and individuals' quality of life scores of 66,000 long-term care residents. Thy found that aphasia had the highest negative relationship with quality of life, even before cancer, Alzheimer's disease, or quadriplegia (Lam & Wodchis, 2010). Helping PWA recover language functions, communication, comorbid NPS, and overall quality of life is thus a critical research priority (Bullier et al., 2020; Crosson et al., 2019). Castellanos-Pinedos et al. (2011) extensively evaluated stroke patients and found that depression and apathy were the most common NPS (Castellanos-Pinedo et al., 2011). The clinical experience of our research group also endorses the high frequency of these two NPS in the aphasic population. Therefore, the introduction will expand further on depressive and apathetic sequelae in terms of incidence, risk factors, and prognosis, specifically aphasia, whenever data are available. In addition, this introduction will cover the pathophysiological mechanisms of aphasia, depression and apathy after stroke, and a final section will be dedicated to the treatment approaches available nowadays for PSA and comorbid NPS.

Post-stroke depression

The current classification of PSD according to the Fifth Edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5) is "*Depressive disorder due to another medical condition*" This disorder is generally characterised by low mood and anhedonia in addition to difficulties in concentration, decreased energy or drive, impaired motor and executive functions, feelings of worthlessness, and general somatic changes (American Psychiatric Association, 2013; De Ryck et al., 2014; Døli et al.,2017; Lenzi et al., 2008; Robinson & Jorge, 2016). PSD is the most common and debilitating NPS after stroke, with a mean prevalence of 33% during the first 5 years (Hackett & Pickles, 2014; Wipprecht & Grötzbach, 2013). This proportion remains stable for the next 10 years, thus constituting a chronic and relapsing disorder (Ayerbe et al., 2014). Stroke patients who suffer from aphasia show an even higher prevalence of depression, with peak levels of 60% at 12 months post-stroke onset (Baker et al., 2018; Kauhanen et al., 2000). In fact, a recent study concluded that PWA are 7.4 times more likely to suffer from depression than stroke survivors without aphasia (Zanella et al., 2022). However, this estimate remains controversial, as most PWAs, especially severe cases, are still excluded from neuropsychiatric observational studies (Kristo & Mowll, 2022; Laures-Gore et al., 2020). PSD also increases the risk of a second stroke and negatively affects the prognosis of rehabilitation after stroke occurrence (Medeiros et al., 2020; Mitchell et al., 2017; Starkstein & Hayhow, 2019; Towfighi et al., 2017; Wei et al., 2014). On the other hand, depression alone causes a four-fold higher risk of a first stroke episode, as shown in the Framingham Heart Study (Kronenberg et al., 2013). Physical health, cognition, and overall quality of life are severely impaired (Fornaro et al., 2017; Thayabaranathan et al., 2022). Suicidal ideation can also increase due to aphasia after a stroke (Carota et al., 2016), but attempts and complete suicide are rare.

The prognosis of PSD, especially in elderly patients, is estimated to be worse than that of non-depressed stroke patients (Espárrago Llorca et al., 2015; Kouwenhoven et al., 2011). The main predictors of PSD are premorbid psychiatric disorders, female sex, older age, cognitive and physical impairment, lack of social support, size of the injury, and specific genotypes (Arzy & Danziger, 2014; Feng et al., 2014; Kutlubaev & Hackett, 2014; Naghavi et al., 2019; Robinson, 2006). Being socially isolated and deprived of family support also increases the probability of developing PSD (Kutlubaev & Hackett, 2014). Therefore, rapid and reliable assessment of depression after stroke is critical. However, in many patients, the diagnosis of PSD is challenging in the presence of aphasia or other cognitive impairments (Townend et al., 2007; Tsarkov & Petlovanyi, 2019). Patients with aphasia cannot reliably respond to standardised clinical interviews (Barrows & Thomas, 2018; Van Dijk et al., 2016), and most instruments for assessing depressive symptoms remain highly language-dependent (Kristo & Mowll, 2022). Consequently, PSA frequently impedes the reliable assessment and diagnosis of depression after stroke (Van Dijk et al., 2016), while the lack of psychological support after PSA is also of concern (Baker et al., 2018; 2020). Clinical observations have shown that PSD is not exclusively the result of premorbid psychopathologies or psychological distress related to stroke, but the result of the interaction of several environmental and biological factors (Castellanos-Pinedo et al., 2011; Nemani & Gurin, 2021). In an early study, Folstein et al. (1997) screened 20 stroke patients for depression two months after hospital admission and compared them with 10 patients with hip fracture, who were matched by physical and motor impairment. Stroke patients had a 45% incidence of depression compared to 10% in the orthopaedic group. The authors concluded that ”mood disorder” is a more specific complication of stroke than a simple response to an accompanying motor disability (hemiparesis) (Folstein et al., 2012). Moreover, older stroke patients with ”asymptomatic” ischaemic white matter lesions and no history of stroke also show higher rates of depression (Flaster et al., 2013). In addition, stroke patients suffering from anosognosia (the lack of ability to perceive the realities of one's condition) may also develop mood disorders, including major depression, after the onset of the stroke (Aybek et al., 2005; Biran & Chatterjee, 2003; Starkstein et al., 1990).

Post-stroke apathy

Post-stroke apathy is the second most common NPS after stroke, characterised by low initiative, flattened or indifferent emotions, difficulty maintaining or completing a goal-directed activity, and low self-activation (Caeiro et al., 2013; Kennedy et al., 2015). Unfortunately, the DSM-5 only acknowledges apathy as a symptom of other disorders, not describing apathy as a stand-alone syndrome and thus potentially limiting its recognition (Tay et al., 2021). Additionally, post-stroke apathy has not received the same attention as depression, although approximately 20 to 25% of patients are affected by this condition after stroke (Jorge et al., 2010; Van Dalen et al., 2013) with symptoms beginning as early as 4 days after stroke (Tay et al., 2021). Prevalence data for post-stroke apathy are limited to patients with minimal language deficits (Kennedy et al., 2015).

However, aphasia is a powerful predictor of apathy at six months of stroke evolution (Pappadis et al., 2019). During the first weeks and months, the proportions are as high as 34% of all stroke patients (Carnes-Vendrell et al., 2019; Mayo et al., 2009), and elderly patients are affected more frequently (Gençer & Hocaoğlu, 2019). Approximately 40% of patients with post-stroke apathy also cope with depression (Sachdev, 2018; Van Dalen et al., 2013), but indeed, in most neurological diseases, apathy is not a result of depression (Levy, 2012).

Post-stroke apathy has severe consequences and is routinely associated with poorer cognitive performance (executive functions), functional recovery, reduced social interaction, increased caregiver burden and overall poorer health and quality of life (Hama et al., 2011; Levy, 2012; Sagen et al., 2010; Tay et al., 2021). For example, even mild symptoms of post-stroke apathy are associated with severe disability in activities of daily living (Mayo et al., 2009). Although apathy alone (as occurs with PSD) represents an important public health problem, progress remains to be made in its pathophysiology (i.e., its neural bases) and clinical approaches (definition, assessment, and treatment) (Levy, 2012). To date, apathy treatment approaches remain unsatisfactory and no specific evidence-based therapeutic approach has been approved by regulatory authorities (Kennedy et al., 2015). Apathy in PSA has received limited attention regarding its incidence, but no studies have included PWA in clinical treatment trials. Generally, treatment should start very soon after a stroke, as this NPS limits the patient's ability to participate in rehabilitation programmes (Mayo et al., 2009).

Neurological mechanisms underlying post-stroke aphasia and neuropsychiatric symptoms

Aphasia and language

From the era of autopsy-driven research in the mid and late 19th century, the classical view of language and the brain primarily focused on two cerebral core areas: The left inferior-posterior frontal region (Broca's area) and the posterior-superior temporal cortex (Wernicke's area). The frontal area was responsible for language production, whereas auditory comprehension was processed in the posterior language cortex. Nowadays, it is known that both areas are connected by the white matter tract named arcuate fasciculus (Fridriksson et al., 2018). However, with the onset of neuroimaging techniques and recent observational studies involving humans and primates, it has become evident that many additional areas are also active during language-related activation, suggesting a widely distributed cortico-subcortical network for language processing (Pulvermüller, 1996; Tremblay & Dick, 2016).

Language function is nowadays understood as the dynamic interaction of temporal, frontal, parietal, and subcortical regions connected by white matter tracts (Cahana-Amitay & Albert, 2015; Fridriksson et al., 2018; Thiel & Zumbansen, 2016). The perisylvian language network engages in dynamic interactions with bilateral, multifaceted domain-general networks responsible for attention and cognitive control (Duncan, 2013). Furthermore, the right hemisphere supports specific processed language, such as automatic and formulaic functions (Ross & Monnot, 2011; Thiel & Zumbansen, 2016; Van Lancker Sidtis & Sidtis, 2018). White matter bundles governing language function are segregated in a dual-stream model of language organisation (Fridriksson et al., 2018; Hickok & Poeppel, 2004). Hickok & Poeppel´s model describes two functionally and structurally differentiated white matter streams. A *dorsal stream*, essential for phonology, responsible for mapping sound to articulation, it connects the superior temporal lobe with the premotor cortex of the frontal lobe through the arcuate fasciculus and the superior longitudinal fasciculus (Hickok & Poeppel, 2004). The *ventral stream* bridges sound to meaning and connects the middle temporal lobe and the ventrolateral prefrontal cortex through the middle longitudinal fascicle and the extreme capsule through the uncinate fasciculus and the inferior longitudinal fasciculus (Hickok & Poeppel, 2004; Nasios et al., 2019) (see Figure 1). PSA results from structural and functional damage to this complex neural network distributed in the cortical and subcortical structures of the dominant left hemisphere (Hartwigsen & Saur, 2019; Thiel & Zumbansen, 2016). Therefore, rather than a language dysfunction resulting from a focal lesion, aphasia must be understood as the consequence of disruptions of functional domain-specific and domain-general complex networks (Blank et al., 2017; Duncan & Small, 2018; Fedorenko & Thompson-Schill, 2014; Fedorenko & Varley, 2016; Gleichgerrcht et al., 2015; López-Barroso & De Diego-Balaguer, 2017; Turken & Dronkers, 2011).

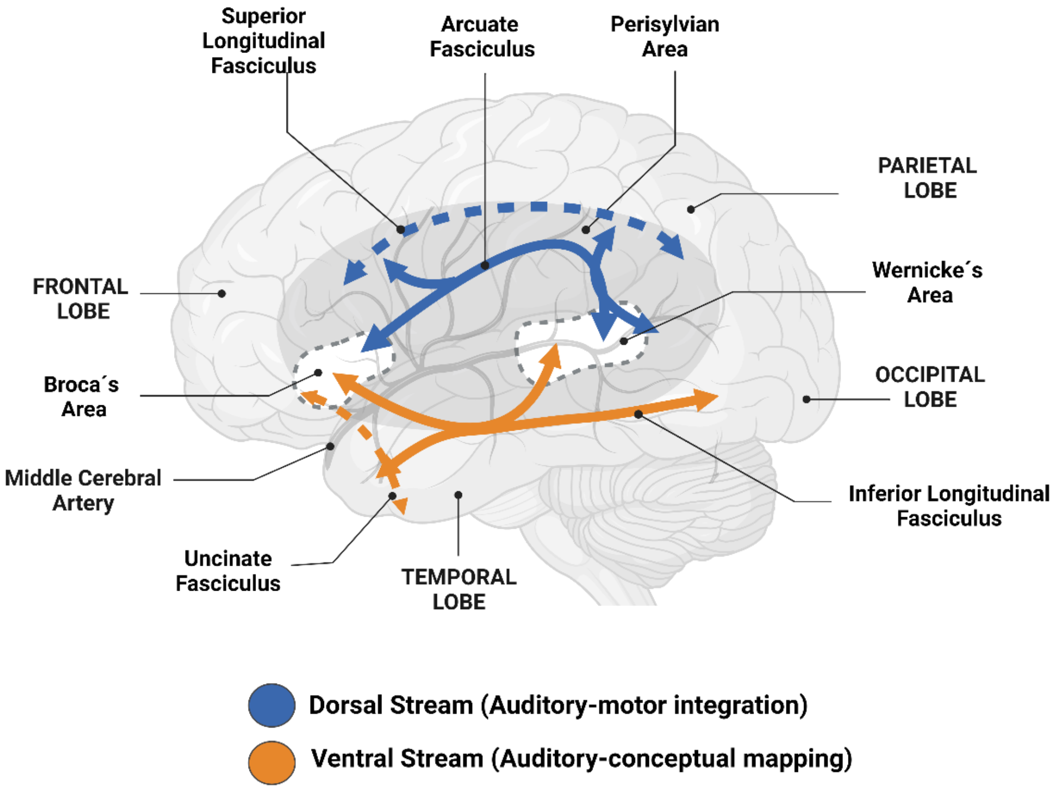

Figure 1. Schematic illustration of the left hemisphere depicting the currently accepted language network model. The perisylvian cortex, which covers the frontal, parietal, and temporal cortices, is shaded in dark grey. The middle cerebral artery is depicted in darker grey. The Broca complex and Wernicke are shown in white in the frontal and caudal zones, respectively. The dorsal language circuit includes the arcuate fasciculus and the superior longitudinal fasciculus (light blue). The ventral language circuit includes the uncinate fasciculus and the inferior longitudinal fasciculus (yellow). Figure adapted from López-Barroso & De Diego-Balaguer, 2017 and Thiel & Zumbansen, 2016 and created with Biorender.com.

Aphasia and other cognitive domains

PSA frequently accompanies a spectrum of cognitive deficits that transcend the domain of language and communication. In this section, insights from several seminal studies are drawn (Fonseca, Raposo, & Martins, 2018; 2019; Akkad et al., 2023; Yao et al., 2020; Bonini & Radanovic, 2015) to provide a more comprehensive grasp of these multifaceted cognitive consequences. First, the study by Bonini and Radanovic (2015) highlights the challenge of evaluating cognitive performance in individuals with aphasia. Their investigation compared the cognitive abilities of aphasic patients to those of non-aphasic individuals with left and right hemisphere lesions. Aphasic patients exhibited poorer performance in various cognitive domains, including attention, verbal and visual memory, executive functions, visuospatial skills, and praxis. These findings underscore the intricate nature of cognitive deficits in aphasia, emphasizing the necessity of comprehensive assessments to optimize therapeutic interventions. On the other hand Yao et al. (2020) conducted a study focusing on non-linguistic cognitive impairments in post-stroke aphasia patients. They identified that individuals with post-stroke aphasia exhibited lower scores in various cognitive domains, particularly those with non-fluent aphasia presenting more severe cognitive impairments.

Akkad et al. (2023) and Fonseca et al. (2018) shed light on the impact of aphasia on executive functions, encompassing planning, problem-solving, and decision-making. Stroke survivors with aphasia often struggle with these cognitive processes, affecting their ability to sequence daily tasks, assess risks, and set goals. These executive deficits not only exacerbate communication challenges but also contribute to a broader cognitive impairment profile observed in aphasic individuals. Working memory, a crucial cognitive mechanism for temporary information storage and manipulation, is also notably affected by post-stroke aphasia (Fonseca et al., 2018). Aphasic individuals encounter challenges in retaining and processing verbal information, hindering their capacity to follow instructions, engage in complex problem-solving, and participate in meaningful conversations. On ther other hand, Akkad et al. (2023) emphasize the substantial influence of post-stroke aphasia on attentional processes. Attention deficits manifest as difficulties in sustaining focus, increased susceptibility to distractions, and diminished multitasking capabilities. Maintaining concentration during verbal exchanges becomes arduous, resulting in communication breakdowns and reduced engagement in tasks requiring sustained attention. Regarding stroke evolution, Fonseca et al. (2019) explored the relationships between cognitive skills and language abilities in individuals with chronic PSA. Their study also revealed that non-linguistic cognitive functions, specifically executive functions and verbal working memory, had a substantial impact on the behavior of aphasic individuals. Furthermore, lesions in the left inferior frontal cortex (LIFC), including Broca's area, were associated with non-language-specific higher-order cognitive deficits in aphasia.

In conclusion, post-stroke aphasia extends its influence well beyond language and communication, affecting executive function, working memory, and attention. Recent studies have illuminated the extensive and interconnected cognitive deficits experienced by aphasic individuals. Understanding the multifaceted nature of these cognitive consequences is vital for tailoring rehabilitation strategies and improving the overall well-being and cognitive outcomes of post-stroke aphasia patients.

Functional and post-stroke depression

Depression is a complex and multifaceted condition that does not neatly align with any single underlying physiological mechanism, as noted by Sarkar et al. (2021) and Spellman & Liston (2020). Functional depression, which is not associated with gross brain damage, can have various potential causes, including genetic, immunologic, endocrine, and neurotransmitter system dysfunctions (Jesulola et al., 2018). However, none of these factors in isolation can comprehensively account for all the manifestations and symptoms of depression, as indicated by Jesulola et al. (2018) and Spellman & Liston (2020). Structural magnetic resonance imaging (MRI) investigations have unveiled structural alterations in the brains of individuals with functional depression. These alterations include cortical thinning in regions such as the anterior cingulate, particularly the subcallosal area, prefrontal cortex, and orbitofrontal cortex, as well as volume reductions in the thalamus, basal ganglia, hippocampus, and amygdala, as described by Riva-Posse et al. (2019) and Spellman & Liston (2020). For instance, the anterior cingulate cortex subgenual area of patients with endogenous depression shows a 35% volume reduction and 24% to 41% fewer glial cells than control non-depressed samples (Hamani et al., 2011). Anatomical changes have also been found in subcortical nuclei that synthesise monoamines (dopamine, serotonin, and norepinephrine), resulting in a decreased availability of these key messengers for mood regulation (Adell, 2015).

On the other hand, differentiated functional activation patterns have been found in the brain of depressed patients involving dysfunction of cognitive and emotion regulation processes (Balaev et al., 2018; Liston et al., 2014; Menon, 2011; Padmanabhan et al., 2019; Peters et al., 2016; Spellman & Liston, 2020). Connectivity magnetic resonance analysis has identified three key networks responsible for complex mood, behaviour, attention, self-awareness, and introspection processes: the Default Mode Network (DMN), the Central Executive Network (CEN), and the Salience Network (SN)(Menon, 2019; Menon, 2011; Palmer, Crewther, & Carey, 2015; Peters et al., 2016; Spellman & Liston, 2020) (see Figure 2). The DMN includes the posterior cingulate cortex (PCC), the medial prefrontal cortex, the nodes in the medial temporal cortex, the precuneus, and the angular gyrus (Menon, 2019; Vicentini et al., 2017). This extensive network is active during wakeful rest and involves internally oriented and self-referential processes, including daydreaming and autobiographical memory (Guha et al., 2021). A meta-analysis of functional magnetic resonance imaging studies shows that depressed patients show a pattern of hyperconnectivity in the DMN (Kaiser et al., 2015). Conversely, a functional pattern of hypoconnectivity was found in the CEN (Menon, 2019). The CEN includes the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex and is involved in high-level cognitive functions such as planning, decision-making, attention, and working memory. The SN, or cingulate-frontal-operculum system, comprises the anterior insula (AI), dorsal anterior cingulate cortex (dACC), amygdala and the substantia nigra/ventral tegmental area. This network is designed to prioritize and respond to significant external stimuli as well as internal events, playing a crucial role in detecting saliency and enabling dynamic cognitive control. In general, the CEN and SN typically exhibit heightened activation during active cognitive and affective stimulus processing, whereas the DMN experiences deactivation during tasks and displays increased activation during periods of rest and stimulus-independent processing. Notably, conditions such as depression and other NPS result in alterations in the coherence of activation patterns within these three networks, as reported by Vicentini et al. in 2017. In simpler terms, functional depression is characterized by abnormalities in the way these three core networks interact with each other.

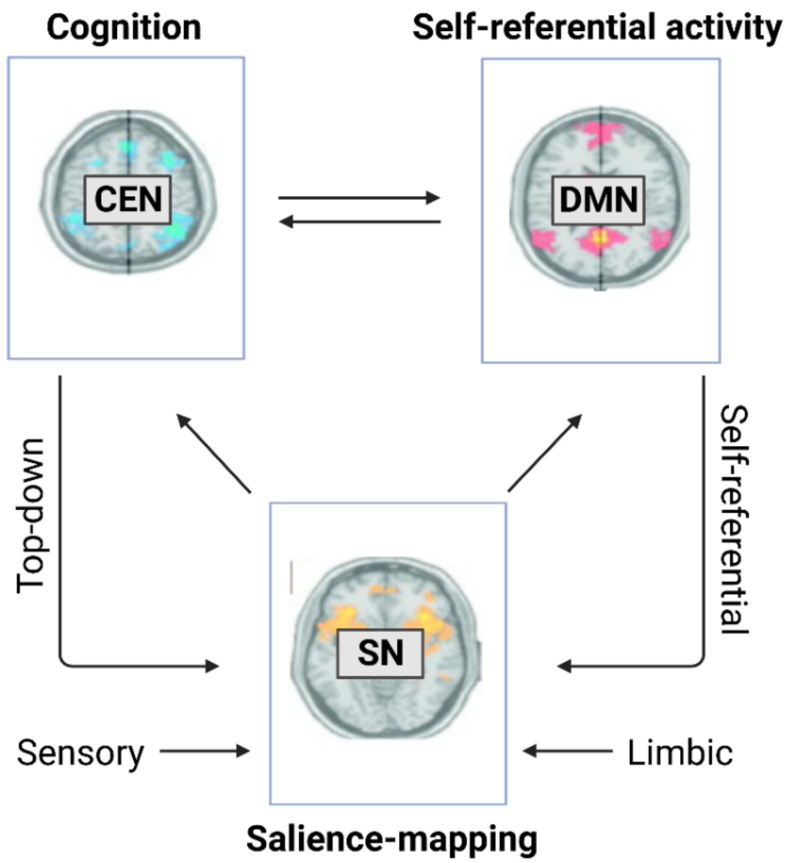

Figure 2. Schematic illustration of the SN, CEN and DMN mainly involved in functional and stroke-induced depression. The atypical intrinsic organization of SN, CEN, and DMN are characteristic of many mental and neurological disorders. Menon (2019) posits that the weak-salience identification and mapping of external stimuli pertaining to the internal mental events of the SN play a pivotal role in psychopathology. The insufficient mapping of the insular-cingulate SN leads to abnormal recruitment of the frontal CEN, thereby impairing cognitive function and adaptive goal-oriented behavior. The atypical organization's inadequate activation or deactivation of the DMN in response to significant events is correlated with alterations in self-referential mental activity. Figure adapted from V. Menon (2011) and created with BioRender.com.

For depression after brain damage due to stroke, the first pathophysiological hypothesis was the role of monoaminergic projection disruptions (dopamine, serotonin, and norepinephrine) (Dulawa & Janowsky, 2019; Laures-Gore et al., 2020). Pioneering studies in the 1970s by Robinson and colleagues in experimental strokes and humans indicated that stroke lesions interrupting ascending monoamine neurotransmitters projections from the brainstem toward the neocortex are responsible for mood disorders, motivation, vigilance, tiredness and lack of energy (fatigue) (Robinson & Jorge, 2016). Over time, other neurotransmitters, such as acetylcholine or glutamate, were also associated with NPS. Since nicotinic receptors of the central cholinergic system have been found to be involved in emotion regulation and the aetiology of major depressive disorders (Loubinoux et al., 2012), the amine hypothesis of post-stroke depression has recently been expanded and called *acetyl-amine hypothesis* (Loubinoux et al., 2012).

Regarding the location of the stroke lesion, the data are inconclusive to effectively state that left hemisphere lesions play a key role in the genesis of PSD, a hypothesis commonly held during the past decades but debated in a recent meta-analysis (Ayerbe et al., 2013; Zhang et al., 2017). However, there are strong data suggesting that more frontal stroke lesions are associated with a higher incidence of PSD (Robinson & Jorge, 2016). In any case and regardless of the site of the injury, PSD has been linked to imbalanced communication amongst the cerebral networks mentioned above, the DMN, the SN and the CEN (Balaev et al., 2018; Kaiser et al., 2015; Riva-Posse et al., 2019; Zhang et al., 2018). Other biological factors associated with PSD include abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis, neuroplasticity and glutamate neurotransmission, and an excess of pro-inflammatory cytokines (Medeiros et al., 2020; Robinson & Jorge, 2016). In summary, the development of a comprehensive pathophysiological framework elucidating the intricate interplay of various factors contributing to PSD remains an unattained objective. Moreover, the intricate nexus between PSA, PSD, and other concomitant NPS remains a subject of limited comprehension within the current body of knowledge.

Functional and post-stroke apathy

Apathy ranks as the second most prevalent NPS following stroke, progressively increasing in frequency over time (Brodaty et al., 2005; Starkstein & Manes, 2000). While the pathophysiological mechanisms underlying PSD have garnered significant research interest, particularly in non-aphasic stroke cohorts, the field of neuropsychiatry has allocated comparatively limited attention to the investigation of apathy, despite its substantial clinical relevance with respect to rehabilitation outcomes (Brodaty et al., 2005). Apathy demonstrates a consistent correlation with structural and functional alterations in both white and grey matter regions responsible for the initiation and regulation of behavior, irrespective of the underlying etiological factors. Apathy has been associated with lesions involving the medial frontal cortex, the anterior dorsal cingulate gyrus, the basal ventral ganglia, the medial nuclei of the thalamus, and the frontostriatal circuits that connect these structures (see Figure 3) (Chong & Husain, 2016; Husain et al., 2018; Le Heron et al., 2019). Apathy thus results from the dysfunction of the systems that provide the affective value of a given behavioural context (Husain et al., 2018; Levy, 2012). The principal neurotransmitter system innervating these anatomical structures is the dopaminergic system. This monoaminergic neurotransmitter exerts a pivotal influence on the regulation of motivation and decision-making processes. Specifically, dopamine plays a critical role in ascribing incentive salience to rewarding stimuli and in facilitating the capacity to surmount the associated effort costs. Consequently, dopamine agonists are the treatment of choice for motivational disorders (Chong & Husain, 2016). However, not all patients with PSA have apathy due to the exclusive deficit of dopamine tone. In fact, some nodes of the meso-cortico-limbic circuit supplied by dopamine are unaffected and can be amenable to pharmacological manipulation with drugs that can strongly interact with dopamine, such as those acting on the cholinergic system. The influence of cholinergic activity on other neurotransmitter systems has been extensively demonstrated (Furey, 2011). In the context of pharmacological interventions for the management of apathy employing cholinergic agents, a plausible mechanistic basis for cholinergic-dopaminergic interplay resides in the putative role of ascending cholinergic projections originating from the pedunculopontine nucleus. These projections extend to critical neuroanatomical locales including the midbrain's ventral tegmental area (VTA) and the forebrain structures encompassing the thalamus and basal ganglia, as elucidated by Mena-Segovia and Bolam (2017).

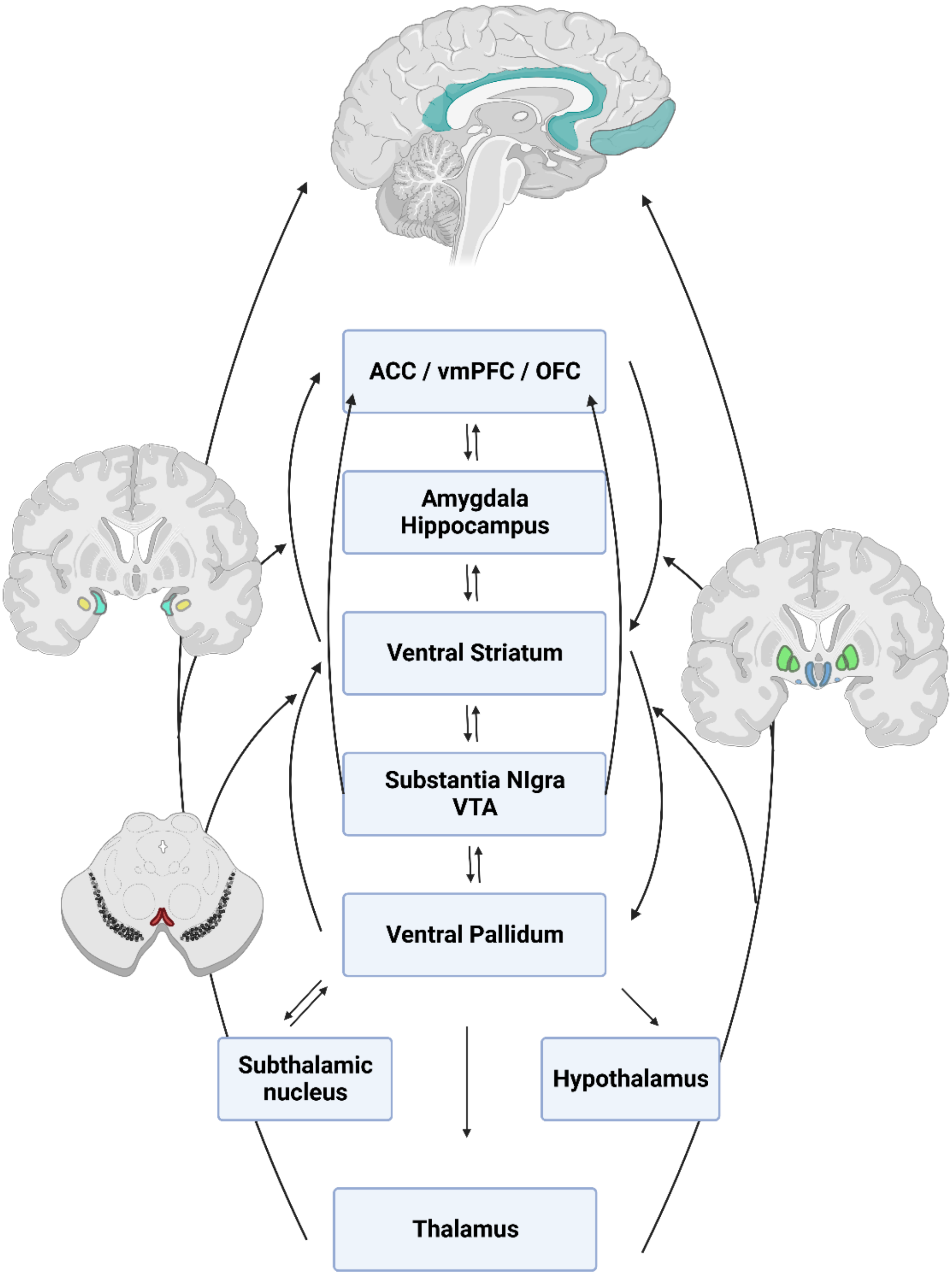

Figure 3. Schematic illustration of the cerebral reward pathway and the interconnected structures mediated by dopamine. The sagittal cross-section (highlighted in light blue) provides a clear view of the anterior cingulate cortex (ACC) in the dorsal region and the ventromedial prefrontal cortex (vmPFC) in the ventral region, while the orbitofrontal cortex (OFC) can be observed on the ventral surface of the frontal lobe. Moving on to the coronal slices, they reveal the distinct nuclei of the amygdala (top left, marked in yellow), the hippocampal formation (top left, represented in turquoise), and the ventral striatum (middle right, appearing in green and blue). In the axial image of the midbrain, one can discern the lateral presence of the substantia nigra, alongside the medial positioning of the ventral tegmental area (VTA) marked in red. Figure adapted from Chong & Husain, 2016 and created with BioRender.com.

Treatment approaches for post-stroke aphasia and neuropsychiatric symptoms

Speech-language therapy (SLT) is the mainstay treatment for PSA. Gains promoted by SLT and neurobiological interventions (pharmacotherapy and non-invasive brain stimulation) are associated with functional and structural changes in the networks discussed previously (Berthier et al., 2011; Fridriksson & Hillis, 2021). There is ample evidence that improving neuroplasticity during aphasia treatment is the result of recruiting dysfunctional, but not irremediably, damaged brain tissue as well as brain areas not fully devoted to language function before the stroke (e.g., Domain-General Multiple Demand Networks) (Berthier et al., 2011; Crosson et al., 2019; J. Duncan, 2013; Hartwigsen & Saur, 2019; Kiran & Thompson, 2019; Stefaniak et al., 2020, 2021, 2022; Watila & Balarabe, 2015). The mean duration of care for affected stroke patients is estimated to be around 5 years (Jones et al., 2020), while the duration of SLT is remarkably shorter in patients with aphasia.

Functional recovery from PSA is highest during the first three to six months after stroke, mainly due to spontaneous recovery. Nevertheless, in the chronic period (> 6 months post-onset), recovery tends to stabilize, usually reaching a plateau. That means that to increase improvement in language and communication, intensive rehabilitation (> 4 hours/week) and biological interventions are required (Berthier, 2005; Lanctôt et al., 2019). However, there are exceptions and improvement may continue for several years (Belagaje, 2017; Breitenstein et al., 2017; Smania et al., 2010). Therefore, it is essential for the patient, family and therapist to be clear about the real expectation of improvement and the key deficits targeted during therapy (Fridriksson et al., 2022). Moreover, the direct effects on language and communication will be translated to other cognitive functions, comorbid NPS, and quality of life (Darkow & Flöel, 2016; Doogan et al., 2018). Indeed, current intervention strategies for PWA focus primarily on the immediate effects of language and communication (aphasia) hoping that reducing these will necessarily have knock-on effects on other cognitive and affective domains (see Figure 4).

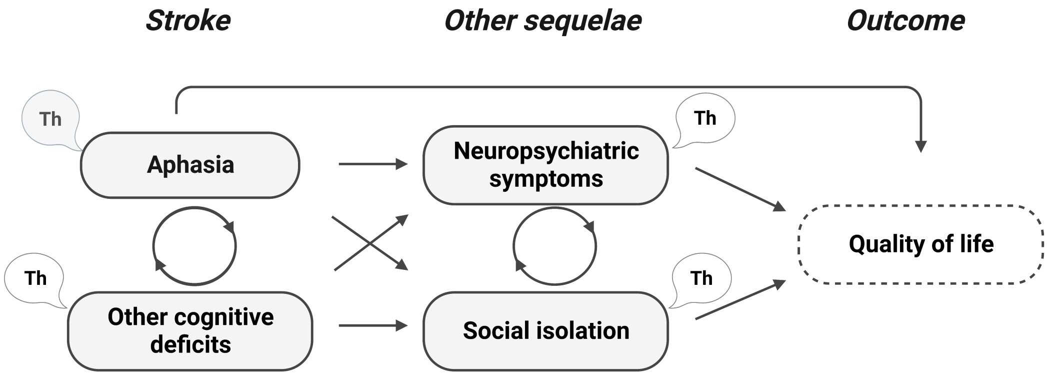

Figure 4. Schematic illustration of the interplay of aphasia and other comorbid factors affecting the quality of life. *Th* refers to "therapy", which in most cases, is applied only to aphasic deficits after stroke. Figure adapted from Doogan et al., 2018 and created with BioRender.com.

Speech-language therapies for post-stroke aphasia and NPS

The gold standard mainstay treatment for language and communication deficits in poststroke aphasia is SLT (Darkow & Flöel, 2016; Doogan et al., 2018; Marshall & Mohapatra, 2017; Vitti & Hillis, 2021). Regardless of the severity of aphasia or the evolution of stroke, patients improve with SLT and show treatment-induced brain plasticity, even months to years after stroke onset (Hillis, 2007; Holland et al., 2017; Vitti & Hillis, 2021). Furthermore, *intensive aphasia therapy* over a short period is more effective than therapy sessions spread over a longer period (Berthier & Pulvermüller, 2011; Brady et al., 2012; Saxena & Hillis, 2017; Zhang et al., 2017). One of the most prominent representatives of SLT is Intensive Language-Action Therapy (ILAT), which is supported by mass and intensive training for a relatively short duration (Difrancesco et al., 2012; Pulvermuller & Berthier, 2008; Stahl et al., 2016). It is a therapeutic approach derived from constraint-induced movement therapies that rehabilitate the upper extremities due to stroke (Difrancesco et al., 2012). This motor therapy is based on the principle of use-dependent learning by preventing the employment of the unaffected arm of the body and forcing the use of the affected side, thus avoiding 'learnt non-use' in patients (Berthier & Pulvermüller, 2011; Difrancesco et al., 2012; Intercollegiate Stroke Working Party, 2016). The method of forced use has shown excellent results in motor rehabilitation (Berthier & Pulvermüller, 2011), and its three main principles have been transferred to the rehabilitation of aphasia.

1. Massed practices in action contexts, including at least 10 days of intervention with 3-hour sessions per day.
2. Shaping, modelling, and gradually increasing the relevant difficulty of the language task for daily life according to the functional performance of the patient.
3. Guiding and focusing patients on verbal communication rather than other nonverbal communication modalities such as gesturing or pointing.

During therapy, speech act sequences are embedded in therapeutic language games. Usually, two to three participants sit around a table with barriers in front of them, hindering the visualisation of the upper limbs and cards of the other participants and, therefore, any non-verbal communication, such as gestures or pointing. Next, each participant receives picture cards that show objects or actions that belong to six different grammatical categories. Then, the sequence of interactions known as Communicative Interaction Language Action Games (LAGs - Difrancesco et al., 2012) is initiated. A LAG consists of several game rounds with the communicative goal of enhancing real-life social interaction. Therapy difficulty is shaped according to the linguistic abilities of each patient. The therapist's role includes introducing, modelling, shaping, adjusting, and tracking communicative success (Difrancesco et al., 2012). ILAT has repeatedly been shown to increase daily communication effectiveness and activities (Marcotte et al., 2012; Pulvermüller et al., 2001b; Zhang et al., 2017). The International Classification of Functioning, Disability, and Health (ICF) calls for rehabilitation methods focusing on social and communicative participation in PWA and less on linguistic deficits (Darkow & Flöel, 2016). NPS in PSA detrimentally affect language/functional communication, rehabilitation outcomes, and vice-versa. Thus, this suggests that intervention approaches designed to improve language and communication deficits after PSA may have a positive carryover effect on NPS, such as depression (Baker et al., 2018).

In this line of work, a recent study showed that ILAT, performed in group settings and targeting social interaction, improves the severity of aphasia, social communication and participation, and low mood in chronic non-fluent aphasia. In a crossover randomised controlled study, Mohr et al. (2017) included 18 PWA with non-fluent chronic aphasia (15 with Broca's aphasia and 3 with global aphasia), randomly assigning them to 2 treatment arms: ILAT or standard intensive naming therapy (INT). All patients received the same number of hours of treatment in a counterbalanced order. Amongst other hypotheses, the study aimed to test (1) whether aphasia therapy, both ILAT and INT, could ameliorate symptoms of depression; and whether (2) improvements in depressive symptoms were associated with specific treatment methods (Mohr et al., 2017). Results showed a significant depression reduction only with ILAT, measured with the Beck Depression Inventory (27%, ILAT *vs* INT 9.8%) (Mohr et al., 2017) (see Figure 5). Additionally, the changes in ILAT in expressive language ability in these PWAs were also more robust with ILAT than with INT. Importantly, the beneficial effects of ILAT on depression were independent of improvements in language deficits. That is the first randomized controlled trial, including participants with chronic aphasia, that shows the efficacy of a specific behavioural language therapy targeting social communication which also improves depressive symptoms. Recently, a study that included 60 participants with subacute aphasia (0.5-6 months of stroke evolution) assigned half of the participants to ILAT and the other half to standard care alone treatment. Again, significant differences between treatments were found between both treatment arms with small to medium effect sizes (Stahl et al., 2022).

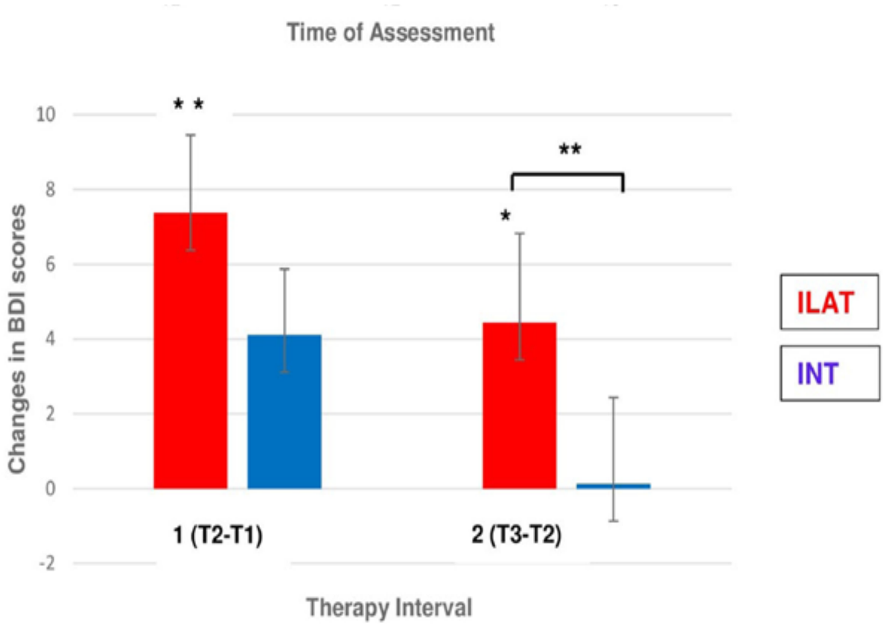

Figure 5. Changes in depression symptoms, as assessed by the Beck Depression Inventory (BDI), in language therapy in chronic aphasia. The reductions in BDI scores during therapy intervals 1 (T2 - T1) and 2 (T3 - T2), combined for both groups, are visually represented with separate bars for each treatment method: ILAT in red and INT in blue. Significant post hoc differences are denoted by asterisks (*P < .05; **P < .01).Figure with permission from Mohr et al., 2017.

In general, ILAT induces improvements in the language of chronic PSA in a short time (Berthier et al., 2009; Pulvermüller et al., 2001a; Stahl et al., 2018) associated with brain plasticity characterised by the rearrangement of activity in both hemispheres after stroke (Basso & Macis, 2011; Brady et al., 2012; Difrancesco et al., 2012; Mohr, 2017; Pulvermüller et al., 2005; Zhang et al., 2017). However, it is unknown whether ILAT also improves depressive symptoms in patients with fluent aphasia. Since many PWA in the chronic post-stroke period still have residual language and mood deficits (Saxena & Hillis, 2017), the potential role of combining therapeutic strategies (SLT and drugs) is currently being explored.

Combining language therapy with pharmacological approaches to target post-stroke aphasia and NPS

To date, no drugs have been approved by regulatory agencies (FDA and EMA) for PSA treatment (Berthier, 2021; Marcotte et al., 2012). However, medications authorised for treating other neurological or neuropsychiatric disorders have been repurposed for PSA use. Treatment with drugs in PSA is beneficial when administered alone (Berthier et al., 2009) and as an adjuvant to SLT (see Berthier, 2021). The theoretical rationale for using drugs in PSA is to leverage the activity of depleted or abnormally released neurotransmitters. This intervention promotes neural plasticity in both cerebral hemispheres, but the specific effect on language systems is still unknown. Low focal agents such as glutamate and GABA, which are widely distributed, may have a more diffuse action. In contrast, other neurotransmitters (serotonin, dopamine, acetylcholine) that innervate more discrete cortical fields may have a selective action, not only in language function but also in other cognitive domains such as arousal, attention, executive function, and memory (Pulvermuller & Berthier, 2008; Saxena & Hillis, 2017). PWA have shown better naming and content of picture description abilities when selective serotonin reuptake inhibitors (SSRIs) were administered after the onset of stroke, and these results were independent of age and level of education (Hillis et al., 2018). Other well-controlled studies do not report significant effects of adjuvant drugs on aphasia outcomes (Breitenstein et al., 2015). In contrast, as early as 2003, Jorge et al. reported a study showing that immediate SSRI antidepressant treatment started independently of the presence of depressive symptoms and could reduce mortality after stroke (Jorge et al., 2013).

Glutamatergic and cholinergic agents such as Memantine and Donepezil have shown profitable results in language and other cognitive domains, enhancing the benefits of SLT in different language domains of PWA in both acute or chronic phases (Bakheit, 2004; Berthier et al., 2006; Berthier et al., 2009; Breining & Sebastian, 2020; Cahana-Amitay & Albert, 2015; Hartwigsen & Saur, 2019; Picano et al., 2021; Saxena & Hillis, 2017). The use of Donepezil, a centrally acting reversible acetylcholinesterase inhibitor, is approved for Alzheimer's disease, although it has also been confirmed to be a promising drug for the treatment of post-stroke cognitive impairment (Berthier et al., 2020), including chronic PSA (Berthier et al., 2006; Neishaboori et al., 2021; Whyte et al., 2008). A double-blind, randomized, placebo-controlled study of Donepezil and distributed SLT (2 hours per week) improved the severity of aphasia, motor aspects of language, input-output phonology, and lexical-semantic processing (Berthier et al., 2006), probably due to reorganization of cortical networks (Berthier et al., 2006) and better regulation of regional blood flow of the cerebral cortex (Román & Kalaria, 2006). Overall, in PWA, the safety and tolerability of short- and long-term treatment with Donepezil have been demonstrated (Berthier, 2005; Berthier et al., 2006; 2014; Hartwigsen & Saur, 2019). Furthermore, physiological evidence shows that the cholinergic system (muscarinic receptor) is overactive or hyperresponsive in depression (Drevets et al., 2013). That would explain, at least in part, the relatively little research on the antidepressant properties of cholinergic agents in depression. However, Donepezil acts primarily on nicotinic receptors and recent experimental studies in rodents show that low doses of Donepezil have antidepressant properties, while high doses induce depression (Fitzgerald et al., 2020). These data, coupled with human studies reporting that Donepezil improves language, depression, and apathy in stroke and dementia (Berthier et al., 2006; Cummings et al., 2006; Whyte et al., 2008), merit further research on the treatment of depression and related NPS in PSA.

Although modulation of brain activity with cognitive enhancing drugs is predominantly directed to a single neurotransmitter (e.g., rotigotine → dopaminergic system), this type of pharmacological stimulation also targets other neurotransmitter systems (Furey, 2011). In support, cholinergic modulation with drugs interacts with monoaminergic neurotransmitter systems traditionally involved in depression treatment (Mena-Segovia et al., 2008; Nestler et al., 2014). High doses of pro-cholinergic drugs seem to promote an antidepressant effect (Dulawa & Janowsky, 2019). The clinical administration of acetylcholinesterase inhibitors to people with mood disorders has shown beneficial effects on depression and, in some cases, reduces mania or hypomania (Reynolds et al., 2006) (see Figure 6). Animal models go in the same direction as a study of chronic stress in rats revealed that chronically administered acetylcholinesterase inhibitors have antidepressant effects (Papp et al., 2016). However, a recent randomised controlled trial in elderly patients with depression and mild cognitive impairment has not shown any benefit of adding Donepezil to ongoing antidepressant treatment (Devanand et al., 2018). Therefore, further studies are warranted on the role of pro-cholinergic drugs in depression after stroke and PSA.

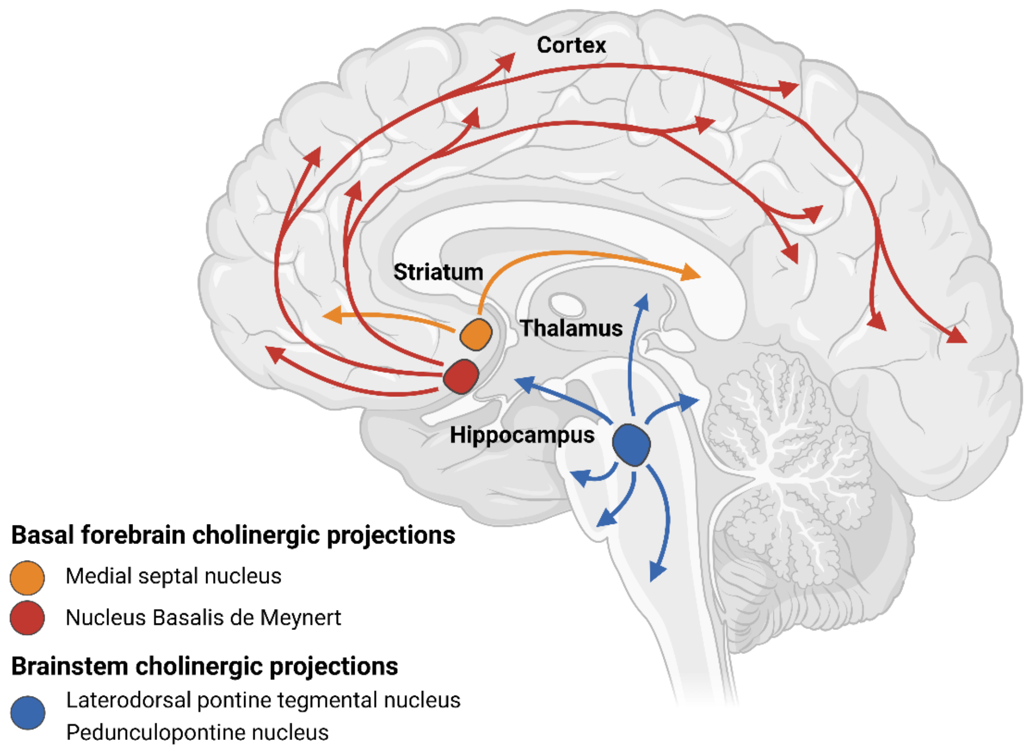

Figure 6. **Schematic illustration of the cholinergic circuit and its main projections in the cerebrum.** A stroke can result in targeted disruptions in neurotransmitter innervation, reducing the availability of messengers in both the neocortex and subcortical structures, ultimately impacting behavior and emotional regulation. The administration of a cognitive-enhancing drug may potentially reverse these degenerative neurotransmitter processes. Figure adapted from Bertrand & Wallace, 2020 and created with BioRender.com.

A recent Cochrane review concludes that SSRIs can improve dependency, disability, neurological impairment, anxiety, and depression after stroke (Allida et al., 2020). However, the review emphasises the broad heterogeneity of existing studies and, at the same time, also points to methodological limitations in a large part of the available studies, as well as the need to conduct more extensive treatment studies before SSRIs can be used routinely in stroke patients (and PWA). It also points out that recurrence is high in patients treated with SSRIs, and these drugs are ineffective in approximately 40% of patients with depression (Dar et al., 2017; M. Jones et al., 2019). Prophylactic prevention of apathy could also occur with escitalopram (Mikami et al., 2013), but the results are based on small-sample studies that need more extensive replication. Cholinergic medications (Donepezil and Galantamine) targeting post-stroke apathy have provided positive preliminary results in stroke patients without aphasia (Mikami et al., 2013; Paranthaman & Baldwin, 2006; Tay et al., 2021; Whyte et al., 2008). Unfortunately, to date, PWAs are excluded from most pharmacological intervention studies aimed at depression, apathy, or other NPS (Mohr et al., 2017; Townend et al., 2007). Psychotherapeutic approaches, on the other hand, namely behavioural activation and cognitive-behavioural therapy, are the mainstay behavioural treatment options for major depression and apathy in stroke patients (Finkenzeller et al., 2009; Hama et al., 2011; Lenzi et al., 2008). Unfortunately, PWAs are once more excluded from most intervention trials due to heavy language restrictions (Baker et al., 2018; Baker, Worrall et al., 2018). Therefore, it must be concluded that no therapy approaches specifically target NPS in PSA.

Conclusion

PSA currently stands as one of the most devastating medical conditions worldwide, and its persistence in this form is expected due to the increasing incidence of strokes. Furthermore, PSA is accompanied by dramatic comorbid consequences, particularly in the realm of secondary NPS. Despite significant strides in the diagnosis and treatment of aphasia, the comorbid neuropsychiatric spectrum has largely been overlooked. The present doctoral dissertation sheds light on several critical questions surrounding the neuropsychiatry of PSA that demand attention and exploration: (1) What are the precise pathophysiological mechanisms that underlie NPS, specifically depression and apathy, in PSA?; (2) Can SLT not only improve aphasia severity but also have a lasting impact on NPS in PSA?; (3) If positive carryover effects exist, can they be enhanced through the administration of cognitive-enhancing drugs like Donepezil? (4) How can SLT, both independently and in conjunction with medication, contribute to functional recovery and the structural modulation of disrupted neuronal networks in PSA and NPS? (5) What are the most effective methods for evaluating depression, apathy and other NPS in individuals with PWA? This doctoral dissertation is dedicated to the exploration and resolution of these vital questions, aiming to advance our understanding of PSA and enhance the care and treatment of individuals affected by this challenging condition.

Chapter 2: Research Aims

Research aims

Chapter 1 (Introduction) summarizes how the neuropsychiatry of PSA has not been adequately explored regarding prevalence, pathophysiology, and treatment data. However, NPS profoundly impact functional rehabilitation and quality of life of people with aphasia and their families. Therefore, the cross-sectional objectives of the present dissertation were to explore the state-of-the-art of NPS in PSA, to provide first data on the prevalence of NPS in chronic aphasic patients, and to further provide data on the effects of ILAT alone and combined with Donepezil in the rehabilitation of linguistic deficits as well as depression and apathy. The present thesis comprises three studies.

Thesis´s objectives:

Study 1 — (A) This study aims to conduct a comprehensive review of the scientific literature regarding the spectrum of NPS in PSA. It will summarize data on prevalence, risk factors, assessment tools, pathophysiology, and available treatment options. Additionally, (B) the feasibility of assessing a broader range of NPS in 20 individuals with chronic PWA will be explored. This will involve examining the frequency, nature, and comorbidity of the neuropsychiatric symptoms using a combination of proxy-based and direct evaluation instruments.

Study 2 — This study will focus on analyzing the effects of two weeks of Intensive Language-Action Therapy (ILAT) on individuals with chronic fluent aphasia. Specifically, changes in aphasia severity and depression scores following the ILAT intervention will be assessed.

Study 3 — (A) The primary objective of this study is to evaluate the outcomes of monotherapy with Donepezil and combined therapy with Donepezil-ILAT in individuals with PWA. We will assess changes in aphasia severity, as well as depression and apathy scores. (B) Furthermore, this study will investigate the functional and structural changes in the brain that may occur as a result of these interventions.

Chapter 3: Main Corpus

Articles included in this thesis

This doctoral dissertation encompasses a collection of original research contributions, including:

Study 1 **Edelkraut, L.**, López-Barroso, D., Torres-Prioris, M. J., Starkstein, S. E., Jorge, R. E., Aloisi, J., Berthier, M. L., & Dávila, G. (2022). Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia. *World Journal of Psychiatry,* 12(3): 450-469. https://doi.org/10.5498/wjp.v12.i3.450.

Study 2 Berthier, M. L., **Edelkraut, L.**, Mohr, B., Pulvermüller, F., Starkstein, S. E., Green-Heredia, C., & Dávila, G. (2022). Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study. *Neuropsychological Rehabilitation*, 32(1): 148–163. https://doi.org/10.1080/09602011.2020.1809463.

Study 3 Berthier, M. L., **Edelkraut, L.**, López-González, F. J., López-Barroso, D., Pulvermuellller, F., Starkstein, S. E., Jorge, R. E., Torres-Prioris M. J., & Dávila, G. (2023). Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study. *Brain and Language,* 236: *1-9.* https://doi.org/10.1016/j.bandl.2022.105205

Study 1

Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia[1]

[1] **Edelkraut, L.**, López-Barroso, D., Torres-Prioris, M. J., Starkstein, S. E., Jorge, R. E., Aloisi, J., Berthier, M. L., & Dávila, G. (2022). Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia. *World Journal of Psychiatry,* 12(3): 450-469. https://doi.org/10.5498/wjp.v12.i3.450

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 450-469

DOI: 10.5498/wjp.v12.i3.450

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Sergio E Starkstein, Ricardo E Jorge, Jessica Aloisi, Marcelo L Berthier, Guadalupe Dávila

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Azocar I, Lin SK

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: July 28, 2021
Revised: August 13, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 19, 2022

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Guadalupe Dávila, Department of Psychobiology and Methodology of Behavioral Science, Faculty of Psychology and Speech Therapy, University of Malaga, Malaga 29071, Spain

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Jessica Aloisi, Marcelo L Berthier, Guadalupe Dávila, Cognitive Neurology and Aphasia Unit, Centro de Investigaciones Médico-Sanitarias, University of Malaga, Malaga 29010, Spain

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Marcelo L Berthier, Guadalupe Dávila, Instituto de Investigación Biomédica de Málaga, University of Malaga, Malaga 29010, Spain

Sergio E Starkstein, School of Psychiatry and Neurosciences, The University of Western Australia, Perth 6009, Australia

Ricardo E Jorge, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX 77030, United States

Corresponding author: Guadalupe Dávila, PhD, Associate Professor, Department of Psychobiology and Methodology of Behavioral Science, Faculty of Psychology and Speech Therapy, University of Malaga, Campus de Teatinos, s/n, Malaga 29071, Spain. mgdavila@uma.es

Abstract

BACKGROUND

Neuropsychiatric symptoms (NPS) have been insufficiently examined in persons with aphasia (PWA) because most previous studies exclude participants with language and communication disorders.

AIM

To report a two-part study consisting of a literature review and an observational study on NPS in post-stroke aphasia.

METHODS

Study 1 reviewed articles obtained from PubMed, PsycINFO, Google Scholar and Cochrane databases after cross-referencing key words of post-stroke aphasia to NPS and disorders. Study 2 examined language deficits and activities of daily

Study 2

Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study[2]

[2] Berthier, M. L., **Edelkraut, L.**, Mohr, B., Pulvermüller, F., Starkstein, S. E., Green-Heredia, C., & Dávila, G. (2022). Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study. *Neuropsychological rehabilitation*, 32(1): 148–163. https://doi.org/10.1080/09602011.2020.1809463

NEUROPSYCHOLOGICAL REHABILITATION
https://doi.org/10.1080/09602011.2020.1809463

Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study

Marcelo L. Berthier[a,b,c], Lisa Edelkraut[a,b,c,d], Bettina Mohr[e,f], Friedemann Pulvermüller[g,h], Sergio E. Starkstein[i], Cristina Green-Heredia[j] and Guadalupe Dávila[a,b,c,d]

[a]Unit of Cognitive Neurology and Aphasia, Centro de Investigaciones Médico–Sanitarias (CIMES), University of Malaga, Málaga, Spain; [b]Research Laboratory on the Neuroscience of Language, Faculty of Psychology and Speech and Language Therapy, University of Malaga, Málaga, Spain; [c]Instituto de Investigación Biomédica de Málaga – IBIMA, Málaga, Spain; [d]Department of Psychobiology and Methodology of Behavioral Sciences, Faculty of Psychology and Speech and Language Therapy, University of Málaga, Málaga, Spain; [e]Department of Psychiatry, Charité Universitätsmedizin, Berlin, Germany; [f]Zentrum für Neuropsychologie und Intensive Sprachtherapie, ZENIS, Berlin, Germany; [g]Brain Language Laboratory, Department of Philosophy and Humanities, WE4, Freie Universität Berlin, Berlin, Germany; [h]Berlin School of Mind and Brain, Humboldt Universität zu Berlin, Berlin, Germany; [i]Division of Psychiatry, School of Medicine, The University of Western Australia, Perth, Australia; [j]Service of Neuropsychology, Hospital Quirón, Malaga, Spain

ABSTRACT

Introduction: Depressive symptoms are a major drawback of aphasia, negatively impacting on functional outcomes. In a previous study, Intensive Language-Action Therapy (ILAT) was effective in improving depression and low mood in persons with chronic non-fluent aphasia. We present a proof-of-concept case–control study that evaluates language and mood outcomes amongst persons with fluent post-stroke aphasia.

Participants: Thirteen Spanish speaking persons with fluent aphasia due to chronic stroke lesions in the left hemisphere participated in the study.

Intervention: Five participants (intervention group) received ILAT for 3 h/day during two consecutive weeks, for an overall of 30 h, and 8 participants (control group) entered a waiting-list no-treatment arm.

Results: The main finding was that participants receiving active treatment showed significant improvements on depression and aphasia severity scores, whereas no significant changes were found in the control group.

Conclusions: The implementation of ILAT was efficient in improving clinical language deficits in people with fluent aphasia and contributes to improvement in mood after therapy.

Trial registration: EUDRACT (2008-008481-12)

ARTICLE HISTORY
Received 12 February 2020
Accepted 8 August 2020

KEYWORDS
Aphasia; Intensive language-action therapy; Post-stroke depression.

CONTACT Marcelo L. Berthier mbt@uma.es Unit of Cognitive Neurology and Aphasia, Centro de Investigaciones Médico–Sanitarias (CIMES), University of Malaga, Spain; Research Laboratory on the Neuroscience of Language, Faculty of Psychology and Speech and Language Therapy, University of Malaga, Spain; Instituto de Investigación Biomédica de Málaga – IBIMA, Spain

Study 3

Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study[3]

[3] Berthier, M. L., **Edelkraut, L.**, López-González, F. J., López-Barroso, D., Pulvermuelller, F., Starkstein, S. E., Jorge, R. E., Torres-Prioris M. J., & Dávila, G. (2023). Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study. *Brain and Language,* 236: 1-9. https://doi.org/10.1016/j.bandl.2022.105205

Brain & Language 236 (2023) 105205

Contents lists available at ScienceDirect

Brain and Language

journal homepage: www.elsevier.com/locate/b&l

Donepezil alone and combined with intensive language-action therapy on depression and apathy in chronic post-stroke aphasia: A feasibility study

Marcelo L. Berthier [a,b], Lisa Edelkraut [a,b,c], Francisco J. López-González [d,e], Diana López-Barroso [a,b,c], Bettina Mohr [f], Friedemann Pulvermüller [g,h], Sergio E. Starkstein [i], Ricardo E. Jorge [j], María José Torres-Prioris [a,b,c], Guadalupe Dávila [a,b,c,*]

[a] Cognitive Neurology and Aphasia Unit, Centro de Investigaciones Médico-Sanitarias, University of Malaga, Malaga, Spain
[b] Instituto de Investigación Biomédica de Málaga - IBIMA, Malaga, Spain
[c] Area of Psychobiology, Faculty of Psychology and Speech Therapy, University of Malaga, Malaga, Spain
[d] Molecular Imaging Unit, Centro de Investigaciones Médico-Sanitarias, General Foundation of the University of Malaga, Malaga, Spain
[e] Molecular Imaging Group, Radiology Department, Faculty of Medicine, University of Santiago de Compostela, Galicia, Spain
[f] Zentrum für Neuropsychologie und Intensive Sprachtherapie – ZeNIS, Berlin, Germany
[g] Brain Language Laboratory, Department of Philosophy and Humanities, WE4, Freie Universität Berlin, Germany
[h] Berlin School of Mind and Brain, Humboldt Universität zu Berlin, Germany
[i] Faculty of Health and Medical Sciences, The University of Western Australia (M704), Perth, Australia
[j] Department of Psychiatry and Behavioural Sciences, Baylor College of Medicine, Houston, TX, United States

A R T I C L E I N F O

Keywords:
Aphasia
Apathy
Depression
Donepezil
Intensive language-action therapy
Neuromaging
Pharmacotherapy
Stroke

A B S T R A C T

This study explored the feasibility and effectiveness of a short-term (10-week) intervention trial using Donepezil administered alone and combined with intensive language action therapy (ILAT) for the treatment of apathy and depression in ten people with chronic post-stroke aphasia. Outcome measures were the Western Aphasia Battery and the Stroke Aphasia Depression Questionnaire-21. Structural magnetic resonance imaging and ^{18}fluorodeoxyglucose positron emission tomography were acquired at baseline and after two endpoints (Donepezil alone and Donepezil-ILAT). The intervention was found to be feasible to implement. Large treatment effects were found. Donepezil alone and combined with ILAT reduced aphasia severity, while apathy and depression only improved with Donepezil-ILAT. Structural and functional neuroimaging data did not show conclusive results but provide hints for future research. Given these overall positive findings on feasibility, language and behavioral benefits, further studies in larger sample sizes and including a placebo-control group are indicated.

1. Introduction

Post-stroke aphasia (PSA) is frequently associated with long-lasting neuropsychiatric symptoms, including apathy and depression (Døli et al., 2017; Edelkraut et al., 2022; Jorge et al., 2010; Laures-Gore et al., 2020). Apathy occurs in more than half of the persons with aphasia (PWA) (Kennedy et al., 2015), and about two-thirds show depression even one year after stroke onset (Laures-Gore et al., 2020). Post-stroke apathy and depression are clinically dissociable and result from disruptions of different subcomponents of networks regulating motivated behavior and mood (Jorge et al., 2010; Kos et al., 2016; Le Heron et al., 2018; Riva-Posse et al., 2019; Starkstein & Brockman, 2018). Yet, the neural signatures of these two symptoms are heterogeneous and do not seem to result from damage to a single brain region (Balaev et al., 2018; Starkstein & Brockman, 2018).

Several studies have shown improved language and communication deficits in chronic PSA after administering intensive language-action therapy (ILAT) (*for a review, see* Pulvermüller et al., 2016). Treatment gains can be augmented and speeded up with cognitive enhancing drugs and non-invasive brain stimulation (Basilakos et al., 2022; Berthier et al., 2009; Berthier, 2021). For instance, a randomized controlled trial (RCT) in chronic PSA showed that the glutamatergic modulator Memantine alone and in combination with ILAT produced significant language and communication benefits, which resulted in an increase of

* Corresponding author at: Unidad de Neurología Cognitiva y Afasia, Centro de Investigaciones Médico-Sanitarias, Universidad de Málaga, Marques de Beccaria 3, 29010 Málaga, Spain.
E-mail address: mgdavila@uma.es (G. Dávila).

https://doi.org/10.1016/j.bandl.2022.105205
Received 17 March 2022; Received in revised form 17 October 2022; Accepted 18 November 2022
Available online 7 December 2022

Chapter 4: Discussion and Thesis Conclusions

Limitations and future directions

Before discussing the results of this doctoral dissertation some limitations are recognised, and potential future research directions highlighted.

First, the studies included in this doctoral dissertation comprised small sample sizes, potentially leading to overestimating treatment effects (Kintz & Wright, 2018). Second, only a small subset of PWAs underwent structural magnetic resonance imaging and ^{18}fluorodeoxyglucose positron emission tomography. Additionally, there was a lack of participants representing culturally and ethnically diverse minority groups in all three studies. Similarly, patients with multiple strokes, premorbid psychiatric illnesses, or pre-stroke dementia were excluded from the studies in this doctoral dissertation. However, small samples are widespread in studies of aphasia. Beeson and Robey (2006) reviewed more than 600 articles published over the past 50 years regarding different aphasia treatment approaches and concluded that more than half of the manuscripts were single-subject designs (Beeson & Robey, 2006). In addition, by clinical experience, it is generally a challenge to reach out to people with aphasia, specifically in the chronic phase, as they are usually no longer in direct contact with the hospital or ambulatory settings and thus difficult to include in longitudinal clinical trials.

Another limitation was that no formal standardised clinical neuropsychiatric diagnosis was made for PWA and only few psychometrically validated instruments were employed to evaluate NPS. A critical gap in the literature still exists regarding the development of reliable and valid instruments to assess NPS in PWA (Kristo & Mowll, 2022). The SADQ has received the most favourable reviews for the neuropsychiatric proxy evaluation of the aphasic cohort and was thus the primary evaluation choice for this work (Kristo & Mowll, 2022; Rose et al., 2022; Van Dijk et al., 2016). On the other hand, the NPI is a commonly chosen instrument in the population with stroke and dementia and was therefore selected to evaluate the general neuropsychiatric spectrum in Study 1. Despite their widespread use, the NPI and the SADQ are brief instruments passed on to a formal caregiver but not to the participant himself. However, most published studies on depression and apathy in PWA are based on caregiver or proxy reports. Although caregivers have a unique view of patients' daily functioning, their evaluation of symptoms may be negatively biased, especially when their mental well-being is compromised. Self-reporting instruments improve autonomy and auto-efficacy in PWA and should generally be preferred when the patient minimally understands spoken and written language (Kristo & Mowll, 2022).

At last, in terms of stability, our participants were evaluated and treated long after the onset of the brain injury. As a result, compensatory mechanisms (both neurological and behaviourally) may have evolved that could have obscured the original relationship between brain injury and NPS. In this thesis it was not possible to include measures of acute infarction, hindering the evaluation of the interaction between acute and chronic brain changes in neuropsychiatric manifestations. Early identification of neuropsychiatric symptoms through screening instruments should be the standard operation to facilitate preventive interventions and stepped psychological care (Thayabaranathan et al., 2022).

In future investigations, it is imperative to undertake a comprehensive examination of the predictive efficacy of clinical variables, necessitating the inclusion of more substantial sample sizes within longitudinal studies. Among the prognostic factors meriting particular scrutiny in the context of aphasia recovery and concurrent amelioration of NPS, temporal dimensions (such as the time of stroke onset, stage of recovery, and number of stroke recurrences), aphasia type (including both fluent and non-fluent varieties), treatment-related variables (encompassing treatment modality, dosage, duration, intensity, and patient compliance), demographic factors (entailing gender, age, socioeconomic status, and family composition), and psychiatric dimensions (comprising pre-stroke mental health conditions, post-stroke psychiatric comorbidities, as well as the severity and temporal evolution of neuropsychiatric symptoms) hold significant research interest.

It is also of special significance to study the relationship between the treatment-specific positive effect of ILAT and the behaviourally decisive action-embedded use of language within rehabilitation of NPS (Mohr, 2017). The intensive social interaction component of ILAT, providing the space for communication between people who cope with similar acquired conditions and leading to positive interactions amongst them, seems to be the main predictor of improved mood (Mohr et al., 2017; Stahl et al., 2022); however, further studies are needed to fill this knowledge gap. In addition, studies are warranted to investigate the long-term treatment effects of ILAT on NPS concerning the best amount, duration and intensity needed to boost low mood and other relevant NPS. Further explorations regarding of cognitive-enhancing drugs' potential effects on NPS in PWA targeting other cerebral neurotransmitters and the synergistic effects of these drugs with ILAT are also warranted. Generally, integrative, inclusive care with speech-language therapy and adjuvant cognitive enhancing drugs should receive future attention from upcoming clinical trials and epidemiological studies.

Another remark must be made on future exploration of brain structures and white matter networks involved in the pathogenesis of specific neuropsychiatric disturbances in PWA and how post-stroke neuronal networks rewire over time, as well as to what extent the lesions affect remote cerebral areas (diaschisis), and thus how behaviour and mood are intensified or inhibited after PSA.

Anxiety and its related conditions shall also be explored in PWA. Anxiety is the second most likely neuropsychiatric condition after stroke, and the prevalence of anxiety in PWA is higher and probably more stable than in patients with non-aphasic stroke (Morris et al., 2017). Consequently, future studies should include anxiety assessment measures and identify specific predictors for improving this condition through ILAT or other behavioural treatment strategies. Furthermore, information is required on the incidence, prevalence, and comorbidity of other NPS in acute, subacute, and chronic aphasic patients, and the neuropsychiatric evolution over time.

Finally, studies focussing on the reliability and validity of self-measured and neuropsychiatric proxy instruments in PWA are of vital interest. Scientific emphasis should also be placed on nonverbal assessment tools with intuitive visuals. The Dynamic Visual Analogous Scale developed by Barrows et al. (Barrows et al., 2021; Barrows & Thomas, 2018) for PWA is a critical step in this direction. A recent study from Ashaie and Cherney (2020) assessed the feasibility of using eye-tracking software to diagnose low mood/depression in PWA, concluding that PWA exhibit differentiated eye patterns on emotional faces compared to healthy controls but that they were not yet predictive of a correct assessment of depression (Ashaie & Cherney, 2020). More research is required to determine whether it is an effective and reliable method of assessing mood.

General discussion and conclusions

The present doctoral dissertation includes three studies that highlight and discern several questions regarding the neuropsychiatry of post-stroke aphasia.

The first part of Study 1 comprises a narrative review that synthesises the neuropsychiatric spectrum in PSA. Most articles that could be included targeted depression, anxiety, and quality of life in PWA, while very little scientific data was available on other neuropsychiatric disturbances. Most of the articles covered evaluation/diagnosis, and behavioural and pharmacological intervention for depression and anxiety. Few articles covered prevalence data for other NPS in PWA, risk factors, or pathophysiological mechanisms. Systematic reviews and meta-analysis accounted for 16.6% of all included articles (from a total of 114 articles). Furthermore, the review highlights that behavioural treatment strategies are often ineffective for PWA as they are highly language dependent. Many important questions regarding the neuropsychiatric spectrum in PWA remain unanswered or unaddressed. The second part of Study 1 consisted of an observational study that evaluated the frequency of NPS in 20 first-time chronic PWA after stroke. This study was the first to incorporate direct and proxy-biased psychometric tools to simultaneously measure the prevalence and comorbidities of a wide range of NPS after post-stroke aphasia. The total number of NPS in patients with chronic PSA is very elevated (median number of 5 symptoms) and appears to exceed the prevalence data reported in the non-aphasic stroke population (Frey et al., 2011). Depression, irritability, agitation/aggression, and anxiety were reported most frequently, followed by appetite/eating disorders, apathy, and sleep disorders, whereas euphoria, delusions, and hallucinations were rare. The severity of these NPS apathy and depressive symptoms was assessed as the most disabling by their caregivers, and in second position were anxiety and agitation. No significant differences were found in the NPS spectrum when controlling for sex, antidepressant intake, or type of aphasia.

Study 2 shows that intensive and massed language intervention strategies (ILAT) targeting aphasia improve aphasia severity and symptoms of depression for the first time in chronic stroke patients with fluent aphasia, even when several years have passed since the onset of stroke. Similarly, significant pre-post differences were found for both language and depression scores in the ILAT-intervention group (5 fluent PWA), while no changes were detected in the 8 PWA randomised to the waiting list without treatment arm control group. These findings positively complement previous publications whose authors found a significant improvement in depression with ILAT in chronic non-fluent aphasic patients (Mohr et al., 2017) and subacute aphasic patients (Stahl et al., 2022). Furthermore, the latter study answers the question of what mood outcomes would be obtained when comparing ILAT with standard speech-language therapy or standard care treatment. Nevertheless, Study 2 of this doctoral dissertation is the first to address the treatment of depressive symptomatology in fluent aphasic patients using intensive language therapy.

In Study 3, ILAT with an adjuvant acetylcholine agonist (Donepezil) improves depression and apathy scores in 10 chronic PWA and chronic strokes. All participants received 5 mg of Donepezil for the first 4 weeks and 10 mg for an additional 6 weeks. ILAT was administered in parallel with the drug during the last two weeks. These results align with Baker et al. (2018), who state that cognitive-enhancing treatments can positively impact affective outcomes (Baker et al., 2018). Furthermore, the scientific literature shows that group therapy provides a naturalized social environment for language rehabilitation in PWA (Mohr et al., 2017; Stahl et al., 2022). Fama et al. (2017) additionally found that acute PWA initiate communication more often during group sessions than individual sessions while employing more vocalizations and facial expressions for social closeness (Fama et al., 2017). These findings support the inclusion of recommendations for routine neuropsychiatric assessment and treatment within clinical guidelines to help optimize the recovery and long-term outcomes in people with stroke and aphasia.

In addition, Study 3 was the first to analyse metabolic and structural brain changes of depression and apathy in PWA. Exploratory data show that combined therapy with Donepezil-ILAT induced structural changes associated with improved depression in the frontal and parietal areas. Many of the affected structures are intrinsic components of the Salience Network, whose aberrant connection pattern with other white matter networks has been consistently associated with endogenous depressive symptoms (Balaev et al., 2018; B. Menon, 2019; V. Menon, 2011, 2015; Tozzi et al., 2021; Vicentini et al., 2017). On the other hand, Donepezil-ILAT increased metabolic activity in the left medial dorsal nucleus of the thalamus and the left subgenual cingulate cortex, which was correlated with a reduction in apathy scores. These changes occurred in structurally spared nodes of the Salience Network and Default Mode Network, showing reduced or average metabolic activity at baseline. Aberrant organisation and connectivity of these networks are characteristic of baseline psychopathology (V. Menon, 2011). The reorganisation of these functional networks appears to be a positive step toward improving neuropsychiatric disturbances in PWA.

The findings within this doctoral dissertation reveal valuable insights into the assessment of NPS in PWA. These studies demonstrate the practicality of conducting such assessments when appropriate psychometric tools are chosen and specialized training is provided. These results underscore the prevalence and significant functional impact of NPS, even in the chronic phase of stroke recovery. Notably, many neuropsychiatric studies continue to exclude PWA due to communication challenges, resulting in underestimated findings and a lack of tailored services for this population. Moreover, the research reveals a marked improvement in depression severity among chronic fluent PWA following Intensive Language-Action Therapy (ILAT). Conversely, combined treatment with Donepezil-ILAT leads to significant improvements in both apathy and depression, accompanied by structural and functional changes in participants' brains. It is essential to highlight that all participants were in a chronic stage of stroke recovery, reducing the likelihood of spontaneous fluctuations in language and neuropsychiatric symptoms. This underscores the crucial role of intensive social interaction within language rehabilitation settings as a key predictor of neuropsychiatric improvement in PWA. The insights and clinical recommendations derived from this comprehensive dissertation have the potential to significantly enhance our understanding and management of neuropsychiatric disorders in individuals with aphasia. As knowledge continues to expand in the fields of epidemiology, assessment, pathogenesis, and treatment of NPS, it will serve as a foundation for shaping global regulations related to diagnosis and treatment. Increasing awareness of the diagnosis and management of neuropsychiatric symptoms in PWA holds promise for reducing functional dependence and alleviating caregiver burden in this population.

Chapter 5: Resumen (en español)

El accidente cerebrovascular (ACV) o ictus ocasionado por un infarto o hemorragia puede provocar alteraciones neurológicas y síndromes clínicos de aparición súbita asociados a daño neuronal (Hankey, 2017). Cada año, 13 millones de personas sufren un ictus en todo el mundo, y dado que la población mundial está envejeciendo y el ictus está aumentando en los países en vías de desarrollo, se espera que la incidencia siga creciendo en las próximas décadas (GBD Stroke Collaborators, 2019). Además, la tasa de supervivencia es cada vez más elevada gracias a importantes avances en la asistencia médica (Feigin et al., 2017). En consecuencia, hoy en día el ictus es la principal causa de discapacidad en todo el mundo, dando lugar a una amplia gama de secuelas neuropsiquiátricas que afectan negativamente a los resultados de la rehabilitación, la participación en las actividades de la vida diaria, la independencia funcional y la autonomía personal (Hilari, 2011; Kauhanen et al., 2000; Laures-Gore et al., 2017, 2020; Wang et al., 2018). Los síntomas neuropsiquiátricos (SNP) más frecuentes tras un ictus son: la depresión, la ansiedad y la apatía, siendo el tratamiento farmacológico y el tratamiento psicológico los métodos de elección para una terapia eficaz de las personas que han sufrido un ictus (Baker, Worrall, Rose, Hudson, et al., 2018; Hankey, 2017).

La afasia post-ictus (API) es un trastorno adquirido del lenguaje causado por un ACV que provoca la pérdida o el deterioro de algunas o de todas las habilidades lingüísticas: el lenguaje espontáneo, la comprensión, la repetición, la lectura, la escritura y la comunicación funcional (Berthier, 2005; Berthier & Pulvermüller, 2011). Aproximadamente un tercio de los supervivientes de un ictus padecen API (Berthier, 2005). Dado que la comunicación es fundamental en aspectos muy diversos de la vida humana, la aparición de la afasia puede inducir y agravar los SNP (por ejemplo, Code et al., 1999; Frey et al., 2011; Jackson, 2013; Pappadis et al., 2019). En la actualidad, la investigación sobre los SNP en la afasia es escasa, ya que la mayoría de los estudios excluyen a las personas con afasia debido a las barreras lingüísticas y de comunicación que presentan (Brady et al., 2013). Aunque se han realizado avances recientes en la validación de cuestionarios de depresión para pacientes afásicos (Barrows et al., 2021; Barrows & Thomas, 2018), incluso cuando se evalúan y diagnostican adecuadamente las personas con afasia (PcA) no se benefician de las intervenciones psicoterapéuticas estándares, ya que estas están basadas principalmente en interacciones lingüísticas.

Las terapias intensivas de lenguaje, como la Rehabilitación Grupal Intensiva de la Afasia (REGIA; ILAT en inglés), consisten en la aplicación de una serie de sesiones de rehabilitación de larga duración (dos a tres horas de entrenamiento al día) concentradas en un breve periodo de tiempo (normalmente 2 semanas), y administrada en un formato grupal (dos o tres participantes más el terapeuta), con el objetivo de estimular el lenguaje hablado a la vez que se restringen modalidades alternativas no-verbales (gestos) de comunicación (Berthier et al., 2014; Difrancesco et al., 2012; Pulvermüller et al., 2016; Pulvermuller & Berthier, 2008). La REGIA ha demostrado ser eficaz para mejorar la gravedad de la afasia, y ha generado resultados preliminares muy positivos en la reducción de sintomatología depresiva de las personas con afasia crónica post-ictus no fluente (con producción del habla muy reducida pero comprensión relativamente preservada; de 6 meses o más de evolución), y en la afasia post-ictus subaguda (entre tres y seis meses de evolución desde el ictus) (Mohr et al., 2017; Stahl et al., 2022). Se ha planteado que el refuerzo de las acciones socio-comunicativas y de los esquemas de interacción interpersonal de esta terapia constituyen un pilar fundamental para la mejoría de la sintomatología depresiva. Sin embargo, hoy en día todavía se desconoce el impacto que la REGIA tiene sobre los síntomas depresivos y otros trastornos neuropsiquiátricos en la afasia crónica post-ictus fluente (con comprensión del lenguaje alterada mientras que la producción lingüística permanece relativamente preservada).

El tratamiento farmacológico, en particular el empleo de los fármacos que potencian la actividad del sistema colinérgico (por ejemplo, el anticolinesterásico Donepezilo), ha mostrado su eficacia en el tratamiento de la afasia (Berthier et al., 2006; 2011; 2020). Sin embargo se desconoce si este potenciador cognitivo tiene un efecto positivo sobre los SNP en la API, aunque los estudios realizados en el campo de las demencias e ictus no asociado a afasia ofrecen resultados prometedores en relación a posibles mejoras de los síntomas de apatía y depresión (Berthier et al., 2006; Cummings et al., 2006; Whyte et al., 2008). En la actualidad, los enfoques terapéuticos multimodales de la afasia con intervenciones conductuales y farmacológicas combinadas se están extendiendo, pues sus beneficios superan las ganancias derivadas de los efectos individuales de cada tratamiento administrado individualmente (Baker et al., 2018). La cuestión que se plantea es si es posible mejorar las secuelas neuropsiquiátricas además de las funciones lingüísticas y de comunicación con tratamientos combinados (REGIA y terapia farmacológica) en PcA. Por otra parte, aunque los estudios de neuroimagen realizados en las últimas décadas en el ámbito de la psiquiatría muestran cambios estructurales y funcionales cerebrales asociados al ictus, la investigación existente en neuroimagen relativa a las secuelas neuropsiquiátricas derivadas de un ictus en las PcA es escasa. Por lo tanto, los objetivos de la presente tesis doctoral fueron los siguientes:

Estudio 1 (A) Este estudio tiene como objetivo llevar a cabo una revisión integral de la literatura científica sobre el espectro de los síntomas neuropsiquiátricos (o NPS, por sus siglas en inglés) en la API. Resumirá datos sobre prevalencia, factores de riesgo, herramientas de evaluación, fisiopatología y opciones de tratamiento disponibles. Además, (B) se explorará la viabilidad de evaluar un rango más amplio de SNP en 20 individuos con API crónica. Esto implicará examinar la frecuencia, naturaleza y comorbilidad de los síntomas neuropsiquiátricos utilizando una combinación de instrumentos de evaluación basados en proxy y evaluación directa.

Estudio 2 Este estudio se centrará en analizar los efectos de dos semanas de REGIA en individuos con afasia fluida crónica. Específicamente, se evaluarán los cambios en la gravedad de la afasia y las puntuaciones de depresión después de la intervención de REGIA.

Estudio 3 (A) El objetivo principal de este estudio es evaluar los resultados de la monoterapia con Donepezilo y la terapia combinada con Donepezilo-REGIA en individuos con API. Se evaluarán los cambios en la gravedad de la afasia, así como las puntuaciones de depresión y apatía. (B) Además, este estudio investigará los cambios funcionales y estructurales en el cerebro que pueden ocurrir como resultado de estas intervenciones.

En el **Estudio 1** se presentan dos apartados diferenciados. En primer lugar, una revisión narrativa sobre SNP y API y en la segunda parte, un estudio original sobre los SNP en la API.

Revisión narrativa de la bibliografía sobre los SNP en la API:

Para la revisión de la literatura científica existente sobre los SNP y la API se incluyeron palabras de búsqueda clave en las bases de datos científicas: PubMed, PsycINFO, Google Scholar y Cochrane databases, abarcando la prevalencia, los factores de riesgo, la fisiopatología, los instrumentos de evaluación y los enfoques de tratamiento, desde el comienzo de las bases de datos hasta el año 2021. En total se incluyeron 114 artículos científicos. Más de la mitad de las publicaciones abordaban la depresión (60 artículos; 52.6 %), 21 artículos (18.4 %) examinaban la ansiedad y 12 artículos (10, 5%) hacían referencia a la calidad de vida en las PcA. Alrededor de una tercera parte de los artículos se centraban en la evaluación/diagnóstico de la depresión y la ansiedad (n = 34; 29.8 %) y una quinta parte se centraban en los enfoques de intervención (n = 24; 20.5 %). Fueron escasos los artículos que informaban sobre la prevalencia de los SNP en las PcA (n = 6; 5.2 %), los factores de riesgo (n = 5; 4.2 %) o los mecanismos fisiopatológicos (n = 7; 6.1 %). Las revisiones sistemáticas y los metaanálisis representaron el 16,6% de todos los estudios incluidos (n = 19).

Estudio observacional sobre los SNP en la API:

Se estudió la prevalencia de los SNP comórbidos en la API. Para ello se evaluó inicialmente la gravedad de la afasia y las actividades de la vida diaria de 20 participantes (edad media: 52.2 ± 12.7 años; duración media desde el ictus: 41 ± 38.6 meses; rango de duración: 6-126 meses) con afasia crónica post-ictus asociada a lesiones perisilvianas izquierdas, empleando como medidas primarias el Western Aphasia Battery y el Índice de Barthel, respectivamente. Los síntomas neuropsiquiátricos se evaluaron con una escala multidominio, el Inventario Neuropsiquiátrico (Neuropsychiatric Inventory - NPI), y escalas de dominio específico, incluido el SADQ-10 para la depresión, la Escala de Apatía de Starkstein (Starkstein Apathy Scale - SAS) para la apatía y la Escala de Ansiedad y Depresión Hospitalaria (Hospital Anxiety and Depression Scale - HADS) para la ansiedad y depresión. Esta última escala fue administrada directamente al paciente mientras que los demás instrumentos de evaluación neuropsiquiátrica fueron pasados a los familiares y/o cuidadores del paciente.

Tabla 1. Perfil demográfico y clínico de los participantes del Estudio 1

Participantes	Edad, Sexo y Dom. Manual	Educación (años)	Duración Ictus (meses)	Índice Barthel	Tipo de Afasia	Antidepresivo
1	50 (M), D	12	80	80	Conducción	Sertralina
2	61 (V), D	14	103	90	Broca	Citalopram
3	49 (V), D	17	61	90	Broca	No
4	42 (V), D	11	45	100	Anómica	Citalopram
5	63 (V), D	8	11	85	Conducción	No
6	58 (M), D	12	126	95	Anómica	No
7	60 (V), D	12	45	60	Anómica	No
8	54 (V), D	14	44	90	Anómica	No
9	51 (V), D	13	7	80	Anómica	Amitriptilina
10	54 (V), D	10	19	90	Wernicke	No
11	58 (M), D	15	66	95	Broca	No
12	61 (M), D	12	17	45	Anómica	Sertralina
13	32 (V), D	18	10	100	Wernicke	Sertralina
14	49 (V), D	8	13	80	Anómica	No
15	28 (M), D	8	6	100	Anómica	No
16	65 (M), D	17	13	100	Wernicke	No
17	64 (V), D	17	120	100	Anómica	No
18	65 (M), D	17	13	75	Broca	No
19	58 (V), D	8	17	100	Wernicke	No
20	63 (V), D	17	10	100	Wernicke	Fluoxetina
Mediana	***58***	***12.5***	***18***	***90***	**-**	-

Abreviaciones = M: Mujer; V: Varón; Dom. Manual: Dominancia Manual; D: Diestro

El WAB-AQ mostró que todos los participantes presentaban afasia crónica con una gravedad de leve a moderada, mientras que el Índice de Barthel indicó que la mayoría de las PcA eran funcionalmente independientes (mediana: 90 puntos; rango: 45-100). El Inventario Neuropsiquiátrico mostró que todas las PcA presentaban más de un SNP, excepto en una mujer de 28 años con afasia leve, que presentó exclusivamente puntuación alta en los cambios del apetito/comportamiento alimentario. El análisis estadístico mostró una mediana de 5 SNP por participante (rango: 1-8) de gravedad leve a moderada. La mayoría de las PcA (75%) presentaban síntomas depresivos, seguidos de agitación e irritabilidad (70%), ansiedad y trastornos del apetito/la alimentación (65%). La mitad de la muestra manifestaban síntomas de apatía, y los trastornos del sueño también fueron relativamente frecuentes (40%). Por el contrario, los síntomas de euforia y los trastornos psicóticos fueron esporádicos. Las escalas de dominios específicos revelaron que el 30% de las PcA superaban la puntuación de corte para depresión y ansiedad (basada en el SADQ-10, HADS-ansiedad), el 40% de los pacientes fueron diagnosticados de depresión sub-umbral (SADQ-10) y el 45% de los participantes presentaban apatía (SAS). Hubo correlaciones significativas entre dos escalas específicas de dominio (SADQ-10 y SAS) y los dominios más frecuentemente reportados por el NPI (por ejemplo, depresión, ansiedad, apatía, agitación e irritabilidad). En cuanto al sexo, la comorbilidad fue ligeramente superior en las mujeres, con una mediana de 6 SNP frente a los hombres que presentaron 5 SNP, si bien, la prueba no paramétrica U de Mann-Whitney no estableció diferencias estadísticamente significativas (p = 0.841). Respecto al análisis de la mediana de SNP en función del tipo de afasia, los participantes con afasia de Broca (afasia no fluida) fueron los que presentaron mayor número de síntomas (6,5), seguidos de los participantes con afasia anómica (5), afasia de conducción (4,5) y afasia de Wernicke (afasia fluida) (3). Sin embargo, la prueba no paramétrica de Kruskal-Wallis no mostró diferencias estadísticamente significativas (p = 0.508).

Las imágenes de RM estructural recogieron una amplia gama de lesiones en la muestra analizada, con afectación predominante del área perisilviana izquierda dominante para el lenguaje. El análisis de la superposición de las lesiones mostró que regiones tradicionalmente implicadas en el lenguaje como el fascículo arqueado, la ínsula y el putamen izquierdos, estaban afectadas en 17 participantes (85%). Además, la corteza insular, junto con el estriado y el giro cingulado anterior, estaba afectado en 6 participantes (30%). Estos son componentes intrínsecos de la Red de Saliencia. Dicha red se ha relacionado con la presencia de apatía y depresión (Balaev et al., 2018), y con la mejora de estos síntomas tras tratamientos específicos (Riva-Posse et al., 2019). Los daños en la Red de Saliencia izquierda de la muestra pueden haber afectado a la autorregulación de la cognición, el comportamiento, la emoción y el arousal autonómico, favoreciendo la aparición de los SNP (Balaev et al., 2018; Guha et al., 2021; Kaiser et al., 2015). En resumen, el espectro de SNP es altamente prevalente en la API crónica, por tanto, futuras evaluaciones exhaustivas de los SNP, utilizando escalas multidominio y de dominio específico, permitirán una mejor caracterización de este amplio espectro favoreciendo el diseño e implementación de terapias adecuadas. En resumen, la literatura sobre trastornos neuropsiquiátricos en las PcA es limitada. El estudio 1 es uno de los primeros artículos publicados en proporcionar un análisis preliminar sobre la prevalencia, naturaleza, fisiopatología, evaluación y tratamiento de los SNP en las PcA. En este estudio, también se informa sobre los resultados de una investigación observacional que incluyó 20 PcA, identificando un amplio espectro de SNP comórbidos, principalmente depresión, irritabilidad, agitación, ansiedad y apatía.

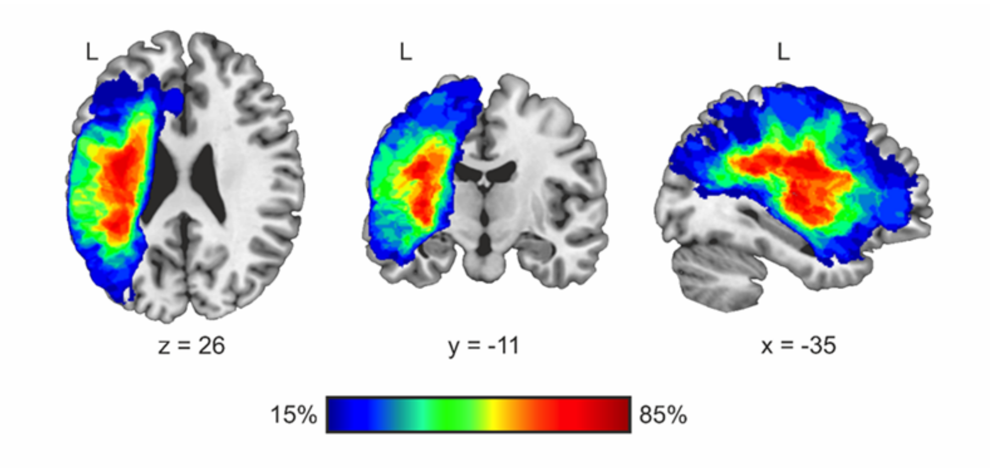

Figura 1. Mapa de superposición de lesiones de los 20 participantes del estudio 1 superpuesto a una plantilla cerebral en el espacio estándar del Instituto Neurológico de Montreal (MNI). La máxima superposición de lesiones (color rojo) (85%, n = 17) afectó a regiones que comprendían el fascículo arqueado izquierdo (segmentos largo y anterior), la ínsula y el putamen. En seis participantes estaban afectados distintos sectores del giro cingulado anterior izquierdo. L: izquierda (Left en inglés).

El **Estudio 2** consiste en un diseño cuasi-experimental de prueba de concepto en el que se evaluaron los efectos de la REGIA sobre el lenguaje y la depresión en 13 participantes (11 varones; edad media: 52.3 años; duración media desde el ictus: 52 meses; rango duración: 7-165 meses) con afasia crónica post-ictus fluida asociada a daño cerebral perisilviano izquierdo. Los participantes fueron incluidos a partir de un reclutamiento prospectivo, cinco participantes fueron asignados al grupo de intervención que recibió REGIA durante dos semanas consecutivas (30 horas de tratamiento), mientras que ocho participantes permanecieron en la lista de espera para recibir el tratamiento en un futuro próximo (grupo control).

Tabla 2. Criterios de inclusión y exclusión para los participantes del Estudio 2

Criterios inclusión	(1) Edad entre 18-70 años.	(2) Lesiones cortico-subcorticales o subcorticales unilaterales por un ictus en el hemisferio izquierdo.	(3) Diagnóstico de afasia según el WAB-AQ.	(4) Presencia de afasia durante más de 6 meses.	
Criterios de exclusión	(1) Jerga fonémica o neologística	(2) Puntuación ≤ 4 en la subprueba de comprensión de la WAB;	(3) Agnosia visual grave	(4) Apraxia ideomotora o ideacional grave	(5) Antecedentes de otro trastorno neurológico o psiquiátrico que afecte al lenguaje y a la capacidad comunicativa.

Abreviaciones = WAB-AQ: Cociente de Afasia de la Batería de Afasia de Western (Western Aphasia Battery Aphasia-Quotient, en inglés)

No se observaron diferencias significativas entre los grupos en ninguna de las variables demográficas o clínicas (prueba U de Mann-Whitney, p = 0,09). Las PcA que estaban recibiendo tratamiento farmacológico para alguna condición médica, incluido el tratamiento con antidepresivo, se mantuvo bajo la misma pauta terapéutica durante todo el estudio.

Tabla 3. Perfiles demográficos y clínicos de los participantes del Estudio 2

Participantes Intervención	**Edad y Sexo**	**Dominancia Manual**	**Educación (años)**	**Duración Ictus (meses)**	**Tipo de Afasia**
1	48 (M)	Diestro	8	70	Conducción
2	47 (M)	Diestro	12	8	Anómica
3	59 (V)	Ambidiestro	16	76	Anómica
4	52 (V)	Diestro	9	165	Anómica
5	51 (V)	Diestro	12	102	Anómica
Media± DE	***51.4 ± 4.7***	**-**	***11.4 ± 3.1***	***84.2 ± 56.8***	**-**
Participantes Control	**Edad (años) y Sexo**	**Dominancia Manual**	**Educación (años)**	**Duración Ictus (meses)**	**Tipo de Afasia**
1	51 (V)	Diestro	10	33	Anómica
2	52 (V)	Diestro	12	7	Anómica
3	47 (V)	Diestro	14	73	Anómica
4	53 (M)	Diestro	10	42	Anómica
5	56 (V)	Diestro	15	53	Anómica
6	60 (V)	Ambidiestro	8	23	Anómica
7	50 (V)	Diestro	15	9	Anómica
8	47 (V)	Diestro	17	16	Anómica
Media± DE	***52 ± 4.4***	**-**	***12.6 ± 3.1***	***32 ± 23.3***	**-**

Abreviaciones = M: Mujer; V: Varón; D.E: Desviación Estándar

Se emplearon el Cociente de Afasia de la Batería de Afasia de Western (Western Aphasia Battery-Aphasia Quotient - WAB-AQ) y el Cuestionario de Depresión por Afasia Post-Ictus-21 (Aphasic Depression Questionnaire 21 – SADQ-21) como medidas primarias de eficacia:

(a) El WAB-AQ mide la gravedad de la afasia presentando buena sensibilidad para detectar cambios longitudinales (Berthier et al., 2006; 2009). Esta prueba fue administrada y puntuada por un neurólogo con amplia experiencia en el campo de la evaluación y tratamiento de las afasias. Las puntuaciones iguales o inferior a 93.8 puntos (de 100 puntos) en el WAB indican afasia, siendo las puntuaciones más bajas indicativas de síntomas afásicos más graves (Kertesz, 2007).
(b) El SADQ-21 fue cumplimentado por cuidadores, familiares o médicos de confianza de las PcA. Las puntuaciones más altas en el SADQ-21 indican una sintomatología depresiva más grave. El SADQ-21 tiene una excelente consistencia interna y una adecuada fiabilidad test-retest en un intervalo de cuatro semanas (Lincoln et al., 2000; Sutcliffe & Lincoln, 1998).

El WAB-AQ y el SADQ-21se aplicaron al grupo tratado y al grupo control en la medida basal (T1, semana 0) e inmediatamente después de las dos semanas de tratamiento (T2, semana 3). A continuación de las evaluaciones basales una terapeuta experta administró la REGIA al grupo de intervención durante dos semanas consecutivas con un total de 30 horas. Esta terapia fue administrada en grupos reducidos formados a partir de la gravedad y tipología de la afasia que presentaron las PcA. Tras la administración de la REGIA se observó en el grupo tratado una mejoría significativa en la gravedad de la afasia medida por el WAB-AQ (T1: 73.84 ± 8.0; T2: 78.76 ± 9.0; $p = 0.050$, prueba de Wilcoxon) y en la gravedad de la depresión medida por el SADQ-21 (T1: 19.8 ± 5.89; T2: 14 ± 6.63; $p = 0.02$, prueba de Wilcoxon). El grupo control no presentó cambios estadísticamente significativos después de dos semanas (WAB-AQ: T1: 76.85 ± 8.0; T2: 77.36 ± 8.16; $p = 0.10$, prueba de Wilcoxon; SADQ-21: T1: 20.25 ± 5; T2: 19.38 ± 8.17; $p = 0.29$, prueba de Wilcoxon).

La depresión se diagnosticó basándose en la versión abreviada de 10 ítems del SADQ-21 (Stroke Aphasia Depression Questionnaire-10; SADQ-10) (Sutcliffe & Lincoln, 1998) que proporciona puntuaciones de corte válidas para detectar depresión y depresión sub-umbral. En el grupo de intervención, tres participantes cambiaron de “depresión” a “depresión sub-umbral”, un participante cambió de “depresión sub-umbral” a “ausencia de depresión” y un participante permaneció estable por debajo del nivel umbral. En el grupo de control, sólo una PcA cambió de categoría (de “depresión” a “depresión subumbral”). Estos resultados replican y amplían hallazgos previos de Mohr et al. (2017) al mostrar que el tratamiento de corta duración con REGIA puede mejorar la depresión en PcA fluida. Por lo tanto, las terapias lingüísticas grupales como la REGIA pueden ser estrategias de rehabilitación eficaces tanto para la recuperación del lenguaje como para la mejora de la sintomatología depresiva en las PcA.

El **Estudio 3** se trata de un ensayo de intervención abierto en el que se estudió la viabilidad y eficacia de un programa de rehabilitación de corta duración (10 semanas) con Donepezilo solo (semanas: 1 – 8) y Donepezilo combinado con REGIA (semanas: 9 – 10) para el tratamiento de la depresión y la apatía en 10 participantes (sexo: 8 varones; edad media: 51.6 ± 8.52 años; duración media de la afasia desde el ictus: 30.1 meses; rango de duración: 7-73 meses) con afasia crónica post-ictus asociada a daño cerebral perisilviano izquierdo.

Tabla 4. Perfil demográfico y clínico de los participantes del Estudio 3

Participantes	Edad, Sexo y Dom. Manual	Educación (años)	Duración Ictus (Meses)	Antidepresivos	Tipo de Afasia
1	51 (V), D	10	33	Escitalopram	Anómica
2	59 (V), D	13	30	No	AMT
3	41 (M), D	8	15	No	AMT
4	52 (V), D	12	7	No	Conducción
5	47 (V), D	14	73	No	Anómica
6	53 (M), D	10	42	No	Anómica
7	50 (V), D	15	9	Escitalopram	Anómica
8	47 (V), D	17	16	Escitalopram	Anómica
9	56 (V), D	15	53	Escitalopram	Anómica
10	60 (V), Am	8	23	Sertraline	Anómica
Media ± D.E.	***51.6 ± 5.82***	***12.2 ± 3.12***	***30.1 ± 21***	**-**	**-**

Abreviaciones = Dom. Manual: Dominancia manual; M: Mujer; V: Varón; D: Diestro; Am: Ambidiestro; AMT: Afasia Motora Transcortical

Los participantes fueron incluidos a partir de un reclutamiento prospectivo siguiendo los criterios de inclusión y criterios de exclusión mencionados previamente en el estudio 2. También se excluyeron las PcA embarazadas o que estuvieran recibiendo alguna medicación que pudiera interferir con el Donepezilo (por ejemplo, anticolinérgicos). Los participantes que estaban recibiendo tratamiento farmacológico para alguna afección médica, incluido el tratamiento con antidepresivo, se mantuvieron bajo la misma pauta terapéutica durante todo el estudio. Todos los participantes recibieron 5 mg de Donepezilo por vía oral durante cuatro semanas. La dosis se ajustó a 10 mg durante otras cuatro semanas y se mantuvo estable durante las dos semanas siguientes de tratamiento combinado (Donepezilo-REGIA). La aplicación de la REGIA se realizó según las pautas comentadas previamente en el estudio 2. Como medidas primarias de eficacia se emplearon el WAB-AQ y el SADQ-21 (ver estudio 2). La depresión se diagnosticó basándose nuevamente en la versión abreviada de 10 ítems del SADQ-21 (Stroke Aphasia Depression Questionnaire-10; SADQ-10) (Sutcliffe & Lincoln, 1998). Para valorar de forma independiente la apatía y los síntomas relacionados con la depresión el SADQ-21 se dividió en 14 ítems para evaluar los síntomas de depresión y 7 ítems para evaluar los síntomas de apatía. Esta división se realizó a partir de un análisis factorial (Sutcliffe & Lincoln, 1998) y el consenso de tres neurólogos expertos en depresión y apatía post-ictus. Se realizaron una evaluación basal (T1, semana 0), una evaluación después del tratamiento con Donepezilo (T2, semana 9) y otra evaluación después del tratamiento combinado con Donepezilo-REGIA (T3, semana 11). En estas tres evaluaciones se adquirieron imágenes de Resonancia Magnética (RM; 3 Teslas) y de Tomografía por Emisión de Positrones con ^{18}fluorodesoxiglucosa (^{18}FDG-PET) para realizar estudios de neuroimagen estructural y funcional, respectivamente. Para evaluar los cambios temporales en el WAB-AQ y los subdominios de apatía y depresión del SADQ-21, se utilizó el ANOVA de medidas repetidas con "tratamiento" (inicio, Donepezilo y Donepezilo-REGIA) como factor intra-sujeto. Cuando se encontró un efecto principal significativo, se realizaron pruebas t post hoc corregidas por Bonferroni.

Los resultados estadísticos del ANOVA de medidas repetidas para el WAB-AQ mostraron un efecto grande del tratamiento ($F(2, 18) = 36.98$, $p = < 0.001$; $\eta 2 = 0.80$). Las pruebas post-hoc revelaron que las puntuaciones de la WAB-AQ aumentaron de forma significativa tras la administración de Donepezilo solo ($p < 0.001$) y tras el tratamiento combinado de Donepezilo-REGIA ($p < 0.001$) en comparación con las medidas basales. Igualmente, mejoraron las puntuaciones de la WAB-AQ después de la administración de Donepezilo-REGIA respecto a la administración de Donepezilo solo ($p = 0.003$). A partir de los cambios temporales de las puntuaciones individuales del WAB-AQ, seis participantes fueron clasificados como respondedores (basándose en un aumento de ≥ 5 puntos en el WAB-AQ) (Berthier et al., 2009) a Donepezilo solo (mejora del AQ [media ± DE]: 6,5 ± 3,6), y ocho participantes fueron respondedores a Donepezilo-REGIA (mejora del AQ [media ± DE]: 9,5 ± 4,6 puntos).

Al considerar los componentes del SADQ-21 separados, se observó un efecto grande del tratamiento tanto para las puntuaciones de apatía ($F (2, 18) = 9.6$, $p = 0.001$; $\eta 2 = 0.52$) como de depresión ($F (2, 18) = 7.0$, $p = 0.005$¸ $\eta 2 = 0.44$). Las pruebas post-hoc mostraron que las puntuaciones de apatía mejoraron significativamente con Donepezilo-REGIA (cambio medio: -2.9 ± 2.2; $p = 0.007$) pero no con Donepezilo solo (cambio medio: -2.0 ± 2.7; $p = .125$) en comparación con las medidas basales. Tampoco se observaron diferencias significativas en las puntuaciones de apatía tras la administración de Donepezilo solo en relación con la administración de Donepezilo-REGIA (cambio medio: -0.9 ± .4; $p = 0.203$). Asimismo, se observó una reducción significativa de la sintomatología depresiva tras la aplicación de Donepezilo-REGIA (cambio medio: -2.6 ± 2.5; $p = 0.028$), pero no con la administración de Donepezilo solo (cambio medio: -0.9 ± 2.5; $p = 0.837$) en comparación con las medidas basales. Además, mejoró de forma significativa de la depresión después de administrar Donepezilo-REGIA en comparación con Donepezilo solo (cambio medio: -1.7 ± 1.6; $p = 0.023$). A partir de la puntuación de corte de la escala SADQ-10, los participantes fueron diagnosticados inicialmente con depresión (4 participantes) o depresión sub-umbral (6 participantes). Sin embargo, al finalizar el ensayo solo 2 participantes seguían presentando depresión, mientras que 4 participantes ya no tenían depresión y otros 4 participantes presentaban síntomas sub-umbrales. Hay que considerar que los 5 participantes que estaban recibiendo inhibidores selectivos de la recaptación de serotonina (ISRS) mostraron mejorías insignificantes en las puntuaciones de depresión (media ± DE: -1 ± 0.9 puntos) mientras que los participantes sin tratamiento con ISRS presentaron una mejoría mayor (media ± DE: -4.2 ± 0.5 puntos).

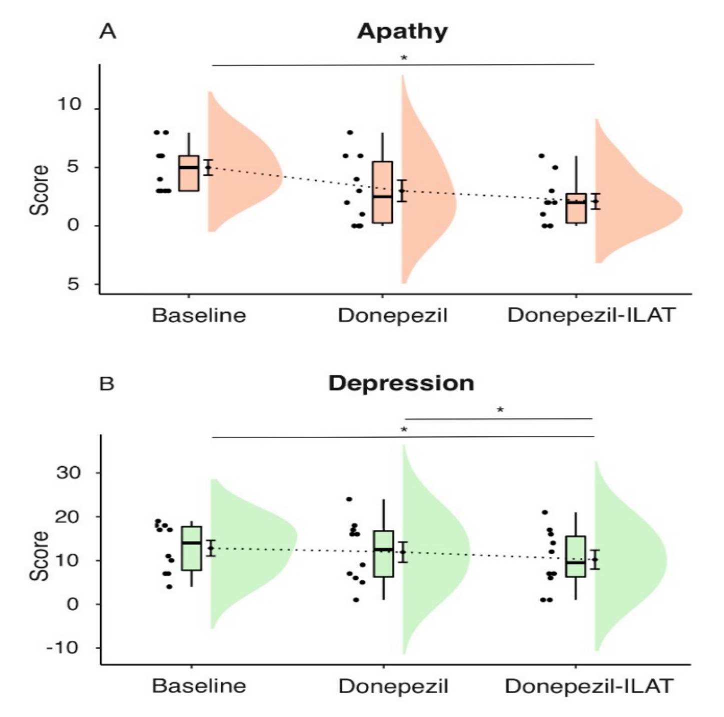

Figura. 2. Gráfico de las puntuaciones de apatía (A) y depresión (B) al inicio, después del tratamiento con Donepezilo solo y después de la administración de Donepezilo-REGIA. Los puntos negros representan la puntuación de cada una de las 10 PcA. En el diagrama de cajas, la línea horizontal que divide la caja representa la mediana del grupo, mientras que las líneas superiore e inferiores representan los cuartiles superiores e inferiores, respectivamente. Los extremos representan los valores más altos y bajos. El punto y las líneas sobre la distribución de probabilidad representan la media y el error estándar, respectivamente. Los asteriscos (*) indican efectos estadísticamente significativos. El gráfico se generó con los scripts de RainClouds R.

En la siguiente figura se muestra el mapa de superposición de lesiones de los 10 participantes. Todas las lesiones afectaron a las regiones perisilvianas izquierdas, lo que presumiblemente comprometió la vía colinérgica lateral en el opérculo frontoparietal, la ínsula y la circunvolución temporal superior (Selden et al., 1998; Simíc et al., 1999). Por otra parte, los datos exploratorios de ^{18}FDG-PET mostraron hipometabolismo en la medida basal de algunos componentes de la Red Neuronal de Saliencia (insula, cabeza del caudado y núcleo talámico dorsomedial), dicha red se ha relacionado con la presencia de apatía y depresión (Balaev et al., 2018) y con la mejora de estos síntomas tras tratamientos específicos (Riva-Posse et al., 2019).

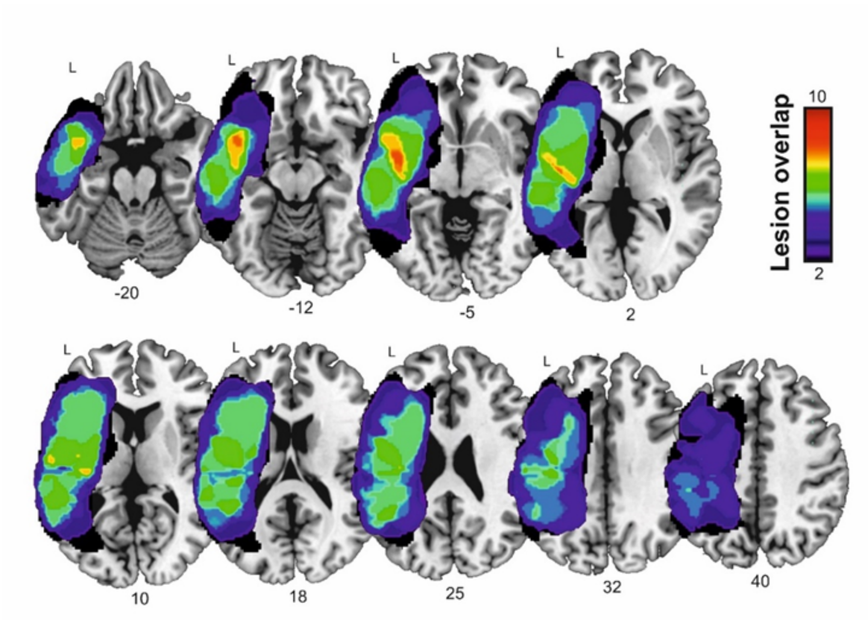

Figura 3. Mapa de superposición de las lesiones por ictus en las PcA (n = 10). Todas las lesiones estaban restringidas al territorio perisilviano de la arteria cerebral media izquierda, mostrando el máximo solapamiento en la ínsula y en la circunvolución temporal superior. Los mapas se superponen a una plantilla estándar. La escala de colores indica el número de participantes con daños en cada localización, de 2 a 10. Las áreas más cálidas indican una mayor superposición de lesiones. Las lesiones se dibujaron manualmente, se binarizaron y se normalizaron al espacio de referencia del MNI. Las coordenadas MNI se indican debajo de cada corte axial. L: Izquierda.

Los análisis no corregidos de la morfometría basada en vóxeles (VBM) en todo el cerebro mostraron cambios en el volumen de la materia gris después del tratamiento con Donepezilo solo y con Donepezilo-REGIA que se asociaron con cambios en las puntuaciones de apatía y depresión. Por ejemplo, los cambios en los síntomas depresivos después del tratamiento con Donepezilo-REGIA correlacionaron con un aumento en el volumen de materia gris en nodos críticos de una amplia red de regulación del estado de ánimo (corteza orbitofrontal bilateral y corteza paracingulada/cingulada anterior) que ha sido implicada en la respuesta positiva al tratamiento de la depresión (Riva-Posse et al., 2019). En la misma línea, los resultados de los análisis de ROI en ^{18}FDG-PET mostraron cambios metabólicos en algunos nodos de dicha red asociados a la mejoría de la apatía y la depresión. No obstante, los datos obtenidos no poseen suficiente potencia estadística, por lo que deberían ser tomados como una guía para futuras investigaciones. En resumen, el tratamiento con Donepezilo solo y en combinación con REGIA mejora significativamente la gravedad de la afasia, mientras que los síntomas de apatía y depresión mejoraron significativamente con el tratamiento combinado de Donepezilo-

REGIA. Por otra parte, datos exploratorios de neuroimagen funcional y estructural muestran que, al combinar la terapia farmacológica con intervenciones conductuales, se inducen cambios cerebrales en las redes que intervienen en la regulación de la motivación y el estado de ánimo.

En síntesis, los resultados obtenidos en los tres estudios presentados en esta tesis doctoral indican que es factible llevar a cabo la evaluación de los síntomas neuropsiquiátricos en personas con API cuando se seleccionan adecuadamente instrumentos psicométricos y se proporciona la formación especializada correspondiente. Estos resultados ponen de manifiesto la alta prevalencia de trastornos neuropsiquiátricos, los cuales conllevan limitaciones significativas en la funcionalidad de la vida cotidiana de los individuos con API, incluso en su fase crónica. Sin embargo, es importante destacar que la mayoría de los estudios en el ámbito neuropsiquiátrico continúan excluyendo a las personas con API debido a las dificultades de comunicación que presentan. Esta exclusión conlleva una subestimación de la prevalencia y gravedad de los trastornos neuropsiquiátricos en la población afectada por un accidente cerebrovascular, lo que a su vez resulta en la falta de servicios adecuados para atender las necesidades específicas de este grupo de pacientes.

Por un lado, los hallazgos de esta tesis doctoral evidencian que la gravedad de la afasia y la sintomatología depresiva experimentan mejoras significativas con la REGIA en personas con API crónica de tipo fluida. Por otro lado, la administración de Donepezilo en combinación con la REGIA genera mejoras significativas en la apatía y la depresión, lo que se traduce en cambios tanto estructurales como funcionales en el cerebro de los participantes. En cualquier caso, es fundamental resaltar que la interacción social intensiva en el contexto de la rehabilitación lingüística emerge como un predictor clave de la mejoría neuropsiquiátrica en las personas con API sometidas a tratamiento con REGIA. En el futuro, es imperativo continuar con la investigación inclusiva de los trastornos neuropsiquiátricos en el contexto de la API, con el objetivo de ampliar nuestra comprensión global de estas condiciones y su impacto en la calidad de vida a corto y largo plazo. Asimismo, es esencial respaldar enfoques de tratamiento integrales y pertinentes. Los descubrimientos y recomendaciones clínicas derivados de esta tesis contribuirán significativamente a la comprensión y el abordaje de los trastornos neuropsiquiátricos en personas con API. En última instancia, estos hallazgos alientan la esperanza de una mejor comprensión y abordaje de los trastornos neuropsiquiátricos en personas con API, lo que podría traducirse en una mejora significativa en su calidad de vida y bienestar a largo plazo.

“Sin emoción no hay proyecto”

Eduard Punset Casals

References

Adell, A. (2015). Revisiting the role of raphe and serotonin in neuropsychiatric disorders. *Journal of General Physiology*, *145*(4), 257–259. https://doi.org/10.1085/jgp.201511389

Akkad, H., Hope, T. M. H., Howland, C., Ondobaka, S., Pappa, K., Nardo, D., Duncan, J., Leff, A. P., & Crinion, J. (2023). Mapping spoken language and cognitive deficits in post-stroke aphasia. *NeuroImage. Clinical*, *39*, 103452. Advance online publication. https://doi.org/10.1016/j.nicl.2023.103452

Allida, S., Cox, K., Hsieh, C., Lang, H., House, A., & Kackett, M. (2020). Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression after stroke. *Cochrane Database of Systematic Reviews*, *1*, 1–223. https://doi.org/10.1002/14651858.CD003437.pub4.www.cochranelibrary.com

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Association.

Angelelli, P., Paolucci, S., Bivona, U., Piccardi, L., Ciurli, P., Cantagallo, A., Antonucci, G., Fasotti, L., Di Santanionio, A., Grasso, M. G., & Pizzamiglio, L. (2004). Development of neuropsychiatric symptoms in poststroke patients: A cross-sectional study. *Acta Psychiatrica Scandinavica*, *110*(1), 55–63. https://doi.org/10.1111/j.1600-0447.2004.00297.x

Arzy, S., & Danziger, S. (2014). The science of neuropsychiatry: Past, present, and future. *Journal of Neuropsychiatry and Clinical Neurosciences*, *26*(4), 392–395. https://doi.org/10.1176/appi.neuropsych.13120371

Ashaie, S. A., & Cherney, L. R. (2020). Eye tracking as a tool to identify mood in aphasia: A feasibility study. *Neurorehabilitation and Neural Repair*, *34*(5), 463–471. https://doi.org/10.1177/1545968320916160

Aybek, S., & Bogousslavsky, J. (2007). Acute behavioral and mood changes. In O. Godefroy & J. Bogousslavsky (Eds.), *The Behavioral and Cognitive Neurology of Stroke* (pp. 520–528). Cambridge University Press. https://doi.org/10.1017/CBO9780511544880.027

Aybek, S., Carota, A., Ghika-Schmid, F., Berney, A., Van Melle, G., Guex, P., & Bogousslavsky, J. (2005). Emotional behavior in acute stroke: The Lausanne emotion in stroke study. *Cognitive and Behavioral Neurology*, *18*(1), 37–44. https://doi.org/10.1097/01.wnn.0000152226.13001.8a

Ayerbe, L., Ayis, S., Crichton, S., Wolfe, C. D. A., & Rudd, A. G. (2014). The long-term outcomes of depression up to 10 years after stroke; The south london stroke register. *Journal of Neurology, Neurosurgery and Psychiatry*, *85*(5), 514–521. https://doi.org/10.1136/jnnp-2013-306448

Ayerbe, L., Ayis, S., Wolfe, C. D. A., & Rudd, A. G. (2013). Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. *British Journal of Psychiatry*, *202*(1), 14–21. https://doi.org/10.1192/bjp.bp.111.107664

Baker, C., Worrall, L., Rose, M., Hudson, K., Ryan, B., & O'Byrne, L. (2018). A systematic review of rehabilitation interventions to prevent and treat depression in post-stroke aphasia. *Disability and Rehabilitation*, *40*(16), 1870–1892. https://doi.org/10.1080/09638288.2017.1315181

Baker, C., Worrall, L., Rose, M., & Ryan, B. (2018). Experiences of mood changes and depression after post-stroke aphasia. *Aphasiology*, *32*(1), 11–12. https://doi.org/10.1080/02687038.2018.1486384

Baker, C., Worrall, L., Rose, M., & Ryan, B. (2020). 'It was really dark': The experiences and preferences of people with aphasia to manage mood changes and depression. *Aphasiology*, *34*(1), 19–46. https://doi.org/10.1080/02687038.2019.1673304

Bakheit, A. M. (2004). Drug treatment of poststroke aphasia. *Expert Review of*

Neurotherapeutics, *4*(2), 211–217. https://doi.org/10.1586/14737175.4.2.211

Balaev, V., Orlov, I., Petrushevsky, A., & Martynova, O. (2018). Functional connectivity between salience, default mode and frontoparietal networks in post-stroke depression. *Journal of Affective Disorders*, *227*, 554–562. https://doi.org/10.1016/j.jad.2017.11.044

Barrows, P. D., & Thomas, S. A. (2018). Assessment of mood in aphasia following stroke: Validation of the Dynamic Visual Analogue Mood Scales (D-VAMS). *Clinical Rehabilitation*, *32*(1), 94–102. https://doi.org/10.1177/0269215517714590

Barrows, P. D., Thomas, S. A., & Van Gordon, W. (2021). Assessing self-reported mood in aphasia following stroke: Challenges, innovations and future directions. *Journal of Stroke and Cerebrovascular Diseases*, *30*(1), 105425. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105425

Basso, A., & Macis, M. (2011). Therapy efficacy in chronic aphasia. *Behavioural Neurology*, *24*(4), 317–325. https://doi.org/10.3233/BEN-2011-0342

Beeson, P., & Robey, R. (2006). Evaluating single-subject treatment research: Lessons learned from the aphasia literature. *Neuropsychological Review*, *23*(1), 161–169. https://doi.org/10.1007/s11065-006-9013-7

Belagaje, S. R. (2017). Stroke Rehabilitation. *Continuum*, *23*(1), 283–253.

Berrios, G. E., & Markova, I. S. (2002). The concept of neuropsychiatry: A historical overview. *Journal of Psychosomatic Research*, *53*, 629–638.

Berthier, M. L., Green, C., Higueras, C., Fernández, I., Hinojosa, J., & Martín, M. (2006). A randomized, placebo-controlled study of donepezil in poststroke aphasia. *Neurology*, *67*(9), 1687–1689. https://doi.org/10.1212/01.wnl.0000242626.69666.e2

Berthier, M. L. (2021). Ten key reasons for continuing research on pharmacotherapy for post-stroke aphasia. *Aphasiology*, *35*(6), 824–858. https://doi.org/https://doi.org/10.1080/02687038.2020.1769987

Berthier, M. L., Dávila, G., García-Casares, N., & Moreno-Torres, I. (2014). Post-stroke aphasia. In *The Behavioral Consequences of Stroke* (pp. 95–117). Springer Science+Business Media. https://doi.org/10.1007/978-1-4614-7672-6

Berthier, M. L, García-Casares, N., & Dávila, G. (2011). Afasias y trastornos del habla. *Medicine*, *10*(74), 5035–5041. https://doi.org/10.1016/S0304-5412(11)70049-X

Berthier, M. L, Green-Heredia, C., Juárez y Ruiz de Mier, R., Lara, J., & Pulvermüller, F. (2014). *REGIA. Rehabilitación Grupal Intensiva de la Afasia*. TEA Ediciones.

Berthier, M. L. (2005). Poststroke aphasia: Epidemiology, pathophysiology and treatment. *Drugs and Aging*, *22*(2), 163–182. https://doi.org/10.2165/00002512-200522020-00006

Berthier, M. L. (2020). Ten key reasons for continuing research on pharmacotherapy for post-stroke aphasia. *Aphasiology*, *35*(6), 824–858. https://doi.org/10.1080/02687038.2020.1769987

Berthier, M. L., Dávila, G., Edelkraut, L., López-Barroso, D., Torres-Prioris, M. J., & Tubío-Ordóñez, J. (2020). Pharmacological treatment of post-stroke cognitive deficits. In R. M. Lazar (Ed.), *Neurovascular Neuropsychology* (pp. 465–500). Springer Nature Switzerland AG. https://doi.org/10.1007/978-3-0348-7842-5_12

Berthier, M. L., Green, C., Lara, J. P., Higueras, C., Barbancho, M. A., Dávila, G., & Pulvermüller, F. (2009). Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. *Annals of Neurology*, *65*(5), 577–585. https://doi.org/10.1002/ana.21597

Berthier, M. L., & Pulvermüller, F. (2011). Neuroscience insights improve neurorehabilitation of poststroke aphasia. *Nature Reviews Neurology*, *7*(2), 86–97. https://doi.org/10.1038/nrneurol.2010.201

Berthier, M. L., Pulvermüller, F., Dávila, G., Casares, N. G., & Gutiérrez, A. (2011). Drug therapy of post-stroke aphasia: A review of current evidence. *Neuropsychology Review*, *21*(3), 302–317. https://doi.org/10.1007/s11065-011-9177-7

Bertrand, D., & Wallace, T. L. (2020). A review of the cholinergic system and therapeutic approaches to treat brain disorders. In M. Shoaib & T. L. Wallace (Eds.), *Behavioral Pharmacology of the Cholinergic System* (pp. 1–28). Springer International Publishing. https://doi.org/10.1007/7854_2020_141

Biran, I., & Chatterjee, A. (2003). Depression with anosognosia following a left subcortical stroke. *Clinical Neurology and Neurosurgery*, *105*(2), 99–101. https://doi.org/10.1016/S0303-8467(02)00113-0

Blank, I. A., Kiran, S., & Fedorenko, E. (2017). Can neuroimaging help aphasia researchers? Addressing generalizability, variability, and interpretability. *Cognitive Neuropsychology*, *34*(6), 377–393. https://doi.org/10.1080/02643294.2017.1402756

Bonini, M. V., & Radanovic, M. (2015). Cognitive deficits in post-stroke aphasia. *Arquivos de neuro-psiquiatria*, *73*(10), 840–847. https://doi.org/10.1590/0004-282X20150133

Brady, M. C., Fredrick, A., & Williams, B. (2013). People with aphasia: Capacity to consent, research participation and intervention inequalities. *International Journal of Stroke*, *8*(3), 193–196. https://doi.org/10.1111/j.1747-4949.2012.00900.x

Brady, M. C., Kelly, H., Godwin, J., & Enderby, P. (2012). Speech and language therapy for aphasia following stroke. *Cochrane Database of Systematic Reviews*, *2012*(5), 1–309. https://doi.org/10.1002/14651858.CD000425.pub3

Breining, B. L., & Sebastian, R. (2020). Neuromodulation in post-stroke aphasia treatment. *Current Physical Medicine and Rehabilitation Reports*, *8*(2), 44–56. https://doi.org/10.1007/s40141-020-00257-5

Breitenstein, C., Grewe, T., Flöel, A., Ziegler, W., Springer, L., Martus, P., Huber, W., Willmes, K., Ringelstein, E. B., Haeusler, K. G., Abel, S., Glindemann, R., Domahs, F., Regenbrecht, F., Schlenck, K. J., Thomas, M., Obrig, H., de Langen, E., Rocker, R., … Bamborschke, S. (2017). Intensive speech and language therapy in patients with chronic aphasia after stroke: A randomised, open-label, blinded-endpoint, controlled trial in a health-care setting. *The Lancet*, *389*(10078), 1528–1538. https://doi.org/10.1016/S0140-6736(17)30067-3

Breitenstein, C., Korsukewitz, C., Baumgärtner, A., Flöel, A., Zwitserlood, P., Dobel, C., & Knecht, S. (2015). L-dopa does not add to the success of high-intensity language training in aphasia. *Restorative Neurology and Neuroscience*, *33*(2), 115–120. https://doi.org/10.3233/RNN-140435

Brodaty, H., Sachdev, P. S., Withhall, A., Altendorf, A., Valenzuela, M. J., & Lorentz, L. (2005). Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - The Sydney Stroke Study. *Psychological Medicine*, *35*(12), 1707–1716. https://doi.org/10.1017/S0033291705006173

Bullier, B., Cassoudesalle, H., Villain, M., Cogné, M., Mollo, C., De Gabory, I., Dehail, P., Joseph, P. A., Sibon, I., & Glize, B. (2020). New factors that affect quality of life in patients with aphasia. *Annals of Physical and Rehabilitation Medicine*, *63*(1), 33–37. https://doi.org/10.1016/j.rehab.2019.06.015

Caeiro, L., Ferro, J. M., & Costa, J. (2013). Apathy secondary to stroke: A systematic review and meta-analysis. *Cerebrovascular Diseases*, *35*(1), 23–39. https://doi.org/10.1159/000346076

Cahana-Amitay, D., & Albert, M. L. (2015). Neuroscience of aphasia recovery: The concept of neural multifunctionality. *Current Neurology and Neuroscience Reports*, *15*(7). https://doi.org/10.1007/s11910-015-0568-7

Cai, W., Mueller, C., Li, Y. J., Shen, W. D., & Stewart, R. (2019). Post stroke depression

and risk of stroke recurrence and mortality: A systematic review and meta-analysis. *Ageing Research Reviews*, *50*(January), 102–109. https://doi.org/10.1016/j.arr.2019.01.013
Campbell Burton, C. A., Murray, J., Holmes, J., Astin, F., Greenwood, D., & Knapp, P. (2013). Frequency of anxiety after stroke: A systematic review and meta-analysis of observational studies. *International Journal of Stroke*, *8*(7), 545–559. https://doi.org/10.1111/j.1747-4949.2012.00906.x
Carnes-Vendrell, A., Deus, J., Molina-Seguin, J., Pifarré, J., & Purroy, F. (2019). Depression and apathy after transient ischemic attack or minor stroke: Prevalence, evolution and predictors. *Scientific Reports*, *9*(1), 1–9. https://doi.org/10.1038/s41598-019-52721-5
Carota, A., Rimoldi, F., & Calabrese, P. (2016). Wernicke's aphasia and attempted suicide. *Acta Neurologica Belgica*, *116*(4), 659–661. https://doi.org/10.1007/s13760-016-0618-1
Carota, A., Staub, F., & Bogousslavsky, J. (2002). Emotions, behaviours and mood changes in stroke. *Current Opinion in Neurology*, *15*(1), 57–69. https://doi.org/10.1097/00019052-200202000-00010
Castellanos-Pinedo, F., Hernández-Pérez, J. M., Zurdo, M., Rodríguez-Fúnez, B., Hernández-Bayo, J. M., García-Fernández, C., Cueli-Rincón, B., & Castro-Posada, J. A. (2011). Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(3), 340–347. https://doi.org/10.1176/jnp.23.3.jnp340
Chong, T., & Husain, M. (2016). The role of dopamine in the pathophysiology and treatment of apathy. *Progress in Brain Research*, *229*, 389–426. https://doi.org/10.1016/bs.pbr.2016.05.007
Code, C., Hemsley, G., & Herrmann, M. (1999). The emotional impact o f aphasia. *Seminars in Speech and Langauge*, *20*(1), 19–31. https://doi.org/https://doi.org/10.1055/s-2008-1064006
Crosson, B., Rodriguez, A. D., Copland, D., Fridriksson, J., Krishnamurthy, L. C., Meinzer, M., Raymer, A. M., Krishnamurthy, V., & Leff, A. P. (2019). Neuroplasticity and aphasia treatments: New approaches for an old problem. *Journal of Neurology, Neurosurgery and Psychiatry*, *90*(10), 1147–1155. https://doi.org/10.1136/jnnp-2018-319649
Cruice, M., Worrall, L., & Hickson, L. (2010). Health-related quality of life in people with aphasia: Implications for fluency disorders quality of life research. *Journal of Fluency Disorders*, *35*(3), 173–189. https://doi.org/10.1016/j.jfludis.2010.05.008
Cummings, J. L., McRae, T., & Zhang, R. (2006). Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. *American Journal of Geriatric Psychiatry*, *14*(7), 605–612. https://doi.org/10.1097/01.JGP.0000221293.91312.d3
Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory. *Neurology*, *44*(1), 2308–2314. https://doi.org/10.1212/WNL.44.12.2308
Dar, S. K., Venigalla, H., Khan, A. M., Ahmed, R., Mekala, H. M., Zain, H., & Shagufta, S. (2017). Post stroke depression frequently overlooked, undiagnosed, untreated. *Neuropsychiatry*, *7*(6), 906–919. https://doi.org/10.4172/neuropsychiatry.1000296
Darkow, R., & Flöel, A. (2016). Aphasie: Evidenzbasierte Therapieansätze. *Nervenarzt*, *87*(10), 1051–1056. https://doi.org/10.1007/s00115-016-0213-y
De Ryck, A., Fransen, E., Brouns, R., Geurden, M., Peij, D., Mariën, P., De Deyn, P. P., & Engelborghs, S. (2014). Poststroke depression and its multifactorial nature:

Results from a prospective longitudinal study. *Journal of the Neurological Sciences*, *347*(1–2), 159–166. https://doi.org/10.1016/j.jns.2014.09.038

Devanand, D. P., Pelton, G. H., D'Antonio, K., Ciarleglio, A., Scodes, J., Andrews, H., Lunsford, J., Beyer, J. L., Petrella, J. R., Sneed, J., Ciovacco, M., & Doraiswamy, P. M. (2018). Donepezil treatment in patients with depression and cognitive impairment on stable antidepressant treatment: A randomized controlled trial. *American Journal of Geriatric Psychiatry*, *26*(10), 1050–1060. https://doi.org/10.1016/j.jagp.2018.05.008

Difrancesco, S., Pulvermüller, F., & Mohr, B. (2012). Intensive language-action therapy (ILAT): The methods. *Aphasiology*, *26*(11), 1317–1351. https://doi.org/10.1080/02687038.2012.705815

Døli, H., Helland, T., & Helland, W. A. (2017). Self-reported symptoms of anxiety and depression in chronic stroke patients with and without aphasia. *Aphasiology*, *31*(12), 1392–1409. https://doi.org/10.1080/02687038.2017.1280595

Doogan, C., Dignam, J., Copland, D., & Leff, A. (2018). Aphasia recovery: When, how and who to treat? *Current Neurology and Neuroscience Reports*, *18*(12), 1–7. https://doi.org/10.1007/s11910-018-0891-x

Drevets, W. C., Zarate, C. A., & Furey, M. L. (2013). Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: A review. *Biological Psychiatry*, *73*(12), 1156–1163. https://doi.org/10.1016/j.biopsych.2012.09.031

Dulawa, S. C., & Janowsky, D. S. (2019). Cholinergic regulation of mood: From basic and clinical studies to emerging therapeutics. *Molecular Psychiatry*, *24*(5), 694–709. https://doi.org/10.1038/s41380-018-0219-x

Duncan, E. S., & Small, S. L. (2018). Changes in dynamic resting state network connectivity following aphasia therapy. *Brain Imaging and Behavior*, *12*(4), 1141–1149. https://doi.org/10.1007/s11682-017-9771-2

Duncan, J. (2013). The structure of cognition: Attentional episodes in mind and brain. *Neuron*, *80*(1), 35–50. https://doi.org/10.1016/j.neuron.2013.09.015

Espárrago Llorca, G., Castilla-Guerra, L., Fernández Moreno, M. C., Ruiz Doblado, S., & Jiménez Hernández, M. D. (2015). Depresión post ictus: Una actualización. *Neurologia*, *30*(1). https://doi.org/10.1016/j.nrl.2012.06.008

Fama, M. E., Baron, C. R., Hatfield, B., & Turkeltaub, P. E. (2017). Group therapy as a social context for aphasia recovery: A pilot, observational study in an acute rehabilitation hospital. *Top Stroke Rehabilitation*, *23*(4), 276–283. https://doi.org/10.1080/10749357.2016.1155277.Group

Fedorenko, E., & Thompson-Schill, S. L. (2014). Reworking the language network. *Trends in Cognitive Sciences*, *18*(3), 120–126. https://doi.org/10.1016/j.tics.2013.12.006

Fedorenko, E., & Varley, R. (2016). Language and thought are not the same thing: Evidence from neuroimaging and neurological patients. *Annals of the New York Academy of Sciences*, *1369*(1), 132–153. https://doi.org/10.1111/nyas.13046

Feigin, V. L., Norrving, B., & Mensah, G. A. (2017). Global burden of stroke. *Circulation Research*, *120*(3), 439–448. https://doi.org/10.1161/CIRCRESAHA.116.308413

Feng, C., Fang, M., & Liu, X. Y. (2014). The neurobiological pathogenesis of poststroke depression. *The Scientific World Journal*, *521349*. https://doi.org/10.1155/2014/521349

Ferro, J. M., Caeiro, L., & Figueira, M. L. (2016). Neuropsychiatric sequelae of stroke. *Nature Reviews Neurology*, *12*(5), 269–280.

Ferro, J. M., & Santos, A. C. (2019). Emotions after stroke: A narrative update. *International Journal of Stroke*, *0*(0), 1–12. https://doi.org/10.1177/1747493019879662

Finkenzeller, W., Zobel, I., Rietz, S., Schramm, E., & Berger, M. (2009). Interpersonelle Psychotherapie und Pharmakotherapie bei post-stroke-Depression: Machbarkeit und Effektivität. *Nervenarzt*, *80*(7), 805–812. https://doi.org/10.1007/s00115-008-2649-1

Fitzgerald, P. J., Hale, P. J., Ghimire, A., & Watson, B. O. (2020). The cholinesterase inhibitor donepezil has antidepressant-like properties in the mouse forced swim test. *Translational Psychiatry*, *10*(1). https://doi.org/10.1038/s41398-020-00928-w

Flaster, M., Sharma, A., & Rao, M. (2013). Poststroke depression: A review emphasizing the role of prophylactic treatment and synergy with treatment for motor recovery. *Topics in Stroke Rehabilitation*, *20*(2), 139–150. https://doi.org/10.1310/tsr2002-139

Flowers, H. L., Skoretz, S. A., Silver, F. L., Rochon, E., Fang, J., Flamand-Roze, C., & Martino, R. (2016). Poststroke aphasia frequency, recovery, and outcomes: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *97*(12), 2188-2201.e8. https://doi.org/10.1016/j.apmr.2016.03.006

Folstein, M., Maiberger, R., McHugh, P., Carson, A. J., Folstein, M., Maiberger, R., & McHugh, P. (2012). Mood disorder as a specific complication of stroke. *Journal of Neurology, Neurosurgery and Psychiatry*, *83*(9), 859. https://doi.org/10.1136/jnnp-2011-301854

Fonseca, J., Raposo, A., & Martins, I. P. (2018). Cognitive performance and aphasia recovery. *Topics in stroke rehabilitation*, *25*(2), 131–136. https://doi.org/10.1080/10749357.2017.1390904

Fonseca, J., Raposo, A., & Martins, I. P. (2019). Cognitive functioning in chronic post-stroke aphasia. *Applied neuropsychology. Adult*, *26*(4), 355–364. https://doi.org/10.1080/23279095.2018.1429442

Fornaro, M., Solmi, M., Veronese, N., De Berardis, D., Buonaguro, E. F., Tomasetti, C., Perna, G., Preti, A., & Carta, M. G. (2017). The burden of mood-disorder/cerebrovascular disease comorbidity: Essential neurobiology, psychopharmacology, and physical activity interventions. *International Review of Psychiatry*, *29*(5), 425–435. https://doi.org/10.1080/09540261.2017.1299695

Frey, K. L., Newman, J. K., Arciniegas, D. B., Alan Anderson, C., & Ramsberger, G. (2011). Assessing neuropsychiatric disturbances associated with post-stroke aphasia. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(4), 4–5. https://doi.org/10.1176/appi.neuropsych.23.4.e4

Fridriksson, J., Basilakos, A., Boyle, M., Cherney, L. R., Dede, G., Gordon, J. K., Harnish, S. M., Hoover, E. L., Hula, W. D., Pompon, R. H., Johnson, L. P., Kiran, S., Murray, L. L., Rose, M. L., Obermeyer, J., Salis, C., Walker, G. M., & Martin, N. (2022). Demystifying the complexity of aphasia treatment: Application of the rehabilitation treatment specification systemx. *Archives of Physical Medicine and Rehabilitation*, *103*(3), 574–580. https://doi.org/10.1016/j.apmr.2021.08.025

Fridriksson, J., & Hillis, E. A. (2021). Current approaches to the treatment of post-stroke aphasia. *Annals of Medicine*, *23*(2), 183–201.

Fridriksson, J., Ouden, D. Den, Hillis, A. E., Hickok, G., Rorden, C., Basilakos, A., Yourganov, G., & Bonilha, L. (2018). Anatomy of aphasia revisited. *Brain*, *January*, 1–15. https://doi.org/10.1093/brain/awx363

Furey, M. L. (2011). The prominent role of stimulus processing: Cholinergic function and dysfunction in cognition. *Current Opinion in Neurology*, *24*(4), 364–370. https://doi.org/10.1097/WCO.0b013e328348bda5.

GBD Stroke Collaborators. (2019). Global, regional, and national burden of stroke, 1990-2016 : A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*, 439–458. https://doi.org/10.1016/S1474-4422(19)30034-1

Gençer, A. G., & Hocaoğlu, Ç. (2019). Post-stroke neuropsychiatric problems. *Current Approaches in Psychiatry*, *11*(4), 419–437. https://doi.org/10.18863/pgy.483540
Gleichgerrcht, E., Kocher, M., Nesland, T., Rorden, C., Fridriksson, J., & Bonilha, L. (2015). Preservation of structural brain network hubs is associated with less severe post-stroke aphasia. *Restorative Neurology and Neuroscience*, *34*(1), 19–28. https://doi.org/10.3233/RNN-150511
Guha, A., Yee, C. M., Heller, W., & Miller, G. A. (2021). Alterations in the default mode-salience network circuit provide a potential mechanism supporting negativity bias in depression. *Psychophysiology*, *58*(12), 1–18. https://doi.org/10.1111/psyp.13918
Hackett, M. L., Köhler, S., O'Brien, J. T., & Mead, G. E. (2014). Neuropsychiatric outcomes of stroke. *The Lancet Neurology*, *13*(5), 525–534. https://doi.org/10.1016/S1474-4422(14)70016-X
Hackett, M. L., & Pickles, K. (2014). Part I. Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *International Journal of Stroke*, *June*, 1017–1025. https://doi.org/10.1111/ijs.12357
Hama, S., Yamashita, H., Yamawaki, S., & Kurisu, K. (2011). Post-stroke depression and apathy: Interactions between functional recovery, lesion location, and emotional response. *Psychogeriatrics*, *11*(1), 68–76. https://doi.org/10.1111/j.1479-8301.2011.00358.x
Hamani, C., Mayberg, H., Stone, S., Laxton, A., Haber, S., & Lozano, A. M. (2011). The subcallosal cingulate gyrus in the context of major depression. *Biological Psychiatry*, *69*(4), 301–308. https://doi.org/10.1016/j.biopsych.2010.09.034
Hankey, G. J. (2017). Stroke. *The Lancet*, *389*(10069), 641–654. https://doi.org/10.1016/S0140-6736(16)30962-X
Hartwigsen, G., & Saur, D. (2019). Neuroimaging of stroke recovery from aphasia-Insights into plasticity of the human language network. *NeuroImage*, *190*, 14–31. https://doi.org/10.1016/j.neuroimage.2017.11.056
Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition*, *92*(1–2), 67–99. https://doi.org/10.1016/j.cognition.2003.10.011
Hilari, K. (2011). The impact of stroke: Are people with aphasia different to those without? *Disability and Rehabilitation*, *33*(3), 211–218. https://doi.org/10.3109/09638288.2010.508829
Hilari, K., Byng, S., Lamping, D. L., & Smith, S. C. (2003). Stroke and aphasia quality of life scale-39 (SAQOL-39): Evaluation of acceptability, reliability, and validity. *Stroke*, *34*(8), 1944–1950. https://doi.org/10.1161/01.STR.0000081987.46660.ED
Hilari, K., Northcott, S., Roy, P., Marshall, J., Wiggins, R. D., Chataway, J., & Ames, D. (2010). Psychological distress after stroke and aphasia: The first six months. *Clinical Rehabilitation*, *24*(2), 181–190. https://doi.org/10.1177/0269215509346090
Hillis, A. (2007). Aphasia: Progress in the last quarter of a century. *Neurology*, *69*(2), 200–213. https://doi.org/10.1212/01.wnl.0000265600.69385.6f
Hillis, A., Beh, Y. Y., Sebastian, R., Breining, B., Bonilha, L., & Basilakos, A. (2018). Predicting recovery in acute post-stroke aphasia. *Annals of Indian Academy of Neurology*, *83*(3), 612–622. https://doi.org/10.1002/ana.25184.Predicting
Holland, AudreyFromm, D., Forbes, M., & MacWhinner, B. (2017). Long-term recovery in stroke accompanied by aphasia: A reconsideration. *Aphasiology*, *31*(2), 152–165. https://doi.org/10.1080/02687038.2016.1184221.Long-term
Huffman, J., & Stern, T. A. (2003). Acute psychiatric manifestations of stroke: A clinical case conference. *Psychosomatics*, *44*(1), 65–75. https://doi.org/10.1176/appi.psy.44.1.65
Husain, M., Roiser, J. P., & Radcliffe, O. J. (2018). Neuroscience of apathy and

anhedonia: A transdiagnostic approach. *Nature Reviews Neuroscience*, *19*, 470–484. https://doi.org/10.1038/s41583-018-0029-9

Intercollegiate Stroke Working Party. (2016). *National clinical guideline for stroke* (5th ed.). Royal College of Physicians.

Jackson, M. C. (2013). *Anxiety, Apathy and Depression in First-Time Stroke Survivors with Aphasia in the Post-Stroke Period (Doctoral Dissertation)*. University of Maryland School of Nursing.

Jesulola, E., Micalos, P., & Baguley, I. J. (2018). Understanding the pathophysiology of depression: From monoamines to the neurogenesis hypothesis model - Are we there yet? *Behavioural Brain Research*, *341*, 79–90. https://doi.org/10.1016/j.bbr.2017.12.025

Jones, A., O'connell, N., David, A., & Chalder, T. (2020). Functional stroke symptoms: A narrative review and conceptual model. *Journal of Neuropsychiatry and Clinical Neurosciences*, *32*(1), 14–23. https://doi.org/10.1176/appi.neuropsych.19030075

Jones, M., Corcoran, A., & Jorge, R. E. (2019). The psychopharmacology of brain vascular disease/poststroke depression. In V. Reus & D. Lindqvist (Eds.), *Handbook of Clinical Neurology Disease. Psychopharmacology of Neurologic Disease* (1st ed., Vol. 165, pp. 229–241). Elsevier. http://dx.doi.org/10.1016/B978-0-444-64012-3.00013-7

Jorge, R. E., Acion, L., Moser, D., Jr, H. P. A., & Robinson, R. G. (2013). Escitalopram and enhancement of cognitive recovery following stroke. *Archives of General Psychiatry*, *67*(2), 187–196. https://doi.org/10.1001/archgenpsychiatry.2009.185.Escitalopram

Jorge, R. E., Starkstein, S. E., & Robinson, R. G. (2010). Apathy following stroke. *Canadian Journal of Psychiatry*, *55*(6), 350–354. https://doi.org/10.1177/070674371005500603

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, *72*(6), 603–611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Katan, M., & Luft, A. (2018). Global burden of stroke. *Seminars in Neurology*, *2*, 208–211. https://doi.org/10.1159/000441085.lifetime

Kauhanen, M., Korpelainen, J., Hintunen, P., Häätä, R., Mononen, H., Brusin, E., Sotaniemi, K., & Myllylä, V. (2000). Aphasia, depression and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Disease*, *10*, 455–461.

Kauhanen ML, Korpelainen JT, Hiltunen P, et al. (2000). Cognitive impairment in non-verbal cognitive impairment in ischaemic stroke. *Cerebrovascular Disease*, *10*, 451–457.

Kennedy, J. M., Granato, D. A., & Goldfine, A. M. (2015). Natural history of poststroke apathy during acute rehabilitation. *Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(4), 333–338. https://doi.org/10.1176/appi.neuropsych.15010001

Kertesz, A. (2007). Western Aphasia Battery-Revised. In *WAB-R: Western Aphasia Battery-R*. PsychCorp.

Kintz, S., & Wright, H. H. (2018). Discourse measurement in aphasia research. *Aphasiology*, *32*(4), 472–474. https://doi.org/10.1080/02687038.2017.1398807

Kiran, S., & Thompson, C. K. (2019). Neuroplasticity of language networks in aphasia: Advances, updates, and future challenges. *Frontiers in Neurology*, *10*, 1–15. https://doi.org/10.3389/fneur.2019.00295

Kouwenhoven, S., Kirkevold, M., Engedal, K., Biong, S., & Kim, H. (2011). The lived experience of stroke survivors with early depressive symptom: A longitudinal perspective. *International Journal of Qualitative Studies on Health and Well-Being*, *6*(4), 10.3402/qhw.v6i4.8491. https://doi.org/https://doi.org/10.3402/qhw.v6i4.8491

Kristo, I., & Mowll, J. (2022). Voicing the perspectives of stroke survivors with aphasia: A rapid evidence review of post-stroke mental health, screening practices and lived experiences. *Health and Social Care*, *4*, 898–908. https://doi.org/10.1111/hsc.13694

Kronenberg, G., Endres, M., & Depression, P. (2013). Schlaganfall und Psyche. *Aktuellle Neurologie*, *40*, 553–556.

Kutlubaev, M. A., & Hackett, M. L. (2014). Part II. Predictors of depression after stroke and impact of depression on stroke outcome: An updated systematic review of observational studies. *International Journal of Stroke*, *9*(8), 1026–1036. https://doi.org/10.1111/ijs.12356

Lam, J. M. C., & Wodchis, W. P. (2010). The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. *Medical Care*, *48*(4), 380–387. https://doi.org/10.1097/MLR.0b013e3181ca2647

Lanctôt, K. L., Lindsay, M. P., Smith, E. E., Sahlas, D. J., Foley, N., Gubitz, G., Austin, M., Ball, K., Bhogal, S., Blake, T., Herrmann, N., Hogan, D., Khan, A., Longman, S., King, A., Leonard, C., Shoniker, T., Taylor, T., Teed, M., … Swartz, R. H. (2019). Canadian stroke best practice recommendations: Mood, cognition and fatigue following stroke, 6th edition. *International Journal of Stroke*, *0*(0), 1–21. https://doi.org/10.1177/1747493019847334

Laska, A. C., Hellblom, A., Murray, V., Kahan, T., & Von Arbin, M. (2001). Aphasia in acute stroke and relation to outcome. *Journal of Internal Medicine*, *249*(5), 413–422. https://doi.org/10.1046/j.1365-2796.2001.00812.x

Laures-Gore, J. S., Dotson, V. M., & Belagaje, S. (2020). Depression in poststroke aphasia. *American Journal of Speech-Language Pathology*, *29*(4), 1798–1810. https://doi.org/10.1044/2020_AJSLP-20-00040

Laures-Gore, J. S., Farina, M., Moore, E., & Russell, S. (2017). Stress and depression scales in aphasia: Relation between the aphasia depression rating scale, stroke aphasia depression questionnaire-10, and the perceived stress scale. *Topics in Stroke Rehabilitation*, *24*(2), 114–118. https://doi.org/10.1080/10749357.2016.1198528

Lazar, R. M., & Boehme, A. K. (2017). Aphasia as a predictor of stroke outcome. *Current Neurology and Neuroscience Reports*, *17*(11), 1–5. https://doi.org/10.1007/s11910-017-0797-z

Le Heron, C., Holroyd, C. B., Salamone, J., & Husain, M. (2019). Brain mechanisms underlying apathy. *Journal of Neurology, Neurosurgery and Psychiatry*, *90*, 302–312. https://doi.org/10.1136/jnnp-2018-318265

Lenzi, G. L., Altieri, M., & Maestrini, I. (2008). Post-stroke depression. *Revue Neurologique*, *164*(10), 837–840. https://doi.org/10.1016/j.neurol.2008.07.010

Levy, R. (2012). Apathy: A pathology of goal-directed behaviour. A new concept of the clinic and pathophysiology of apathy. *Revue Neurologique*, *168*(8–9), 585–597. https://doi.org/10.1016/j.neurol.2012.05.003

Lincoln, N., Sutcliffe, L., & Unsoworth, G. (2000). Validation of the Stroke Aphasic Depression Questionnaire (SADQ) for use with patients in hospital. *Clinical Neuropsychological Assessment*, *1*, 88–96.

Liston, C. C., Chen, A. C., Zebley, B. D., Drysdale, A. T., Gordon, R., Leuchter, B., Voss, H. U., Casey, B. J., Etkin, A., Dubin, M. J., & Marc, J. (2014). Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological Psychiatry*, *76*(7), 517–526. https://doi.org/10.1016/j.biopsych.2014.01.023

López-Barroso, D., & De Diego-Balaguer, R. (2017). Language learning variability within the dorsal and ventral streams as a cue for compensatory mechanisms in aphasia recovery. *Frontiers in Human Neuroscience*, *11*(9), 1–7.

https://doi.org/10.3389/fnhum.2017.00476
Loubinoux, I., Kronenberg, G., Endres, M., Schumann-Bard, P., Freret, T., Filipkowski, R. K., Kaczmarek, L., & Popa-Wagner, A. (2012). Post-stroke depression: Mechanisms, translation and therapy. *Journal of Cellular and Molecular Medicine*, *16*(9), 1961–1969. https://doi.org/10.1111/j.1582-4934.2012.01555.x
Luengo-Fernandez, R., Violato, M., Candio, P., & Leal, J. (2020). Economic burden of stroke across Europe: A population-based cost analysis. *European Stroke Journal*, *5*(1), 17–25. https://doi.org/10.1177/2396987319883160
Marcotte, K., Adrover-Roig, D., Damien, B., de Préaumont, M., Généreux, S., Hubert, M., & Ansaldo, A. I. (2012). Therapy-induced neuroplasticity in chronic aphasia. *Neuropsychologia*, *50*(8), 1776–1786. https://doi.org/10.1016/j.neuropsychologia.2012.04.001
Marshall, R. S., & Mohapatra, B. (2017). Integrative intervention: A new perspective and brief review in aphasia. *Disability and Rehabilitation*, *39*(19), 1999–2009. https://doi.org/10.1080/09638288.2016.1212283
Mayo, N. E., Fellows, L. K., Scott, S. C., Cameron, J., & Wood-Dauphinee, S. (2009). A longitudinal view of apathy and its impact after stroke. *Stroke*, *40*(10), 3299–3307. https://doi.org/10.1161/STROKEAHA.109.554410
Mcneil, M. R., & Pratt, S. R. (2001). Defining aphasia: Some theoretical and clinical implications of operating from a formal definition. *Aphasiology*, *15*(10), 901–911. https://doi.org/10.1080/02687040143000276
Medeiros, G. C., Roy, D., Kontos, N., & Beach, S. R. (2020). Post-stroke depression: A 2020 updated review. *General Hospital Psychiatry*, *66*(3), 70–80. https://doi.org/10.1016/j.genhosppsych.2020.06.011
Mena-Segovia, J., Winn, P., & Bolam, J. P. (2008). Cholinergic modulation of midbrain dopaminergic systems. *Brain Research Reviews*, *58*(2), 265–271. https://doi.org/10.1016/j.brainresrev.2008.02.003
Menon, B. (2019). Towards a new model of understanding – The triple network, psychopathology and the structure of the mind. *Medical Hypothesis*, *133*, 1–7. https://doi.org/10.1212/01.wnl.0000304109.18563.81
Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003
Menon, V. (2015). Salience Network. In A. Toga (Ed.), *Brain Mapping: An Encyclopedic Reference* (Vol. 2, pp. 597–611). Academic Press: Elsevier. https://doi.org/10.1016/B978-0-12-397025-1.00052-X
Mikami, K., Jorge, R. E., Moser, D. J., Arndt, S., Jang, M., Solodkin, A., Small, S. L., Fonzetti, P., Hegel, M. T., & Robinson, R. G. (2013). Prevention of poststroke apathy using escitalopram or problem-solving therapy. *American Journal of Geriatric Psychiatry*, *21*(9), 855–862. https://doi.org/10.1016/j.jagp.2012.07.003
Mitchell, A. J., Sheth, B., Gill, J., Yadegarfar, M., Stubbs, B., Yadegarfar, M., & Meader, N. (2017). Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. *General Hospital Psychiatry*, *47*, 48–60. https://doi.org/10.1016/j.genhosppsych.2017.04.001
Miyoshi, K., Morimura, Y., & Maeda, K. (2010). Neuropsychiatric disorders. *Neuropsychiatric Disorders*, 1–351. https://doi.org/10.1007/978-4-431-53871-4
Mohr, B. (2017). Neuroplasticity and functional recovery after intensive language therapy in chronic post stroke aphasia: Which factors are relevant? *Frontiers in Human Neuroscience*, *11*(6), 1–5. https://doi.org/10.3389/fnhum.2017.00332
Mohr, B., Stahl, B., Berthier, M. L., & Pulvermüller, F. (2017). Intensive communicative

therapy reduces symptoms of depression in chronic nonfluent aphasia. *Neurorehabilitation and Neural Repair*, *31*(12), 1053–1062. https://doi.org/10.1177/1545968317744275

Morris, R., Eccles, A., Ryan, B., & Kneebone, I. I. (2017). Prevalence of anxiety in people with aphasia after stroke. *Aphasiology*, *31*(12), 1410–1415. https://doi.org/10.1080/02687038.2017.1304633

Naghavi, F. S., Koffman, E. E., Lin, B., & Du, J. (2019). Post-stroke neuronal circuits and mental illnesses. *International Journal of Physiology, Pathophysiology and Pharmacology*, *11*(1), 1–11.

Nasios, G., Dardiotis, E., & Messinis, L. (2019). From Broca and Wernicke to the neuromodulation era: Insights of brain language networks for neurorehabilitation. *Behavioural Neurology*, *2019*. https://doi.org/10.1155/2019/9894571

Neishaboori, A. M., Maleki, S. N., Pirouz, M. S., Golmohammadi, S., Nazarinia, D., & Aboutaleb, N. (2021). Donepezil attenuates injury following ischaemic stroke by stimulation of neurogenesis, angiogenesis, and inhibition of inflammation and apoptosis. *Inflammopharmacology*, *29*(1), 153–166. https://doi.org/10.1007/s10787-020-00769-5

Nemani, K., & Gurin, L. (2021). Neuropsychiatric complications after stroke. *Seminars in Neurology*, *41*, 85–100. https://doi.org/10.1055/s-0040-1722723

Nestler, E., Hyman, S., Holtzman, D., & Malenka, R. (2014). Widely projecting systems: Monoamines, acetylcholine, and orexin. In E. J. Nestler, P. j: Kenny, S. J. Russo, & A. Schaefer (Eds.), *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*. McGraw Hill.

O'Sullivan, M., Brownsett, S., & Copland, D. (2019). Language and language disorders: Neuroscience to clinical practice. *Practical Neurology*, *19*(5), 380–388. https://doi.org/10.1136/practneurol-2018-001961

Ojagbemi, A., Bello, T., Owolabi, M., & Baiyewu, O. (2021). Prevalence, predictors, and prognoses of prestroke neuropsychiatric symptoms at 3 months poststroke. *International Psychogeriatrics*, *33*(8), 827–834. https://doi.org/10.1017/S1041610220003816

Padmanabhan, J. L., Cooke, D., Joutsa, J., Siddiqi, S. H., Ferguson, M., Darby, R. R., Soussand, L., Horn, A., Kim, N. Y., Voss, J. L., Naidech, A. M., Brodtmann, A., Egorova, N., Gozzi, S., Phan, T. G., Corbetta, M., Grafman, J., & Fox, M. D. (2019). A Human Depression Circuit Derived From Focal Brain Lesions. *Biological Psychiatry*, *86*(10), 749–758. https://doi.org/10.1016/j.biopsych.2019.07.023

Palmer, S. M., Crewther, S. G., & Carey, L. M. (2015). A meta-analysis of changes in brain activity in clinical depression. *Frontiers in Human Neuroscience*, *8*(1), 1–19. https://doi.org/10.3389/fnhum.2014.01045

Papp, M., Gruca, P., Lason-Tyburkiewicz, M., & Willner, P. (2016). Antidepressant, anxiolytic and procognitive effects of rivastigmine and donepezil in the chronic mild stress model in rats. *Psychopharmacology*, *233*(7), 1235–1243. https://doi.org/10.1007/s00213-016-4206-0

Pappadis, M. R., Krishnan, S., Hay, C. C., Jones, B., Sander, A. M., Weller, S. C., & Reistetter, T. A. (2019). Lived experiences of chronic cognitive and mood symptoms among community-dwelling adults following stroke: A mixed-methods analysis. *Aging and Mental Health*, *23*(9), 1227–1233. https://doi.org/10.1080/13607863.2018.1481927

Paranthaman, R., & Baldwin, R. C. (2006). Treatment of psychiatric syndromes due to cerebrovascular disease. *International Review of Psychiatry*, *18*(5), 453–470. https://doi.org/10.1080/09540260600935462

Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-striatal-thalamic loop circuits of the salience network: A central pathway in psychiatric disease and treatment. *Frontiers in Systems Neuroscience*, *10*(12), 1–23. https://doi.org/10.3389/fnsys.2016.00104

Picano, C., Quadrini, A., Pisano, F., & Marangolo, P. (2021). Adjunctive approaches to aphasia rehabilitation: A review on efficacy and safety. *Brain Sciences*, *11*(1), 1–29. https://doi.org/10.3390/brainsci11010041

Popkin, M. K., & Tucker, G. J. (1992). " Secondary " and mood, anxiety, psychotic, catatonic, personality disorders: A review of the literature. *The Journal of Neuropsychiatry and Clinical Neuroscience*, *4*, 369–385.

Pulvermüller, F. (1996). Hebb´s concept of cell assemblies and the psychophysiology of word processing. *Psychophysiology*, *33*, 317–333.

Pulvermuller, F., & Berthier, M. L. (2008). Aphasia therapy on a neuroscience basis. *Aphasiology*, *22*(6), 563–599. https://doi.org/10.1080/02687030701612213

Pulvermüller, F., Hauk, O., Zohsel, K., Neininger, B., & Mohr, B. (2005). Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. *NeuroImage*, *28*(2), 481–489. https://doi.org/10.1016/j.neuroimage.2005.06.038

Pulvermüller, F., Mohr, B., & Taub, E. (2016). Constraint-Induced Aphasia Therapy: A neuroscience-centered translational method. *Neurobiology of Language*, 1025–1034. https://doi.org/10.1016/B978-0-12-407794-2.00082-1

Pulvermüller, F., Neininger, B., Elbert, T., Mohr, B., Rockstroh, B., Koebbel, P., & Taub, E. (2001). Constained-Induced Therapy of chronic aphasia after stroke. *Stroke*, *32*, 2–7. https://doi.org/doi.org/10.1161/01.str.32.7.1621

Reynolds, C. F., Dew, M. A., Pollock, B. G., Mulsant, B. H., Frank, E., Miller, M. D., Houck, P. R., Mazumdar, S., Butters, M. A., Stack, J. A., Schlernitzauer, M. A., Whyte, E. M., Gildengers, A., Karp, J., Lenze, E., Szanto, K., Bensasi, S., & Kupfer, D. J. (2006). Maintenance treatment of major depression in old age. *New England Journal of Medicine*, *354*(11), 1130–1138. https://doi.org/10.1056/nejmoa052619

Riva-Posse, P., Holtzheimer, P. E., & Mayberg, H. S. (2019). Cingulate-mediated depressive symptoms in neurologic disease and therapeutics. In *Handbook of Clinical Neurology* (1st ed., pp. 371–379). Elsevier B.V. https://doi.org/10.1016/B978-0-444-64196-0.00021-2

Robinson, R. G. (2006). *The clinical neuropsychiatry of stroke, 2nd ed.* Cambridge University Press.

Robinson, R. G., & Jorge, R. E. (2016). Post-stroke depression: A review. *American Journal of Psychiatry*, *173*(3), 221–231. https://doi.org/10.1176/appi.ajp.2015.15030363

Román, G. C., & Kalaria, R. N. (2006). Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. *Neurobiology of Aging*, *27*(12), 1769–1785. https://doi.org/10.1016/j.neurobiolaging.2005.10.004

Rose, A. E., Cullen, B., Crawford, S., & Evans, J. J. (2022). A systematic review of mood and depression measures in people with severe cognitive and communication impairments following acquired brain injury. *Clinical Rehabilitation*, *37*(5), 1–22. https://doi.org/10.1177/02692155221139023

Ross, E. D., & Monnot, M. (2011). Affective prosody: What do comprehension errors tell us about hemispheric lateralization of emotions, sex and aging effects, and the role of cognitive appraisal. *Neuropsychologia*, *49*(5), 866–877. https://doi.org/10.1016/j.neuropsychologia.2010.12.024

Sachdev, P. S. (2018). Post-stroke cognitive impairment, depression and apathy: Untangling the relationship. *American Journal of Geriatric Psychiatry*, *26*(3), 301–303. https://doi.org/10.1016/j.jagp.2017.12.002

Sagen, U., Finset, A., Moum, T., Mørland, T., Vik, T. G., Nagy, T., & Dammen, T. (2010). Early detection of patients at risk for anxiety, depression and apathy after stroke. *General Hospital Psychiatry*, *32*(1), 80–85. https://doi.org/10.1016/j.genhosppsych.2009.10.001

Santo Pietro, M. J., Marks, D. R., & Mullen, A. (2019). When words fail: Providing effective psychological treatment for depression in persons with aphasia. *Journal of Clinical Psychology in Medical Settings*, *26*(4), 483–494. https://doi.org/10.1007/s10880-019-09608-4

Sarkar, A., Sarmah, D., Datta, A., Kaur, H., Jagtap, P., Raut, S., Shah, B., Singh, U., Baidya, F., Bohra, M., Kalia, K., Borah, A., Wang, X., Dave, K. R., Yavagal, D. R., & Bhattacharya, P. (2021). Post-stroke depression: Chaos to exposition. *Brain Research Bulletin*, *168*(September 2020), 74–88. https://doi.org/10.1016/j.brainresbull.2020.12.012

Saxena, S., & Hillis, A. E. (2017). An update on medications and noninvasive brain stimulation to augment language rehabilitation in post-stroke aphasia. *Expert Review of Neurotherapeutics*, *17*(11), 1091–1107. https://doi.org/10.1080/14737175.2017.1373020

Selden, N. R., Gitelman, D. R., Salamon-Murayama, N., Parrish, T. B., & Mesulam, M. M. (1998). Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain : a journal of neurology*, *121 (Pt 12)*, 2249–2257. doi.org/10.1093/brain/121.12.2249

Sheppard, S. M., & Sebastian, R. (2021). Diagnosing and managing post-stroke aphasia. *Expert Review of Neurotherapeutics*, *21*(2), 221–234. https://doi.org/10.1080/14737175.2020.1855976

Simić, G., Mrzljak, L., Fucić, A., Winblad, B., Lovrić, H., & Kostović, I. (1999). Nucleus subputaminalis (Ayala): the still disregarded magnocellular component of the basal forebrain may be human specific and connected with the cortical speech area. *Neuroscience*, *89*(1), 73–89. doi.org/10.1016/s0306-4522(98)00304-2

Smania, N., Gandolfi, M., Aglioti, S. M., Girardi, P., Fiaschi, A., & Girardi, F. (2010). How long is the recovery of global aphasia? Twenty-five years of follow-up in a patient with left hemisphere stroke. *Neurorehabilitation and Neural Repair*, *24*(9), 871–875. https://doi.org/10.1177/1545968310368962

Spellman, T., & Liston, C. (2020). Toward circuit mechanisms of pathophysiology in depression. *American Journal of Psychiatry*, *177*(5), 381–390. https://doi.org/10.1176/appi.ajp.2020.20030280

Stahl, B., Millrose, S., Denzler, P., Lucchese, G., Jacobi, F., & Flöel, A. (2022). Intensive social interaction for treatment of poststroke depression in subacute aphasia: The CONNECT trial. *Stroke*, *1*(12), 1–8. https://doi.org/10.1161/strokeaha.122.039995

Stahl, B., Mohr, B., Büscher, V., Dreyer, F. R., Lucchese, G., & Pulvermüller, F. (2018). Efficacy of intensive aphasia therapy in patients with chronic stroke: A randomised controlled trial. *Journal of Neurology Neurosurgery and Psychiatry*, *89*, 586–592. https://doi.org/10.1136/jnnp-2017-315962

Stahl, B., Mohr, B., Dreyer, F. R., Lucchese, G., Pulvermüller, F., & Pulvermu, F. (2016). Using language for social interaction: Communication mechanisms promote recovery from chronic non-fluent aphasia. *Cortex*, *85*, 90–99. https://doi.org/10.1016/j.cortex.2016.09.021

Starkstein, S. E., Berthier, M. L., Fedoroff, P., Price, T. R., & Robinson, R. G. (1990). Anosognosia and major depression in 2 patients with cerebrovascular lesions. *Neurology*, *40*(9), 1380–1382. https://doi.org/10.1212/wnl.40.9.1380

Starkstein, S. E., & Hayhow, B. D. (2019). Treatment of post-stroke depression. *Current Treatment Options in Neurology*, *21*(7), 1–10. https://doi.org/10.1007/s11940-019-

0570-5
Starkstein, S. E., & Manes, F. (2000). Apathy and depression following stroke. *CNS Spectrums*, *5*(3), 43–50. https://doi.org/10.1017/S1092852900012955
Stefaniak, J. D., Alyahya, R. S., & Lambon Ralph, M. A. (2021). Language networks in aphasia and health: A 1000 participant activation likelihood estimation meta-analysis. *NeuroImage*, *233*(February), 117960. https://doi.org/10.1016/j.neuroimage.2021.117960
Stefaniak, J. D., Geranmayeh, F., & Lambon Ralph, M. A. (2022). The multidimensional nature of aphasia recovery post-stroke. *Brain*, *145*(4), 1354–1367. https://doi.org/10.1093/brain/awab377
Stefaniak, J. D., Halai, A. D., & Lambon Ralph, M. A. (2020). The neural and neurocomputational bases of recovery from post-stroke aphasia. *Nature Reviews Neurology*, *16*(1), 43–55. https://doi.org/10.1038/s41582-019-0282-1
Stein, L. A., Goldmann, E., Zamzam, A., Luciano, J. M., Messé, S. R., Cucchiara, B. L., Kasner, S. E., & Mullen, M. T. (2018). Association between anxiety, depression, and post-traumatic stress disorder and outcomes after ischemic stroke. *Frontiers in Neurology*, *9*(NOV), 1–9. https://doi.org/10.3389/fneur.2018.00890
Stolwyk, R. J., O'Connell, E., Lawson, D. W., Thrift, A. G., & New, P. W. (2018). Neurobehavioral disability in stroke patients during subacute inpatient rehabilitation: Prevalence and biopsychosocial associations. *Topics in Stroke Rehabilitation*, *25*(7), 527–534. https://doi.org/10.1080/10749357.2018.1499301
Sutcliffe, L. M., & Lincoln, N. B. (1998). The assessment of depression in aphasic stroke patients: The development of the Stroke Aphasic Depression Questionnaire. *Clinical Rehabilitation*, *12*(6), 506–513. https://doi.org/10.1191/026921598672167702
Tay, J., Morris, R. G., & Markus, H. S. (2021). Apathy after stroke: Diagnosis, mechanisms, consequences, and treatment. *International Journal of Stroke*, *0*(0), 1–9. https://doi.org/10.1177/1747493021990906
Thayabaranathan, T., Baker, C., Andrew, N. E., Stolwyk, R., Thrift, A. G., Carter, H., Moss, K., Kim, J., Wallace, S. J., Brogan, E., Grimley, R., Lannin, N. A., Rose, M. L., Baker, C., Andrew, N. E., Stolwyk, R., Thrift, A. G., Carter, H., Moss, K., … Cadilhac, D. A. (2022). Exploring dimensions of quality-of-life in survivors of stroke with communication disabilities- A brief report. *Topics in Stroke Rehabilitation*, *00*(00), 1–7. https://doi.org/10.1080/10749357.2022.2095087
Thiel, A., & Zumbansen, A. (2016). The pathophysiology of post-stroke aphasia: A network approach. *Restorative Neurology and Neuroscience*, *34*(4), 507–518. https://doi.org/10.3233/RNN-150632
Towfighi, A., Ovbiagele, B., El Husseini, N., Hackett, M. L., Jorge, R. E., Kissela, B. M., Mitchell, P. H., Skolarus, L. E., Whooley, M. A., & Williams, L. S. (2017). Poststroke depression: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *48*(2), e30–e43. https://doi.org/10.1161/STR.0000000000000113
Townend, E., Brady, M., & McLaughlan, K. (2007). Exclusion and inclusion criteria for people with aphasia in studies of depression after stroke: A systematic review and future recommendations. *Neuroepidemiology*, *29*(1–2), 1–17. https://doi.org/10.1159/000108913
Tozzi, L., Zhang, X., Chesnut, M., Holt-Gosselin, B., Ramirez, C. A., & Williams, L. M. (2021). Reduced functional connectivity of default mode network subsystems in depression: Meta-analytic evidence and relationship with trait rumination. *NeuroImage: Clinical*, *30*. https://doi.org/10.1016/j.nicl.2021.102570
Tremblay, P., & Dick, A. S. (2016). Broca and Wernicke are dead, or moving past the classic model of language neurobiology. *Brain and Language*, *162*, 60–71.

https://doi.org/10.1016/j.bandl.2016.08.004
Trimble, M. (2021). The intentional brain - A short history of neuropsychiatry. *CNS Spectrums*, *21*(2016), 223–229. https://doi.org/10.1017/S1092852916000195
Tsarkov, A., & Petlovanyi, P. (2019). Neuropsychiatric aspects of a common problem: Stroke. *European Journal of Medical and Health Sciences*, *1*(3), 1–6. https://doi.org/10.24018/ejmed.2019.1.3.64
Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: Converging evidence from lesion and connectivity analyses. *Frontiers in System Neuroscience*, *5*, 1. https://doi.org/10.3389/fnsys.2011.00001
Ueki, H., Washino, K., Fukao, T., Inoue, M., Ogawa, N., & Takai, A. (1999). Mental health problems after stroke. *Psychiatry and Clinical Neurosciences*, *53*(6), 621–627. https://doi.org/10.1046/j.1440-1819.1999.00616.x
Van Dalen, J. W., Van Charante, E. P. M., Nederkoorn, P. J., Van Gool, W. A., & Richard, E. (2013). Poststroke apathy. *Stroke*, *44*(3), 851–860. https://doi.org/10.1161/STROKEAHA.112.674614
Van Dijk, M. J., De Man-Van Ginkel, J. M., Hafsteinsdóttir, T. B., & Schuurmans, M. J. (2016). Identifying depression post-stroke in patients with aphasia: A systematic review of the reliability, validity and feasibility of available instruments. *Clinical Rehabilitation*, *30*(8), 795–810. https://doi.org/10.1177/0269215515599665
Van Lancker Sidtis, D., & Sidtis, J. J. (2018). Cortical-subcortical production of formulaic language: A review of linguistic, brain disorder, and functional imaging studies leading to a production model. *Brain and Cognition*, *126*(August), 53–64. https://doi.org/10.1016/j.bandc.2018.08.003
Van Rijsbergen, M. W., Mark, R. E., Kop, W. J., de Kort, P. L. M., & Sitskoorn, M. M. (2019). Psychological factors and subjective cognitive complaints after stroke: Beyond depression and anxiety. *Neuropsychological Rehabilitation*, *29*(10), 1671–1684. https://doi.org/10.1080/09602011.2018.1441720
Vicentini, J. E., Weiler, M., Almeida, S. R. M., de Campos, B. M., Valler, L., & Li, L. M. (2017). Depression and anxiety symptoms are associated to disruption of default mode network in subacute ischemic stroke. *Brain Imaging and Behavior*, *11*(6), 1571–1580. https://doi.org/10.1007/s11682-016-9605-7
Vitti, E., & Hillis, A. E. (2021). Treatment of post-stroke aphasia: A narrative review for stroke neurologists. *International Journal of Stroke*, *0*(0), 1–7. https://doi.org/10.1177/17474930211017807
Wafa, H. A., Wolfe, C. D. A., Emmett, E., Roth, G. A., Johnson, C. O., & Wang, Y. (2020). Burden of stroke in Europe: Thirty-year projections of incidence, prevalence, deaths, and disability-adjusted life years. *Stroke*, *51*(8), 2418–2427. https://doi.org/10.1161/STROKEAHA.120.029606
Wallace, S. J., Worrall, L., Dorze, G. Le, Brandenburg, C., Foulkes, J., Rose, T. A., Wallace, S. J., Worrall, L., Dorze, G. Le, & Brandenburg, C. (2020). Many ways of measuring: A scoping review of measurement instruments for use with people with aphasia. *Aphasiology*, *0*(0), 1–66. https://doi.org/10.1080/02687038.2020.1836318
Wang, S., Wang, C. X., Zhang, N., Xiang, Y. T., Yang, Y., Shi, Y. Z., Deng, Y. M., Zhu, M. F., Liu, F., Yu, P., Ungvari, G. S., & Ng, C. H. (2018). The association between post-stroke depression, aphasia, and physical independence in stroke patients at 3-month follow-up. *Frontiers in Psychiatry*, *9*, 1–6. https://doi.org/10.3389/fpsyt.2018.00374
Watila, M. M., & Balarabe, B. (2015). Factors predicting post-stroke aphasia recovery. *Journal of the Neurological Sciences*, *352*(1–2), 12–18. https://doi.org/10.1016/j.jns.2015.03.020

Wei, N., Yong, W., Li, X., & Zhou, Y. (2014). Post-stroke depression and lesion location: A systematic review. *Journal of Neurology*, *262*(1), 81–90. https://doi.org/10.1007/s00415-014-7534-1

Whyte, E. M., Lenze, E. J., Butters, M., Skidmore, E., Koenig, K., Dew, M. A., Penrod, L., Mulsant, B. H., Pollock, B. G., Cabacungan, L., Reynolds, III, C. F., & Munin, M. C. (2008). An open-label pilot study of acetylcholinesterase inhibitors to promote functional recovery in elderly cognitively impaired stroke patients. *Cerebrovascular Diseases*, *26*(3), 317–321. https://doi.org/10.1159/000149580

Whyte, E. M., Mulsant, B. H., Vanderbilt, J., Dodge, H. H., & Ganguli, M. (2004). Depression after stroke: A prospective epidemiological study. *Journal of the American Geriatrics Society*, *52*(5), 774–778. https://doi.org/10.1111/j.1532-5415.2004.52217.x

Wijenberg, M. L., Van Heugten, C. M., Van Mierlo, M. L., Visser-Meily, J. M., & Post, M. W. (2019). Psychological factors after stroke: Are they stable over time? *Journal of Rehabilitation Medicine*, *51*(1), 18–25. https://doi.org/10.2340/16501977-2488

Wipprecht, M., & Grötzbach, H. (2013). Poststroke Depression bei Aphasie: Diagnose- und Behandlungsmöglichkeiten. *Neurologie Und Rehabilitation*, *19*(5), 310–320.

Wong, A., Lau, A. Y., Yang, J., Wang, Z., Liu, W., Lam, B. Y., Au, L., Shi, L., Wang, D., Chu, W. C., Xiong, Y. Y., Lo, E. S., Law, L. S., Leung, T. H., Lam, L. C., Chan, A. Y., Soo, Y. O., Leung, E. Y., Swong, L. K., & Mok, V. C. (2016). Neuropsychiatric symptom clusters in stroke and transient ischemic attack by cognitive status and stroke subtype: Frequency and relationships with vascular lesions, brain atrophy and amyloid. *PLoS ONE*, *11*(9), 1–12. https://doi.org/10.1371/journal.pone.0162846

Worrall, L., Ryan, B., Hudson, K., Kneebone, I., Simmons-Mackie, N., Khan, A., Hoffmann, T., Power, E., Togher, L., & Rose, M. (2016). Reducing the psychosocial impact of aphasia on mood and quality of life in people with aphasia and the impact of caregiving in family members through the Aphasia Action Success Knowledge (Aphasia ASK) program: Study protocol for a randomized controlled. *Trials*, *17*(153), 1–7. https://doi.org/10.1186/s13063-016-1257-9

Worrall, L., Sherratt, S., Rogers, P., Howe, T., Hersh, D., Ferguson, A., Davidson, B., Worrall, L., Sherratt, S., Rogers, P., Howe, T., Hersh, D., Worrall, L., Sherratt, S., Rogers, P., Howe, T., Ferguson, A., & Davidson, B. (2011). What people with aphasia want: Their goals according to the ICF. *Aphasiology*, *25*(3), 309–322. https://doi.org/10.1080/02687038.2010.508530

Yao, J., Liu, X., Liu, Q., Wang, J., Ye, N., Lu, X., Zhao, Y., Chen, H., Han, Z., Yu, M., Wang, Y., Liu, G., & Zhang, Y. (2020). Characteristics of Non-linguistic Cognitive Impairment in Post-stroke Aphasia Patients. Frontiers in Neurology, 11, 1038. https://doi.org/10.3389/fneur.2020.01038

Zanella, C., Laures-Gore, J., Dotson, V. M., & Belagaje, S. R. (2022). Incidence of post-stroke depression symptoms and potential risk factors in adults with aphasia in a comprehensive stroke center. *Topics in Stroke Rehabilitation*, *1*, 1–11. https://doi.org/10.1080/10749357.2022.2070363

Zhang, J. J., Yu, J., Bao, Y., Xie, Q., Xu, Y., Zhang, J. J., & Wang, P. (2017). Constraint-Induced Aphasia Therapy in post-stroke aphasia rehabilitation: A systematic review and meta-analysis of randomized controlled trials. *PLoS ONE*, *12*(8), 1–15. https://doi.org/10.1371/journal.pone.0183349

Zhang, P., Wang, J., Xu, Q., Song, Z., Dai, J., & Wang, J. (2018). Altered functional connectivity in post-ischemic stroke depression: A resting-state functional magnetic resonance imaging study. *European Journal of Radiology*, *100*(June 2017), 156–165. https://doi.org/10.1016/j.ejrad.2018.01.003

Zhang, S., Xu, M., Liu, Z.-J., Feng, J., & Ma, Y. (2020). Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications. *World Journal of Psychiatry*, *3206*(6), 125–138.

Zhang, Y., Zhao, H., Fang, Y., Wang, S., & Zhou, H. (2017). The association between lesion location, sex and poststroke depression: Meta-analysis. *Brain and Behavior*, *7*(10), 1–11. https://doi.org/10.1002/brb3.788

Zhou, H. X., Chen, X., Shen, Y. Q., Li, L., Chen, N. X., Zhu, Z. C., Castellanos, F. X., & Yan, C. G. (2020). Rumination and the default mode network: Meta-analysis of brain imaging studies and implications for depression. *NeuroImage*, *206*(June 2019). https://doi.org/10.1016/j.neuroimage.2019.116287

Zhu, Z., Wang, Y., Lau, W. K. W., Wei, X., Liu, Y., Huang, R., & Zhang, R. (2022). Hyperconnectivity between the posterior cingulate and middle frontal and temporal gyrus in depression: Based on functional connectivity meta-analyses. *Brain Imaging and Behavior*, *0123456789*. https://doi.org/10.1007/s11682-022-00628-7