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DIAGNOSES AND RECOVERY PATTERNS IN PATIENTS WITH APRAXIA OF SPEECH AFTER STROKE

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Diagnosis and recovery patterns in patients with apraxia of speech after stroke

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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SVENSK SAMMANFATTNING

Bakgrund: En av de vanligaste följderna efter stroke är en kommunikationsstörning. Kommunikationsstörningar innefattar vanligtvis afasi (en språkstörning) och motoriska talststörningar såsom dysartri, men även förvärvad talapraxi. Talapraxi är en neurologisk motorikstörning som drabbar planeringen och programmeringen av talet. Svårigheterna kan variera, från mindre artikulationsproblem till en total oförmåga att uttrycka sig via tal. I kliniska verksamheter saknas valida och reliabla bedömningsinstrument för talapraxi som kan användas för bedömning av talapraxi av alla svårighetsgrader. Den vanligaste orsaken till talapraxi är en stroke i vänster arteria cerebri media, en artär som försörjer områden i hjärnan som är involverade i både talmotorik, språkfunktion och handmotorik. Trots omfattande forskning är kunskapen om de neurofysiologiska mekanismerna bakom talapraxi begränsad. Få studier har undersökt talapraxi i ett tidigt skede efter stroke samt följt talapraxi longitudinellt, och det saknas information om vad som kan förutsäga förloppet. Effekterna av fokala hjärnskador vid talapraxi har studerats relativt rikligt, men däremot är kunskapen om hur en skada i ett område kan påverka andra områden i hjärnans språk- och talmotoriska nätverk begränsad. Trots ett nära samband mellan talmotorik, språkliga funktioner och handmotorik har endast ett fåtal studier undersökt återhämtningsförloppet efter en stroke inom dessa tre domäner tillsammans.

Syfte: Det övergripande målet för denna avhandling var att öka kunskapen om diagnostiken och återhämtningsförloppet hos personer med talapraxi i ett tidigt skede efter stroke. De specifika målen med delstudierna var:

Studie I: Att undersöka intra- och interbedömarreliabiliteten hos Apraxia of Speech Rating Scale (ASRS) vid bedömning av personer med talapraxi i ett tidigt skede efter stroke. ASRS är ursprungligen framtagen för forskningsändamål, och dess reliabilitet när skattningarna utförs av kliniskt aktiva logopeder har inte studerats. Ett ytterligare syfte var att undersöka hur väl ASRS kunde fånga upp svårigheter hos personer med grava tal- och språkstörningar.

Studie II: Att beskriva och utvärdera preliminära mått på reliabilitet och validitet hos ett kliniskt bedömningsprotokoll för talapraxi. Testet ska vara kliniskt tillämpbart, inklusive ha adekvat bedömarreliabilitet och kunna användas för att bedöma talapraxi av alla svårighetsgrader.

Studie III: Att undersöka förekomsten av talapraxi och afasi hos personer med nedsatt handfunktion i ett subakut skede efter stroke, och att jämföra återhämtning vid sex månader mellan talmotoriska, språkliga och handmotoriska domäner. Ett ytterligare syfte var att undersöka faktorer som kan förutsäga återhämtning av talapraxi.

Studie IV: Att undersöka longitudinella förändringar av funktionell konnektivitet i hjärnans nätverk för språk och talmotorik hos individer med talapraxi efter stroke, från den subakuta fasen till den kroniska fasen, i syfte att identifiera prediktorer av återhämtning av talapraxi. Ytterligare syften var att studera sambandet mellan funktionell konnektivitet och svårighetsgrad av talapraxi, samt att jämföra funktionell konnektivitet i talmotoriska nätverk hos personer med talapraxi efter en stroke i vänster hjärnhalva mot den hos personer med en vänstersidig skada efter en stroke, men som inte har en tal- och språkstörning.

Metoder: För att undersöka intra- och interbedömarreliabiliteten hos ASRS i **studie I** deltog fem legitimerade logopeder från olika kliniker som bedömare. Alla arbetade med neurogena kommunikationsstörningar hos vuxna. Skattningarna på ASRS baserades på videoinspelningar av tio deltagare som alla var i ett tidigt skede efter stroke och som visade lindriga till svåra symtom på talapraxi. För att undersöka intrabedömarreliabilitet genomfördes en ny skattning efter minst tre veckor. Det kliniska bedömningsprotokollet i **studie II** bestod av tio uppgifter, varav fem var operationaliserade uppgifter baserade på kvantifierbara mått och de övriga fem var perceptuella skattningar av karakteristika förknippade med talapraxi. Interbedömarreliabiliteten för bedömningsprotokollet analyserades utifrån videoinspelningar av fem individer som visade olika grader av symtom förknippade med talapraxi. Bedömare var elva legitimerade logopeder som alla arbetade med neurogena kommunikationsstörningar hos vuxna. Som mått på validitet jämfördes den totala poängen på bedömningsprotokollet från 39 studiedeltagare i en subakut fas efter stroke med logopedernas kliniska beslut om patienterna hade talapraxi. I **studie III** undersöktes förekomsten av talapraxi och afasi hos personer med nedsatt handmotorik i en subakut fas efter stroke i en grupp om 70 deltagare. Hälften av dessa hade en skada i vänster hjärnhalva, och övriga en skada i höger hjärnhalva. Återhämtning av talapraxi, afasi och nedsatt handmotorik vid sex månader undersöktes hos 15 av dessa deltagare som hade en skada i vänster hjärnhalva. För undersökning av funktionell konnektivitet i **studie IV** användes resting state funktionell magnetresonanstomografi. Tal och språkfunktion samt funktionell konnektivitet i hjärnans nätverk för språk och talmotorik undersöktes hos nio deltagare med talapraxi och afasi efter stroke i vänster hjärnhalva, samt jämfördes med data från sex deltagare med en vänstersidig skada som inte hade talapraxi eller afasi. Mätningar gjordes fyra veckor efter insjuknande samt vid sex månader. Funktionell konnektivitet undersöktes i ett nätverk av områden för talproduktion: gyrus frontalis inferior (eng. inferior frontal gyrus, (IFG)), anteriora insula (aINS) och ventrala premotoriska cortex (vPMC), alla bilateralt för att studera förändringar i båda hjärnhalvorna.

Resultat: I **studie I** var intrabedömarreliabiliteten för totalpoängen för ASRS i genomsnitt måttlig. Interbedömarreliabiliteten för totalpoängen på ASRS var låg. Resultaten för de olika uppgifterna på ASRS varierade mellan måttlig och låg, med fler resultat i den lägre kategorien. Hög oenighet sågs särskilt vid bedömningar av deltagare med svår talapraxi, men varierande överensstämmelse sågs även för deltagare med lindrigare nedsättningar. Då vissa av uppgifterna på ASRS kräver en talproduktion med flerstaviga ord och fraser för att kunna skattas säkert utifrån de formulerade skalstegen sågs begränsningar av ASRS vid bedömning av deltagare med svåra tal- och språkstörningar. I **studie II** var interbedömarreliabiliteten för det kliniska bedömningsprotokollets totalpoäng god, medan resultaten på uppgiftsnivå varierade. Högst reliabilitet noterades för uppgifter baserade på operationaliserade mått, medan de flesta av uppgifterna med perceptuella skattningar visade måttlig överensstämmelse. Indikationer på hög validitet sågs då totalpoängen på bedömnings-protokollet jämfördes mot den kliniska bedömningen. I **studie III** hade 57 % av deltagarna med en skada i vänster hjärnhalva talapraxi, medan 71 % hade afasi. Alla deltagare med talapraxi hade också afasi. Ingen av studiedeltagarna med en skada i höger hjärnhalva hade talapraxi eller afasi. Parallella återhämtningsmönster av talapraxi, afasi och nedsatt handmotorik noterades, vilket även gällde personer med grava nedsättningar. Den starkaste prediktorn av återhämtning av talapraxi vid sex månader var resultatet på afasitestet i det subakuta skedet. I **studie IV** korrelerade återhämtningen av talapraxi vid sex månader med den interhemisfäriska funktionella konnektiviteten mellan vänster och höger IFG i den subakuta fasen. Deltagare med talapraxi hade en signifikant svagare funktionell konnektivitet mellan bilaterala vPMC jämfört med deltagare utan talapraxi och afasi efter en skada i vänster hjärnhalva. Nedsättningsgraden av talapraxi vid sex månader var relaterad till styrkan av funktionell konnektivitet mellan bilaterala aINS.

Slutsats: Resultaten i de två första studierna stödjer tidigare forskning som påtalat brister vid diagnostisering av talapraxi som endast baseras på perceptuella skattningar. Behovet av att använda objektiva mått för att diagnostisera talapraxi noterades. Vissa av diagnoskriterierna för talapraxi går inte att säkert identifiera hos personer med svår talapraxi, vilket gör det svårt att följa talapraxi longitudinellt utifrån samma diagnostiska kriterier och samma bedömningsinstrument. Ett behov av att bättre identifiera och beskriva personer med svår talapraxi konstaterades. I **studie III** sågs en hög samförekomst av afasi och talapraxi hos personer med nedsatt handmotorik efter stroke. Parallella återhämtningskurvor för talapraxi, afasi och nedsatt handmotorik vid sex månader sågs, med tecken på gemensamma bakomliggande plastiska mekanismer bakom förloppet. Grad av afasi i den subakuta fasen kan vara en viktig prediktor för grad av återhämtning av talapraxi vid sex månader. Resultaten i **studie IV** visade att grad av funktionell konnektivitet mellan vänster och höger IFG i det subakuta skedet kunde förutsäga grad av återhämning av talapraxi vid sex månader, och att en ökad aktivering av det språkliga och talmotoriska nätverket i höger hjärnhalva var gynnsamt för återhämtning av talapraxi. Den nedsatta funktionella konnektiviteten mellan vänster och höger vPMC hos deltagarna med talapraxi är i linje med tidigare studier, och bekräftar rådande teorier angående en central roll för vPMC vid programmering av talmotoriska rörelser.

ABSTRACT

Background: Stroke is a leading cause of adult disability. One of its most common consequences is a communication disorder. Beside aphasia (a language disorder), a motor speech disorder may occur, manifested as dysarthria or apraxia of speech (AOS). AOS has been defined as a motor speech disorder that affects an individual's ability to transform a linguistic message into speech motor plans. The most common symptoms associated with AOS include slow rate of speech, impaired articulation with sound errors that are predominately distortions, and disturbed prosody. The effects of AOS vary, from subtle articulation deviations to a complete inability to communicate through speech. AOS is most frequently caused by infarcts in the left middle cerebral artery, which supplies areas involved in both speech, language, and hand motor function. Despite a large amount of research, our knowledge of the exact nature and neurophysiological mechanisms of AOS is limited. Few studies have investigated AOS in an early phase after stroke as well as its resolution longitudinally, and factors predicting recovery are largely unknown. While the effects of focal brain lesions induced by stroke have been frequently studied, less is known about alterations in network connectivity in patients with AOS. Despite a close relationship between speech motor, language, and hand motor function, only few studies have addressed the relation between recovery in these multiple behavioral domains. In clinical settings, there is a lack of valid and reliable assessment instruments for AOS diagnosis that are applicable at all severity levels.

Aim: The overall aim of this thesis was to gain more knowledge on the diagnosis and recovery patterns of AOS in individuals in an early phase after stroke. The specific aims for the four studies were:

Study I: To study the intra- and interrater reliability of the Apraxia of Speech Rating Scale (ASRS) in assessment of individuals with speech and language impairments in an early phase after stroke. The ASRS was developed for research purposes, and its reliability for clinically active SLPs is unknown. An additional aim was to investigate the applicability of the ASRS in assessment of individuals with severe speech and language impairments.

Study II: To describe and evaluate preliminary measures of reliability and validity of a clinical assessment protocol for AOS diagnosis, developed as part of a clinical study with the aims to be applicable in clinical settings and to be valid in the assessment of individuals with speech and language impairments at all severity levels.

Study III: To investigate the prevalence of AOS and aphasia in individuals with a hand motor impairment in a subacute phase after stroke, and to compare recovery at six months in speech, language, and hand motor domains. An additional aim was to explore factors predicting recovery from AOS.

Study IV: To investigate longitudinal changes in functional connectivity (FC) in speech-language networks in individuals with AOS after stroke, from the subacute to the chronic phase, specifically to identify predictors of AOS recovery. Additional aims were to study the

relation between FC and degree of severity in AOS and to compare FC strength in patients with AOS after a left hemisphere stroke to that in left hemisphere lesioned stroke patients without speech-language impairment.

Methods: For intra- and interrater reliability of the ASRS in **study I**, five certified speech-language pathologists (SLPs) from different hospital departments participated as raters. All worked with neurogenic communication disorders in adults. The ratings were based on video recordings of ten participants in an early phase after stroke showing varying degrees of AOS symptoms, from mild to severe. For measures of intrarater reliability, a rescoring was carried out after a minimum of three weeks. The clinical assessment protocol in **study II** included ten items, five of which were based on operationalized measures and five were perceptual ratings of AOS characteristics. Interrater reliability for the assessment protocol was based on video recordings of five individuals with varying degrees of AOS symptoms being assessed with the assessment protocol. Eleven certified SLPs participated as raters, all of whom worked with neurogenic communication disorders in adults. For measures of validity, the total scores of the assessment protocol from 39 participants in a subacute phase after stroke were compared against the clinical judgement of an AOS diagnosis. In **study III,** the prevalence of AOS and aphasia in individuals with a hand motor impairment in a subacute phase after stroke was investigated in a group of 70 participants. Half of the group had a left hemispheric lesion and the other half a right hemispheric lesion. Recovery of AOS, aphasia, and hand motor impairment at six months was investigated in 15 of these participants with a left hemispheric lesion. For measures of functional connectivity in **study IV**, resting state functional magnetic resonance imaging was applied. Assessments of speech and language impairment and FC in speech-language networks were obtained in nine participants with AOS and concomitant aphasia after a left hemispheric stroke and compared to six left hemispheric lesioned stroke participants without speech-language impairment. Measurements were performed at four weeks and six months after stroke. Functional connectivity was investigated in a network of key regions for speech production: inferior frontal gyrus (IFG), anterior insula (aINS) and ventral premotor cortex (vPMC), all bilaterally to investigate signs of adaptive or maladaptive changes in both hemispheres.

Results: In **study I**, the intrarater reliability for the ASRS total score was moderate on average. The interrater reliability for the total score was poor. The item level values varied between moderate and poor, with lack of agreement on several items. High disagreement was especially noted in ratings of participants with severe speech-language impairments, but varying agreement were also found for participants with milder impairments. In addition, because some of the items on the ASRS require speech output consisting of multisyllabic words and phrases to target the diagnostic marker, limitations when assessing participants with signs of severe AOS with the ASRS were noted. In **study II,** the interrater reliability for the clinical AOS assessment protocol total score was good, but varied at an item level. The highest reliability was found for items with operationalized measures, while most items with perceptual ratings showed moderate agreement. A high index of validity was found when comparing the total score against the clinical judgement of an AOS diagnosis. In **study III,**

57% of the participants with a left hemispheric lesion had AOS, while 71% had aphasia. All participants with AOS also had aphasia. Recovery in AOS, aphasia and hand motor impairment at six months correlated positively across speech, language and hand motor domains. The strongest predictor for AOS recovery at six months was the initial aphasia test score. In **study IV**, recovery of AOS at six months correlated positively with the interhemispheric FC between left and right IFG in the subacute phase. Participants with AOS had a significantly reduced FC between bilateral vPMC in comparison to participants with a left hemispheric lesion without a language impairment, while severity of AOS at six months was related to the FC between bilateral aINS.

Conclusion: The results of the two first studies add to the growing body of research that highlights the limitations of diagnosis of AOS solely based on perceptual characteristics, and call for the need to include objective measures in the diagnosis. In addition, if the same set of diagnostic AOS criteria cannot be applied during the course of the disease, it makes it difficult to study its longitudinal course and to identify predictors of recovery. In **study III**, a high prevalence of AOS with concomitant aphasia was noted in participants with a left hemisphere lesion and a hand motor impairment. Recovery of AOS, aphasia and hand motor followed a parallel trajectory, indicating that shared plasticity mechanisms are driving the recovery. For predictors of AOS recovery, indications that measures of aphasia at the subacute phase may be an important predictor was noticed. **In study IV**, the degree of AOS recovery at six months was strongly associated with the interhemispheric IFG connectivity strength at the subacute phase, indicating that increased activation in homologous speech-language areas in the right hemisphere in the subacute phase is positive for the recovery of AOS at six months. The reduced FC between the interhemispheric vPMC in participants with AOS is in line with earlier findings and confirms the current opinion about the left vPMC as a key region for speech motor programming.

LIST OF SCIENTIFIC PAPERS

I. **Hybbinette, H**., Östberg, P., & Schalling, E. (2021). Intra-and interjudge reliability of the Apraxia of Speech Rating Scale in early stroke patients. *Journal of Communication Disorders*, *89*, 106076.

II. **Hybbinette, H**., Schalling, E., & Östberg, P. Assessing apraxia of speech in patients early after stroke: description of an initial version of a clinical assessment protocol and preliminary findings. Manuscript

III. **Hybbinette, H**., Schalling, E., Plantin, J., Nygren-Deboussard, C., Schütz, M., Östberg, P., & Lindberg, P. G. (2021). Recovery of apraxia of speech and aphasia in patients with hand motor impairment after stroke. *Frontiers in Neurology*, *12*, 398

IV. **Hybbinette, H**., Östberg, P., Schalling, E., Nygren-Deboussard, C., Plantin, J., Borg, J., & Lindberg, P. Longitudinal changes in functional connectivity in speech motor networks in patients with apraxia of speech after stroke. Manuscript.

INNEHÅLL

LIST OF ABBREVIATIONS

aINS	Anterior Insula
A-ning	Neurolinguistic Aphasia Examination
ASRS	The Apraxia of Speech Rating Scale
BNT	Boston Naming Test
DIVA	Directions Into Velocities of Articulators
FC	Functional connectivity
FMA-UE	The Fugl-Meyer Assessment for the Upper Extremity
GODIVA	Gradient Order Directions Into Velocities of Articulators
ICC	Intraclass correlation coefficient
ICF	International Classification of Functioning, Disability and Health
IFG	Inferior frontal gyrus
MRI	Magnetic resonance imaging
ROI	Region of interest
rs- fMRI	Resting state magnetic resonance imaging
SLP	Speech language pathologist
TAX	Clinical assessment protocol for apraxia of speech
vPMC	Ventral premotor cortex

1 INTRODUCTION

For most of us, talking is a fast and seemingly uncomplicated activity. Yet, communicating through speech is one of the most complex processes performed by humans. A stroke may harm the ability to communicate in several different ways. When the programming of speech motor movements is impaired, it is defined as apraxia of speech (AOS). There are many challenges associated with the AOS diagnosis. This applies especially to individuals with severe AOS in an early phase after a stroke. The aim of this thesis project is to address some of these questions.

1.1 COMMUNICATION DISORDERS AFTER STROKE

Globally, stroke is a leading cause of adult disability and the third most common cause of death (Global Burden of Disease Stroke Collaborators, 2021).In Sweden 2020, approximately 25 400 individuals had a stroke (Socialstyrelsen i Sverige, 2022). For approximately 65% of these individuals, the stroke led to a communication disorder, which is in line with findings by Michell et al. (2020). Neurogenic communication disorders is an umbrella term used to describe different speech and language disabilities caused by disease or damage to the central and/or peripheral nervous system. In the American Psychological Association (APA) dictionary, neurogenic communication disorders are defined as “any speech or language problem due to nervous system impairment that causes some difficulty or inability in exchanging information with others.” Neurogenic communication disorders after stroke generally include aphasia, dysarthria and cognitive-communication disorders (CCD). Aphasia has been defined as a multimodal impairment of the capacity for interpretation and formulation of language symbols, due to brain damage and disproportionate to impairment of other intellectual functions (Darley, 1982). Aphasia may cause impairments across spoken, written and auditory modalities, such as difficulty in naming or producing correct and complex syntax, difficulty in reading a text or writing single words (Papathanasiou et al., 2016). Dysarthria has been defined as disturbances in muscular control of the speech mechanism due to damage of the central or peripheral nervous systems (Darley, 1996). Dysarthria includes a group of motor speech disorders that can be characterized by "abnormalities in the strength, speed, range, steadiness, tone, or accuracy of movements required for breathing, phonatory, resonatory, articulatory, or prosodic aspects of speech production" (Duffy, 2020, p. 3). The term cognitive-communication disorders (CCD) was first used to describe communication impairments following a traumatic brain injury, but is also associated with dementia (Bayles et al., 2018) and with impairments following predominantly a right hemisphere stroke (Blake, 2016; Hewetson et al., 2017). Cognitive-communication impairments can result in difficulties in conversational interaction and social communication, with problems when reading, writing, and understanding a context. The impairments occur because of deficits in cognition, such as attention, orientation, memory, executive functions, and self-regulation (Benton & Bryan, 1996; Côté et al., 2007). In addition to these three disorders, neurogenic communication disorders after stroke also include apraxia of speech. In the following section, the theoretical framework and research field of apraxia of speech will be described.

1.2 APRAXIA OF SPEECH

1.2.1 Definition and theoretical foundation

One the most frequently applied definitions of apraxia of speech (AOS) states that "AOS is a neurologic speech disorder that reflects an impaired capacity to plan or program sensorimotor commands necessary for directing movements that result in phonetically and prosodically normal speech" (Duffy, 2020, p.4). Unlike in dysarthria, AOS may exist without any impairments in the muscular execution of speech movements (i.e., respiration, articulation, phonation, resonance, and prosody). AOS may also occur without any impairment involving the structure of the linguistic message, as in aphasia (Cherney & Small, 2009). The severity may vary, from minor articulation problems and slightly deviating prosody to a complete inability to communicate through speech (Duffy, 2020 p. 67). In a psycholinguistic framework, it is postulated that an individual with AOS can complete the linguistic processing for speech production, including the lexical retrieval and phonological encoding, but fails to transform the retrieved phonological representation into articulatory specification and planning/programming of speech motor movements (Croot et al., 2012). Although AOS may appear as an isolated communication disorder, it is most often accompanied by aphasia and/or dysarthria (Duffy, 2020).

A distinct clinical entity that equals impaired speech planning and/or programming in the presence of preserved language skills and unimpaired muscular function was first proposed by Broca in 1861. Broca used the term aphemia to describe this disorder, claiming that patients with aphemia had lost "the memory of the procedures for the production of words." In Broca's opinion, the ability to articulate spoken language was based on procedural knowledge of how each word of a language is generated by adequate movements of the speech organs. Aphemia resulted from a corruption of this knowledge after lesions to left posterior inferior frontal cortex (Broca, 1861, 1865; as cited in Ziegler, 2008). Several alternative theories and explanation models of speech production and language were later proposed, as for example by Marie (1906) and Dejerine (1914), as cited in Ogar et al. (2005). Duffy (2020, p. 261) notes that since 1861, over twenty different terms have been suggested as an alternative to Broca's original term aphemia, as for example cortical dysarthria, expressive aphasia, and afferent motor aphasia.

Current research on AOS is rooted in the heritage of the American speech and language pathologist Frederic L. Darley (1918-1999). His introduction in 1968 of the disorder as an "apraxia of speech" was guided by phenomenological similarities between the speech disorder and limb apraxia, such as its error inconsistency, or the groping/searching behavior of apraxic patients who are confronted with a (speech or motor) task they had trouble to perform (Darley, 1968; as cited in Ziegler, 2008). The concept of apraxia had earlier been introduced in 1871 by the German linguist Heymann Steinthal, who was the first to use the term apraxia to describe a disturbance in skilled limb movements following brain damage. Since Darley's original definition of the diagnosis, several researchers have questioned the accuracy of his theoretical definition and clinical description of AOS. The debate over the AOS diagnosis persisted for a long time (and to some extent still exists), often regarding questions if AOS is truly a specific disorder and about its diagnostic demarcations towards aphasia and dysarthria (Knollman-Porter, 2008; Strand, 2001). Although a total consensus on theoretical definition and diagnostic criteria has not yet been reached, there is today general agreement that AOS is indeed a separate disorder that is theoretically and clinically separable from both aphasia and dysarthria (McNeil et al., 2016).

1.2.2 Etiology and prevalence

A stroke in the language-dominant hemisphere is the most common cause of AOS, often by infarcts involving territories supplied by the precentral (pre-Rolandic) artery or superior division of the left middle cerebral artery (Mohr et al., 1978; Hillis et al., 2004; Trupe et al., 2013; for a comprehensive review of middle cerebral artery territory syndromes, see Mohr and Kejda-Scharler, 2012). Less frequent etiologies are traumatic brain injury, tumors, and neurosurgery. In contrast to certain dysarthria subtypes, AOS is not common in toxic-metabolic and infectious disorders (Duffy, 2020; Duffy & Josephs, 2012). AOS can also be caused by a degenerative process, often together with the neurodegenerative syndrome of primary progressive aphasia (PPA), but sometimes in the absence of other neurological impairments. When progressive AOS is the only or the primary neurological deficit, it is referred to as primary progressive apraxia of speech (PPAOS) (Josephs et al., 2012). Pathologically, PPAOS is most often associated with tauopathies such as progressive supranuclear palsy or corticobasal degeneration (Josephs et al., 2021). Unlike in AOS after a stroke or an acquired brain injury, AOS in degenerative diseases has a subtle onset and progresses over time, sometimes culminating in mutism (Josephs et al., 2012).

Reliable data on the prevalence of AOS is missing. The absence of information relates to challenges in differential diagnosis between aphasia and AOS and a lack of reliable and valid assessment instruments for AOS diagnosis (Basilakos, 2018; Strand et al., 2014). Duffy (2020, p. 258) reported that in the Mayo Clinic Speech Pathology practice, 4.7% of the patients with motor speech disorders were documented as having AOS as the primary communication disorder. This percentage would be considerably higher if co-occurring AOS was included in the data (Duffy, 2020, p. 258). It is acknowledged that individuals with aphasia, most often Broca's or nonfluent aphasia, often may have AOS as well (Duffy, p. 261), but closer information regarding its comorbidity is missing. Because a stroke in the territory supplied by the middle cerebral artery often affects a range of areas involved in both motor and language functions, many patients with aphasia and AOS also have right-sided motor impairments. According to Duffy (2020, p. 356), the association between AOS and a right-sided motor impairment might even be stronger than the association between aphasia and right-sided motor impairments.

1.2.3 Studies of AOS in an early phase after stroke

Most studies of AOS concern individuals in the chronic phase after a stroke, and very few have investigated AOS in subacute stroke patients (Basilakos, 2018; Duffy, 2020). In a recent review, Baker et al. (2021) reported that out of a sample of 129 articles that included patients with a communication disorder in the first 90 days after stroke, aphasia was by far the most frequently addressed communication disability. Only two studies concerned patients with AOS. The authors speculated that the high comorbidity and unclear diagnostic criteria for AOS may contribute to this low number. The lack of studies that concern patients with AOS in a subacute phase after stroke hinders information on its incidence and prevalence. The insufficient information also limits the understanding of long-term recovery and prognosis for patients with AOS (Baker et al., 2021; Haley et al., 2016).

1.2.4 Characteristics and diagnosis of AOS

Since the presumed speech motor programming impairment in AOS cannot be investigated neurophysiologically, the AOS diagnosis must instead be based on characteristics that can be observed to draw inferences about underlying functional pathology (Haley et al., 2021). The clinical descriptions of AOS have to some extent changed over the years, moving from being considered a pure articulatory disorder to an articulatory disorder with secondary prosodic compensations (Darley et al., 1975), to the current opinion that both articulatory and prosodic impairments are primary characteristics of AOS (McNeil et al., 2016). The characteristics that most often are proposed as primary criteria for an AOS diagnosis are: (1) slow speech rate with segment and pause prolongation; (2) the presence of distortions and distorted substitutions, and (3) abnormal prosody with syllable and word segmentation that leads to the perception of an impaired stress assignment (Ballard et al., 2015; Duffy, 2020; Haley et al., 2012). Other characteristics that have been proposed to be included in the diagnostic criteria are articulatory groping and speech initiation difficulties (Wertz et al., 1984) and articulatory speech errors that tend to increase with increasing word length and/or articulatory complexity (Strand et al., 2014). Individuals with AOS are also presumed to be aware of their own speech errors (Wertz et al., 1984). Because several of the suggested speech behaviors are not perceptually discriminative between AOS, aphasia, and dysarthria, the relationship between observed characteristics and underlying speech-language pathology needs careful consideration (Basilakos, 2018; Strand et al., 2014). McNeil et al. (2016, p. 201) emphasized that “[i]t is the specific perceptually derived *cluster* of behaviors that is claimed to differentiate AOS from its clinical neighbors.” There is however no absolute consensus about which symptoms that must be present for an AOS diagnosis (Allison et al., 2020; Croot, 2002). Molloy and Jagoe (2019) used a scoping review methodology which included both a review of 157 published studies and an online survey with 190 international speech-language pathologist (SLP) respondents. They found that different sets of diagnostic criteria for AOS were applied, both between research groups and in clinical settings. The selection was not influenced by the geographical location, but differed between those that are commonly used in research and those that clinically active SLPs consider most indicative of AOS (Molloy & Jagoe, 2019).

1.2.4.1 Severe AOS

Individuals with severe AOS often have a very restricted speech output. Their speech production can be limited to a few short utterances with varying intelligibility. In some individuals, the ability to imitate and produce isolated speech sounds may be in error and even difficulties to phonate may occur. Some of the characteristics that an AOS diagnosis traditionally are based upon may therefore be hard to identify and measure. In addition, severe AOS is often accompanied by severe aphasia which further complicates the assessment (Duffy, 2020; Hickok et al., 2014). Individuals with AOS often demonstrate impaired movement of the articulators during nonspeech tasks (Ballard et al., 2010). Nonverbal oral apraxia (NVOA) is diagnosed when an individual has an impaired capacity to use intact sensory motor systems for voluntary oral movements, such as blowing, coughing, or smacking the lips, on command or by imitation (Whiteside et al., 2015). According to Duffy (2020), severe AOS is nearly always accompanied with NVOA, a view supported by recent findings in acute stroke patients (Conterno et al., 2021). The frequent association indicates that the mechanisms for oromotor and speech motor control to some degree depend upon shared substrates (Ballard et al., 2003). In the study by Conterno et al. (2021), concomitant AOS and NVOA was predominantly related to injuries in the insula region.

1.2.5 Assessment procedure

The diagnostic procedure for AOS is not well established (Haley et al., 2012). For many decades, the only formal assessment instrument was the Apraxia Battery for Adults (ABA) (Dabul, 1979) and its later version, The ABA-2 (Dabul, 2000). However, differential diagnosis between AOS and aphasia using the ABA-2 has been questioned as it incorrectly includes phonemic paraphasias as an apraxic symptom, which limits its use in research and clinical settings (Basilakos et al., 2017; Mumby et al., 2007). In the absence of standardized assessment instruments, the AOS diagnosis is most often based upon perceptual observations of a collection of proposed AOS characteristics (Haley et al., 2012). This unstandardized approach entails several problems, both in research and in a clinical context. The lack of shared diagnostic standards impedes synthesis of information between different research groups. Above all, it entails major limitations to clinical communication and hinders that reliable information can follow an individual with AOS through the course of the disease (Allison et al., 2020; Haley et al., 2012; Wambaugh et al., 2006).

1.2.5.1 The Apraxia of Speech Rating Scale

The Apraxia of Speech Rating Scale (ASRS) presented by Strand et al. (2014) was originally created as a research instrument, to aid quantification and description of AOS characteristics in individuals with neurodegenerative (progressive) aphasia and progressive AOS. Its potential for differential diagnosis and as a clinical assessment instrument was also recognized, and indices of high validity were reported. High to excellent intra- and interrater reliability was found with ratings made by the creators of the scale. The ASRS has been used in several studies of progressive AOS (e.g., Botha et al., 2018; Josephs et al., 2021) and later versions of the scale have also been used in studies of AOS after stroke (e.g., Bislick, 2020; Haley et al., 2019). Wambaugh et al. (2019) reported high interrater reliability for the total score of the ASRS 3.0 in assessment of individuals with AOS in the chronic stage after stroke. The raters in this study were two expert researchers with long mutual experience in the field of AOS. However, because its reliability and validity might depend on perceptual training and calibration among experienced researchers, the applicability of the ASRS in clinical settings was still questioned (Wambaugh et al., 2019).

1.3 SPEECH PRODUCTION

1.3.1 Theoretical models of speech production

A considerable amount of research in psycholinguistics and neurolinguistics has focused on the processes involved in speech production. A common method has been to delineate a multistage process by which a conceptualization of an idea and generation of a communicative goal ultimately is transformed into a spoken word or a sentence (Bohland et al., 2010). In the majority of psycholinguistic and neurocomputational speech production models, as for example the Directions Into Velocities of Articulators (DIVA) model (Guenther et al., 2006) and its extended version, the Gradient Order DIVA (GODIVA) model (Bohland et al., 2010), the different stages in the process are considered to be functionally distinct with both feedforward and feedback mechanisms at each stage of processing. According to these models, AOS can be the consequence of weak feedforward commands and an overreliance on feedback (Bohland et al., 2010). Based on theories from the dual-stream model of visual processing (Milner & Goodale, 2006), Hickok (2012) presented an analog model of language organization. The dual-route model claims that a ventral stream is involved in processing speech signals for comprehension, while a dorsal stream is involved in transforming acoustic signals into speech production. In contrast to the common opinion that language processing is mainly left-hemisphere dependent, the dual-route model proposes that the ventral stream is more bilaterally organized, while the dorsal stream is described as strongly left-hemisphere dominant (Hickok, 2012). Speech motor programming has long been acknowledged as a critical stage in the speech production process, enabling the transformation of abstract linguistic codes into highly specified motor commands that can be executed by the motor system (Miller & Guenther, 2020). With the increasing integration of theories of language production and speech motor control, neurocomputational modeling and neuroimaging methods, AOS has been proposed as a theoretically important condition in studies of how the interaction between language and speech motor production can be disrupted (Ziegler et al., 2012).

1.4 NEUROANATOMICAL SUBSTRATES OF APRAXIA OF SPEECH

Speech and language impairments after a stroke have classically been attributed to focal brain damage (Benson & Ardila, 1996; Kertesz, 1979). Several different brain regions, mainly in the left frontal lobe, have been proposed to play an important role in motor speech programming and AOS, as for example the inferior frontal gyrus (Broca's area) (Hillis et al., 2004; Richardson et al., 2012), the anterior insula (Dronkers, 1996; Ogar et al., 2006) and premotor cortex and supplementary motor areas (Graff-Radford et al., 2014; Botha et al., 2018; Hartwigsen et al., 2013). AOS has also been reported after lesions of the basal ganglia (Peach & Tonkovich, 2004) and cerebellum (Mariën et al., 2014). While fundamental understanding is provided by these findings, there is an increased focus on the functional contributions of the respective brain areas, and how the interaction within a network of regions can be impacted by a lesion. Nowadays, there is wide agreement that the pathogenesis of AOS is associated with disturbance in a network of regions, with all the above-mentioned structures included that are supported by other cortical and subcortical regions and pathways (McNeil et al., 2016). While structural connectivity refers to the anatomical organization of white matter fiber tracts, functional connectivity is defined as the temporal coincidence of spatially distant neurophysiological events (Eickhoff & Grefkes, 2011; Friston, 1994).

1.5 RESTING STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING

To study functional connectivity (FC), the use of resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as a powerful method. Functional magnetic resonance imaging (fMRI) is based on the close link between neuronal activity and blood flow and uses the variability of the Blood Oxygen Level Dependent (BOLD) signal as a sensitive measure of cortical activity (Fox & Raichle, 2007). Biswal et al. (1995) showed that during rest, the left and right hemispheric regions of the primary motor network showed a high correlation between their fMRI BOLD time-series, suggesting ongoing information processing between anatomically separated brain regions. This relationship is believed to reflect networks that typically are engaged in shared function (Damoiseaux et al., 2006). The fMRI time series are obtained in the absence of a stimulus and do not require any specific activity from the individual in the scanner. This technique is therefore considered particularly suitable for individuals who may have difficulty to perform a certain task, as for example individuals with speech-language impairments (Eickhoff & Grefkes, 2011). There are several methods to analyze rs-fMRI data. In a seed-based analysis, cross-correlation is computed between different regions of interest (ROI). This analysis method requires *a priori* selection of ROIs, with different brain regions considered to be of specific importance for the studied function or phenomenon included in the model (van den Heuvel & Hulshoff Pol, 2010). In contrast, whole brain analysis does not require an a priori hypothesis regarding regions but has the disadvantage of requiring stringent multiple comparison procedures (since 1000s of voxels are included in the brain). This can sometimes make whole brain analysis procedures less sensitive for detection of pathological patterns of functional connectivity (Smitha et al., 2017).

1.5.1 Functional connectivity in speech and language networks

The speech and language network in healthy subjects has been investigated by FC methods in several studies (e.g., Cordes et al., 2000; Klingbeil et al., 2019; Tomasi & Volkow, 2012), revealing an extended and highly interconnected network including temporal, parietal, and prefrontal as well as subcortical regions. A rich amount of research has also explored the feasibility of extracting language network from rs-fMRI in preoperative mapping, reporting overall promising results using the method for this purpose (e.g., Sair et al., 2017; Tie et al., 2014). An increasing number of studies have applied rs-fMRI to investigate FC in patients with aphasia after stroke. Sharp et al. (2010) found a correlation between an increased frontoparietal integration and language recovery after stroke. Zhu et al. (2014) reported that disrupted FC after stroke was significantly associated with the degree of language impairment and that aphasia therapy affected the FC between language related areas. An increased FC, predominantly within the left hemisphere, was observed in after language treatment in individuals with aphasia in a chronic phase (van Hees et al., 2014). Siegel et al. (2018) studied a large cohort of 132 patients in the first two weeks after stroke onset, 33 of which had aphasia. A major finding in this study was that both lesion location and the interhemispheric FC could explain a significant variance in severity of aphasia, suggesting that the involvement of homotopic right hemisphere language areas in the subacute phase may contribute to aphasia recovery.

Currently, only one published study has specifically investigated network connectivity in patients with AOS after stroke. New et al. (2015) included 32 chronic aphasia patients, 15 of which had concomitant AOS, and 18 healthy age-matched controls. The main finding in this study was a reduced FC between bilateral premotor cortex in individuals with AOS that also related to AOS severity (New et al., 2015). Functional network connectivity methods have also been applied in studies of individuals with PPAOS. Botha et al. (2018) used a hybrid method based on nine predefined networks that included areas associated with AOS. A reduced FC between the right supplementary motor area and left posterior temporal lobe was found that correlated with measures of articulation impairments. Although it is still not fully understood how observed FC measures in speech and language networks are associated with behavioral deficits and recovery, there is increasing support for rs-fMRI as a valuable method in studies of underlying neural mechanisms, indicating that FC analyses are vital for the understanding of how neural networks are affected in AOS (Basilakos, 2018; Duncan & Small, 2018).

1.6 BRAIN PLASTICITY AND POST STROKE RECOVERY

Brain plasticity has been defined as "the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections" (Mateos-Aparicio & Rodriguez-Moreno, 2019, p.1). These changes are highly involved in learning, adaption to new environments and in the mechanism of aging (Alia et al., 2017). Brain plasticity mechanisms are also considered to be the basis for adaptive changes in response to brain damage (Nudo, 2006). Neural plasticity after an acquired brain injury has been described in a sequence of phases: the acute phase, the subacute phase, and a chronic phase (Cramer, 2008). The duration of these phases may vary, depending on pathological severity and conditions, such as lesion size and location, age and comorbidity (Zao et al., 2018). In the acute phase, a series of events associated with disruption of neurophysiological and metabolic processes occur, with changes in blood flow (perfusion) that may result in hypoperfusion in perilesional regions. The subacute phase is generally described as the period between the first six weeks to three or six months after stroke onset (Donnan et al., 2008; van Delden et al., 2012). The plasticity process is then initiated, both to compensate for the lesion itself but also for its remote effects. Changed neural activity and connectivity can occur, both in perilesional regions but also in the contralateral hemisphere, (Kiran & Thompson, 2019; Small et al., 2013). The chronic phase begins three to six months after stroke, when spontaneous recovery generally is considered to have reached a plateau (Cramer, 2008: Wade et al., 1985). There is however growing evidence that significant improvements also may also occur much later (Hope et al., 2013; Smania et a., 2010) and a need for providing therapy to patients also in the chronic and late chronic stages (Ballester et al., 2019; Berthier et al., 2011).

1.6.1 Speech and language recovery after stroke

A fundamental issue relates to whether speech and language improvement after a stroke is sustained by left hemisphere zones spared by the lesion, or by recruitment of homologous right hemisphere regions (Cherney & Small, 2009). According to a hierarchical model of aphasia recovery, patients with small left hemisphere lesions often recover well due to normal restitution of perilesional language networks. Patients with more expansive lesions recruit areas surrounding the lesion and tend to show a good, but often incomplete recovery. In patients with a severely damaged left hemisphere, there will be an activation of the homologous right hemisphere. This activation appears to occur especially during early recovery and has also been argued to be less efficient, for example by Heiss and Thiel (2006) and Naeser et al. (2005). It is debated whether this activation is favorable (Hartwigsen et al., 2013) or a maladaptive response, reflecting loss of active transcallosal inhibition (Fernandez et al., 2004; Watila & Balarabe, 2015). In the chronic stage of aphasia, it is still unclear to what degree a permanent recruitment of the right hemisphere is beneficial (Kiran, 2012; Klingbeil et al., 2019).

1.6.2 Measures of recovery

A common approach to examine recovery of function is to study the difference between initial and final performance on a standardized test. An alternative method was introduced by Prabhakaran et al. (2008). The researchers focused on the change in results from the Upper Extremity motor section of the Fugl-Meyer Assessment Protocol (FMA–UE) (Fugl-Meyer et al., 1975) rather than the final FMA-UE score, claiming that the recovery process essentially implies a change in state rather than just an endpoint. Recovery was defined as the percentage that a patient improves over time on a test in relation to the possible maximum improvement on that specific measure. It was also argued that the initial score was highly correlated with the proportional recovery score, and that motor recovery in the first six months after stroke could be characterized into two different patterns: a majority of patients recover about 70% of the maximum potential change, whereas a subgroup of patients with severe initial deficits show very little or no improvement at all (Prabhakaran et al., 2008). The theory of the proportional recovery rule then became widespread in stroke rehabilitation research. Lazar et al. (2010) reported that the proportional recovery rule also applied to patient with mild-moderate aphasia. These patterns were also observed by Marchi et al. (2017) in studies of patients with aphasia and visuospatial neglect. However, the theories behind the proportional recovery rule were later questioned in some respects. Hawe et al. (2019) argued that previous results presented as the proportional recovery rule were biased because of the mathematical properties of how the proportional recovery rule is derived. Hope at al. (2018) had earlier pointed out that there is a risk of a false correlation between the initial impairments and amount of change when there is a ceiling effects on the scale used to measure the impairment. However, Hope and colleagues concluded that the procedure to study recovery could still be a valid method. To minimize the ceiling effects, a recommended approach was to remove results that are at ceiling at the initial assessment (Hope et al., 2018).

1.7 SPEECH-LANGUAGE FUNCTION AND HAND MOTOR FUNCTION

1.7.1 Concepts and theories

It has been claimed that our ability to communicate through speech evolved from manual gestures, and that hand motor movement preceded spoken language (Ardila, 2015; Corballis, 2003; cf. MacNeilage, 2003). A close relationship between the organization of the neural substrates subserving skilled hand motor actions and speech production has been observed in several studies. Neuroimaging studies (e.g., Binkofski et al., 1999; Eickhoff & Grefkes, 2011; Gerardin et al., 2000; Kroliczak et al., 2021) have shown that regions in the inferior frontal gyrus (IFG), corresponding to Broca's area, are recruited during manual action, demonstrating that this region is not language specific. According to Binkofski and Buccino (2006), areas within Broca's region also subserve complex function of hand motor movements, associative sensorimotor learning, and sensorimotor integration. This area is also a part of a specialized parieto-premotor network that interacts with the adjacent premotor areas (Binkofski & Buccino, 2006). The ventral premotor cortex, proposed to be a key region for speech motor planning and a lesion correlate of AOS, is also assumed to be involved in the control and coordination of sequential movements in hand motor activities (Halsband et al., 1993; Heim et al., 2012). Based on the observations of shared correlates for manual activity and speech motor planning, AOS has been proposed as a link between motor and language processing functions (Primaßin et al., 2015).

1.7.2 Recovery in multiple domains

A stroke in the left middle cerebral artery often affects regions involved in both speech and language functions and in motor functions. As a result, many patients have both motor and speech and language impairments. According to Anderlini et al. (2019), around 80% of individuals with a Broca's aphasia also have right-side hemiplegia. Motor recovery is considered to operate on similar principles as speech and language recovery. Regardless of domain, most spontaneous recovery is considered to occur within the first three months after stroke (Rijntjes, 2006; Wade et al., 1985). Studies on simultaneous speech-language and motor impairments after stroke are however rare. Most studies of recovery have focused on a single domain within selected patient groups and determinants of concurrent recovery of language and motor functions are largely unknown (Corbetta et al., 2015; Ramsey et al., 2017). In several studies of motor recovery, aphasia has actually been a criterion for exclusion (Dalemans et al., 2009). Because cortical reorganization after stroke in language and motor systems may depend on many mutual factors, an integrative view could be valuable for investigations of either of them (Rijntjes & Weiller, 2002).

1.8 RATIONALE FOR THE INCLUDED STUDIES

After a stroke, early assessment and diagnosis of speech and language impairment are crucial for selecting and initiating proper treatment interventions. There is an established need for improved assessments of AOS and further understanding of neural mechanisms explaining the variable recovery patterns observed clinically. However, few studies have investigated AOS in early stroke patients as well as its resolution longitudinally, and factors predicting recovery are largely unknown. While the effects of stroke-induced focal brain lesions have been frequently studied, less is known about alterations in network connectivity in patients with AOS. Despite a close relationship between speech, language and hand motor function, only a few studies have addressed the issue of recovery in these behavioral domains. In clinical settings, there is a lack of valid and reliable assessment instruments for AOS diagnosis that are applicable at all severity levels.

2 RESEARCH AIMS

2.1 GENERAL AIM

The overall aim of this thesis was to gain more knowledge on the diagnosis and the recovery patterns of AOS in individuals in a subacute phase after stroke.

2.2 SPECIFIC AIMS

The specific aims for the four studies were:

Study I: To study the intra- and interrater reliability of the Apraxia of Speech Rating Scale 2.0 (ASRS 2.0), an instrument for assessment of AOS created for research purposes, in a group of clinically active SLPs in assessment of individuals with speech and language impairments in an early phase after stroke. An additional aim was to investigate the applicability of the ASRS 2.0 in the assessment of individuals with severe speech and language impairments after stroke.

Study II: To describe and evaluate measures of reliability and validity for a clinical assessment protocol for AOS diagnosis, developed with the aim of being applicable in clinical settings and valid in assessment of individuals with speech and language impairments of all severity levels.

Study III: To investigate the prevalence of AOS and aphasia in individuals with an upper limb impairment in a subacute phase after stroke and to compare recovery across speech, language and hand motor domains.

Study IV: To investigate longitudinal changes in functional connectivity (FC) in individuals with AOS after stroke, from the subacute to the chronic phase, in order to identify predictors of AOS recovery. Additional aims were to study the relation between FC and the degree of severity in AOS, and to compare FC strength in patients with AOS after a left hemisphere stroke to that in left hemisphere lesioned stroke patients without a speech and language impairment.

3 MATERIALS AND METHODS

An overview of the methods applied in the four studies is presented in Table 1.

Table 1. Summary of study design, research questions, number of participants and principal methods of the four studies.

Study	Study design	Research question	Participants	Principal methods
Study I	Clinical validation study	(i) What is the reliability of the ASRS in assessment of patients in an early phase after stroke? (ii) Can the ASRS 2.0 be rated reliably by SLPs without long common experience and joint training?	Ten individuals with speech-language impairments in an early phase after stroke (patient sample), Five SLPs from different hospital departments (raters)	Intraclass Correlation Coefficient (ICC)
Study II	Clinical validation and observational study	(i) What is the applicability of the TAX assessment protocol, in a clinical setting in the assessment of individuals in an early phase after stroke? (ii) What is the reliability and the validity of the TAX assessment protocol in the clinical assessment of a group of individuals with speech and language impairments at all severity levels?	Reliability: Five individuals with speech-language impairment after stroke (patient sample), eleven SLPs (raters). Validity: Thirty-nine individuals with speech- language impairments in a sub-acute phase after stroke (patient sample), Seven practicing SLPs (raters)	Intraclass Correlation Coefficient, (ICC), Binary logistic regression analysis, ROC curve analysis
Study III	Prospective longitudinal observational study	(i) What is the prevalence of AOS and aphasia in a cohort of patients with arm and hand motor impairment in an early phase after first ever stroke? (ii) How does recovery at six months in speech-language domains relate to recovery in hand motor domains? (iii) Can any of the measures predict AOS recovery?	Prevalence: Seventy individuals with a hand motor impairment in a subacute phase after first ever stroke. Recovery: Fifteen individuals with a hand motor impairment in a subacute phase after first ever stroke.	Relation between behavioral data and imaging data analyzed by recovery ratios and correlation/ regression methods
Study IV	Prospective longitudinal observational study	(i) Can AOS recovery at six months after stroke be predicted by measures of FC in speech-language networks at four weeks after stroke? (ii) How do measures of FC relate to severity in AOS? (iii) How do measures of FC in patients with AOS after stroke relate to that in left hemisphere lesioned stroke patients without a speech-language impairment?	Nine individuals with AOS and aphasia in a subacute phase after stroke, six individuals with left hemisphere lesions in a subacute phase after stroke without a speech-language impairment.	Relation between behavioral data and FC measures analyzed by correlation methods and recovery ratios

Note: ASRS 2.0 = The Apraxia of Speech Rating Scale, version 2, TAX assessment protocol = Clinical assessment protocol for apraxia of speech (study specific), FC = functional connectivity

3.1 STUDY SETTING

Patients for all four studies were recruited from an inpatient clinic at the University Department of Rehabilitation Medicine at Danderyd Hospital, Stockholm, Sweden. The clinic provides multi-professional, team-based rehabilitation within the biopsychological framework of the International Classification of Functioning, Disability and Health (ICF) for individuals of working age, the majority being in a subacute phase after an acquired brain injury. The ICF framework is a central component in rehabilitation medicine that promotes the description of health conditions among the three domains; body function and structure, activity, and participation. All data collection for study III and IV were carried out in collaboration with the ProHand Study (section 3.3.8), a longitudinal prospective cohort study performed at the University Department of Rehabilitation Medicine at Danderyd Hospital between February 2015 and June 2021 (ClinicalTrials.gov Identifier: NCT02878304). The patient sample for study II was recruited from patients admitted to inpatient care at the same clinic between November 2017 and August 2021. The participating speech-language pathologists (SLPs) in this study worked at the University Department of Rehabilitation Medicine at Danderyd Hospital during this period. Speech-language pathologists participating as raters in study I were recruited from different hospital units in Stockholm.

3.2 INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria for the participant sample for study I, III and IV were according to the ProHand study: Individuals aged ≥ 18 years admitted to inpatient care after first ever-stroke, between 2 and 6 weeks after stroke onset with clinical evidence of hand motor deficits, and alert and capable of participating in assessment procedures. Exclusion criteria were: Inability to understand and comply with instructions (presented in an adapted format for patients with aphasia), cerebellar lesions, report of claustrophobia or metal object in body, presence of other neurological, psychiatric, or medical conditions that preclude active participation. In addition to the ProHand criteria, the participants in the present studies had to have Swedish as their first language to be eligible. In study II, individuals ≥ 18 years admitted to inpatient care, between 2 and 6 weeks after an acquired brain injury and with Swedish as first language were eligible. Exclusion criteria included ongoing psychiatric or medical conditions that prevented active participation in the assessment procedure. All participants gave informed consent prior to participation. To enable the recruitment of individuals with aphasia, both oral and written information was modified and presented in an aphasia-friendly manner (further described in section 3.5., Ethical considerations).

3.3 ASSESSMENT METHODS

3.3.1 The Apraxia of Speech Rating Scale 2.0

In this thesis, the ASRS version 2.0 was used. It was investigated for measures of reliability in study I. In study III and IV, the ASRS 2.0 was used as an assessment instrument with the modifications presented in section 3.3.1.2. and in Table 2. The ASRS 2.0 includes ratings of thirteen characteristics on a 5-point graded scale. Total maximum score is 52, with higher scores reflecting greater severity. The recommended cut-off value for an AOS diagnosis is 8 points. The descriptors for each level of rating are: (0) 'not observed in any task/no more than one occurrence'; (1) 'infrequent/noted more than once'; (2) 'frequent but not pervasive/noted in 20 –50 % of all utterances, but not on most tasks or utterances'; (3) 'nearly always evident but not marked in severity/noted on many utterances on most tasks but not enough to decrease overall intelligibility' and (4) 'nearly always evident and marked in severity/noted on most utterances on most tasks and severe enough to impact intelligibility.' The Swedish translation was made by Ellika Schalling and Per Östberg, in collaboration with the original authors. The Swedish version was back translated by a bilingual speaker and compared to the original version. The ASRS 2.0 can be seen in study I (table 4 at page 8).

3.3.1.1 Material for ratings with the ASRS 2.0

As a basis for the ratings on the ASRS 2.0, speech production was elicited by use of a motor speech protocol developed at the Mayo Clinic, the Supplemental Tasks for Assessing Motor Speech Abilities. The protocol includes measurements of vowel prolongation, word repetition × 3, sentence repetition, alternating motion rates (AMRs) and sequential motion rates (SMRs), and has frequently been applied in studies reporting on motor speech disorders (the protocol is presented in Duffy et al., 2015). The speech sample also contained conversational speech and a picture description task by use of material from the Swedish aphasia assessment instrument A-ning (described in section 3.3.4.). The procedure was carried out by the doctoral student and two certified SLP colleague of hers at the same clinic. The video recordings also contained information on nonverbal oral apraxia according to the nonverbal oral apraxia (NVOA) protocol described in section 3.3.3.

3.3.1.2 Modifications of the level descriptors of the ASRS 2.0

To enable ratings that reflected the observed severity levels in individuals with a limited speech output with the ASRS 2.0 (motivated and described in section 4.1.2 and 5.1.1. and in study I), modifying strategies were used for ratings in four of the thirteen items on the ASRS 2.0. These adjustments were used in study III and IV and are presented in table 2. The rating procedure with the ASRS 2.0 is presented in section 3.4.5.

Table 2. Applied modifications for ratings with the ASRS 2.0

0	1	2	3	4
Not observed in any task	**Infrequent**	**Frequent but not pervasive**	**Nearly always evident but not marked in severity**	**Nearly always evident and marked in severity**
No more than one occurrence	Noted more than once	Noted 20-50% of all utterances, but not on most tasks or utterances	Noted on many utterances on most tasks but not enough to decrease overall intelligibility	Noted on most utterances on most tasks and severe enough to impact intelligibility

Items on the ASRS 2.0	Applied modifications
1.3 Increased sound distortions or distorted sound substitutions with increased utterance length or increased syllable/word articulatory complexity	For observations of individuals who cannot produce phrases or multisyllabic words but these symptoms are noticed in monosyllabic word and isolated speech sounds, rating value 4 is given.
2.1 Syllable segmentation within words > 1 syllable (Brief silent interval between syllables and/or inappropriate equalized stress across syllables)	For observations of individuals who cannot produce multisyllabic words but show other apraxic symptoms*, a rating value between 1- 4 is given.
2.2 Syllable segmentation across words in phrases/sentences (Increased inter-word intervals and/or inappropriate equalized stress across words)	For observations of individuals who cannot produce phrases or sentences but shows other apraxic symptoms*, a rating value between 1- 4 is given.
3.1 **RATE ONLY FOR SMRs:** Deliberate, slowly sequenced, segmented (gaps between sequences), and/or distorted (including distorted substitutions) speech SMRs in comparison to AMRs. *Rate the best effort* Score on severity only: 0 = not noted, SMRs normal; 1 = slow, 2 = mildly segmented and/or distorted; 3 = moderately segmented and/or distorted, 4 = severely segmented and/or distorted	For observations of individuals with major problems to produce both alternating motion rates (AMRs) and sequential motion rates (SMRs), and shows other apraxic symptoms*, a rating value between 1- 4 is given.

* Rating value corresponding to degree of other observed AOS characteristics, decided in consensus between 2 raters and discussed with the participants' clinical SLP

3.3.2 The TAX assessment protocol

An initial version of a clinical assessment protocol for AOS was investigated in study II. The assessment protocol, called TAX (from the Swedish word for AOS, 'Talapraxi'), includes ratings of ten characteristics that are widely considered to reflect speech motor impairments related to the AOS diagnosis. The protocol was developed with the aims to be: (1) applicable and sensitive also for symptoms related to severe AOS impairments; (2) feasible to use in a clinical setting, and (3) that as many as possible of the characteristics should be assessed by objective measures. All items are rated on a 4-graded scale, from zero to three. The TAX assessment protocol has two sections. The first section consists of five items where all ratings are based on task results with quantitative measures. All these items have individually operationalized descriptors for each level of rating. The second part comprises perceptual ratings of five symptoms associated with the AOS diagnosis. All ratings in this section are made by use of the same level descriptors. The assessment protocol is operationalized with standardized instructions. Presented by shortened item descriptor, the items in the first section are: (1) Repetition of sequential motion rates (SMRs) in comparison to repetition of alternating motion rates (AMRs); (2) Ability to imitate isolated speech sounds; (3) Repetition of monosyllabic words in comparison to repetition of multisyllabic words; (4) Presence and severity of nonverbal oral apraxia. The items in the second section are: (5) Awareness of errors – self-judgement of word production accuracy; (6) Slow speech rate with segment and pause prolongation; (7) Sound distortions; (8) Prosodic abnormalities; (9) Articulatory groping; (10) Attempts at self-correction. A detailed description is presented in study II.

3.3.3 Assessment protocol for nonverbal oral apraxia

Applied in all four studies: For presence and severity of nonverbal oral apraxia (NVOA), a screening protocol developed by Josephs et al. (2012) and Botha et al. (2014) was used. This protocol includes observations of four different gestures that shall be repeated twice; ‘click your tongue’, ‘blow’, and ‘smack your lips’. Total maximum score is 32, whereas the recommended cut-off for an NVOA diagnosis is < 29.

3.3.4 Neurolinguistic Aphasia Examination (A-ning)

Applied in all four studies: For assessment of aphasia, the Swedish standardized assessment instrument Neurolinguistic Aphasia Examination (A-ning) (Lindström & Werner, 1995) was applied. A-ning includes evaluation of seven linguistic modalities: ‘oral expression abilities’, ‘repetition’, ‘auditory comprehension’, ‘reading comprehension’, ‘reading aloud’, ‘dictation’ and ‘informative writing.’ The maximum total score result is 220 points (= no language impairment), with a corresponding aphasia index of 5.0. The cut-off value for an aphasia diagnosis is 208 (index 4.8).

3.3.5 Boston Naming Test

Applied in all four studies: Visual confrontation naming ability was assessed by use of the Boston Naming Test (BNT). The BNT is frequently used, both in clinical settings and research. Maximum result is 60, and scoring was done according to Swedish target words by Tallberg (2005).

3.3.6 Dysarthria Assessment

Applied in all four studies: Presence, degree and type of dysarthria was assessed by the Swedish assessment instrument Dysartribedömning (Dysarthria Assessment; Hartelius, 2015). Dysartribedömning is a standardized clinical assessment instrument which includes measurements of respiration, phonation, oromotor function, articulation, prosody and intelligibility. A scale ranging from 0 (= normal function) to 3 (= severe deviation or no function) is used. Both quantitative results and qualitative descriptions are used to capture level of severity and subtypes of dysarthria according to the Mayo classification.

3.3.7 The Fugl-Meyer assessment for the Upper Extremity

A*pplied in study III and IV:* To assess hand motor function, the Fugl-Meyer assessment for the upper extremity (FMA-UE) was used (Fugl-Meyer et al, 1975). The FMA-UE is a standard outcome measure in clinical stroke research and has shown excellent inter- and intrajudge reliability and construct validity (Gladstone et al., 2016). The maximum total score is 60 (with the three reflex items excluded) (Woodbury et al., 2007). Upper extremity motor impairment level was classified as severe impairment (FMA-UE < 19), moderate (FMA-UE 19 − 47), and mild (FMA-UE > 47) (Woodbury et al., 2013).

3.3.8 Recording equipment

For all video recordings, a Sony HDR-CX450 Camcorder with a 5.1 channel microphone was used.

3.3.9 The ProHand study protocol

A summary of all applied assessment instruments in the ProHand study is presented in table 3.

Table 3. The ProHand study protocol

ICF Level	Methods	~3 weeks	3 months	6 months
Body function and structure	NIH stroke scale (NIHSS), BNI screen for Higher Cerebral Functions (BNIS), Hospital anxiety and depression scale (HADS)	x		
	Somatosensory function	x	x	x
	Maximum pinch and whole hand grip strength	x	x	x
	Fugl-Meyer Assessment	x	x	x
	Modified Ashworth scale	x	x	x
	NeuroFlexor ©	x	x	x
	Strength Dexterity Test	x	x	x
	Visuomotor Grip Force Tracking	x	x	x
	Magnetic resonance imaging	x		x
Speech- and language function	A-ning Neurolinguistic aphasia examination	x		x[a]
	Boston Naming Test	x		x[a]
	The Apraxia of Speech Rating Scale 2.0 (ASRS 2.0)	x[b]		x[b]
	Nonverbal oral apraxia screening protocol (NVOA)	x[b]		x[b]
Activities and participation	Assisting Hand Assessment	x	x	x
	Box & Block Test	x	x	x
	Action Research Arm Test	x	x	x
	ADL - Barthel Index	x		x
	ABILHAND	x	x	x
	Life satisfaction (LiSat)			x
Health outcome	Quality of life (EQ5D)	x		x

Note [a] Follow-up assessment with A-ning and Boston Naming Test added in 2014. [b]Assessments by use of ASRS and NVOA screening protocol added in 2015.

3.3.9.1 The ProHand study imaging protocol

Brain imaging was carried at two times; the first occasion at 2–6 weeks after the stroke and the follow-up at 6 months in conjunction with the behavioural assessments. It was performed with an Ingenia 3.0T MR system (www.usa.philips.com) with an 8HR head coil. Three structural imaging sequences were included: (1) T1-weighted anatomical images using a 3-

dimensional gradient echo-based sequence (field of view 250×250×181 mm; matrix 228×227; slice thickness 1.2 mm; slice spacing 0.6 mm; and number of slices 301 (echo time [TE] = 3.456 milliseconds; repetition time [TR] = 7.464 ms). This sequence provides high-resolution anatomical images contrasting white and grey matter in the brain; (2) T2-fluid attenuated inversion recovery images (FLAIR; field of view 250×250×157 mm; matrix 224×224; slice thickness 2.5 mm; TR 4800 ms; TE 30 ms). This sequence provides high contrast between uninjured and injured tissue (hyper-intense lesions); (3) T2-weighted fast field echo (FFE) images (field of view 230×183×149 mm; matrix 256×163; slice thickness 4 mm; TR 500 ms; TE 16 ms). This sequence also highlights hyperintense lesions, for example areas containing oedema, infarction and subacute haemorrhage.

The resting-state functional MRI protocol consisted of a gradient echo-planar sequence (echo time [TE] = 35 milliseconds, flip angle = 90°, voxel size of 1.8 × 1.8 × 4 mm, repetition time [TR] = 3000 ms) sensitive to Blood Oxygen-Level Dependent (BOLD) contrast. The acquisition time was 6 minutes and the total number of volumes acquired were 160. Patients were instructed to keep the eyes closed, to think about nothing in particular and not to fall asleep.

3.4 PARTICIPANTS AND PROCEDURES

3.4.1 Study I

3.4.1.1 Patient sample for investigations of reliability for the ASRS 2.0

Ten individuals considered as representative of the patient group at the actual inpatient ward were selected for reliability analysis. The individuals were collected from the group of participants in the ProHand study, and included both participants with severe aphasia and signs of severe AOS, as well as two participants with very subtle or no obvious AOS characteristics. Their mean age was 46.3 (SD 12.9). Two of the participants were females (20 %), while eight were males (80 %).

3.4.1.2 Raters for investigations of reliability for the ASRS 2.0

Five certified SLPs from different clinics and departments in Stockholm were recruited as raters. The SLPs had graduated between three and 34 years ago and were between 27 and 61 years of age. All worked primarily with neurogenic communication disorders in adults.

3.4.1.3 Reliability of the ASRS 2.0: Rating procedures

Before the rating period started, three of the raters attended a one-day course and/or a short training session with the ASRS 2.0 held by one of the creators of the scale. Two raters did not participate in any training with the ASRS 2.0 and had instead general written information and/or short oral instructions from the doctoral student. All five raters performed their ratings independently, by individually viewing the video recordings and rated the presence and severity of AOS using the ASRS 2.0. The speech samples on the video recordings were based on a material described in section 3.3.1.1. None of the raters had prior knowledge about the individuals in the sample, and no information was given about the participants in the video clips. No restrictions were given concerning how many times the raters were allowed to watch and listen to the recordings. After the first round of ratings were completed, all results were handed in. For measures of intrarater reliability, rescoring was carried out after at least three weeks.

3.4.2 Study II

3.4.2.1 Patient sample for investigations of reliability for the TAX assessment protocol

The patient sample included five individuals displaying varying degrees of AOS symptoms, from mild to severe. The participants were recruited by the doctoral student and all participants provided informed consent. There was one female in the group and four were males. Two of the participants were in a chronic phase (> 6 months post stroke onset), while three were in a subacute phase, 2–8 weeks after a stroke.

3.4.2.2 Raters for investigations of reliability for the TAX assessment protocol

Eleven certified SLPs participated as raters, all working in different units at the University Department of Rehabilitation Medicine at Danderyd Hospital. The group varied regarding seniority levels as an SLP, with the majority having over ten years of professional experience.

3.4.2.3 Reliability of the TAX assessment protocol: Rating procedures

The reliability ratings were carried out at two joint sessions with the participating SLPs gathered. At the first occasion, a short introduction of the TAX assessment protocol was given by the doctoral student, followed by joint training of one video recorded individual displaying several characteristics associated with the AOS diagnosis. The clinicians then independently completed the protocol for the video recorded participants. The video clips displayed the five participants being assessed with the TAX assessment protocol by the doctoral student. The procedure and the participants performances for the first five items on the assessment protocol that are task-based were shown. Conversational speech about the patients’ own experience and thoughts about their communication ability (limited for the participants with more severe speech-language impairments) were also included in the recordings.

3.4.2.4 Patient sample for investigations of validity of the TAX assessment protocol

Validity was investigated in a group of 39 participants. All were in a subacute phase, 2 − 6 weeks after a stroke. There were 11 women (28.2%) and 28 (71.8%) men. The mean age was 51.1 years (SD 10.9), and the median age was 53 years. Thirty-three participants (84.6%) had left hemisphere lesions, while 2 participants (5.1%) had right hemisphere lesions. Three of the participants had bilateral lesions.

3.4.2.5 Clinical speech-language pathologists for investigation of validity for the TAX assessment protocol

The clinical assessments were carried out by seven certified SLPs working at the inpatient clinic at the University Department of Rehabilitation Medicine at Danderyd hospital. The years of professional experience covered a range with one newly graduated SLP up to one SLP with over 20 years of experience in the profession.

3.4.2.6 Validity of the TAX assessment protocol

The TAX assessment protocol (presented in section 3.3.2) was added to the regular speech and language assessment battery used at the actual inpatient ward (presented in section 3.3.4 – 3.3.6). All participant assessments with the TAX assessment protocol were carried out as part of the clinical routine by the SLP in charge of the respective participants. In the clinical assessment, the SLPs were encouraged to interpret the results from the TAX assessment protocol with careful consideration regarding comorbidity and perceptual overlap. It was emphasized that the TAX total score should not be regarded as a direct measure of the presence and severity of AOS, since several of the perceptual characteristics on the assessment protocol can also be found in dysarthria or aphasia. The clinicians were requested to report the quantitative results from all ten items in the protocol separately. They were then asked to report how these measures were used to base a possible AOS diagnosis on in relation to eventual co-existing aphasia and/or dysarthria, and to report on the level of AOS severity with one of the terms 'mild', 'moderate' or 'severe'. For estimation of validity, the TAX total score was then compared to the binary clinical decision on the presence or absence of an AOS diagnosis. Owing to missing data and the small sample size, it was not possible to analyze the correlation between the TAX total score and the clinical severity level ('mild', 'moderate' or 'severe').

3.4.3 Study III

3.4.3.1 Patient sample for the prevalence of AOS and aphasia in post stroke patients with an upper limb impairment.

The prevalence of AOS was investigated in 70 of the 89 participants in the ProHand study (= all participants in the ProHand study with Swedish as first language). The mean age in the group was 51.9 (SD 9.5); 16 (16.8%) were female, and 54 (56.8%) were men. Half of the group (n=35) had right hemisphere lesions, whereas 35 participants (50 %) had left hemisphere (LH) lesions. The mean age in the group with LH lesions was 53.3 years (SD 8.4). Six of the participants in this group (17%) were females and 29 participants (83%) were males.

3.4.3.2 Patient sample for recovery of AOS, aphasia and hand motor impairment

Recovery of AOS, aphasia, and hand motor impairment was investigated in 15 of the 35 LH lesioned participants with aphasia at the first assessment occasion (A1). Twelve of these (80%) also had AOS at A1. The mean age in the group was 50.3 years (SD 9.4). Three of the participants (20%) were females, 12 participants (83%) were males. All participants had middle cerebral artery lesions.

3.4.3.3 Procedures

Behavioral measurements and imaging data were obtained according to the ProHand study protocol. Assessments were carried out at two occasions, the first (A1) between 2 – 6 weeks after first ever stroke with a follow-up occasion (A2) at 6 months (Table 3).

3.4.4 Study IV

3.4.4.1 Patient sample for investigation of longitudinal changes in FC

Investigations by use of FC methods were carried out in a group of nine participants in the ProHand study with AOS at the first assessment occasion (A1). All these participants also had aphasia and NVOA, all also had mild to severe upper limb motor impairment. The mean age in this group was 49.6 years (SD 11.3). Two of the participants (22 %) were females, and seven participants (78 %) were males.

3.4.4.2 Patient sample for investigation of group differences

For investigations of group differences between LH lesioned stroke patients with AOS and LH lesioned stroke patients without AOS, six LH lesioned participants without speech-language impairment were added to the analysis. The mean age in the group was 56.7 years (SD 5.1). One of the participants (17 %) was female and five participants (83%) were males.

3.4.4.3 Procedures

Behavioral measurements and imaging data were obtained according to the ProHand study protocol (Table 3). For investigations of FC, three ROIs regarded as key areas for AOS were selected: inferior frontal gyrus (IFG), anterior insula (aINS), and ventral premotor cortex (vPMC), with both hemispheres included in the model. The coordinates for the selected ROIs were selected from Eickhoff et al. (2009).

3.4.5 Rating procedure with the ASRS 2.0

In study III and IV, ratings of the presence and severity of AOS by use of the ASRS 2.0 was made by the doctoral student. All ratings were also compared against the results from an external SLP with long clinical and research experience in both aphasia and AOS, who independently watched the video recordings and completed the ASRS 2.0 for all participants. When disagreement occurred, consensus was reached via discussions and joint review of the video recordings. The ASRS 2.0 results were also discussed and controlled with the clinical SLP for the respective participant, who in some cases also had completed the ASRS 2.0 for the participant. Modifications of the level definitions in four of the thirteen items on the ASRS 2.0 are presented in Table 2.

3.4.6 Statistical analysis

All statistical analysis was made in IBM SPSS Statistics, Version 26.0 (in study I and III) and 27.0 (in study II and IV). For estimates of intra- and interrater reliability, the intraclass correlation coefficient (ICC) was calculated. The selected ICC formula for interrater analysis (in study I and II) was a 2-way random-effects model with single measurement and absolute agreement. The selected formula for intrarater analysis (in study I) was a 2-way mixed-effects model with single measurement and absolute agreement. For qualitative interpretation of the ICC results, guidelines by Koo and Li (2016) were applied with ICC values below 0.50 indicative of poor reliability, values between 0.50 and 0.75 indicative of moderate reliability, values between 0.75 and 0.90 good reliability, and values greater than 0.90 indicative of excellent reliability. The magnitude of recovery (in study III and IV) was defined as the percentage that a participant improved over time on a test in relation to the possible maximum improvement on that specific measure. Recovery ratio was calculated as the absolute amount of recovery (change from the subacute score, A2–A1) divided by the amount corresponding to full recovery (difference between subacute score and maximum score, max−A1). To minimize known ceiling effects, patients with results at ceiling at the initial assessment were excluded from the analysis. To avoid a strong influence of possible outliers in the relatively small datasets, non-parametric options were mainly used in all studies. To test the strength between groups, Spearman’s correlation coefficients was applied. Between-group differences were tested using the Mann-Whitney *U* test and Kruskal-Wallis test. For within-group differences, the Wilcoxon signed-rank test was applied. To investigate predictors of AOS recovery in study III, univariate regression analyses were performed. For estimates of validity (in study II), a binary logistic regression analysis was performed. The model accuracy was also investigated by use of a receiver operating characteristic curve (ROC) analysis.

3.5 ETHICAL CONSIDERATIONS

This project included individuals with varying degree of neurological impairments after a first ever stroke. Several of the participants had moderate to severe speech and language disabilities, with an impaired ability to process regular written and oral study information. It has been recognized that individuals with aphasia, and especially those with severe aphasia, often are excluded from research (Dalemans et al., 2009). This relates to assumptions that the language impairments hinder the ability to provide informed consent and thereby to participate in research (Kagan & Kimelman, 1995). However, there is increasing support for that also individuals with severe aphasia can make informed decisions and give consent to participate in research projects (Jayes & Palmer, 2014). To enable the inclusion of individuals with severe aphasia, the procedure to obtain informed consent can be supported by use of 'aphasia friendly principles' (Rose et al., 2003). The principles include adapted information with modifications to both language expressions and layout, as for example using simplified terms and sentence structures, limiting the amount of text on each page, and adding pictures that illustrate the principal information in the written information (Worrall et al., 2005). Such methods were applied in this project. The overall aim of the studies was to improve the knowledge about individuals with AOS in an early phase after stroke. The risk of adverse events by participating was considered low. All assessments in study II were carried out as part of the clinical routine and did not require any further testing activities. One possible risk in study III and IV was that the assessment protocol could be exhausting and time consuming, and thereby absorb time needed for other interventions and time to rest. To counteract this, all research assessments were scheduled in cooperation with the members of the patient's medical team, taking other rehabilitation activities into account. Another possible risk was that the radiological examinations, lasting around 30 minutes, could provoke feelings of discomfort or claustrophobia. In most cases, the participants were therefore accompanied by a person from the research group or the medical team. The participants were informed about the procedure and ensured that they could stop the examination at any time without any hesitations. This project involves potentially identifiable human material. All data were therefore stored and treated in accordance with standard ethical rules and protocols. With the means taken to protect the interests of the participating patients in this research project, the potential benefits could be considered to outweigh the potential risks.

4 RESULTS

This section summarizes the main findings of the four studies in this thesis.

4.1 STUDY I

4.1.1 Reliability of the ASRS 2.0

The main finding in Study I was a high disagreement among clinically practicing SLPs in their perceptual rating of 13 speech characteristics associated with the AOS diagnosis. The interrater reliability of the total score on the ASRS 2.0 was ICC = 0.42, 95% CI [0.35, 0.50] which should be regarded as poor (Koo & Li, 2016). High disagreement was especially noted in ratings of individuals with severe speech-language impairments, but varying rating agreement were also found for individuals with milder impairments, indicating general shortcomings of perceptual ratings on AOS characteristics and on this number of items. Also on an item level, the reliability was mainly moderate to low. None of the items on the ASRS 2.0 reached an ICC value that indicated good reliability (i.e., an ICC ≥ 0.75). The intrarater reliability for the total score was moderate on average, varying between excellent for one rater to moderate for three of the raters.

4.1.2 Applicability of the ASRS 2.0 in assessment of severe AOS

Limitations in the ASRS 2.0 when assessing individuals with severe language impairments were noticed. Several items on the ASRS require a certain level of speech production in order to be ratable in accordance with the formulations of level definitions. As an example, item 2.2. concerns rating of the characteristic “Syllable segmentation across words in phrases/sentences.” The definition for response value 4 is “Nearly always evident and marked in severity/noted on most utterances on most tasks and severe enough to impact intelligibility,” while response value/level definition 0 in the ASRS 2.0 is “Not observed in any task/no more than one occurrence”. Some of the participants in this sample had a very restricted speech output, consisting of mainly monosyllabic words with very limited ability to produce or imitate multisyllabic words or phrases. Several of the raters in this study therefore chose to rate this as a “0” (since this characteristic was not possible to observe, these ratings were in a way “true”), although a rating of 4 would possibly better reflect the severity level of AOS. The raters also noted problems to properly rate impairments that reflected the observed severity by use of the level definitions on the ASRS. Similar problems occurred in ratings of the items 1.3, 2.1 and 3.1 on the ASRS 2.0. These observations were also a contributing factor to the adjustments/applied strategies described in section 3.3.1.1 and presented in Table 2 for the continued use of the ASRS in study III and IV of this project. The Swedish version of the ASRS 2.0, SkaFTA 2.0, is presented in Appendix A. The ASRS 2.0 can be seen in Study I.

4.2 STUDY II

4.2.1 Development of a clinical assessment protocol for AOS diagnosis

The second study is part of an ongoing project with the final aim to develop a clinical assessment protocol for AOS diagnosis. Preliminary results of evaluations of reliability and validity that will guide the continued work are presented below.

4.2.2 Reliability of the TAX assessment protocol

An ICC analysis indicated a good, but not satisfactory interrater reliability for the total score: ICC 0.76, 95% CI [0.68, 0.83]. When calculating the two different sections separately, high to excellent reliability was found for the first section with ratings based on tasks with quantitative measures: ICC 0.91, 95% CI [0.86, 0.95]. The interrater reliability of the second section, with perceptual rating of five items, was lower with an ICC value indicating a moderate agreement: ICC 0.62, 95% CI [0.48, 0.77]. For the ten separate items on the protocol, the interrater reliability varied between excellent for the item on NVOA (ICC 0.97, 95% CI [0.93, 0.99]) to poor on the perceptual rating of attempts at self-correction (ICC 0.40, 95% CI [0.40, 0.86]).

4.2.3 Validity of the TAX assessment protocol

The results from a binary logistic regression analysis indicated that the TAX protocol total score predicted the presence of a clinical AOS diagnosis ($\chi^2 = 41.22$, $p < 0.001$), with an overall correct classification rate at 92.3%. A receiver operating characteristic curve (ROC) analysis yielded an area under the curve (AUC) model accuracy of 0.98, 95% CI [0.95, 1.00], indicating excellent discrimination ability. According to the curve and table of coordinates, the sensitivity for the TAX protocol would be 100% with a cut-of set at 10 points, with a specificity of 91%.

4.3 STUDY III

4.3.1 Prevalence of AOS and aphasia in patients with a hand motor impairment in a subacute phase after stroke

In a sample of 70, none of the participants with a RH lesion (n = 35) had AOS or aphasia. In the group with LH lesions (n = 35), the prevalence of aphasia was 71% and of AOS 57%. All participants with AOS also had aphasia, while 80% of the participants with aphasia also had AOS. There was a statistically significant group difference in FM-UE results between the three participant groups (Kruskal Wallis test, $H = 7.8$, $p = 0.02$), with a significantly lower median FM-UE score in the group with AOS plus aphasia than in the groups with aphasia only or in the group without a speech and language impairment.

4.3.2 Recovery of AOS and aphasia in patients with a hand motor impairment in a subacute phase after stroke

Measured in a group of 15 participants, a parallel recovery pattern with significant correlations between recovery ratio in hand motor and speech-language domains was found. At the 6-months follow up, the FM-UE total score also correlated significantly with the ASRS 2.0 total score (rho = -0.57, $p < 0.03$) and the A-ning total score (rho = 0.83, $p < 0.001$). The lesion volume did not correlate with the recovery ratio or behavioral results in any of the domains.

4.3.3 Predictors of AOS recovery

In a univariate linear regression analysis, the initial total score of A-ning was found as the strongest predictor of AOS recovery at six months, with 84% of the variance explained. The initial ASRS score accounted for 52% of the variance, while the initial FM-UE score showed no explanatory power (0.6%).

4.4 STUDY IV

4.4.1 AOS recovery predicted by measures of FC

For prediction of recovery by use of FC methods, a strong correlation between the interhemispheric IFG connectivity at the first assessment (A1) and the individual AOS recovery ratios at six months follow-up (A2) was found (Figure 3). Thus, participants with higher FC between left and right IFG in the subacute phase showed a better recovery to six months than participants with lower FC between these seeds.

4.4.2 Measures of FC in relation to AOS severity

At A1, no significant correlations between FC and behavioral scores were found. At A2, the severity level of AOS correlated with the bilateral aINS connectivity strength at six months (rho -0.88, $p = 0.002$).

4.4.3 Measures of FC in individuals with AOS a in comparison to FC measures in individuals without a speech and language impairment

At A1, the participants with AOS had a significantly reduced interhemispheric homotopic vPMC seed connection in comparison with LH lesioned without a speech-language impairment (Fisher's z-score 0.08 versus 0.78, Mann-Whitney *U* test $p = 0.001$). Participants with AOS also displayed a significantly stronger FC between the right aINS and right vPMC compared to the participants without a speech-language impairment (Fisher's z-score 0.32 versus 0.06, Mann-Whitney *U* test $p = 0.025$). At A2, the interhemispheric vPMC connectivity was still lower in the participants group with AOS, but the difference did not reach significance (Fisher’s z-score 0.46 versus 0.12, Mann-Whitney *U* test $p = 0.059$).

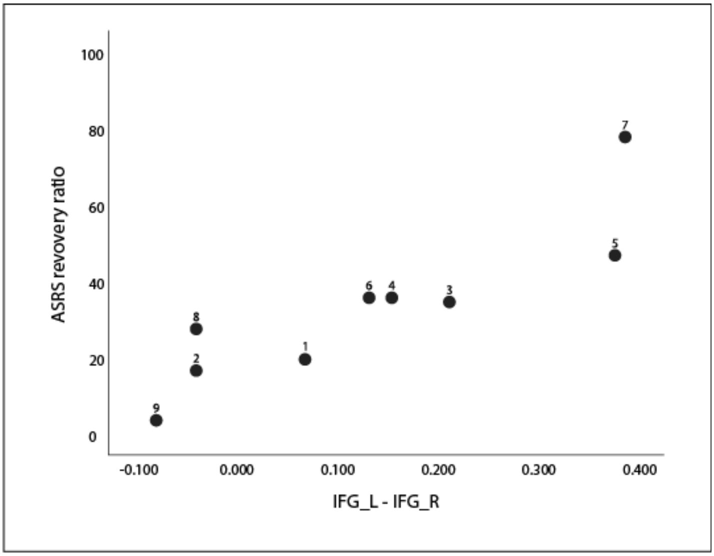

Figure 3. Correlation between ASRS recovery ratio at 6 months (A2) and FC between left and right IFG at A1 (rho = 0.92, $p = 0.001$) in nine patients with AOS.

5 DISCUSSION

The two fundamental questions addressed in this thesis concern how to confidently identify and diagnose individuals with AOS in an early phase after a stroke – and why some individuals recover better than others. Concerning the first question, the psychometric properties of an assessment instrument for AOS diagnosis was investigated in study I, with focus on measures of reliability. The findings in study I led on to the second study, a methodological report where feasibility, measures of reliability and validity for the development of a clinical assessment protocol for AOS were described. The second theme, regarding how to explain different recovery profiles of AOS, was explored in the two other studies. The first of these studies characterized recovery of AOS in relation to recovery in aphasia and upper limb recovery. In the last study of this thesis, neural mechanisms for prediction of AOS recovery were investigated by longitudinally studying connectivity in brain areas using functional MRI, and by relating this to AOS recovery.

This thesis is one of the first longitudinal investigations of individuals with AOS in an early phase after stroke. The observations made by a combination of standardized and detailed behavioral assessments and the imaging protocol may provide some new scientific and clinical insights. The main findings in the four studies will be discussed below.

5.1 DIAGNOSIS AND ASSESSMENT

5.1.1 Study I

The rationale for the first study was the recognized need for more information on the prevalence and severity of AOS in patients in an early phase after stroke. The original purpose of study I was to find an assessment instrument for AOS diagnosis that could be used for this purpose. The reliability results presented in study I showed that the use of the ASRS for this purpose may be limited. The low ICC values indicated that a high reliability of the ASRS might depend upon extensive mutual training and calibration of the ratings with experienced SLPs and/or researchers as raters. In line with previous findings, as for example by Duncan et al. *(*2020), shortcomings related to difficulties with perceptual ratings of thirteen different AOS characteristics on a 5-graded scale were noticed. These results add to the growing amount of research that highlights the limitations of diagnosis solely based on perceptual characteristics and call for the need to include objective measures in the diagnosis (Allison et al., 2020; Duncan et al., 2020; Haley et al., 2012). In addition, issues of concern were noticed regarding the assessment of individuals with signs of severe AOS with the ASRS. As noted by Malloy and Jagoe (2019), when the speech output is restricted to monosyllabic utterances, confident conclusions regarding overall prosody and observations of more distortions in multisyllabic word in comparison to monosyllabic words are not possible. Such observations preclude the use of some of the proposed discriminatory criteria for an AOS diagnosis. The findings in this study do not contradict the ASRS as a valid assessment instrument when conditions such as video recorded material and opportunities for mutual calibration between experienced researchers or SLPs, are given. The ASRS has been frequently used across several research groups (e.g., Bislick, 2020; Haley et al., 2019; Wambaugh et al., 2020) and has become a standard instrument in the AOS literature (Mailend et al., 2021). Because of the limitations discussed above and the severity level of AOS in the present participant sample, the modifications of the definitions of the different response alternatives were applied for measurement with the ASRS 2.0 in study III and IV of this thesis (presented in Table 2). The observations in study I were also a large part of the rationale for the second study of this thesis.

5.1.2 Study II

Study II is a report, written to present and discuss methodological considerations and preliminary measures of reliability and validity that will guide the ongoing development of a clinical assessment protocol for AOS. The current assessment protocol (called TAX) comprises a combination of item types, with five items based on operationalized metrics (as e.g., the percentage of correct repetition of mono- and multisyllabic words, and frequency counts of the ability to repeat isolated speech sounds), and five items with perceptual ratings of AOS characteristics.

During the development of the present assessment protocol, several different methods to objectively measure AOS characteristics were tested in a clinical setting. These have included, for example, measures of prosody using the Pairwise Variability Index (PVI), for quantification of the relative vowel duration in polysyllabic words (Ballard et al., 2016) and word syllable duration (WSD) (Haley & Jacks, 2019; Haley et al., 2012) for measures of speech rate in word repetition tasks. In one of the items, the self-awareness of speech production/repetition accuracy was investigated with quantitative measurements with methods in line with those described in Wambaugh et al. (2016). However, some of the objective methods showed a limited applicability in the assessment of individuals in an early phase after stroke, since they require a speech output with multisyllabic words to be confidently measured. In the current assessment protocol, measures of speech rate and prosody are therefore still based upon perceptual ratings. In future versions, options like digital sound recordings that are feasible to apply in clinical setting are to be considered. As some of the five perceptual ratings may be redundant, limiting the number of perceptual ratings on the assessment protocol may also be an alternative.

In a preliminary reliability trial, acceptable to good interrater reliability was found for the TAX total score. The highest reliability values were observed for items with operationalized measures, while most items based on perceptual ratings showed moderate agreement. Concerns have been raised regarding how characteristics suggested to be diagnostic of AOS are defined, and that they may be interpreted differently across researchers and clinicians (Molloy & Jagoe, 2019). In accordance with these considerations, the lowest agreement in the reliability trial was found for perceptual ratings on 'Attempts at self-correction.' Perceptual ratings of 'Groping' and 'Prosodic abnormalities' were also among the items with no more than moderate agreement. A revision of these items is needed, and alternative approaches are to be considered (further discussed below).

As a preliminary estimation of validity, the results from the TAX assessment protocol were compared against the clinical binary judgement of an AOS diagnosis. Although all SLPs involved were encouraged to interpret all the separate item results of the assessment protocol in relation to the comorbidity of aphasia and dysarthria in every separate patient, their decision may still have been guided by the total score. The diagnostic decisions were also based on the same characteristics that are included in the TAX assessment protocol. The high index of validity for this assessment protocol is thereby probably confounded by the circularity of such methods and needs to be further investigated by other options in future studies. An acknowledged challenge is to find such options. This might especially concern this patient group, since some of the earlier used methods, as for example the comparison against measures of word intelligibility (used in Wambaugh et al., 2019) are problematic to use in studies of individuals with concomitant (severe) aphasia. As discussed in study II, for the TAX protocol to be diagnostically valid, all measures need to be considered in relation to the comorbidity in every individual that is observed. The continued work includes revision of the items and further data collection to obtain larger data that allows for more statistical investigations. Future plans also include a follow-up assessment with the assessment protocol at six months.

5.2 PREDICTORS AND RECOVERY PATTERNS

The second theme of this thesis, investigations of recovery patterns and predictors of AOS, was in focus in study III and IV. Both these studies were carried out in collaboration with the ProHand study. The ProHand study protocol (Table 3) included several commonly used clinical assessment instruments in combination with new, fine-graded hand motor measurements, as well as a multimodal neuroimaging protocol. Measurements of aphasia, by use of the standardized Neurolinguistic aphasia examination (A-ning) and naming ability by the Boston Naming Test, were also included in the study protocol. The ASRS 2.0, with its modifications (described in section 4.1.2 and table 2), was added to this protocol in 2015. This allowed possibilities to study early AOS from different research angles, and to investigate AOS recovery after stroke in concurrent domains.

5.2.1 Study III

The focus of study III was the relation between hand function and speech and language function. As a first part in this study, the prevalence of AOS was examined in a group of participants with an upper limb impairment in a subacute stage after first ever stroke. Half of this group had a left hemispheric lesion, while the other half had a right hemisphere lesion. In line with the leading view that the speech motor programming impairments in AOS is caused by lesions in left lateral premotor areas (Miller & Guenter, 2020; New et al., 2015), none of the participants with a right-sided lesion were found to have AOS. Instead, in left hemisphere lesioned, over half of the group (57%) had AOS, while the prevalence of aphasia was even higher (71%). No participant with isolated AOS was found. These results confirm the common co-occurrence of aphasia and a hand motor impairment after a left hemisphere stroke (Anderlini, 2019: Duffy, 2020, p. 356) and add new quantitative information on the prevalence of AOS.

In study III, we also tested the hypothesis that speech and language recovery and recovery of hand motor function are driven by the same plasticity mechanism. In a group of fifteen participants, parallel recovery trajectories for AOS, aphasia and hand motor impairment were found. The similar pattern was observed in participants with severe impairments and a limited amount of recovery, indicating that general brain plasticity mechanisms are operating at all severity levels. No indications of a “fight for resources,” referred to in Ginex et al. (2020) and Primaßin et al. (2015) were noticed, and the parallel patterns that were found when comparing the different levels of change (i.e., recovery ratios) were also supported by correlated behavioral test results of AOS, aphasia and upper limb impairments. In line with reports of aphasia and hand motor recovery after stroke (e.g., Gerstenecker & Lazar, 2019; Hillis et al., 2018; Riley et al., 2011), the lesion volume could not explain the degree of recovery in any of the domains. These findings do not offer any suggestions whether the parallel recovery patterns are indicative of a specific relation, with shared neural correlates for speech motor programming (in AOS), language (aphasia) and hand motor function. As an alternative, the concurrent recovery patterns may also reflect anatomical proximity in areas supplied by the middle cerebral artery or be related to brain-wide plasticity mechanism driving the recovery.

Although the initial ASRS result could explain about 50% of the variation of recovery of AOS at six months, an even stronger predictor was the initial aphasia result. This observation could indicate that the tight link between language and speech motor function is central for AOS recovery. According to the GODIVA theory (Miller & Guenther, 2020), AOS impairments relates to disturbances of the feedforward mechanisms in speech production, and a reliance on feedback mechanisms. If these feedback mechanisms also are impaired because of concomitant aphasia, recovery of AOS would also be affected. Study IV in this thesis included the same participants and is an attempt to investigate these questions further with methods of functional connectivity.

5.2.2 Study IV

In study IV, changes in a network of regions were investigated by functional connectivity (FC) methods. The model included regions considered central to the AOS impairments, namely the inferior frontal gyrus (IFG), ventral premotor cortex (vPMC), and regions in the anterior insula (aINS). Since the effect of activation in the right hemisphere is unclear in terms of recovery after a stroke (Kiran et al., 2019: Sims et al., 2016), homologous regions in the right hemisphere were included in the analysis. Theories of motor control propose a close coupling between feedforward and feedback systems, in which the development and maintenance of motor programs depend upon monitoring and integrating sensory feedback. A stroke could result in damage to the (speech) motor programs themselves, or it could hinder the interaction in sensorimotor networks connected to the affected area (Eickhoff et al., 2009; Simonyan & Fuertinger, 2015). Functional connectivity methods allow investigations that move beyond questions of where the damage is, to investigations of how this damage may affect the speech production network (Ballard et al., 2014; New et al., 2015).

The main finding in study IV was a strong correlation between the interhemispheric IFG connectivity in the subacute phase and the individual AOS recovery ratios at six months. In line with contemporary speech production models, as for example Eickhoff et al. (2009), this result could suggest that a lesion in the left IFG, considered a key region for the phonological representation of the intended speech act, would impair the information that is transformed into motor speech programming in premotor areas. In these cases, a facilitating role of the homologous area in the right hemisphere can be present. These findings are in accordance with studies by Hartwigsen et al. (2013), Hillis et al. (2004) and Turkeltaub et al. (2011), reporting that the right IFG can support speech production when the left IFG is lesioned. In a recent longitudinal study by Landin-Romero et al. (2021) that included individuals with primary progressive aphasia with progressive apraxia of speech, a critical role of the right IFG was found. A major finding in this study was that deterioration of AOS was significantly correlated with greater progressive cortical thinning in the right IFG. In line with New et al. (2015) in studies of AOS in the chronic phase after stroke, the participants in the present study had a significantly reduced FC between the left and right vPMC in comparison to left hemisphere lesioned participants without AOS and aphasia. Unlike in New et al. (2015), this reduction was not correlated to the severity of AOS in at the subacute phase. At six months follow-up, the correlation between AOS severity and bilateral vPMC connectivity was strengthened and almost reached a significance level. At this timepoint, a significant correlation between bilateral aINS connectivity strength and AOS severity was found. New et al. (2015) suggested that for some individuals with AOS, an upregulation of the right vPMC region may not be sufficient. In such cases, the right aINS may also be recruited to compensate (New et al., 2015). The findings in study IV suggest that even if areas in premotor regions are the key regions for speech programming and the severity of AOS, the role of the IFG in the speech production network is important for the recovery of AOS. These results, together with the observations in study III, could indicate that recovery from (early) post stroke AOS may be closely related to phonological mechanisms in IFG regions, and that both motor and language components drive the recovery of AOS.

5.3 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

An obvious methodological dilemma of this thesis concerns the use of the ASRS in study III and IV. Considering the findings in study I, indicating limitations in assessment of individuals with severe AOS with the ASRS, this choice may seem irrational. However, because of the increasing use and support for the ASRS in the AOS literature, and a lack of other standardized alternatives, the ASRS was regarded as the best option. To adjust the ratings in line with our findings and severity level in the study sample, the modifications presented in table 2 were applied. All ratings with the ASRS were carried out in consensus by at least two raters. High attention on the influence of comorbidity and risk for perceptual overlap was taken for every item rating with the ASRS. Since this study was carried out in the clinical setting, the ratings were also discussed with the clinical SLPs and compared with the clinical judgement.

Recovery in this thesis was studied only by measures of function, with focus on the amount of change on a behavioral test result at two different timepoints. It is fully acknowledged that, in accordance with the framework of ICF, it is not sufficient to assess a function on a clinical assessment instrument without also considering how changes (recovery) in this function affects activities of daily communication and degree and of involvement across social communication contexts. These aspects were not considered in this thesis, which is a major shortcoming.

The resting-state fMRI findings are valuable since they provide the first preliminary evidence on how functional connectivity patterns relate to AOS recovery after stroke. However, the sample size was small. There are also common questions regarding difficulties to study patients with large lesions in speech and language areas by such methods, particularly in the early phase after stroke. Studies with larger sample size are indicated to confirm our findings.

The setting for this thesis was at a rehabilitation university clinic for team-based specialized rehabilitation for patients in working age. The study cohorts in all four studies were therefore younger compared to the overall stroke population, which limits the generalization of these findings to the stroke population as a whole. In addition, information on the prevalence of AOS in study III is based on a selected sample (inclusion an upper-limb impairment in the ProHand study), these measures does not hold for the general stroke population.

The multidisciplinary design of the ProHand study protocol entailed many possibilities to study and describe this patient group out of different research questions. The absolute focus of the ProHand study protocol was obviously on hand motor function, but already from the start in 2013, measurements of aphasia was collected at the first assessment in the subacute phase. By adding follow-up assessments of aphasia (in 2014) and of AOS (in 2015), it was also possible to collect longitudinal data on AOS and aphasia. Despite the broad and time consuming ProHand study protocol, including an MRI examination, all participants in this thesis that were included after 2015 showed up at the follow up at six months and participated in all the assessments of speech and language function. The missing data in study IV relates to artefacts in the MRI sequences for measures of FC, not to dropouts from any of the participants. By adapting study information and consent forms to an aphasia friendly format, individuals with severe speech and language impairments were also included.

6 CONCLUSIONS

This thesis set out to gain a better understanding of a group of patients about which the knowledge of diagnosis and prognosis is still incomplete. Despite its exploratory nature and limited sample sizes, some new insights may have been provided. The overall result in the first two studies adds to the body of research that emphasize the need for valid and reliable assessment instruments for AOS diagnosis, both for clinical settings and in research. In addition, the need for an instrument that can follow a patient with AOS, from the subacute phase into the chronic phase, was especially noted. The use of different AOS criteria, depending on severity level and phases in a disease, hinders information on longitudinal courses and identification of predictors for AOS recovery.

Regarding recovery of AOS, the findings of this thesis confirms the close link between language and speech motor function. Although the AOS sensorimotor impairments are truly separate impairments that interrupts the execution of a linguistic message, these two functions are closely intertwined. The observations made in the third and fourth study indicate that although the severity level of AOS primarily might relate to a speech-motor programming impairment in premotor regions, recovery of AOS is also related to the phonological output and to the influence of linguistic aphasia impairments.

Individuals with communication disability after stroke need appropriate rehabilitation interventions. An early, integrated assessment for AOS is needed, where the comorbidity of language and speech motor impairment in every separate individual is considered, to optimize rehabilitation outcomes and facilitate a return to premorbid communication activities.

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8 REFERENCES

Alia, C., Spalletti, C., Lai, S., Panarese, A., Lamola, G., Bertolucci, F., . . . Caleo, M. (2017). Neuroplastic changes following brain ischemia and their contribution to stroke recovery: Novel approaches in neurorehabilitation. *Frontiers in Cellular Neuroscience, 11*, 76. doi:10.3389/fncel.2017.00076

Allison, K. M., Cordella, C., Iuzzini-Seigel, J., & Green, J. R. (2020). Differential diagnosis of apraxia of speech in children and adults: A scoping review. *Journal of Speech, Language, and Hearing Research*, *63*(9), 2952-2994. doi:10.1044/2020_JSLHR-20-00061

Anderlini, Deanna, Wallis, Guy, & Marinovic, Welber. (2019). Language as a predictor of motor recovery: The case for a more global approach to stroke rehabilitation. *Neurorehabilitation and Neural Repair, 33*(3), 167-178. doi:10.1177/1545968319829454

Ardila, A. (2015). A proposed neurological interpretation of language evolution. *Behavioural Neurology, 2015*, 872487. doi:10.1155/2015/872487

Baker, C., Foster, A. M., D'Souza, S., Godecke, E., Shiggins, C., Lamborn, E., . . . Rose, M. L. (2021). Management of communication disability in the first 90 days after stroke: a scoping review. *Disability and Rehabilitation*, 1-15. doi:10.1080/09638288.2021.2012843

Ballard, K. J., Azizi, L., Duffy, J. R., McNeil, M. R., Halaki, M., O'Dwyer, N., . . . Robin, D. A. (2016). A predictive model for diagnosing stroke-related apraxia of speech. *Neuropsychologia, 81*, 129-139. doi:10.1016/j.neuropsychologia.2015.12.010

Ballard, K. J., Tourville, J. A., & Robin, D. A. (2014). Behavioral, computational, and neuroimaging studies of acquired apraxia of speech. *Frontiers in Human Neuroscience, 8*, 892. doi:10.3389/fnhum.2014.00892

Ballard, K. J., Wambaugh, J. L., Duffy, J. R., Layfield, C., Maas, E., Mauszycki, S., & McNeil, M. R. (2015). Treatment for acquired apraxia of speech: A systematic review of intervention research between 2004 and 2012. *American Journal of Speech-Language Pathology*, *24*(2), 316-337. doi:10.1044/2015_AJSLP-14-0118

Ballard, K. J., Robin, D. A., & Folkins, J. W. (2003). An integrative model of speech motor control: A response to Ziegler. *Aphasiology*, *17*(1), 37-48.

Ballard, K. J., Granier, J. P., & Robin, D. A. (2000). Understanding the nature of apraxia of speech: Theory, analysis, and treatment. *Aphasiology*, *14*(10), 969-995.

Ballester, B. R., Maier, M., Duff, A., Cameirão, M., Bermúdez, S., Duarte, E., ... & Verschure, P. F. (2019). A critical time window for recovery extends beyond one-year post-stroke. *Journal of neurophysiology*.

Basilakos, A. (2018). Contemporary approaches to the management of post-stroke apraxia of speech. In *Seminars in speech and language* (Vol. 39, No. 01, pp. 025-036). Thieme Medical Publishers. doi:10.1055/s-0037-1608853

Basilakos, A., Yourganov, G., den Ouden, D. B., Fogerty, D., Rorden, C., Feenaughty, L., & Fridriksson, J. (2017). A multivariate analytic approach to the differential diagnosis of apraxia of speech. *Journal of Speech, Language, and Hearing Research*, *60*(12), 3378-3392. doi:10.1044/2017_JSLHR-S-16-0443

Bayles, K., McCullough, K., & Tomoeda, C. K. (2018). *Cognitive-communication disorders of MCI and dementia. Definition, assessment, and clinical management*. Third edition.Plural Publishing.

Benson, D. F., & Ardila, A. (1996). *Aphasia: A clinical perspective*. Oxford University Press on Demand.

Benton, E., & Bryan, K. (1996). Right cerebral hemisphere damage: Incidence of language problems. *International Journal of Rehabilitation Research, 19*(1), 47–54.

Berthier, M. L., Garcia-Casares, N., Walsh, S. F., Nabrozidis, A., de Mier, R. J. R., Green, C., ... & Pulvermueller, F. (2011). Recovery from post-stroke aphasia: lessons from brain imaging and implications for rehabilitation and biological treatments. *Discovery medicine*, *12*(65), 275-289.

Binkofski, F., & Buccino, G. (2006). The role of ventral premotor cortex in action execution and action understanding. *Journal of Physiology-Paris*, *99*(4-6), 396-405. doi:10.1016/j.jphysparis.2006.03.005

Binkofski, F., Buccino, G., Posse, S., Seitz, R. J., Rizzolatti, G., & Freund, H. J. (1999). A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *European Journal of Neuroscience*, *11*(9), 3276-3286. doi:10.1046/j.1460-9568.1999.00753.x

Bislick, L. (2020). A phonomotor approach to apraxia of speech treatment. *American Journal of Speech-Language Pathology*, *29*(4), 2109-2130. doi:10.1044/2020_AJSLP-19-00116

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic resonance in medicine*, *34*(4), 537-541.

Bohland, J. W., Bullock, D., & Guenther, F. H. (2010). Neural representations and mechanisms for the performance of simple speech sequences. *Journal of cognitive neuroscience*, *22*(7), 1504-1529. doi:10.1162/jocn.2009.21306

Botha, H., Duffy, J. R., Strand, E. A., Machulda, M., Whitwell, J. L., & Josephs, K. A. (2014). Nonverbal oral apraxia in primary progressive aphasia and apraxia of speech. *Neurology, 82*(19), 1729-1735. doi:10.1212/WNL.0000000000000412

Botha, H., Utianski, R. L., Whitwell, J. L., Duffy, J. R., Clark, H. M., Strand, E. A., ... & Jones, D. T. (2018). Disrupted functional connectivity in primary progressive apraxia of speech. *NeuroImage: Clinical*, *18*, 617-629. doi:10.1016/j.nicl.2018.02.036

Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bulletin et Memoires de la Societe anatomique de Paris*, *6*, 330-357.

Broca, P. (1865). Sur le siège de la faculté du langage articulé. *Bullentin de la societé anthropologique 6,* 377-393. E. A. Berker, A. H. Berker, & A. Smith (trans.) (1986): Translation of Broca's 1865 report, *Archives of Neurology 43,* 1065-1072.

Cherney, L. R., & Small, S. L. (2009). Aphasia, apraxia of speech, and dysarthria. In Stein J., Harvey, R.L., Macko, R. F., Winstein, C.J., Zorowitz, R.D. *Stroke recovery and rehabilitation*, New York: Demos Medical Pub.

Code, C. (2021). Contemporary issues in apraxia of speech. *Aphasiology*, *35*(4), 391-396.

Corballis, M. C. (2003). From mouth to hand: gesture, speech, and the evolution of right-handedness. *Behavioral and brain sciences*, *26*(2), 199-208. doi:10.1017/s0140525x03000062

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C. D., Siegel, J. S., . . . Shulman, G. L. (2015). Common behavioral clusters and subcortical anatomy in stroke. *Neuron, 85*(5), 927-941. doi:10.1016/j.neuron.2015.02.027

Cordes, D., Haughton, V. M., Arfanakis, K., Wendt, G. J., Turski, P. A., Moritz, C. H., ... & Meyerand, M. E. (2000). Mapping functionally related regions of brain with functional connectivity MR imaging. *American journal of neuroradiology*, *21*(9), 1636-1644.

Côté, H., Payer, M., Giroux, F., & Joanette, Y. (2007). Towards a description of clinical communication impairment profiles following right-hemisphere damage. *Aphasiology*, *21*(6-8), 739-749.

Cramer, S. C. (2008). Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Annals of neurology*, *63*(3), 272-287.

Croot, K. (2002). Diagnosis of AOS: definition and criteria. In *Seminars in speech and language* (Vol. 23, No. 04, pp. 267-280). Thieme Medical Publishers, New York, NY .

Croot, K., Ballard, K., Leyton, C. E., & Hodges, J. R. (2012). Apraxia of speech and phonological errors in the diagnosis of nonfluent/agrammatic and logopenic variants of primary progressive aphasia. *Journal of speech, language, and hearing research, 55*(5). doi:10.1044/1092-4388(2012/11-0323)

Dabul, Barbara (1979). *Apraxia battery for adults*. In. Tigard, Or. C.C. Publications.

Dabul, Barbara. (2000). *ABA-2: Apraxia battery for adults*: Pro-ed Austin, TX.

Dalemans, R., Wade, D. T., Van den Heuvel, W. J., & De Witte, L. P. (2009). Facilitating the participation of people with aphasia in research: a description of strategies. *Clinical Rehabilitation*, *23*(10), 948-959.

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the national academy of sciences*, *103*(37), 13848-13853.

Darley, Frederic L., Brown, Joe R., & Aronson, Arnold E. (1975). *Motor speech disorders*. Philadelphia: Saunders.

Donnan, G. A., Fisher, M., Macleod, M.,, & Davis, S. M. (2008). Stroke. *Lancet*, *371,* 1612-1623

Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature, 384*(6605), 159-161. doi:10.1038/384159a0

Duffy, J. R., Strand, E. A., Clark, H., Machulda, M., Whitwell, J. L., & Josephs, K. A. (2015). Primary progressive apraxia of speech: Clinical features and acoustic and neurologic correlates. *American journal of speech-language pathology*, *24*(2), 88-100. doi:10.1044/2015_AJSLP-14-0174

Duffy, J. R. (2020). *Motor speech disorders : substrates, differential diagnosis, and management*. Missouri: Elsevier.

Duffy, J. R., & Josephs, Keith A. (2012). The diagnosis and understanding of apraxia of speech: Why Including Neurodegenerative Etiologies May Be Important. *Journal of speech, language, and hearing research, 55*(5). doi:10.1044/1092-4388(2012/11-0309)

Duncan, E. S., Donovan, N. J., & Sajjadi, S. A. (2020). Clinical assessment of characteristics of apraxia of speech in primary progressive aphasia. *American journal of speech-language pathology*, *29*(1S), 485-497. doi:10.1044/2019_AJSLP-CAC48-18-0225

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

Eickhoff, S. B., & Grefkes, C. (2011). Approaches for the integrated analysis of structure, function and connectivity of the human brain. *Clinical EEG and neuroscience, 42*(2), 107-121. doi:10.1177/155005941104200211

Eickhoff, S. B., Heim, S., Zilles, K., & Amunts, K. (2009). A systems perspective on the effective connectivity of overt speech production. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 367*(1896), 2399-2421. doi:10.1098/rsta.2008.0287

Fox, M, & Raichle, M. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature reviews. Neuroscience, 8*(9), 700-711. doi:10.1038/nrn2201

Friston, K. (2002). Functional integration and inference in the brain. *Progress in neurobiology*, *68*(2), 113-143. doi:10.1016/s0301-0082(02)00076-x

Friston, K. (1994). Functional and effective connectivity in neuroimaging: a synthesis. *Human brain mapping*, *2*(1-2), 56-78.

Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., & Steglind, S. (1975). The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scandinavian journal of rehabilitation medicine, 7*(1), 13-31.

Gajardo-Vidal, A., Lorca-Puls, D. L., Hope, T. M., Parker Jones, O., Seghier, M. L., Prejawa, S., ... & Price, C. J. (2018). How right hemisphere damage after stroke can impair speech comprehension. *Brain*, *141*(12), 3389-3404.

GBD 2019 Stroke Collaborators. (2021). Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet. Neurology*, *20*(10), 795.

Gerardin, E., Sirigu, A., Lehéricy, S., Poline, J. B., Gaymard, B., Marsault, C., ... & Le Bihan, D. (2000). Partially overlapping neural networks for real and imagined hand movements. *Cerebral cortex*, *10*(11), 1093-1104. doi:10.1093/cercor/10.11.1093

Gerstenecker, A., & Lazar, R. M. (2019). Language recovery following stroke. *The Clinical Neuropsychologist*, *33*(5), 928-947.

Ginex, V., Gilardone, G., Viganò, M., Monti, A., Judica, E., Passaro, I., ... & Corbo, M. (2020). Interaction between recovery of motor and language abilities after stroke. *Archives of physical medicine and rehabilitation*, *101*(8), 1367-1376.

Gladstone, David J., Danells, Cynthia J., & Black, Sandra E. (2016). The Fugl-Meyer assessment of motor recovery after stroke: A critical review of its measurement properties. *Neurorehabilitation and Neural Repair, 16*(3), 232-240. doi:10.1177/154596802401105171

Graff-Radford, J., Jones, D. T., Strand, E. A., Rabinstein, A. A., Duffy, J. R., & Josephs, K. A. (2014). The neuroanatomy of pure apraxia of speech in stroke. *Brain and language*, *129*, 43-46. doi:10.1016/j.bandl.2014.01.004

Grefkes, C., & Fink, G. R. (2020). Recovery from stroke: current concepts and future perspectives. *Neurological research and practice*, *2*(1), 1-10.

Grindrod, C. M., & Baum, S. R. (2005). Hemispheric contributions to lexical ambiguity resolution in a discourse context: Evidence from individuals with unilateral left and right hemisphere lesions. *Brain and cognition*, *57*(1), 70-83.

Guenther, F. H., Ghosh, S. S., & Tourville, J. A. (2006). Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain and language*, *96*(3), 280-301.

Guenther, F. H., Tourville, J. A., & Bohland, J. W. (2015). Speech production. In *Brain Mapping* (pp. 435-444).

Haley, K. L., & Jacks, A. (2019). Word-level prosodic measures and the differential diagnosis of apraxia of speech. *Clinical linguistics & phonetics*, *33*(5), 479-495. doi:10.1080/02699206.2018.1550813

Haley, K. L., Jacks, A., Jarrett, J., Ray, T., Cunningham, K. T., Gorno-Tempini, M. L., & Henry, M. L. (2021). Speech metrics and samples that differentiate between nonfluent/agrammatic and logopenic variants of primary progressive aphasia. *Journal of Speech, Language, and Hearing Research*, *64*(3), 754-775. doi:10.1044/2020_JSLHR-20-00445

Haley, K. L., Shafer, J. N., Harmon, T. G., & Jacks, A. (2016). Recovering with acquired apraxia of speech: The first 2 years. *American Journal of Speech-Language Pathology*, *25*(4S), S687-S696. doi:10.1044/2016_AJSLP-15-0143

Haley, K. L., Jacks, A., de Riesthal, M., Abou-Khalil, R., & Roth, H. L. (2012). Toward a quantitative basis for assessment and diagnosis of apraxia of speech. *Journal of speech, language, and hearing research, 55*(5). doi:10.1044/1092-4388(2012/11-0318

Haley, K. L., Smith, M., & Wambaugh, J. L. (2019). Sound distortion errors in aphasia with apraxia of speech. *American Journal of Speech-Language Pathology*, *28*(1), 121-135. doi:10.1044/2018_ajslp-17-0186

Halsband, U., Ito, N., Tanji, J., & Freund, H. J. (1993). The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain*, *116*(1), 243-266. doi:10.1093/brain/116.1.243

Hartelius, L. (2015). Dysartri-bedömning och intervention. *Lund: Studentlitteratur*.

Hartwigsen, Gesa, Saur, Dorothee, Price, Cathy J., Baumgaertner, Annette, Ulmer, Stephan, & Siebner, Hartwig R. (2013). Increased facilitatory connectivity from the Pre-SMA to the left dorsal premotor cortex during pseudoword repetition. *Journal of cognitive neuroscience, 25*(4), 580-594. doi:10.1162/jocn_a_00342

Hawe, Rachel L., Scott, Stephen H., & Dukelow, Sean P. (2019). Taking proportional out of stroke Recovery. *Stroke, 50*(1), 204-211. doi:10.1161/strokeaha.118.023006

Heim, S., Amunts, K., Hensel, T., Grande, M., Huber, W., Binkofski, F., & Eickhoff, S. B. (2012). The role of human parietal area 7A as a link between sequencing in hand actions and in overt speech production. *Frontiers in psychology*, *3*, 534. doi:10.3389/fpsyg.2012.00534

Heiss, W. D., & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language, 98*(1), 118-123. doi:10.1016/j.bandl.2006.02.002

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature reviews neuroscience*, *8*(5), 393-402.

Hickok, G. (2012). The cortical organization of speech processing: feedback control and predictive coding the context of a dual-stream model. *Journal of Communication Disorders, 45*(6), 393-402. doi:10.1016/j.jcomdis.2012.06.004

Hickok, G. (2014). The architecture of speech production and the role of the phoneme in speech processing. *Language, Cognition and Neuroscience*, *29*(1), 2-20. doi:10.1080/01690965.2013.834370

Hickok, G., Rogalsky, C., Chen, R., Herskovits, E. H., Townsley, S., & Hillis, A. E. (2014). Partially overlapping sensorimotor networks underlie speech praxis and verbal short-term memory: evidence from apraxia of speech following acute stroke. *Frontiers in Human Neuroscience*, *8*, 649. doi:10.3389/fnhum.2014.00649

Hillis, A. E., Beh, Y. Y., Sebastian, R., Breining, B., Tippett, D. C., Wright, A., ... & Fridriksson, J. (2018). Predicting recovery in acute poststroke aphasia. *Annals of neurology*, *83*(3), 612-622.

Hillis, A. E., Work, M., Barker, P. B., Jacobs, M. A., Breese, E. L., & Maurer, K. (2004). Re-examining the brain regions crucial for orchestrating speech articulation. *Brain, 127*(7), 1479-1487. doi:10.1093/brain/awh172

Hope, T. M., Seghier, M. L., Leff, A. P., & Price, C. J. (2013). Predicting outcome and recovery after stroke with lesions extracted from MRI images. *Neuroimage Clinical, 2*, 424-433. doi:10.1016/j.nicl.2013.03.005

Horwitz, Barry, Amunts, Katrin, Bhattacharyya, Rajan, Patkin, Debra, Jeffries, Keith, Zilles, Karl, & Braun, Allen R. (2003). Activation of Broca's area during the production of spoken and signed language: a combined cytoarchitectonic mapping and PET analysis. *Neuropsychologia, 41*(14), 1868-1876. doi:10.1016/s0028-3932(03)00125-8

Jayes, M., & Palmer, R. (2014). Initial evaluation of the Consent Support Tool: a structured procedure to facilitate the inclusion and engagement of people with aphasia in the informed consent process. *International journal of speech-language pathology*, *16*(2), 159-168. doi:10.3109/17549507.2013.795999

Josephs, K. A., Duffy, J. R., Clark, H. M., Utianski, R. L., Strand, E. A., Machulda, M. M., ... & Whitwell, J. L. (2021). A molecular pathology, neurobiology, biochemical, genetic and neuroimaging study of progressive apraxia of speech. *Nature Communications*, *12*(1), 1-17. doi:10.1038/s41467-021-23687-8

Josephs, K. A., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Master, A. V., . . . Whitwell, J. L. (2012). Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. *Brain, 135*(Pt 5), 1522-1536. doi:10.1093/brain/aws032

Josephs, K. A., Duffy, J. R., Strand, E. A., Whitwell, J. L., Layton, K. F., Parisi, J. E., . . . Petersen, R. C. (2006). Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain, 129*(6), 1385-1398. doi:10.1093/brain/awl078

Kagan, A., & Kimelman, M. D. (1995). Informed consent in aphasia research: Myth or reality. *Clinical aphasiology*, *23*, 65-75.

Kertesz, A. (1979). *Aphasia and associated disorder: Taxonomy, localization and recovery*. Grune & Stratton. Inc., New York.

Kiran, S. (2012). What is the nature of poststroke language recovery and reorganization?. *International Scholarly Research Notices*, *2012*. doi:10.5402/2012/786872

Kiran, S., & Thompson, C. K. (2019). Neuroplasticity of language networks in aphasia: Advances, updates, and future challenges. *Frontiers in Neurology*, *10*, 295. doi:10.3389/fneur.2019.00295

Klingbeil, J., Wawrzyniak, M., Stockert, A., & Saur, D. (2019). Resting-state functional connectivity: An emerging method for the study of language networks in post-stroke aphasia. *Brain and Cognition, 131*, 22-33. doi:10.1016/j.bandc.2017.08.005

Knollman-Porter, K. (2008). Acquired apraxia of speech: a review. *Topics in stroke rehabilitation*, *15*(5), 484-493. . doi:10.1310/tsr1505-484

Koo, T. K., & Li, M. Y. (2016). A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *Journal of chiropractic medicine*, *15*(2), 155-163.

Kroliczak, G., Buchwald, M., Kleka, P., Klichowski, M., Potok, W., Nowik, A. M., . . . Piper, B. J. (2021). Manual praxis and language-production networks, and their links to handedness. *Cortex, 140*, 110-127. doi:10.1016/j.cortex.2021.03.022

Lazar, R. M., Minzer, B., Antoniello, D., Festa, J. R., Krakauer, J. W., & Marshall, R. S. (2010). Improvement in aphasia scores after stroke is well predicted by initial severity. *Stroke, 41*(7), 1485-1488. doi:10.1161/STROKEAHA.109.577338

MacNeilage, P. F. (2003). Mouth to hand and back again? Could language have made those journeys? *Behavioral and Brain Sciences, 26*(02). doi:10.1017/s0140525x03490067

Mailend, M. L., Maas, E., & Story, B. H. (2021). Apraxia of speech and the study of speech production impairments: Can we avoid further confusion? Reply to Romani (2021). *Cognitive neuropsychology*, 1-9. doi:10.1080/02643294.2021.2009790

Mailend, M.L., & Maas, E. (2020). To lump or to split? Possible subtypes of apraxia of speech. *Aphasiology*, 1-22. doi:10.1080/02687038.2020.1836319

Marchi, N. A., Ptak, R., Di Pietro, M., Schnider, A., & Guggisberg, A. G. (2017). Principles of proportional recovery after stroke generalize to neglect and aphasia. *European Journal of Neurology, 24*(8), 1084-1087. doi:10.1111/ene.13296

Marien, P., Ackermann, H., Adamaszek, M., Barwood, C. H., Beaton, A., Desmond, J., . . . Ziegler, W. (2014). Consensus paper: Language and the cerebellum: an ongoing enigma. *Cerebellum, 13*(3), 386-410. doi:10.1007/s12311-013-0540-5

Mateos-Aparicio, P., & Rodríguez-Moreno, A. (2019). The impact of studying brain plasticity. *Frontiers in cellular neuroscience*, *13*, 66.

McNeil, M. R., Ballard, K., Duffy, J. R., & Wambaugh, J. (2016). Apraxia of speech: theory, assessment, differential diagnosis and treatment: past, present and future, chapter 9. In P. van Lieshout, Maassen, B., Terband, H. (Ed.), *Speech motor control in normal and disordered speech: Future developments in theory and methodology*. Rockville, MD: ASHA Press.

Miller, Hilary E., & Guenther, Frank H. (2020). Modelling speech motor programming and apraxia of speech in the DIVA/GODIVA neurocomputational framework. *Aphasiology*, 1-18. doi:10.1080/02687038.2020.1765307

Milner, D., & Goodale, M. (2006). *The visual brain in action*. Oxford: Oxford University Press.

Mitchell, Claire, Gittins, Matthew, Tyson, Sarah, Vail, Andy, Conroy, Paul, Paley, Lizz, & Bowen, Audrey. (2020). Prevalence of aphasia and dysarthria among inpatient stroke survivors: describing the population, therapy provision and outcomes on discharge. *Aphasiology, 35*(7), 950-960. doi:10.1080/02687038.2020.1759772

Mohr, J. P., & Kejda-Scharler, J. (2012). Middle cerebral artery territory syndromes. In L. R. Capland &J. van Gijn (Eds.), Stroke syndromes (pp. 314-363). New York, NY: Cambridge University Press.

Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W., & Davis, K. R. (1978). Broca aphasia: pathologic and clinical. *Neurology*, *28*(4), 311-311.

Molloy, J., & Jagoe, C. (2019). Use of diverse diagnostic criteria for acquired apraxia of speech: A scoping review. *International journal of language & communication disorders*, *54*(6), 875-893. doi:10.1111/1460-6984.12494

Moser, D., Basilakos, A., Fillmore, P., & Fridriksson, J. (2016). Brain damage associated with apraxia of speech: evidence from case studies. *Neurocase, 22*(4), 346-356. doi:10.1080/13554794.2016.1172645

Mumby, K., Bowen, A., & Hesketh, A. (2007). Apraxia of speech: how reliable are speech and language therapists' diagnoses?. *Clinical Rehabilitation*, *21*(8), 760-767.

Naeser, M. A., Martin, P. I., Nicholas, M., Baker, E. H., Seekins, H., Helm-Estabrooks, N., . . . Pascual-Leone, A. (2005). Improved naming after TMS treatments in a chronic, global aphasia patient--case report. *Neurocase, 11*(3), 182-193. doi:10.1080/13554790590944663

New, A. B., Robin, D. A., Parkinson, A. L., Duffy, J. R., McNeil, M. R., Piguet, O., . . . Ballard, K. J. (2015). Altered resting-state network connectivity in stroke patients with and without apraxia of speech. *Neuroimage Clin, 8*, 429-439. doi:10.1016/j.nicl.2015.03.013

Nudo, R. J. (2006). Mechanisms for recovery of motor function following cortical damage. *Current opinion in neurobiology*, *16*(6), 638-644.

Ogar, J., Slama, H., Dronkers, N., Amici, S., & Luisa Gorno-Tempini, M. (2005). Apraxia of speech: an overview. *Neurocase*, *11*(6), 427-432.

Ogar, J., Willock, S., Baldo, J., Wilkins, D., Ludy, C., & Dronkers, N. (2006). Clinical and anatomical correlates of apraxia of speech. *Brain and Language, 97*(3), 343-350. doi:10.1016/j.bandl.2006.01.008

Papathanasiou, I., Coppens, P., Potagas, C. *Aphasia and Related Neurogenic Communication Disorders*. Burlington, VT: Jones & Bartlett Learning (2016).

Peach, R. K., & Tonkovich, J. D. (2004). Phonemic characteristics of apraxia of speech resulting from subcortical hemorrhage. *Journal of Communication Disorders, 37*(1), 77-90. doi:10.1016/j.jcomdis.2003.08.001

Prabhakaran, S., Zarahn, E., Riley, C., Speizer, A., Chong, J. Y., Lazar, R. M., ... & Krakauer, J. W. (2008). Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehabilitation and neural repair*, *22*(1), 64-71.

Primaßin, A., Scholtes, N., Heim, S., Huber, W., Neuschäfer, M., Binkofski, F., & Werner, C. J. (2015). Determinants of concurrent motor and language recovery during intensive therapy in chronic stroke patients: four single-case studies. *Frontiers in neurology*, *6*, 215.

Ramsey, L. E., Siegel, J. S., Lang, C. E., Strube, M., Shulman, G. L., & Corbetta, M. (2017). Behavioural clusters and predictors of performance during recovery from stroke. *Nature human behaviour*, *1*(3), 1-10.

Richardson, J. D., Fillmore, P., Rorden, C., Lapointe, L. L., & Fridriksson, J. (2012). Re-establishing Broca's initial findings. *Brain and Language, 123*(2), 125-130. doi:10.1016/j.bandl.2012.08.007

Rijntjes, M. (2006). Mechanisms of recovery in stroke patients with hemiparesis or aphasia: new insights, old questions and the meaning of therapies. *Current opinion in neurology*, *19*(1), 76-83. doi:10.1097/01.wco.0000203886.28068.38

Rijntjes, M., & Weiller, C. (2002). Recovery of motor and language abilities after stroke: the contribution of functional imaging. *Progress in neurobiology*, *66*(2), 109-122.

Riley, J. D., Le, V., Der-Yeghiaian, L., See, J., Newton, J. M., Ward, N. S., & Cramer, S. C. (2011). Anatomy of stroke injury predicts gains from therapy. *Stroke*, *42*(2), 421-426.

Rose, T., Worrall, L., & McKenna, K. (2003). The effectiveness of aphasia-friendly principles for printed health education materials for people with aphasia following stroke. *Aphasiology*, *17*(10), 947-963.

Sair, H. I., Agarwal, S., & Pillai, J. J. (2017). Application of resting state functional MR imaging to presurgical mapping: Language mapping. *Neuroimaging Clinical, 27*(4), 635-644. doi:10.1016/j.nic.2017.06.003

Sharp, D. J., Turkheimer, F. E., Bose, S. K., Scott, S. K., & Wise, R. J. (2010). Increased frontoparietal integration after stroke and cognitive recovery. *Annals of neurology*, *68*(5), 753-756.

Sheppard, S. M., & Hillis, A. E. (2018). That's right! Language comprehension beyond the left hemisphere. *Brain*, *141*(12), 3280-3289.

Siegel, J. S., Ramsey, L. E., Snyder, A. Z., Metcalf, N. V., Chacko, R. V., Weinberger, K., ... & Corbetta, M. (2016). Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proceedings of the National Academy of Sciences*, *113*(30), E4367-E4376.

Simmons-Mackie, N., & Kagan, A. (2007). Application of the ICF in aphasia. In *Seminars in speech and language* (Vol. 28, No. 04, pp. 244-253).Thieme Medical Publishers.

Simonyan, K., & Fuertinger, S. (2015). Speech networks at rest and in action: interactions between functional brain networks controlling speech production. *Journal of neurophysiology*, *113*(7), 2967-2978.

Sims, J. A., Kapse, K., Glynn, P., Sandberg, C., Tripodis, Y., & Kiran, S. (2016). The relationships between the amount of spared tissue, percent signal change, and accuracy in semantic processing in aphasia. *Neuropsychologia*, *84*, 113-126.

Small, S. L., Buccino, G., & Solodkin, A. (2013). Brain repair after stroke—a novel neurological model. *Nature Reviews Neurology*, *9*(12), 698-707. doi:10.1038/nrneurol.2013.222

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.

Smitha, K. A., Akhil Raja, K., Arun, K. M., Rajesh, P. G., Thomas, B., Kapilamoorthy, T. R., & Kesavadas, C. (2017). Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. *The neuroradiology journal*, *30*(4), 305-317.

Stephan, K. E., Harrison, L. M., Penny, W. D., & Friston, K. J. (2004). Biophysical models of fMRI responses. *Current opinion in neurobiology*, *14*(5), 629-635. doi:10.1016/j.conb.2004.08.006

Strand, E. A., Duffy, J. R., Clark, H. M., & Josephs, K. (2014). The Apraxia of Speech Rating Scale: a tool for diagnosis and description of apraxia of speech. *Journal of Communication Disorders, 51*, 43-50. doi:10.1016/j.jcomdis.2014.06.008

Strand, E. A. (2011). Darley's contributions to the understanding and diagnosis of developmental apraxia of speech. *Aphasiology, 15*(3), 291-304. doi:10.1080/02687040042000278

Tallberg, I. M. (2005). The Boston Naming Test in Swedish: normative data. *Brain and Language, 94*(1), 19-31. doi:10.1016/j.bandl.2004.11.004

Tie, Y., Rigolo, L., Norton, I. H., Huang, R. Y., Wu, W., Orringer, D., ... & Golby, A. J. (2014). Defining language networks from resting-state fMRI for surgical planning—A feasibility study. *Human brain mapping*, *35*(3), 1018-1030. doi:10.1002/hbm.22231

Tomasi, D., & Volkow, N. D. (2012). Resting functional connectivity of language networks: characterization and reproducibility. *Molecular psychiatry*, *17*(8), 841-854. doi:10.1038/mp.2011.177

Trupe, L. A., Varma, D. D., Gomez, Y., Race, D., Leigh, R., Hillis, A. E., & Gottesman, R. F. (2013). Chronic apraxia of speech and Broca's area. *Stroke, 44*(3), 740-744. doi:10.1161/STROKEAHA.112.678508

Turkeltaub, P. E., Messing, S., Norise, C., & Hamilton, R. H. (2011). Are networks for residual language function and recovery consistent across aphasic patients? *Neurology*, *76*(20), 1726-1734.

van Delden, A. E. Q., Peper, C. E., Beek, P. J., & Kwakkel, G. (2012). Unilateral versus bilateral upper limb exercise therapy after stroke: a systematic review. *Journal of rehabilitation medicine*, *44*(2), 106-117.

van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology, 20*(8), 519-534. doi:10.1016/j.euroneuro.2010.03.008

van der Vliet, R., Selles, R. W., Andrinopoulou, E. R., Nijland, R., Ribbers, G. M., Frens, M. A., ... & Kwakkel, G. (2020). Predicting upper limb motor impairment recovery after stroke: a mixture model. *Annals of neurology*, *87*(3), 383-393.

van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., Read, S., & Copland, D. A. (2014). A functional MRI study of the relationship between naming treatment outcomes and resting state functional connectivity in post-stroke aphasia. *Human brain mapping*, *35*(8), 3919-3931.

Wade, D. T., Wood, V. A., & Hewer, R. L. (1985). Recovery after stroke--the first 3 months. *Journal of Neurology, Neurosurgery & Psychiatry*, *48*(1), 7-13. doi:10.1136/jnnp.48.1.7

Wambaugh, J. L., Bailey, D. J., Mauszycki, S. C., & Bunker, L. D. (2019). Interrater reliability and concurrent validity for the Apraxia of Speech Rating Scale 3.0: Application with persons with acquired apraxia of speech and aphasia. *American Journal of Speech-Language Pathology*, *28*(2S), 895-904. doi:10.1044/2018_AJSLP-MSC18-18-0099

Wambaugh, J. L., Duffy, J. R., McNeil, M. R., Robin, D. A., & Rogers, M. A. (2006). Treatment guidelines for acquired apraxia of speech: A synthesis and evaluation of the evidence. *Journal of Medical Speech-Language Pathology*, *14*(2)

Wambaugh, J., Shuster, L., Bailey, D. J., Mauszycki, S., Kean, J., Nessler, C., . . . Brunsvold, J. (2016). Self-judgments of word production accuracy in acquired apraxia of speech. *American Journal of Speech-Language Pathology, 25*(4S), 716-728.

Wambaugh, J. L., Wright, S., Nessler, C., Mauszycki, S. C., Bunker, L., Boss, E., ... & Doyle, P. J. (2020). Further study of the effects of treatment intensity on outcomes of sound production treatment for acquired apraxia of speech: Does dose frequency matter?. *American journal of speech-language pathology*, *29*(1), 263-285. doi:10.1044/2019_AJSLP-19-00005

Watila, M. M., & Balarabe, S. A. (2015). Factors predicting post-stroke aphasia recovery. *Journal of the neurological sciences*, *352*(1-2), 12-18. doi:10.1016/j.jns.2015.03.020

Weiss, P. H., Ubben, S. D., Kaesberg, S., Kalbe, E., Kessler, J., Liebig, T., & Fink, G. R. (2016). Where language meets meaningful action: a combined behavior and lesion analysis of aphasia and apraxia. *Brain Structure and Function*, *221*(1), 563-576. doi:10.1007/s00429-014-0925-3

Wertz, Robert T., LaPointe, Leonard L., & Rosenbek, John C. (1984). *Apraxia of speech in adults the disorder and its management*. Orlando: Grune & Stratton.

Whiteside, S. P., Dyson, L., Cowell, P. E., & Varley, R. A. (2015). The relationship between apraxia of speech and oral apraxia: association or dissociation?. *Archives of Clinical Neuropsychology*, *30*(7), 670-682. doi:10.1093/arclin/acv051

Woodbury, M. L., Velozo, C. A., Richards, L. G., & Duncan, P. W. (2013). Rasch analysis staging methodology to classify upper extremity movement impairment after stroke. *Archives of physical medicine and rehabilitation*, *94*(8), 1527-1533. doi:10.1016/j.apmr.2013.03.007

Worrall, L., Rose, T., Howe, T., Brennan, A., Egan, J., Oxenham, D., & McKenna, K. (2005). Access to written information for people with aphasia. *Aphasiology*, *19*(10-11), 923-929.

Zhao, L. R., & Willing, A. (2018). Enhancing endogenous capacity to repair a stroke-damaged brain: An evolving field for stroke research. *Progress in neurobiology*, *163*, 5-26.

Zhu, D., Chang, J., Freeman, S., Tan, Z., Xiao, J., Gao, Y., & Kong, J. (2014). Changes of functional connectivity in the left frontoparietal network following aphasic stroke. *Frontiers in Behavioral Neuroscience*, *8*, 167.

Ziegler, W. (2008). Apraxia of speech, chaper 13. *Handbook of clinical neurology*, *88*, 269-285.

Ziegler, Wolfram, Aichert, Ingrid, & Staiger, Anja. (2012). Apraxia of Speech: Concepts and controversies. *Journal of speech, language, and hearing research, 55*(5). doi:10.1044/1092-4388(2012/12-0128)