Aphasia after stroke. From admission to one-year post-stroke

Lesion location, lesion size, and self-reported symptoms of anxiety and depression

Hedda Døli

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Scientific environment

I have been employed as a Ph.D. research fellow at the Department of Biological and Medical Psychology, The Faculty of Psychology, University of Bergen during my work with the present thesis (2013-2017). During this period, I have been a member of the International Graduate School on Integrated Neuroscience (IGSIN), and the Bergen Logopedic Research Group (B.LOG).

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My main supervisor has been Professor Wenche Andersen Helland, while co-supervisors have been Professor Turid Helland, Professor Karsten Specht and Professor Halvor Næss. Turid Helland, Wenche Andersen Helland and Karsten Specht are all employed at the Department of Biological and Medical Psychology, University of Bergen. Specht is also affiliated with the Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway. Wenche Andersen Helland is also affiliated with Helse Fonna. Halvor Næss is a professor of medicine at the University of Bergen and a medical doctor at Haukeland University Hospital.

Prior to the present thesis I received funding from Helse Bergen to plan and write my project description. The data collection in the present thesis was derived from clinical data from the NORSTROKE registry at the Neurology Department at Haukeland University Hospital, and the Early Supported Discharge after Stroke in Bergen-project. The Early Supported Discharge after Stroke in Bergen-project was supported by grants from the Norwegian Research Council, the Western Norway Regional Health Trust, the Ministry of Health, and the Sophies Minde Foundation. Haukeland University Hospital and the Municipality of Bergen have contributed financially to carry out the Early Supported Discharge after Stroke in Bergen-project.

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Abstract in English

Aphasia is an acquired communication disorder that deeply affects the life of the person, and his or her surroundings. Aphasia is most commonly a result of stroke. Lesion location and lesion size affects the severity and recovery of aphasia, but there is no clear consensus as to which variables that precisely predict aphasia outcome.

The main aim of this thesis was to investigate the relationships between lesion size, lesion location, and aphasia in acute, subacute, and chronic stages post-stroke. Further aims were to investigate the emotional consequences of aphasia by investigating symptoms of anxiety and depression and quality of life in persons with and without aphasia after stroke. The aims were investigated in three papers, of which two papers assessed lesion size and lesion location in acute and chronic stroke, and one paper addressed the emotional consequences of aphasia in the chronic stages post-stroke.

All three papers were based on data from the Bergen NORSTROKE registry and the Early Supported Discharge after Stroke in Bergen – study (ESD-study). The Bergen NORSTROKE study is a large stroke registry at Haukeland University Hospital. The ESD-study was a randomized controlled trial that started in 2008 and was finalized in 2014. In the present thesis, the data were collected at three different time points, in the acute stages post-stroke (within seven days post-onset of initial symptoms), three months post-stroke, and finally, twelve months post-stroke.

In Paper I we investigated the associations between lesion location, lesion size, and aphasia severity in patients with aphasia in the acute stages post-stroke. We used a voxel-based lesion-symptom mapping method to explore the statistical relationship between aphasia severity and lesion location. The main finding of this study was that lesion size was significantly associated with overall aphasia severity, and all subtests from the Norwegian Basic Aphasia Assessment (NBAA). Our lesion analyses yielded that performance in naming was associated with lesions within the Rolandic operculum and the superior temporal gyrus. To investigate the patients further, we divided the patients into two groups based on their performance on the auditory

comprehension subtest from the NBAA. The high comprehension group consisted of patients with mild auditory comprehension deficits, while the low comprehension group consisted of patients with moderate to severe auditory comprehension deficits. The patients in the high comprehension group, had lesions within Broca's area, insula, the superior temporal gyrus, and Heschl's gyrus that were associated with overall aphasia severity, difficulties with repetition, naming, and reading aloud. For all subtests, except naming, lesions within the supramarginal gyrus, postcentral gyrus, angular gyrus, inferior parietal lobule, and superior parietal lobule were significant regions. Although different lesion patterns, the findings support current views that these language functions are related to both speech production and comprehension, thus dependent on interactions within the ventral and dorsal streams. Interestingly, the group with more severe auditory comprehension deficits did not have specific lesioned areas that were associated with their performance on the language subtests. Also, the patients in this group had a wider spread in lesion patterns than in the high comprehension group. This result is on its own interesting as it suggests that lesions at various places within the language network can cause severe auditory comprehension deficits.

Paper II was a longitudinal study where we followed the same patients from Paper I at three- and twelve-months post-stroke. We investigated the associations between lesion location, lesion size, initial stroke and aphasia severity, and their associations to aphasia at the three time points. As in Paper I, we performed a voxel-based lesion-symptom analysis to investigate the statistical relationship between aphasia severity and lesion location. The findings from Paper II showed that initial lesion size and aphasia severity were associated with aphasia severity at three months post-stroke. However, neither initial lesion size, stroke severity, nor aphasia severity at admission was associated with aphasia severity at one-year post-stroke. However, aphasia severity at three months was strongly associated with aphasia severity at one-year post-stroke. The lesion analyses yielded that damage within the left postcentral gyrus and left inferior parietal gyrus were associated with the patients' overall aphasia severity one-year post-stroke. Further, auditory comprehension and reading comprehension deficits at twelve-months post-stroke were both associated to lesions

within the postcentral gyrus, thus indicating a significant role of the postcentral gyrus in comprehension tasks. Lesions within the Rolandic operculum were associated with repetition deficits. Finally, deficits in reading aloud were associated with lesions within the Rolandic operculum, the insula, the superior temporal gyrus, and the supramarginal gyrus. In sum, the findings from Paper II indicate that lesions within the left inferior and postcentral parietal regions are crucial when investigating long-term overall language performance.

Finally, in Paper III we compared two groups of patients (with and without aphasia after stroke) and their differences in self-reported symptoms of depression and anxiety, and quality of life at one-year post-stroke. For the patients with aphasia, we explored the relationships between aphasia severity at admission, after three months, and after one year, and their symptoms of anxiety and depression one-year post-stroke. Finally, we investigated the relationship between symptoms of anxiety and depression and the patients' performance on the subtests from the NBAA (total score, auditory comprehension, repetition, naming, reading aloud, syntax and writing). The main findings of Paper III were that there were no significant differences in reported symptoms of anxiety and depression between the patients with aphasia and the patients without aphasia. However, we did find that aphasia severity was associated with more symptoms of depression, thus indicating that the patients with more severe aphasia also experienced more depressive symptoms. Finally, we found that difficulties on the repetition and reading comprehension tasks were associated with more symptoms of both anxiety and depression.

Abstract in Norwegian

Afasi er en erverva kommunikasjonsvanske som påvirker livet til personen som rammes, og hans eller hennes omgivelser. Afasi er som oftest et resultat av et hjerneslag. Skadelokalisasjon og skadestørrelse påvirker alvorlighetsgraden og bedringen av afasi, men det er ingen klar enighet om hvilke variabler som predikerer utfallet av afasi.

Hensikten med denne avhandlingen var å undersøke sammenhengene mellom skadestørrelse, skadelokalisasjon og afasi i akuttfasen, subakutt fase og kronisk fase etter et hjerneslag. Ytterligere hensikter var å undersøke de følelsesmessige konsekvensene av å leve med afasi, ved å undersøke symptomer på angst og depresjon og livskvalitet hos personer med og uten afasi etter hjerneslag. Disse hensiktene ble undersøkt i tre artikler, hvorav to artikler undersøkte skadestørrelse og skadelokalisasjon i akuttfasen og i kronisk fase etter hjerneslag. En tredje artikkel undersøkte de følelsesmessige konsekvensene av afasi i kronisk fase etter hjerneslag.

Alle artiklene bygger på datamateriale fra Bergen NORSTROKE-studien og Early Supported Discharge after Stroke in Bergen-studien (ESD-studien). Bergen NORSTROKE er et slagregister ved Haukeland Universitetssykehus. ESD-studien var en randomisert-kontrollert studie som startet i 2008, og ble avsluttet i 2014. Datainnsamlingen til denne avhandlingen ble gjennomført ved tre forskjellige tidspunkt etter at pasientene fikk hjerneslag. I det akutte stadiet etter hjerneslag (innen syv dager etter symptomstart), etter tre måneder, og til slutt tolv måneder etter hjerneslaget.

I artikkel I undersøkte vi forholdene mellom skadelokalisasjon, skadestørrelse og graden av afasi hos pasienter med afasi i akuttfasen. Vi brukte «voxel-based lesion-symptom mapping» som er metode for å kartlegge det statistiske forholdet mellom symptomer og graden av afasi og skadelokalisasjon. Hovedfunnet i denne studien var at skadestørrelse hadde en signifikant sammenheng med graden av afasi i akuttfasen, samt alle deltester fra Norsk Grunntest for Afasi. Analysene av skadelokalisasjon viste at vansker med benevning var assosiert med skader i Rolandic operculum, og

superior temporal gyrus. For å undersøke dataene videre, delte vi pasientene inn i to grupper basert på skåren deres på deltesten auditiv forståelse fra Norsk Grunntest for Afasi. I analysene av pasientene med bedre bevart auditiv forståelse fant vi at skader innen Brocas område, insula, superior temporal gyrus og Heschl's gyrus var assosiert med graden av afasi, samt vansker innen deltestene gjentagelse, benevning og høytlesning. For alle deltestene, utenom benevning, var skader innen supramarginal gyrus, postcentral gyrus, inferior parietal lobule og superior parietal lobule signifikante områder. Funnene støtter opp om nåværende teorier om at språklige oppgaver som krever både språkproduksjon og språkforståelse er avhengige av samhandlingen mellom en ventral og dorsal strøm i språknettverket. Et annet interessant funn var at det i gruppen med personer med større auditive forståelsesvansker ikke ble funnet signifikante sammenhenger mellom skadelokalisasjon og prestasjoner på deltester fra Norsk Grunntest for Afasi. I tillegg fant vi at pasientene i denne gruppen hadde en større spredning på skaden enn i gruppen med bedre bevart auditiv forståelse. Dette resultatet er i seg selv interessant da det tyder på at alvorlige auditive forståelsesvansker kan oppstå fra skade i ulike deler av språknettverket.

Artikkel II var en longitudinell studie hvor vi fulgte de samme pasientene som i artikkel I i tre og tolv måneder etter hjerneslaget. I artikkel II undersøkte vi forholdet mellom skadelokalisasjon, skadestørrelse, alvorlighetsgraden av hjerneslaget ved innkomst, alvorlighetsgraden av afasi ved innkomst, og forholdene mellom disse variablene og grad og symptomer på afasi ved de ulike testpunktene. I likhet med artikkel I brukte vi voxel-based lesion-symptom mapping for å undersøke sammenhengen mellom afasi og skadelokalisasjon. Funnene fra artikkel II viste at skadestørrelse i akuttfasen og graden av afasi i akuttfasen var assosiert med graden av afasi etter tre måneder, men at dette ikke var tilfelle etter ett år. Kun graden av afasi etter tre måneder hadde et signifikant forhold til graden av afasi etter ett år. Hovedfunnet fra analysene av skadelokalisasjon var at skader i venstre postcentral gyrus og inferior parietal gyrus var assosiert med pasientenes grad av afasi etter ett år. Videre fant vi at pasientenes ferdigheter innen auditiv forståelse og leseforståelse var

assosiert med skader i postcentral gyrus. Disse funnene indikerer dermed at postcentral gyrus spiller en viktig rolle innen oppgaver som krever språkforståelse. Skader i Rolandic operculum var assosiert med vansker innen gjentagelse. Til sist fant vi at vansker med høytlesing kunne tilskrives skader innen Rolandic operculum, insula, superior temporal gyrus og supramarginal gyrus. Samlet sett viser funnene fra artikkel II at skader innen venstre inferior og postcentral parietale områder kan være viktige områder når en skal undersøke bedringen av afasi etter ett år.

I artikkel III sammenlignet vi to grupper med pasienter, en med afasi og en uten afasi etter hjerneslag, og deres forskjeller i selvrapporterte symptomer på angst og depresjon, og deres livskvalitet ett år etter hjerneslaget. For personene med afasi, undersøkte vi forholdene mellom graden av afasi ved innkomst, og etter tre og tolv måneder, og deres symptomer på angst og depresjon etter ett år. Til sist undersøkte vi også forholdet mellom symptomer på angst og depresjon, og pasientenes skårer fra deltestene fra Norsk Grunntest for Afasi. Hovedfunnene i artikkel III var at vi ikke fant statistisk signifikante forskjeller mellom gruppen med afasi og gruppen uten afasi. Men vi fant at pasienter med mer alvorlig afasi rapporterte flere symptomer på depresjon enn de med mildere afasi. Til slutt fant vi at pasienter med større vansker innen gjentagelse og leseforståelse opplevde flere symptomer på både angst og depresjon.

List of Publications

I. Døli, H., Helland, W.A, Helland, T., & Specht, K. (2021) Associations between lesion size, lesion location and aphasia in acute stroke. *Aphasiology, 35(6),* 745-763. doi: 10.1080/02687038.2020.1727838

II. Døli, H., Helland, W.A., Helland, T., Næss, H., Hofstad, H. & Specht, K. (2021) Associations between stroke severity, aphasia severity, lesion location and lesion size in acute stroke, and aphasia severity one year post stroke. *Aphasiology,* 1-23. doi: 10.1080/02687038.2021.2013430

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

List of abbreviations

BA	Brodmann Area
BI	Barthel Index
CLSM	Connectome lesion-symptom mapping
CT	Computerized tomography
DWI-MRI	Diffusion-weighted magnetic resonance imaging
ESD	Early Supported Discharge After Stroke in Bergen – study
GLM	General Linear Model
HADS	Hospital Anxiety and Depression Scale
HUS	Haukeland University Hospital
ICF	International Classification of Functioning
IFG	Inferior Frontal Gyrus
IFGpOrb	Inferior Frontal Gyrus pars Orbitalis
IFGpTri	Inferior Frontal Gyrus pars Triangularis
MMSE	Mini Mental State Examination
MNI	Montreal Neurologic Institute
mRS	Modified Rankin Scale
MTG	Middle Temporal Gyrus
NBAA	Norwegian Basic Aphasia Assessment

NIHSS	National Institute of Health Stroke Scale
NORSTROKE	The Bergen NORSTROKE registry
NPM	Non-parametric mapping
PLORAS	Predicting Language Outcome and Recovery after Stroke
RO	Rolandic operculum
ROI	Region of interest
RSLM	Region-wise lesion-symptom mapping
SIS	Stroke Impact Scale version 2.0
SLF	Supralongitudinal fasciculus
SLT	Speech and language therapist
SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus
SPSS	Statistical Package for the Social Sciences
SPM	Statistical Parametric Mapping
SSRI	Selective Serotonin Reuptake Inhibitors
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
T1	Admission to the hospital
T2	Three-month follow-up
T3	Twelve-month follow-up

VLSM	Voxel-based lesion symptom mapping
WAB	Western Aphasia Battery
WHO	World Health Organization

Contents

1. Introduction

Aphasia is an acquired communication disorder that deeply affects the life of the person affected, and their surroundings. Aphasia is most commonly a result of stroke (Hallowell & Chapey, 2008). Lesion location and lesion size affect the severity and recovery of aphasia, but there is no clear consensus on which variables that precisely predict aphasia outcome (Kristinsson et al., 2022; Thye & Mirman, 2018). However, regardless of lesion location and lesion size, the impact of aphasia in a person's life is immense and impacts the entire life of the person with aphasia. Therefore, in the present thesis, I present three studies on patients with aphasia. Two of the studies investigated the associations between lesion location and lesion size and aphasia in the acute, subacute, and chronic stages post-stroke, and one study investigated the emotional consequences of acquiring aphasia after stroke, and the impact aphasia has on quality of life.

To encompass these aspects, two theoretical approaches are presented as the overall theoretical backgrounds of the thesis, the clinical framework of the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001), and a cognitive neuroscientific approach to aphasia. As stated by Worrall et al. (2015), the future strategy of aphasia clinicians and researchers should be that the brain, the person, and their environment is treated holistically to ensure the best aphasia rehabilitation.

The ICF is a framework for describing and organising information on functioning and disability, and is based on a biopsychosocial approach to understanding disability, which integrates social and medical models (World Health Organization, 2001). The ICF therefore provides a holistic framework for understanding the implications of living with disease, including the medical and symptomatic perspective.

Cognitive neuroscience can be defined as the study of the underlying neural substrates of mental processes. It converges the field of psychology and neuroscience, and overlaps with physiological-, cognitive- and neuropsychology (Nature portfolio,

2022). A discussion of the theoretical frameworks will be presented in the following chapters (c.f. 1.4, 1.6 and 1.7).

1.1 Overall aims

The overall aim of the thesis is to contribute to clinical and theoretical insights for persons with aphasia, their caregivers, health-care providers, researchers, and others within the field of aphasia.

The thesis includes three papers with different theoretical and methodological approaches to aphasia, thus providing a broad view into the field of aphasiology. In the following chapter, the theoretical background of the present thesis is discussed. Recent and relevant findings from the field are presented and highlighted. Thereafter, methods and results are presented. Finally, a discussion of the work is provided, as well as clinical implications and directions for future research.

1.2 Stroke

Stroke, or a cerebrovascular accident (CVA), is defined either as ischemic (thrombosis and emboli) where a blood vessel is blocked, or as haemorrhagic stroke where a blood vessel ruptures, as an aneurysm or haemorrhage (Halpern & Goldfarb, 2013). On a global measure, ischemic stroke is the most common type of stroke, responsible for approximately 80% of all stroke cases, while haemorrhagic stroke accounts for about 20% (Boehme et al., 2017).

Stroke is the third most common cause of death in Norway, and the most common reason for disabilities among elders (Ellekjær & Selmer, 2007). From a population of 5.4 million people, approximately 11000 individuals in Norway suffer from stroke each year, with a median age of 75 years (Kvåle et al., 2018). Persons who

experience stroke might exhibit a range of symptoms, such as difficulties with movement, coordination and motor control of the body, cognitive deficits, swallowing difficulties, as well as speech and language problems, such as aphasia (Hallowell & Chapey, 2008). The degree and nature of impairments depend on several factors, such as type of stroke, lesion site, lesion size, as well as premorbid factors and environmental factors. About half of the stroke survivors will experience long-term disabilities (Lv et al., 2021).

1.3 Aphasia

Aphasia is an acquired communication disorder caused by a focal damage to the brain. There is no universal definition of aphasia within research or clinical practice, and recent efforts to achieve a consensus have failed (Berg et al., 2022). The definition of aphasia proposed by Papathanasiou, Coppens and Davidson (2017) is chosen in the present thesis, because it includes the impact aphasia has on social functioning, the quality of life of the person with aphasia and significant others, as well as acknowledging that the localization of the lesion is of importance. The definition is in line with the framework of the ICF (World Health Organization, 2001) encompassing the biological, physiological, psychological and social perspective on aphasia.

Aphasia can be defined as:

> an acquired selective impairment of language modalities and functions resulting from a focal brain lesion in the language-dominant hemisphere that affects the person's communicative and social functioning, quality of life, and the quality of life of his or her relatives and caregivers (Papathanasiou, Coppens, & Davidson, 2017, p. 4).

Aphasia is most commonly the result of left hemispheric stroke (Hallowell & Chapey, 2008). However, aphasia can also occur after e.g. traumatic brain injury,

brain tumours, and degenerative neurological diseases (Damasio, 1992). Aphasia can affect all language modalities, that is auditory comprehension, verbal expression, reading and writing, and may cause deficits in semantic, phonological, morphological, syntactic and pragmatic processing (Papathanasiou, Coppens, & Davidson, 2017).

The frequency of aphasia after stroke varies across studies from 15% to 40% (Denier et al., 2015; Engelter et al., 2006; Laska et al., 2001). The variation can be explained by different methodological approaches that yield different answers and results, such as type of stroke, differences in aphasia assessment tools, differences in time of assessment and so forth (Crinion et al., 2013). Roughly, it is estimated that 1/3 of the stroke population will experience aphasia, either fluctuating or chronic (Flowers et al., 2016).

1.4 The Classic Model of aphasia

From a historical perspective, aphasia has been referenced in the ancient past in the form of medical records of patients with brain damage in the Edwin Smith Surgical Papyrus (3000-2200 B.C.) (Breasted, 1930). The term “speechlessness” was used to describe several patients with brain injuries and other injuries, such as head and jaw fractures (Tesak & Code, 2008). From the ancient past to the 19th century many attempts were made to describe the localization of mental faculties and descriptions of speech and language impairments (e.g. Aristotle (384-322 BC); Hippocrates (460 BC – c. 370 BC), da Vinci (1472-1519), Johann Gessner (1738-1801)) (Tesak & Code, 2008).

To understand the evolvement of the cognitive neuroscientifical approach to aphasia a historical background can give perspective. The modern history of aphasiology emerged with the findings of Pierre Paul Broca in 1861 (Tesak & Code, 2008). The French anthropologist and surgeon was the first to discover and document the relationship between a brain lesion and specific language functions. Broca provided

evidence that speech production was dependent of regions in the left inferior frontal cortex (posterior inferior frontal gyrus). Later Carl Wernicke, a german doctor and neuropathologist, published "The symptom complex of aphasia: A psychological study on an anatomical basis" (1874) which established the *Classic Model* of language processing. Wernicke's' studies determined that aphasia was a consequence of lesions within specific language centers and/or their connections, and their neural pathways in the brain (Tesak & Code, 2008). Today, Wernicke's classification of aphasia still is commonly used in clinical and research settings.

The *Wernicke-Lichtheim model* was a systematization and abstract representation of Wernicke's Classic Model, proposed by Luis Lichtheim in 1885 (Code, 2017). The model became the standard neuropsychological theory and dominated aphasia theory into the 20th century (Code, 2017; Graves, 1997). Within the Wernicke-Lichtheim model, normal higher cognitive functions were explained in terms of neural pathways. The goal of the model was to be predictive, where pathological syndromes were associated to damage to specific places within the neural pathways (Graves, 1997).

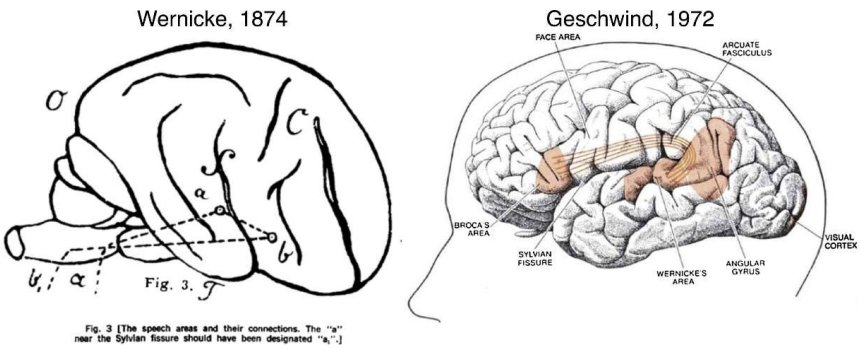
The findings from Broca, Wernicke, and the model of Lichtheim have influenced and impacted current models within neuroscience and neuropsychology. Today, they are still acknowledged and referred to, but modern neuroscience provides a more complex picture of the neural localization of speech and language functions. To understand current views of speech and language processing, the reintroduction of the Classic Model is presented below.

1.4.1 Neoclassicism - the return of the Classic Model

Several schools and theoretical approaches to aphasia received attention from the emergence of the Classic Model in 1874 (e.g Luria (1966)). However, in 1965 the Classic Model was reintroduced and further developed by the American neurologist Norman Geschwind (Geschwind 1965). Geschwind reintroduced the notion of

language processing as dependent of specific brain structures in the left hemisphere, namely Broca's and Wernicke's area. This model is also commonly referred to as the *Wernicke-Geschwind model*. Geschwind hypothesized that the posterior temporal area was necessary for language processing (referred to as Wernicke's area), which was considered responsible for auditory comprehension, storage, synthesis, and overall language comprehension. Within the Wernicke-Geschwind model of language, the specific location of Wernicke's area comprised the posterior third of the superior temporal gyrus (STG), on the border between the temporal and parietal lobe. Broca's area was defined within the anterior inferior frontal area and considered crucial in oral and written language production. The angular gyrus, which is situated within the inferior parietal lobe, was considered significant for the connection between visual and auditory information. Also, Geschwind postulated that the arcuate fasciculus as essential for the flow of information from the posterior to the anterior language areas making language processing possible (Geschwind 1965; Geschwind, 1972). To illustrate the differences between the models, Tremblay and Dick (2016) made a comparison of the original model from Wernicke (1874) to the left, and the model proposed by Geschwind (1972) to the right. The STG is mislabeled as the angular gyrus in the figure.

Figure 1. From "Broca and Wernicke are dead, or moving past the classic model of language neurobiology" by P. Tremblay and S.A. Dick, 2016, *Brain and Language,* 162, p. 62 (http://dx.doi.org/10.1016/j.bandl.2016.08.004).



Geschwind's reintroduction of the Classic Model of aphasia was a modern perspective of the early theories of Wernicke. The attribution of modern anatomical brain scans provided a novel approach to aphasia and speech and language processing in the 1960s. Since then, the development of newer imaging techniques and analyses, newer and more detailed models of speech and language processing have emerged. In chapter 1.7 recent and relevant models and research investigating the neural localization of language functions will be highlighted and discussed.

1.5 Assessment and classification of aphasia

The assessment of aphasia varies across research, languages, theoretical traditions, and schools. Aphasia can be conceptualized dichotomously, such as fluent versus non-fluent aphasia, or Broca's versus Wernicke's aphasia and so forth (Hallowell & Chapey, 2008). In the present thesis, the Norwegian Basic Aphasia Assessment (NBAA) (Reinvang & Engvik, 1980) was used to assess the patients' aphasia symptoms and severity in all three papers. Aphasia was not conceptualized dichotomously, nor as aphasia types, but rather as a continous variable to investigate the patients' aphasia severity within each subtest, as well as their overall aphasia severity.

The NBAA is based on the Boston classification of aphasia, and the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1972). This is also referred to as a neoclassical approach to aphasia described in chapter 1.4.1. The BDAE and the NBAA were designed to classify patients into localization-based classifications of aphasia, such as Broca's, Wernicke's, anomic, conduction, transcortical motor, transcortical sensory, and global aphasia syndromes. In the Boston-classification of aphasia, the different aphasia syndromes have certain hallmark symptoms dependent on lesion location (Hallowell & Chapey, 2008), and each aphasic syndrome is thought to indicate lesion location in the brain.

Even though newer classifications and theories on language processing and aphasia have emerged, the Boston-classification of aphasia is still commonly used in clinical and research settings, and has been reported to be the most widely used aphasia assessment in Norway (Lind & Haaland-Johansen, 2013). To this date, there is no universal consensus on the classification of aphasia syndromes, however, the classifications of the Boston-school are still widely used and adopted within both clinical and research settings. Although the limitations of the classification system are accepted, newer neuroimaging techniques have discarded the idea that certain aphasic syndromes can predict lesion location. The table surely has turned, whereas clinicians and researchers are now more interested in predicting aphasia symptoms based on the location of the lesion in the brain and investigating the course of aphasia recovery based on neural mechanisms.

1.6 The International Classification of Functioning, Disability and Health

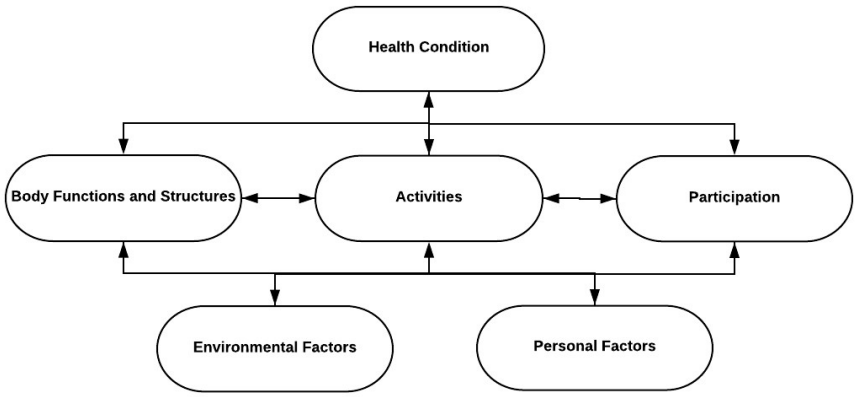
Historically, as described above, aphasia has been viewed through different theoretical frameworks. However, the past few decades an increased focus on a holistic view on health conditions, and the social consequences of disease has emerged. As argued by Worrall et al. (2015), therapists working with aphasia cannot rely on neuroscience alone, one has to consider the brain, the person, and their environment as one. Further, research on aphasia should seek to transfer knowledge from neuroscience to improve the outcomes and lives of persons with aphasia (Worrall et al., 2015).

The World Health Organization (WHO) developed the ICF as a standard framework and classification of health and health-related domains (2001). The framework was introduced to increase awareness and to implement a more holistic approach within health-care delivery than the classic biomedical models (Papathanasiou, Coppens, & Davidson, 2017). The framework provides a unified terminology that can be used

across disciplines, health conditions, and health systems (World Health Organization, 2001). The ICF has become the most acknowledged and commonly used framework within rehabilitation of aphasia and rehabilitation research on aphasia (Ma et al., 2007).

Figure 2 is a visual overview of the ICF-model from Ritchie (2018).

Figure 2. The ICF-model



Two main domains are categorized within the ICF, (a) body structures and functions, and (b) activities and participation. The framework can be applied to a person with acquired aphasia after stroke. The person with aphasia has a health condition, and loss of functions that are referred to as (a) body structures and functions within the ICF. Within the ICF, one acknowledges that the loss of body structures and functions is related to changes within a person's (b) activities and participation. These concepts include a holistic approach, thus emphasizing that living with aphasia causes changes in a person's entire life, and that all aspects are important for the person living with aphasia. To exemplify, for an individual with aphasia, (b) activities and participation

can refer to actions that require listening, speaking, reading and writing, as well as everyday communication, such as reading the newspaper, watching television, and participating in conversations, or participating in sports and leisure activities (Papathanasiou, Coppens, & Davidson, 2017). Another important concept of the ICF-model is that the environment of the patient also is affected, which involves the person's relationship with others, local and national policies and regulations, physical environmental factors, and the use of assistive technology. The implementation of the ICF in rehabilitation has led to an increased focus on the psychosocial consequences of disease in both clinical and research settings, with the focus and goal of enhancing quality of life for persons with aphasia.

Viewing aphasia through the ICF-framework emphasizes the importance of the social impact aphasia has on not only the person himself, but also the role of the persons and environment surrounding the individual with aphasia. The framework acknowledges and highlights the importance of the interaction between variables, from medical factors, such as risk factors, etiologies and genetics, to social and environmental factors (Papathanasiou, Coppens, & Davidson, 2017).

The current thesis incorporates a focus on (a) body structures and functions, such as the brain lesion and aphasic symptoms, and (b) activities and participation, such as the psychosocial consequences of living with aphasia after stroke. Acknowledging that these variables influence each other and viewing aphasia through a holistic perspective will benefit persons with aphasia in future rehabilitation.

1.7 Anatomical models of the neurobiology of language

In recent years, several studies have investigated the neuroanatomical basis of language processing and proposed new models of language comprehension and production (Ardila et al., 2016; Dronkers et al., 2004; Hickok & Poeppel, 2007). The notion of Broca's and Wernicke's area being the two main language centers of the brain have been challenged, and the language processes that occur in the regions are

not enough to explain what goes on in speech and language production and comprehension (Damasio, 2008).

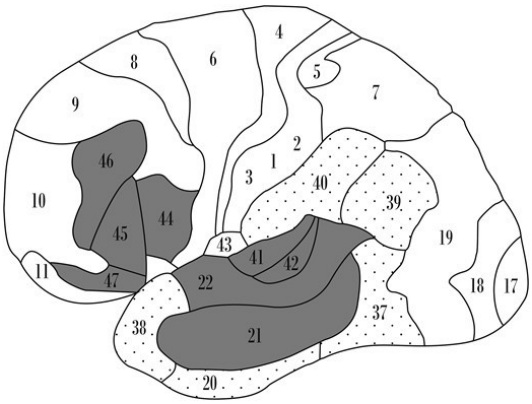
1.7.1 The neural underpinnings of speech and language production and comprehension

Several brain regions are suggested to be relevant for language. Based on earlier findings from lesion analysis (Dronkers et al., 2004), fiber tractography and functional connectivity analysis, Turken and Dronkers (2011) suggested a language comprehension network that included the left middle temporal gyrus (MTG), the anterior STG (BA22), the pars orbitalis (IFGpOrb/BA47), and the superior temporal sulcus (STS/BA39). Further, the inferior occipito-frontal fasciculus, the arcuate fasciculus, and the middle and inferior longitudinal fasciculi, and transcallosal projections via the tapetum, were the most significant white matter pathways bridging the areas crucial in language comprehension. Finally, the authors suggested the MTG as a core region in the language comprehension network.

Ardila et al. (2016) conducted a meta-analysis of the Brodmann areas (BA) involved in language. An extended Wernicke's' area was suggested as a crucial region for auditory comprehension. This area included the traditional core areas as the planum temporale, the posterior thirds of the STG (BA22), the posterior part of the MTG (BA21), and the auditory cortex (BA41/42). Ardila et al. (2016) further suggested to include corresponding areas as the inferior temporal gyrus (BA20), the fusiform gyrus (BA37), the angular gyrus (BA39), and the supramarginal gyrus (SMG/BA40). Accordingly, Ardila and colleagues also suggested the borders of Broca's area were extended. While Broca's area traditionally includes the pars opercularis (IFGpOp/BA44), and the pars triangularis (IFGpTri/BA45), Ardila et al. (2016) suggested the area to also include the dorsolateral prefrontal cortex (BA46), the IFGpOrb, the supplementary motor area (SMA/BA6), and extending the area subcortically towards the basal ganglia. Ardila and colleagues referred to this region as the Broca's complex. Finally, the insula (BA13) was suggested to have a crucial

coordinating role in both language production and comprehension (Ardila et al., 2016). Figure 3 is an illustration of the Brodmann Areas involved in language proposed by Ardila et al. (2016).

Figure 3. "Brain language areas. The frontal language area (Broca's complex: language production and grammar: BA44, BA45, BA46, BA47) also partially includes BA6 and extends subcortically to the basal ganglia. The posterior language area (language reception and understanding: lexical-semantic system) includes a core Wernicke's area (BA21, BA22, BA41, and BA42) and an "extended Wernicke's area" also including BA20, BA37, BA38, BA39, and BA40." From: "How Localized are Language Brain Areas? A Review of Brodmann Areas Involvement in Oral Language" by A. Ardila, B. Bernal & M. Rosselli, 2016, 31, p. 120 (https://doi.org/10.1093/arclin/acv081).



To summarize, regions within the left inferior frontal, temporal, and parietal lobe are considered the most significant areas for speech and language functions. However, studies also show that several other brain regions and pathways are involved in language, such as the cerebellum (Ackermann & Brendel, 2016), white matter

pathways, such as the arcuate fasciculus and the lateral longitudinal fasciculus (Duffau, 2016), as well as regions within the right hemisphere (Friederici, 2011).

For reading, a larger area referred to as the visual word form area has been suggested as crucial (Dehaene, 2009). The visual word form area is considered a large reading network, comprising the occipital cortex for processing written information, the left anterior temporal cortex for processing meaning, the left posterior parietal cortex for top-down processing and serial reading, and the left inferior frontal and insular regions for reading aloud (Baldo et al., 2018; Dehaene, 2009). Purcell et al. (2011) conducted a comprehensive meta-analysis examining the neural substrates of written word production, suggesting that the most relevant brain regions for writing are the left inferior temporal/fusiform gyri, and the left inferior frontal gyrus. Clearly, speech and language deficits can arise from lesions to a large number of regions within the left hemisphere.

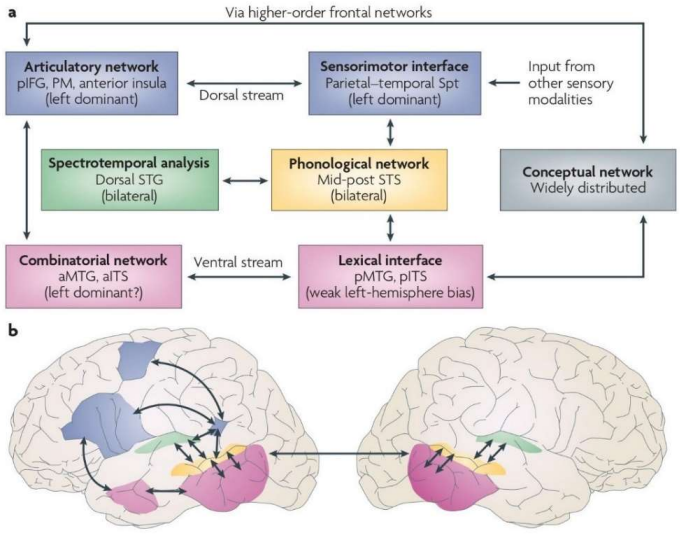
1.7.2 The dual-stream theory – the neural basis of speech processing

To understand the neural organization of speech and language it is essential to understand how underlying linguistic processes are processed in the brain. Imaging techniques on both healthy and lesioned brains have provided more precise anatomical definitions and newer models of speech and language processing. Gregory Hickok and David Poeppel proposed the dual-stream theory of the cortical organization of speech processing based on evidence from both functional neuroimaging and lesion studies (Hickok & Poeppel, 2007). In paper I and II we used the dual-stream theory as a model to understand and interpret and discuss our findings.

The dual-route model suggests that a ventral stream processes signals for auditory comprehension, from sound to meaning. The ventral stream is considered bilaterally organized and involves structures within the superior and middle portions of the

temporal lobe where it interacts with the dorsal stream. The dorsal stream maps acoustic speech signals to the articulatory networks in the frontal lobe. Assumably, the dorsal stream is motor-speech driven, it maps sounds to action, and it involves structures in the posterior frontal lobe, the posterior dorsal region of the temporal lobe, as well as the parietal operculum. Both streams share neural tissue in the left posterior STG. While the ventral stream is considered bilaterally organized, the dorsal stream is left-hemisphere dominant (Hickok & Poeppel, 2007). Further, Hickok and Poeppel (Hickok & Poeppel, 2007) suggest the planum temporale as responsible for sensorimotor integration related to the vocal-tract. Fridriksson et al. (2018) formulated that it is the harmony of the interaction of the streams that makes communication possible. The precise anatomical areas which comprise the ventral and dorsal stream, and where the two streams diverge is however still a debate (Specht, 2014). Figure 4 is the original model proposed by Hickok and Poeppel (2007).

Figure 4. The dual-stream model of the functional anatomy of language from "The cortical organization of speech processing", by G. Hickok & D. Poeppel, 2007, *Nat Rev Neurosci*, 8, p. 395 (https://doi.org/10.1038/nrn2113).



Fridriksson et al. (2018) used lesion data from patients with aphasia to reveal the anatomical borders of the dorsal and ventral stream. Their results showed that language measures of motor-speech impairments involved primarily lesions within the dorsal stream, while measures of speech comprehension deficits were associated with lesions within the ventral stream. One key point from their study was that clinical language tests assessing naming, repetition, or grammatical processing rely on the interactions between the dorsal and ventral stream. Therefore, patients with aphasia, with completely different lesion locations, may exhibit identical symptoms of aphasia since their lesion affects a broad network relevant for the given speech or language tasks. Based on this, Fridriksson et al. (2018) argue that this is a more appropriate way of viewing speech and language processes than assuming that specific lesion locations are responsible for specific language tasks, such as the historical models of aphasia described earlier (c.f. 1.4).

Fridriksson et al. (2018) stated that even though the model has been highly influential in neuropsychological research on normal subjects, the model has received limited attention within research on patients with aphasia. Therefore, in the present thesis, the dual-stream model is used as a theoretical model for speech and language processing in patients with aphasia, to further explore and investigate the the anatomical borders of the model.

1.8 Lesion-symptom mapping in aphasia

The present thesis includes two studies using lesion-symptom mapping in patients with aphasia. In the following chapter recent and relevant studies on lesion mapping in patients with aphasia will be discussed and highlighted.

The development within neuroimaging and imaging-analysis the past few decades has given new insights into the neuroanatomical organization of language in patients with aphasia. Lesion studies aim to investigate the statistical relationships between brain

lesions and linguistic or psychological phenomena (Hickok & Small, 2016). The overarching goals in lesion studies are to enhance the prognostication and treatment of aphasia, as well as understanding how lesions affect speech and language processes.

In Paper I and II in the present thesis *voxel-based lesion-symptom mapping* (VLSM) (Bates et al., 2003) was used as a method to investigate the statistical relationships between the patients' lesions and the patients' aphasia symptoms and severity. VLSM has a binary approach to investigating lesions, each voxel in the brain is either lesioned, or not. A lesioned voxel is given the value of 1, while the non-lesioned voxel is valued as 0.

Some key advantages of the VLSM-approach are that the behavioural data can be continuous, which makes it possible to include patients with a wide range of performances on language measures. Furthermore, VLSM allows an investigation of several lesions at once, thus providing information about possible networks that are involved in specific language processes (Baldo, Wilson, et al., 2012).

Several recent studies have investigated the relationships between lesioned areas of the brain and language deficits in patients with aphasia (Baldo, Katseff, et al., 2012; Bates et al., 2003; Dronkers et al., 2004; Døli, Helland, Helland, & Specht, 2021; Fridriksson et al., 2018; Schwartz et al., 2009).

In Paper I the relationships between the patients' initial aphasia severity and symptoms, and their specific lesion location and lesion size was investigated, while Paper II reported on the patients' recovery the first-year post-stroke based on their initial lesions, as well as their initial stroke and aphasia severity and aphasic symptoms. The current chapter will focus on the relationships between lesioned regions of the brain and symptoms of aphasia. Predictions about the recovery of aphasia will be discussed in chapter 1.9.

1.8.1 The role of Broca's and Wernicke's area in aphasia

Bates et al. (2003) were the first to report findings from a study using a VLSM-approach. They investigated speech fluency and auditory-verbal comprehension deficits in 101 patients with aphasia. The fluency subtest from the Western Aphasia Battery (WAB) (Kertesz, 1982) was used as a behavioural measure, assessing the patients' performance on articulatory, word-finding and sentence-production tasks. Bates et al. (2003) found lesions within the anterior insula to be associated with fluency deficits in aphasia, while lesions within the middle temporal areas of the left hemisphere were associated with auditory comprehension deficits. Interestingly, Bates et al. (2003) also found lesions limited to Broca's area not being able to explain fluency deficits in their sample. Further, lesions within the MTG were strongly associated with the patients' auditory comprehension difficulties, especially when Wernicke's area was factored out. Finally, fluency and comprehension difficulties were associated with lesions within peri-Sylvian regions, suggesting that they account for core language functions.

Accordingly, Dronkers et al. (2004) did a lesion study on language comprehension deficits in 64 patients with aphasia. Lesions within the posterior MTG and underlying white matter, the anterior STG, the STS, and the angular gyrus were associated with the patients' auditory comprehension deficits. However, their results also yielded differences in between single word comprehension and sentence level comprehension, whereas the MTG was identified as significant for single word comprehension, while the mid-frontal cortex and IFG, the posterior MTG, anterior STG, STS, and angular gyrus were related to sentence level comprehension deficits. Finally, neither lesions within Broca's or Wernicke's area accounted for the patients language comprehension difficulties in the study (Dronkers et al., 2004).

The role of specific lesion locations in relation to verbal fluency deficits in patients with aphasia was also investigated by Baldo et al. (2006). They used two different measures of verbal fluency, letter fluency, which requires phonological and lexical retrieval, and category fluency, which is dependent on semantic processing. VLSM was performed in patients with aphasia at least nine months post-stroke. The authors

reported that letter fluency deficits were associated with lesions within anterior regions of the left frontal cortex, while reduced category fluency was associated with lesions within posterior regions of the left temporal cortex. Their findings also showed that impairments within fluency tasks were associated with lesions within the insula, putamen, and the inferior parietal cortex (Baldo et al., 2006). Their results suggest that phonological fluency tasks are more dependent of the frontal regions of the left hemisphere, while semantic fluency tasks are located within posterior temporal regions of the left hemisphere.

The findings from Bates et al. (2003), Dronkers et al. (2004) and Baldo et al. (2006) challenge the assumption about the significance of Broca's and Wernicke's area in language production and comprehension. Bonilha & Fridriksson (2009) suggest a more pragmatic approach by acknowledging that Broca's area is crucial for speech production, but damage and disconnection from surrounding areas might also result in fluency disorders (Bonilha & Fridriksson, 2009).

Schwartz et al. (2009) also questioned the role of Wernicke's area in semantic error production. In their study of 64 individuals with post-stroke aphasia, the authors used VLSM to investigate semantic naming errors. Their results showed that the left anterior temporal lobe is crucial for mapping concepts to words in speech production. The authors hypothesized that the left anterior temporal lobe is important for the transfer of semantic distinctions to the lexical system (Schwartz et al., 2009).

In another VLSM-study, Baldo, Katseff, et al. (2012) investigated the neural basis of repetition and auditory-verbal short-term memory in 84 individuals with aphasia after left hemispheric stroke. Repetition and auditory-verbal short-term memory deficits were reported to be associated with lesions in cortical regions within the left posterior temporo-parietal cortex. Surprisingly, the authors did not find that the white matter pathway, the arcuate fasciculus, was critical for repetition and auditory-verbal short-term memory (Baldo, Katseff, et al., 2012). Their findings challenge earlier assumptions about the role of the arcuate fasciculus in repetition, such as the neoclassical model proposed by Geschwind (1972).

1.8.2 Lesion size in aphasia

Thye and Mirman (2018) used VLSM with sparse canonical correlation analysis to test the relative predictive role of lesion size and lesion location on different language deficits in patients with aphasia after left hemisphere stroke, at least one-month post-stroke. The authors found that speech production deficits and speech recognition deficits in patients with aphasia was predicted by both lesion size and lesion location. Interestingly, their findings suggest that more comprehensive deficits, such as aphasia severity, as well as naming, were mainly predicted by lesion size and not lesion location. The authors argue that controlling for lesion size in lesion studies investigating aphasia is essential. Further, some language deficits might be so broad that they can be better predicted by overall lesion size, while other, more neurally-localized cognitive systems that support language are more suitable for lesion-symptom predictions. However, studies have also contradicted these findings showing that lesion size is not a significant predictor of aphasia recovery (Lazar et al., 2010).

1.8.3 The dual-stream model in aphasia

A recent study by Fridriksson et al. (2018) investigated the anatomical borders of the dorsal and ventral stream using lesion data from patients with aphasia and their performances on given language tasks. They included 159 chronic stroke patients, with an average time since post-stroke of 36.4 months. The authors used region-wise lesion-symptom mapping (RLSM) to investigate the relationships between lesions within specific regions and language performance, and connectome lesion-symptom mapping (CLSM) to investigate lesions involving white matter connections between brain regions and performance on language tests. Using RLSM the authors found that lesions within the pars opercularis, the STG, and the SMG were predictors of performance on fourteen of the sixteen language tests included in the study. Further, their CLSM analyses showed that overall aphasia severity (measured by the WAB

(Kertesz, 1982)), and speech fluency were predicted by lesions primarily within the dorsal stream, with fewer connections to the ventral stream. The authors argue that this finding was to be expected as the WAB mainly consists of speech production tasks (fluency, repetition, naming). Further, their results yielded deficits in auditory word recognition to mainly involve regions within the ventral stream, with fewer connections to the dorsal stream. Finally, they reported that performance on speech repetition and naming was associated with lesions in both the dorsal and ventral stream. Fridriksson et al. (2018) argue that chronic aphasia can occur even due to small strokes within the language network, and lesions affecting both the dorsal and ventral stream is likely to cause long-lasting language deficits because of the damage to the neural pathways.

1.8.4 Future approaches for predicting aphasia outcome

The Predicting Language Outcome and Recovery after Stroke database (PLORAS) (Price et al., 2010; Seghier et al., 2016) has generated important studies on predicting the recovery of aphasia post-stroke. Price et al. (2010) sought to predict language outcome and recovery after stroke based on brain scans. The authors discuss two approaches, one model-led approach and one data-led approach. In a model-led approach one must understand the role of every region in the brain involved in every language task, as well as the functions of the subregions, and the alternative neural systems for the same language function. The authors state that we still do not know enough about language and the brain to make model-led predictions. Therefore, they suggest a data-led approach, which allows the clinician to draw conclusions based on data from other patients with similar brain lesions. Price et al. (2010) argue that this is an available approach, because it only requires proof of efficacy, safety, and reproducibility.

In their comprehensive review Price et al. (2010) reported that auditory comprehension deficits in aphasia were associated with lesions within the left posterior superior temporal and/or left middle temporal regions. Further, the authors

reported that non-fluent speech production in patients with aphasia was associated with damage within the left inferior and/or middle frontal gyri and underlying white matter (Price et al., 2010). The authors argue that there still is no method to accurately predict recovery from aphasia, but the main determinant is lesion site. Finally, the authors argue that an international database will enhance the predictive validity of a data-led approach when predicting language outcomes and recovery post-stroke.

Nonetheless, the rapid scientifical development of cognitive neuroscience has challenged the 160-year-old findings from Broca and Wernicke and given newer and more detailed models of speech and language processing. However, clear answers about the cortical organization of language in the brain remain. The findings from Papers I and II in the present thesis will hopefully serve as a contribution to the understanding of the neural organization of language.

1.9 Predicting recovery of aphasia

In the present thesis, lesion size and lesion location in the acute stages post-stroke and their relationship to aphasia severity and symptoms three- and twelve-months post-stroke was investigated in Paper II. In the following chapter earlier studies investigating variables that predict the recovery of aphasia will be discussed.

Recovery is an important goal for every patient with aphasia, and for every clinician working with aphasia. The recovery of aphasia has been found to be influenced by several factors. Studies have shown that initial aphasia severity (El Hachioui et al., 2015), lesion site, lesion size (Plowman et al., 2012), psychosocial factors (Worrall, Hudson, et al., 2017), age (Ali et al., 2021) and therapy (Brady, 2016) are among the most important predictors of aphasia recovery. Nonetheless, there is still unexplained variance in the therapeutic effects of speech and language therapy at the individual level. Therefore, planning individual therapy for persons with aphasia, and prognostication of outcome is a challenging endeavour for clinicians and researchers (Cheng et al., 2020; Kristinsson et al., 2022)

The time course post-stroke is commonly described as acute, subacute, and chronic; however, a clear-cut definition of these stages does not exist. In the present thesis, I use the definitions as proposed by Wittler (2009), where the recovery of aphasia is divided into three stages based on the underlying neural mechanisms that occur post-stroke. Wittler suggests that within aphasia recovery, the acute stage is defined as the first month post-stroke (0-6 weeks), the subacute stage as one month to one year after stroke, and the chronic stage as one-year post-stroke and further (Wittler, 2009). There is no clear-cut distinction between the three stages, but an overlap.

1.9.1 Mechanisms of recovery

In aphasia, recovery involves changes in the brain. These changes can be described within two levels, the microlevel and the macrolevel, both levels associated to plasticity and recovery (Papathanasiou, Coppens, Durand, et al., 2017). Plasticity refers to the brain's ability to change on a microlevel, thus referring to cellular change which is called neuroplasticity, and on a macrolevel, which refers to the brain's responses to environmental and behavioural changes, called behavioural plasticity (Papathanasiou, Coppens, Durand, et al., 2017). Recovery refers to all behavioural changes that occur post-stroke, and is a result of the interaction between neuroplasticity and behavioural plasticity (Papathanasiou, Coppens, Durand, et al., 2017). The most important neural mechanism of recovery in aphasia is neuroplasticity. Language recovery after stroke is not a linear process, large differences are seen in recovery processes across patients with aphasia (Kiran & Thompson, 2019). Spontaneous recovery, which occurs during the acute stages post-stroke, is a natural recovery mechanism not influenced by specific treatment. It is likely due to the reduction of oedema, absorption of damaged tissue, and improvement of local circulation (Cherney & Robey, 2008). Several repair-mechanisms in the brain contribute to neuroplasticity in the acute and subacute stages post-stroke. These mechanisms should be considered when predicting the course of post-stroke recovery. Synaptogenesis involves unmasking of pathways or the

formation of new pathways, resulting in new connections (Cherney & Robey, 2008; Kiran & Thompson, 2019). Diaschisis, which refers to depressed function or hypometabolism of structurally normal cortical regions distant from the lesion, is a result of the sudden interference of synaptic connections with the region. Other mechanisms are regenerative and collateral sprouting which refers to the changes in connections between neurons from healthy cells to denervated regions (Cherney & Robey, 2008). The result of these neurobiological processes will influence the pattern of recovery in aphasia.

There is no theoretical model that can predict how patients with aphasia will recover after stroke. However, the recovery of aphasia has been suggested to follow the principles of proportional recovery (Krakauer & Marshall, 2015; Marchi et al., 2017). These principles were originally used to describe motor recovery after stroke, suggesting that most patients recover 70% of their initial impairment, and some patients show no or little recovery (Krakauer & Marshall, 2015; Marchi et al., 2017). Marchi et al. (2017) suggest that patients with aphasia show the same proportional recovery as patients with motor deficits. They argue that the reason for this is the common underlying mechanisms of neuroplasticity, which apply to both motor and cognitive functions. The empirical support for the principles of proportional recovery have however been criticized for being weak and not sufficient to stand as a model of aphasia recovery (Hope et al., 2019).

Even though there is no model that can accurately predict the course of aphasia recovery, several studies have found variables that are significant when forecasting the long-term outcome of aphasia, such as lesion size, lesion location, age and initial aphasia severity (Ali et al., 2021; El Hachioui et al., 2013; Hillis et al., 2018; Plowman et al., 2012; Price et al., 2010; Sul et al., 2019).

1.9.2 Initial stroke and aphasia severity

Initial aphasia severity has been found to predict aphasia recovery (El Hachioui et al., 2013; Laska et al., 2001; Lazar et al., 2010; Pedersen et al., 2004). In a review

Plowman et al. (2012) investigated the long-term prognosis of aphasia after stroke. Lesion site, lesion size and initial aphasia severity were found to be associated with aphasia recovery. Initial aphasia severity was the most predictive variable of post-stroke aphasia (Plowman et al., 2012). This finding was also confirmed by Lazar et al. (2010) where the authors found initial impairment to be the most predictive variable of aphasia recovery at three-months post-stroke.

Aphasia type has also been suggested to be predictive of aphasia outcome, and aphasia type is also associated with lesion size and location (Kristinsson et al., 2022). In a large treatment study by Kristinsson et al. (2021) the authors found that patients with milder language impairments with fluent speech were more likely to respond well to semantic treatment, than patients with more nonfluent aphasias. Their results indicate differences in therapeutic effects between patients with fluent and nonfluent aphasia types. The authors argue that aphasia type is a possible predictor of aphasia therapy, but the effects must be considered along with aphasia severity, lesion size, and lesion location.

1.9.3 Neural predictors of aphasia recovery

The role of lesion size and lesion location in aphasia recovery has been investigated in several studies (Benghanem et al., 2019; Døli, Helland, Helland, Næss, et al., 2021; Forkel & Catani, 2018; Hillis et al., 2018; Lazar et al., 2010; Plowman et al., 2012; Seghier et al., 2016; Sul et al., 2019; Thye & Mirman, 2018; Watila & Balarabe, 2015). There seems to be an agreement that lesion location might be more important to consider than lesion size when predicting aphasia outcome (Cherney & Robey, 2008; Crinion et al., 2013), but studies also emphasize the predictive role of lesion size in aphasia recovery (Thye & Mirman, 2018).

Lesion location and aphasia recovery

Similar to Paper II in the present thesis, Sul et al. (2019) also investigated lesion location and the recovery of fluency, comprehension, naming, and repetition deficits

in patients with aphasia one-year post-stroke. Specific lesion locations were associated with long-term outcomes for the different language impairments that were assessed in the study. Lesions within the frontal inferior triangularis, frontal inferior operculum, supramarginal cortex and insula were associated with the patients' fluency deficits. Further, comprehension deficits were associated with lesions within the parietal cortex, angular cortex, temporal middle cortex, sagittal stratum, and temporal superior cortex. Lesions within the angular cortex, supramarginal cortex, posterior corona radiata, the supralongitudinal fasciculus (SLF), internal capsule, temporal superior cortex, and temporal middle cortex were associated with naming deficits. Deficits within repetition were associated with lesions within the temporal superior cortex, posterior corona radiata and the SLF. Finally, Sul et al. (2019) reported that lesions within the Rolandic cortex, Heschl's gyrus, posterior corona radiata, supramarginal cortex, superior longitudinal fasciculus, STG, and insula were associated with overall poor language outcomes.

White matter pathways in aphasia recovery

Forkel et al. (2014) investigated anatomical predictors of aphasia using tractography in both hemispheres. Tractography is a specific MRI sequence which infers long-range fibre pathways in the brain (Jeurissen et al., 2019). Forkel et al. (2014) found that the volume of the long segment of the arcuate fasciculus in the right hemisphere was a strong predictor of better aphasia recovery in patients with aphasia six months post-stroke. Forkel et al. (2014) hypothesize that a larger long segment might facilitate direct communication between the left and right hemisphere homologues of Broca's and Wernicke's area. However, the overall strongest predictor of aphasia recovery was the patients' initial lesion size, where larger lesions predicted lesser recovery. Forkel et al. (2014) findings emphasize that both hemispheres play a significant role in the recovery of aphasia after stroke.

1.9.4 Other factors related to the recovery of aphasia

Even though there is a strong consensus that initial aphasia severity and lesion location is a strong predictor of aphasia recovery, several other variables seem to be relevant (Ali et al., 2021; Forkel et al., 2014; Watila & Balarabe, 2015). In a recent systematic review and meta-analysis of aphasia recovery Ali et al. (2021) found that improvement from baseline diminished with patients increasing age and aphasia chronicity. Younger patients were favourable of larger changes in aphasia scores (<55 years). Forkel et al. (2014) also found that younger age was a predictor of recovery in aphasia six months post-stroke, as well as being female. The role of gender in aphasia recovery has been investigated in several studies, but there is no converging evidence indicating that one gender is favourable of greater recovery (Watila & Balarabe, 2015).

Cognitive functions in aphasia recovery

Patients with aphasia often exhibit deficits affecting other cognitive domains and processes (Fonseca et al., 2019; Lambon Ralph et al., 2010). Cognitive deficits, such as impaired semantic memory, constructive abilities, attention and processing speed (Fonseca et al., 2019), and deficits in executive control (Simic et al., 2019) have been reported to co-occur in patients with aphasia. Lambon Ralph et al. (2010) investigated patients with aphasia and their gains after anomia therapy. Their results suggest that both cognitive and phonological skills were predictors of overall improvement. However, as Simic et al. (2019) points out in their literature review, the tasks used when investigating executive control vary, as well as the theoretical models defining executive control. Therefore, further research is needed to investigate the role of the various cognitive domains that might have a predictive role in the recovery of aphasia.

Pharmacological treatment in aphasia

Hillis et al. (2018) investigated the role of lesion locations, the use of selective serotonin reuptake inhibitors (SSRIs), and the recovery of naming impairments (single word and picture description) in aphasia. The authors reported that lesion load in the left posterior STG, and/or superior longitudinal fasciculus/arcuate fasciculus was associated with poorer recovery of naming. However, when these areas were damaged and the patient used SSRIs, the patients had a better recovery of their naming deficits, independent of lesion volume, time since stroke, and depression. Also, if the patient had preserved these areas, they had a good recovery of naming deficits, even without the use of SSRIs. The authors emphasize the need for larger randomized controlled trials on the use of SSRIs in aphasia recovery (Hillis et al., 2018).

Post-stroke dementia in patients with aphasia

Stroke has been found to be a risk factor for developing post-stroke dementia (Leys et al., 2005; Mijajlović et al., 2017; Pendlebury & Rothwell, 2009). Post-stroke dementia affects up to 30% of all stroke survivors (Leys et al., 2005; Mijajlović et al., 2017). A clear understanding of the mechanisms and causes underlying the cognitive decline remains uncertain (Mijajlović et al., 2017). Left hemisphere lesions, as well as multiple strokes, have been found to increase the risk of post-stroke dementia (Zhou et al., 2004). The most common determinants of post-stroke dementia are increasing age, lower educational levels, pre-stroke dependency, and pre-stroke cognitive decline (Leys et al., 2005; Rasquin et al., 2004).

In a study by Zhou et al. (2004) the authors found that patients with aphasia were more likely to develop post-stroke dementia. Fonseca et al. (2017) conducted a systematic review on the topic and argue that it is not clear whether acquiring aphasia enhances the risk of post-stroke dementia. However, the authors found that patients with aphasia have lower scores than patients with left hemisphere strokes without aphasia on non-verbal neurobehavioral tools assessing cognitive functions.

Finally, a supportive environment has been found to decrease the consequences of aphasia (Simmons-Mackie, 2008). Patients suffering from stroke who are aware of their impairments and receive good social support, are more motivated and more likely to have better recovery post-stroke (Basso, 1992). Educating family and caregivers in helpful communication strategies and how to adapt to the situation is of essence for the SLT and might facilitate better recovery in aphasia.

Aphasia therapy

The current thesis does not investigate the effects of aphasia therapy, however, the findings from Papers I and II may serve as a background for future tailoring of neuroscience-based interventions in aphasia, while Paper III emphasizes the need for a focus on emotional well-being and quality of life in persons with aphasia. In the past chapter an integrated approach to understanding some of the mechanisms related to aphasia in the acute, subacute, and chronic stages post-stroke has been endeavoured.

Aphasia therapy can be direct or indirect, but a clinical approach implementing both is likely to be the most beneficial (Worrall, Sherratt, et al., 2017). Direct treatment can be described as face-to-face treatment of the specific aphasic deficit, while indirect treatment can be described as working the contextual factors surrounding the individual with aphasia, such as informing caregivers, fascilitating better communication with caregivers, and so forth (Worrall, Sherratt, et al., 2017) . In order to ensure a holistic approach to the person with aphasia, the ICF can be used in aphasia therapy to create a treatment plan to ensure the optimal treatment for each patient and their families (Worrall, Sherratt, et al., 2017). As mentioned earlier, aphasia may lead to a lesser quality of life and emotional difficulties. Treatment approaches that focus on improving both the language impairment and the quality of life of the person with aphasia, should therefore be the overarching goal of every clinician.

There seems to be a majority of studies investigating direct therapy in aphasia, and the recovery of aphasia has been found to be associated with the frequency, type, and amount of language therapy (Brady et al., 2016; Cherney et al., 2011). Also, Ali et al. (2021) conducted a comprehensive study that showed that improvement in aphasia was

associated with earlier language intervention. In the Cochrane-review by Brady et al. (2016) the authors reported that language therapy for people with aphasia following stroke improved functional communication, reading, writing, and expressive language functions compared with no therapy. The authors argue that there is some evidence that therapy at high intensity, and with a high dosage, or over a longer period might be more beneficial. However, this might not apply to every person with aphasia.

Summary

The cognitive neuroscientific approach to aphasia has embossed both research and the clinical approach to aphasia for hundreds of years, although several treatments and therapies that evolved during the 20th century opposed these theoretical approaches. The notion that aphasia can have a significant emotional and psychosocial impact has received more attention the last half-century (Papathanasiou, Coppens, & Davidson, 2017), and a more holistic approach, converging both neuroscience and the emotional and social consequences of aphasia, is promoted (Worrall et al., 2015).

In the present thesis both the neuroscientific and biopsychosocial approach to aphasia is emphasized. In Paper III the aims were to investigate patients' emotional consequences after stroke, as well as their quality of life. Therefore, in the following chapter (c.f. 1.10), recent studies within the field of quality of life and emotional difficulties after aphasia will be presented and discussed.

1.10 Quality of life in persons with aphasia

Aphasia affects several aspects of a person's social life and may lead to considerable emotional difficulties (Code et al., 1999). In the present thesis the term "quality of life" is used in line with the definition proposed by the WHO: "an individual's perception of their position in life in the context of the culture and value systems in

which they live and in relation to their goals, expectations, standards and concerns" (World Health Organization, 2001, para. 1.). The terms "quality of life" and "health-related quality of life" are frequently reported within aphasia research, and the latter is considered a more narrow term referring to the impact of a specific health state on a person's ability to lead a fulfilling life (Hilari et al., 2015). The terms are used interchangeably, and there is an ongoing discussion about whether the use of the term health-related quality of life is inappropriate because the term is not well-defined, nor clearly differentiated from the term quality of life (Karimi & Brazier, 2016).

Several studies have investigated the quality of life in patients with aphasia (Bullier et al., 2020; Gainotti, 1997; Hilari, 2011; Hilari et al., 2015; Ross & Wertz, 2003; Spaccavento et al., 2014). Aphasia severity, emotional difficulties, as well as functional limitations have been found to be associated with poor quality of life in persons with aphasia after stroke (Bullier et al., 2020). Furthermore, Bullier et al. (2020) also reported that in addition to aphasia severity, symptoms of anxiety and depression, and functional limitations, post-stroke fatigue might play a significant role to explain poor quality of life for persons with aphasia.

Ross and Wertz (2003) reported that individuals with aphasia engage in fewer social activities than stroke patients without aphasia. They also found that individuals with aphasia experienced less independence, and fewer and less meaningful social relationships compared to stroke patients without aphasia (Ross & Wertz, 2003). This has also been confirmed in a follow-up study by Hilari (2011), where persons with aphasia reported participating in fewer activities and had a poorer quality of life than persons without aphasia. Interestingly, Hilari (2011) also found that persons with aphasia at three-months post-stroke reported higher levels of psychological distress compared to others without aphasia. Surprisingly, the difference in psychological distress diminished after six months post-stroke, whereas persons with aphasia reported lower levels of distress, and those without aphasia reported the same levels of psychological distress.

This finding is contradictive to other studies investigating more long-term psychosocial consequences of aphasia, as several studies show that persons with aphasia have a higher prevalence of emotional difficulties which is found to be highly associated with quality of life (Kauhanen et al., 2000; Shehata et al., 2015). Hilari (2011) argues that the mood of the person with aphasia changes during the time course post-stroke due to the person's perceived social support. After three months there is a need for social support to cope with the new situation of being communicatively impaired. However, after six months the person with aphasia does not experience the same need for social support. Finally, after one year the aphasia has become chronic and the differences between patients with and without aphasia reappear (Hilari, 2011). The time of the assessment of the quality of life and emotional status in patients with aphasia is therefore necessary to bear in mind.

Worrall, Hudson, et al. (2017) addressed possible factors that contribute to living well at different time points in the first-year post-stroke. Aphasia severity, as in milder aphasia, was found to be a predictor of successfully living with aphasia, but it was one of the least significant predictors. The most important predictive variables were having a higher household income, being female, and a larger social network. Having a low mood was negatively associated with living well with aphasia. Psychosocial factors should be implemented in aphasia rehabilitation to contribute to positive outcomes, both in maximizing the outcomes following therapy (Kristinsson et al., 2022) and by enhancing the quality of life of the person with aphasia (Worrall, Hudson, et al., 2017).

1.10.1 Emotional consequences of stroke

Emotional difficulties are highly associated with a lower quality of life (Kauhanen et al., 2000). Therefore, to understand all aspects of a person's quality of life, it is necessary to bear in mind the emotional state after suffering from a stroke.

According to Fure (2007) emotional difficulties post-stroke are one of the most ignored sequelae after stroke in Norway. This is due to the lack of systematic clinical

investigation (Fure, 2007). Suffering from emotional difficulties after stroke has been found to have an adverse effect on the recovery and prognosis of stroke rehabilitation (Robinson & Jorge, 2015). This should serve as a strong incentive to assess and treat patients at risk of emotional difficulties to optimize stroke rehabilitation and quality of life.

Poststroke depression has been found to be a common sequalae after stroke, and can be characterized by symptoms such as low mood, anhedonia, decreased energy, appetite and concentration (De Ryck et al., 2014). Studies have estimated that 39-52% of the stroke population suffer from depression within the first five years following stroke (Robinson & Jorge, 2015). Several risk factors have been found to associated with poststroke depression, such female gender smoking, and mild cognitive impairment (Shi et al., 2015), history of mental illness, severity of stroke and level of handicap (Shi et al., 2017). Studies on anxiety and depression following stroke vary in their inclusion and exclusion criteria, and often exclude patients with aphasia, thus decreasing the generalizability of the results (Morris et al., 2017; Townend et al., 2007).

In Paper III, symptoms of anxiety and depression in stroke patients with and without aphasia was assessed using the Hospital Anxiety and Depression scale (HADS) (Zigmond & Snaith, 1983), which is a non-diagnostic screening tool for assessing symptoms of anxiety and depression, and the Stroke Impact Scale Version 2.0 (SIS) (Duncan et al., 1999) which is a self-report questionnaire that evaluates disability and health-related quality of life in persons with stroke (Mulder & Nijland, 2016). The clinical diagnosis of anxiety and depression as described in the Diagnostic and Statistical Manual of Mental Disorders - 5 (American Psychiatric Association, 2014) was not used as a clinical benchmark in the present thesis, as the assessment of anxiety and depression in the thesis is not based on a diagnostic test of depression and anxiety. Emotional difficulties are therefore hereafter used as a term referring to the symptoms of anxiety and depression as measured in the HADS.

1.10.2 Emotional consequences of aphasia

Within aphasiology, the emotional consequences of acquiring aphasia have been given more attention both in the scientific and clinical setting the past half-century (Sarno & Gainotti, 1998). Studies have reported a high incidence of emotional difficulties in patients with aphasia post-stroke (Hilari, 2011; Shehata et al., 2015; Starkstein & Robinson, 1988). The prevalence of depression in persons with aphasia has been found to be higher than in the overall stroke population, and patients with aphasia seem to be more likely to develop depressive symptoms (Hilari, 2011; Shehata et al., 2015; Starkstein & Robinson, 1988). Studies report that up to 60% of all patients with aphasia suffer from depression one-year post-stroke (Cruice et al., 2010; Kauhanen et al., 1999). Symptoms such as depression, anxiety, and other symptoms like fear, despair, social isolation, embarrassment, and frustration are frequently reported among persons with aphasia (Halpern & Goldfarb, 2013; Shehata et al., 2015; Spaccavento et al., 2014).

The cooccurrence of aphasia and depression has an adverse effect on stroke outcome (Laures-Gore et al., 2020). Acquiring aphasia is associated with worse outcomes in the acute and chronic stages post-stroke, poorer function in activities of daily living, longer rehabilitation processes, and increased mortality (Lazar & Boehme, 2017).

However, it is not clear whether the reason for the higher prevalence is due to the experience of acquiring aphasia, or if it is the lesion location itself that is the primary cause of the higher prevalence (Døli et al., 2017; Starkstein & Robinson, 1988). Understanding the relationship between post-stroke aphasia and depression requires a broad understanding of neural mechanisms of depression and stroke, in addition to psychological and psychosocial mechanisms. To this date, there is no clear understanding of the interplay between post-stroke depression and aphasia.

A study by Starkstein and Robinson (1988) reported that depression was more common in patients with non-fluent aphasia than patients fluent aphasia. The authors found left hemisphere lesions within the basal ganglia and the frontal regions of the brain to be associated with depression after stroke. However, the authors argue that

aphasia and depression are two separate outcomes of brain lesions that coexist, sometimes independently, and sometimes not (Starkstein & Robinson, 1988). Code et al. (1999) hypothesized that one explanation is that persons with aphasia with poor comprehension do not always realize the severity of their language deficits, but those with milder comprehension deficits are more self-aware.

Most studies investigating emotional difficulties following stroke focus on depressive symptoms. There is, however, some evidence showing that anxiety is as common as depression in stroke patients (Kneebone et al., 2012). Unfortunately, there is a lack of proper tools for assessing anxiety in patients with aphasia, which again makes it difficult to assess and determine the best treatment for persons with aphasia and emotional difficulties. Over the past years, several assessment measures have been found to be appropriate to assess emotional difficulties in persons with aphasia (van Dijk et al., 2015), however few are implemented into clinical practice. The development of proper assessment measures of emotional difficulties in persons with aphasia should be a priority for researchers and clinicans within the field of aphasia.

To assess and advocate for persons with aphasia and emotional difficulties it is essential that speech and language therapists (SLTs) understand the mechanisms and consequences of emotional difficulties in patients with aphasia as a result of stroke, and that the SLT participates in the treatment of emotional difficulties. Also, it is of essence to other health-care professionals that there is a clear understanding of the communicative abilities of the person with aphasia so that proper guidance and treatment is given. An assessment of the person's speech and language abilities should therefore be a basis before assessing and treating emotional difficulties in persons with aphasia.

2. Research questions and aims

In the following chapter the overall aim and the specific aims and research questions of each paper are presented.

2.1 Overall aim

The overall aim of this thesis was to investigate the associations between lesion size and lesion location in acute, subacute, and chronic aphasia, and to investigate the emotional consequences of aphasia one-year post-stroke. The theoretical background of the thesis is the framework of the ICF (World Health Organization, 2001), and the cognitive neuroscientific approach to aphasia. The aim is to provide a holistic and broad approach in the understanding of acquiring and living with aphasia.

2.2 Specific aims and hypotheses

Paper I

In Paper I the aim was to investigate the relationships between brain lesions in patients with aphasia after acute ischemic stroke, and the associations to aphasia severity and aphasic symptoms within one-week post-stroke. We wanted to investigate which lesioned regions of the brain that were related to the patients' aphasic symptoms and aphasia severity. Moreover, we wanted to know if aphasia severity and aphasic symptoms could be explained by certain lesion patterns in the brain, and if these patterns would align with the dual-stream model of speech and language processing.

A VLSM-method was performed to investigate the data. The main hypothesis was that lesions associated with speech comprehension deficits mainly would involve regions within the posterior superior and middle temporal lobe, and that speech production deficits would mainly be associated to lesions within the inferior frontal areas of the left hemisphere.

Paper II

In Paper II we wanted to explore relevant variables from the acute stages that were associated with the patients' aphasia outcome and symptoms twelve-months post-stroke. Further, we wanted to investigate specific lesions and lesion patterns that were associated with aphasia severity and aphasic symptoms after one year.

To do so, we investigated the statistical relationships between lesion location, lesion size, aphasia severity and initial stroke severity and their associations to aphasia and aphasic symptoms in the subacute (three months) and chronic stages post-stroke (twelve months). We hypothesized that initial stroke and aphasia severity was associated with the patients' aphasia outcome after one year.

As in Paper I, we used a VLSM-approach to investigate the relationships between the patients' lesions and their performance on the aphasia assessment at three- and twelve-months post-stroke. We also performed a region of interest-analysis (ROI) to investigate possible significant regions. We expected that lesions within the left frontotemporal regions were associated with aphasia severity in the chronic stages post-stroke, as this would be in line with current views of the dual-stream model proposed by Hickok and Poeppel (2007).

Paper III

In Paper III we wanted to explore differences in self-reported symptoms of anxiety and depression in one group of patients with aphasia, and one group with stroke, but

without aphasia. We also wanted to investigate if the groups differed in a measure of quality of life one year after their stroke.

Further aims were to investigate the relationships between the patients' aphasia severity and aphasia symptoms, and self-reported symptoms of depression and anxiety. We expected to find that patients with aphasia reported more symptoms of anxiety and depression than patients without aphasia. Further, we expected that aphasia severity was adversely associated with more self-reported symptoms of anxiety and depression.

Paper III was carried out in line with the famework of the ICF and incorporated a holistic and broad view on aphasia as a health condition, aphasia symptoms as limitations of functioning, and the consequences this might have on a person's activities and participation in life.

3. Methods

To answer the research questions, the aims and hypotheses postulated above (c.f. 2.0), three studies were planned and carried out. The following chapter will discuss the study designs, give an overview of the participants, assessment measures, and data analyses of each study.

3.1 Study design

This PhD-project collected data through the Bergen Stroke registry (NORSTROKE) and the Early Supported Discharge After Stroke – Bergen study (ESD) (Hofstad et al., 2013), both conducted at Haukeland University Hospital (HUS), Bergen, Norway.

The Bergen NORSTROKE study was initiated by Dr. Halvor Næss in 2006. The Bergen NORSTROKE study registers all patients admitted to the Stroke Unit at HUS diagnosed with ischemic stroke. The data collection for the present thesis included patients admitted to the Stroke Unit within the same period as the ESD-study, from 2008-2011. The NORSTROKE registry includes an extensive amount and range of data, from demographics and medical history to clinical findings and parameters during the patients' hospital stay, from admission to discharge.

The ESD-study was a clinical trial that started in 2008 and was completed in 2014. The study was led by Dr. Jan Sture Skouen and Dr. Håkon Hofstad. The study was a randomized controlled trial with two intervention arms and one control arm. The study consisted of 306 patients with stroke. The patients were randomized into one of three different treatment arms, where they received physical and/or occupational therapy; day unit with until 4 hours a day for up to 5 weeks, home rehabilitation with until 4 hours a day for up to 5 weeks, or a conventional rehabilitation treatment, with a longer hospital stay, but without specific treatment or follow-up after discharge (Hofstad et al., 2013).

Some of the patients in the study likely received speech and language therapy within all three arms, but in the present thesis data on where the patients with aphasia were randomized is not reported. However, it is important to clarify, the patients with aphasia received speech and language therapy regardless of the treatment arms.

The main objectives of the ESD-study were to compare the effects of the three intervention arms. The purpose was to evaluate the possible benefits of early supported discharge in the rehabilitation of stroke patients with either day unit rehabilitation or home rehabilitation. The results from the ESD-study showed that the patients in the ESD-groups tended to be more independent than controls at three and six months, but the authors did not find clear statistical differences between the groups (Hofstad et al., 2014).

The present PhD-project collected data from the two projects, from the patients' admission to the hospital, three months post-stroke, and finally one-year post-stroke. An overview of the data that was used in the present thesis is presented in figure 5.

The Regional Committee for Medical Research Ethics in Western Norway (REK Vest) approved the project.

3.2 Participants

As mentioned above, the patients in the present study were all part of the NORSTROKE registry, as well as included in the ESD-study at admission to the Stroke Unit at HUS. In the ESD-study all patients admitted to the Stroke Unit with suspicion of ischemic or hemorrhagic stroke during the period of the 8th of December 2008 – the 21st of December 2011, were assessed for inclusion following the inclusion criteria of the ESD-protocol. Inclusion to the study was paused during Easter, summer, and the Christmas Holiday periods. Table 1 is a presentation of the inclusion and exclusion criteria from the ESD-study originally made by Hofstad et al. (2013) .

Table 1. Inclusion and exclusion criteria in the ESD-study (Hofstad et al., 2013)

Inclusion criteria
Patient home-dwelling and living in the Municipality of Bergen
Recent stroke verified by CT or MRI
Inclusion within one to seven days after symptom onset
Inclusion within six hours to five days after admission to stroke unit
NIHSS score 2-26 at inclusion, or mRS score 2 or higher
Patient awake and able to consent; if not consent must be obtained by next-of-kin
No age limit
Exclusion criteria
Serious psychiatric disorders
Alcohol or substance abuse
Other serious conditions interfering with subsequent rehabilitation process
Insufficient knowledge of the Norwegian language pre-stroke

A total of 306 patients with stroke were included in the ESD-study. Of these, 114 patients were referred to a SLT based on initial suspicion of aphasia. Of these 114 patients, 66 patients were confirmed to have aphasia by a SLT at the Stroke Unit. Aphasia was diagnosed based on the convergence of clinical symptoms and by assessment with the NBAA within seven days post-admission (T1). The patients were thereafter summoned for a follow-up with the NBAA after three- (T2) and 12-months (T3). All patients signed informed consent forms prior to the inclusion in the ESD-study. If the patient was unable to sign, a next-of-kin was asked to sign the consent form.

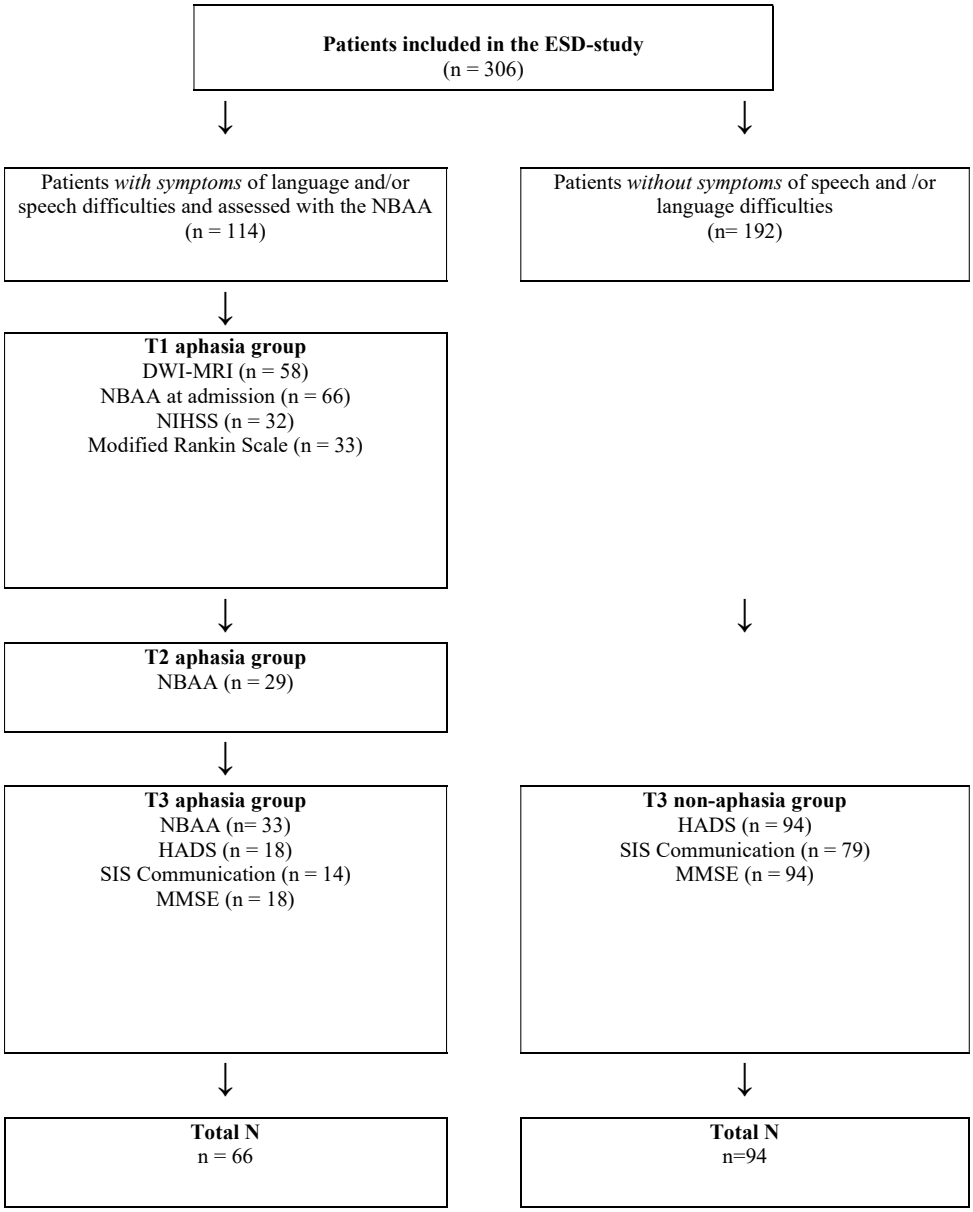
In study I and II we investigated patients with aphasia and their scans from the diffusion-weighted magnetic resonance imaging (DWI-MRI) at admission. Of the initial 66 patients with aphasia, eight patients were excluded because MRI was not

performed. Also excluded were six patients with inconclusive findings on their MRI-scans, three patients with earlier episodes of stroke, four patients with cerebral haemorrhage, and three patients with right hemispheric lesions. Therefore, a total of forty-two patients with aphasia after left hemispheric stroke were included with the NBAA and DWI-MRI at admission.

In Paper I we also divided the patients into two groups based on their median scores on the auditory comprehension subtests from the NBAA. The high comprehension group consisted of patients with mild to no auditory comprehension deficits, while the low comprehension group consisted of patients with moderate to severe auditory comrepehension. The division of the groups was based on the notion that we would find more damage to dorsal regions within the low auditory comprehension group, than the high comprehension group.

In Paper III we also included patients with stroke without aphasia as a control group to investigate the differences in self-reported symptoms of anxiety and depression between the patients with and without aphasia. Figure 5 is an overview of the patients that were included in all three studies.

Figure 5. Flow-chart of participants in the thesis



3.3 Assessment measures

Clinical information regarding the patients' stroke, comorbidities, demographics, and medical data were registered into the Bergen NORSTROKE registry database as standard procedure at the Stroke Unit. Additional examinations were carried out through the ESD-study at several time points. The data used in the present thesis are presented below.

3.3.1 The Norwegian Basic Aphasia Assessment

Patients were assessed with the NBAA (Reinvang & Engvik, 1980) at three time points, at admission, after three months, and finally, twelve months post-stroke. The NBAA was used to assess the patients' aphasia severity, aphasia symptoms, and to confirm the diagnosis of aphasia. The patients were not divided into aphasia syndromes, as this was not clinical procedure at the hospital.

The NBAA was used as a measure of aphasia severity and symptoms in all three papers. When the data for the present project was collected, the NBAA was the only standardized aphasia test in Norway and was performed as standard clinical procedure at the Stroke Unit at HUS for patients with suspicion of aphasia.

The NBAA, as previously described (c.f. 1.5), is based on the The Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1972). The test consists of seven subtests measuring auditory comprehension, repetition, naming, reading comprehension, reading out loud, syntax, and writing. The BDAE has been widely used and dominated the clinical assessment of aphasia in English speaking countries, as well as in Norway (Katz et al., 2000; Lind & Haaland-Johansen, 2013).

The overall aphasia score on the NBAA suggests an aphasia profile indicating both aphasia severity and aphasia type. The score on the NBAA ranges from 0-217 where

217 is the maximum of correct responses. A high score does not necessarily imply that the patient does not have aphasia, it implicates that the patient does not have severe aphasia. Therefore, clinical observation was also of importance when diagnosing aphasia after admission to the hospital. Table 2 is an overview of the subtests and their minimum and maximum scores.

Table 2. Subtests from the Norwegian Basic Aphasia Assessment

Subtest	**Minimum score**	**Maximum score**
Auditory comprehension	0	71
Repetition	0	40
Naming	0	41
Reading comprehension	0	23
Reading aloud	0	26
Syntax comprehension	0	10
Writing	0	10

The NBAA measures different language processes through the seven subtests. In the subtest *auditory comprehension,* the patient is asked to identify, describe, and conduct instructions. The subtest *repetition* investigates the patient's ability to repeat words, non-words, and sentences of increasing difficulty. In the subtest *naming*, the patient is asked to name body-parts and actions. There are three subtests that measure the patient's ability to read and write. *Reading aloud* is examined by reading words, letters, and sentences aloud. Similar is done while examining *reading comprehension*

where the patient is asked to match words and objects, words and letters, and words and sentences. In the subtest *syntax comprehension,* the patient is asked to organize cards with several words on each card to produce correct sentences. The last subtest examines the patient's *writing* skills. The patient is asked to write words and sentences by copying, after dictation and after naming (Reinvang & Engvik, 1980).

In all three papers we used the patients' total score from the NBAA, and the scores on each subtest as a measure of the patients' aphasia severity. We did not divide the patients into aphasia subgroups because we wanted to investigate the patients' aphasia severity within each subtest, as well as the overall aphasia severity score. Another important reason was when using VLSM, continuous scores are more adequate to use, and enhances the overall power and sensitivity of the study (Baldo, Wilson, et al., 2012). In Paper II we also used the patients' change in scores as a measure of aphasia recovery.

At T1 the NBAA was performed within seven days post-onset of their initial symptoms. The NBAA was assessed by SLTs at the Stroke Unit at HUS. At T2 and T3 the NBAA was assessed by SLTs at the Department of Physical Medicine and Rehabilitation at HUS.

3.3.2 The National Institute of Health Services Scale

The National Institute of Health Services Scale (NIHSS) (Brott et al., 1989) was included as a measure of the patient's overall stroke severity at admission to the Stroke Unit. Within the framework of the ICF, the NIHSS assesses body functions. We included the NIHSS in Paper I and II.

The NIHSS is a scale that measures neurological deficits common in acute stroke. The modified version (Lyden et al., 2001) consists of 11 subtests investigating level of consciousness, gaze, visual fields, fascial palsy, left and right motor arm, left and right motor leg, ataxia, sensory, language, dysarthria and neglect. Results from the affected side (left/right) were reported in Paper I and II. The NIHSS was performed at

several time points from admission and until seven days post-onset of initial symptoms or earlier if the patient was discharged. We used the Norwegian version of the NIHSS score from admission to the Stroke Unit. The score ranges from 0 to 34 points, a higher score indicates more severe stroke symptoms.

3.3.3 The Modified Rankin Scale

The Modified Rankin Scale (mRS) (Rankin, 1957) is a widely used global disability measure (Banks & Marotta, 2007). The mRS measures functional independence, and thereby incorporates the ICF components of body function, activity and participation (Kasner, 2006). The mRS was included in Paper I as a measure of functional independence at admission to the hospital. The mRS is shown to have high validity, however the due to the few items the reliability of the measure is debated (Kasner, 2006). The score ranges from 0-6, where zero indicates no symptoms at all, and six is given if the patient is dead. In Paper III we used the mRS scores from day seven post-stroke, or on discharge if the patient was discharged earlier.

3.3.4 The Barthel Index

The Barthel Index (BI) (Mahoney & Barthel, 1965) assesses a patient's performance in daily life activities. It consists of ten items that is divided into self-care tasks (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and items related to mobility (ambulation, transfers, and stair climbing). The maximal score is one hundred, indicating that the patient has no difficulties in daily activities, and the lowest score is zero, indicating that the patient is dependent on constant nursing care and attention. In Paper III we used the BI as a measure of functional status at seven days post-stroke or at discharge if discharged earlier.

3.3.5 The Hospital Depression and Anxiety Scale

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was developed to investigate if patients with somatic disease experience symptoms of anxiety and depression. The HADS consists of fourteen items, whereas seven of the items relate to the experience of anxiety and the remaining seven items relate to the experience of depression. The test consists of written questions, and the patient can mark his or hers answers independently or with help. Each item is scored on a 3-2-1 ordinal-scale, with a total score of 21 for either anxiety or depression. Higher scores indicate more reported symptoms of anxiety and/or depression.

The cut-off for both scales is a score of eight out of 21, whereas a score above eight on each scale indicates the need for further diagnostics of anxiety and/or depression. When summarizing the two scales into a total-score, a score above 15 suggests the need for further diagnostics. We included the HADS in Paper III to investigate the patients' symptoms of anxiety and depression after stroke.

3.3.6 The Stroke Impact Scale Version 2.0

The Stroke Impact Scale (Duncan et al., 1999) was developed to evaluate how stroke has affected the health and life of stroke survivors. The SIS, which was used in Paper III, investigates how acquiring stroke impacts a person's health-related quality of life. However, in the present thesis, the term quality of life is used when reporting the findings from the SIS. The SIS consists of 64 questions divided into eight subscales. In Paper III the subscales *communication, daily activities* and *social/leisure activities* were included. Each item is rated in a 5-point Likert scale that indicates to what extent the patients have experienced difficulties regarding the question asked. The scores on the subscale *communication* ranges from 0-35, the *daily activities* subscale ranges from 0-50, and the *social/leisure* subscale ranges from 0-40. A high score indicates no difficulties and a low score indicating severe difficulties (Duncan et al., 1999).

3.3.7 The Mini Mental State Examination

The Mini Mental State Examination (MMSE) is a short global cognitive functioning questionnaire which consists of different measures within cognition, such as episodic memory, language skills, orientation, memory and attention (Folstein et al., 1975). The questionnaire was performed at the twelve-month follow-up and was included in Paper I as a measure of cognitive functioning. The questionnaire consists of eleven questions. The test was administered and scored by a skilled practitioner. The MMSE score ranges from 0-30, where a high score indicates a high level of cognitive functioning. The cut-off is <24, a score of 24-30 indicates no cognitive impairment, 18-23 indicates mild cognitive impairment and 0-17 indicates severe cognitive impairment.

3.4 Magnetic resonance imaging

According to the clinical routine at the Stroke Unit, all patients were referred to diffusion-weighted magnetic resonance imaging (DWI-MRI) within 24 hours post-onset of stroke symptoms. The imaging data were collected on a Siemens 1.5 Tesla Symphony using a DWI-sequence with TR 3200 ms, TE 94 ms, field of view 230mm, 128x128 matrix, in-plane voxel size 1.8 x 1.8 mm^2, and slice thickness 5mm as specification parameters.

3.4.1 Data pre-processing for voxel-based lesion-symptom mapping

Lesions were traced manually slice-by-slice directly onto the patients' DWI-images in MRIcron (Rorden et al., 2007). Uncertain or unclear cases were excluded. Both the DWI images as well as the lesion maps were normalised into standard Montreal Neurological Institute (MNI) stereotactic space, using the "old normalisation" procedure of the Statistical Parametric Mapping (SPM) software, version 12. First,

DWI-images were normalised into the MNI space using an EPI-template, as provided by SPM12. To achieve the most optimal normalisation, the transformation was based on the non-lesioned tissue by masking the individual DWI-images with the respective lesion maps (Brett et al., 2001). Thereafter, the transformation was applied to the lesion map, and images were resampled to a voxel size of $2mm^3$.

3.5 Data Analyses

Paper I

Paper I was a cross-sectional study where we investigated the associations between lesion location, lesion size, initial stroke severity and aphasia severity in patients with aphasia in the acute stages post-stroke. We used a VLSM-method to investigate the statistical relationship between aphasia severity and lesion location. We used the non-parametric mapping (NPM) software package in MRIcron. We used a general linear model (GLM) where the predictor variable was the lesion, and the outcome variable was the patient's scores from the NBAA. We carried out independent samples t-tests to investigate differences in lesion size between the high and low comprehension groups. Descriptive statistics, t-tests, correlations, and frequencies were all calculated using the Statistical Package for the Social Sciences version 20 (SPSS).

Paper II

Paper II was a follow-up study that investigated the associations between lesion location, lesion size, aphasia severity, and initial stroke severity and aphasia at three- and twelve-months post-stroke. As in Paper I, we used the NPM-software package in MRIcron for the VLSM-analysis to investigate the statistical relationship between aphasia severity and lesion location. We used a GLM where the predictor variable was the lesion, and the outcome variable was the patient's scores from the NBAA. To explore the lesion data further, we performed a post-hoc ROI-analysis, which included the insula, the IFG triangularis, the IFG opercularis, and the posterior and

anterior divisions of the STG. We performed a drop-out analysis to investigate differences in initial scores between the dropouts at T3 and the ones who attended the retesting. To investigate associations between initial stroke and aphasia severity, and lesion size and aphasia at three- and twelve-months post-stroke, correlation analysis was performed. To investigate changes in the patients' scores over time, we performed an ANOVA. All analyses were calculated using SPSS version 25.

Paper III

Paper III was a correlational study. First, we compared the two groups of patients (with and without aphasia after stroke). We used independent samples t-tests to investigate group differences in self-reported symptoms of depression and anxiety, and scores from the SIS. Second, we used Pearson's correlation to investigate the relationships between aphasia severity at admission, after three months, and after one year, and the patients' symptoms of anxiety and depression, the SIS, the mRS, and their cognitive functioning at one-year post-stroke. We also used Pearson's correlation to investigate associations between symptoms of anxiety and depression and the patients' scores from the subtests from the NBAA (total score, auditory comprehension, repetition, naming, reading aloud, syntax and writing). All analyses were performed using SPSS version 23.

Please refer to the individual papers for further information and details on the data analyses.

4. Results

The following chapter provides a summary of the papers included in the thesis.

Paper I

Paper I, *Associations between lesion size, lesion location and aphasia in acute stroke*, investigated the relationships between the patients' lesion locations and size, and the aphasia symptoms and severity in the acute stages post-stroke. This was investigated using a VLSM-method. The results showed that in the whole group analysis, lesion size was significantly associated with all subtests of the NBAA. Further, difficulties naming was associated with lesions within the Rolandic operculum (RO), and the STG. In the analysis of patients in the high comprehension group, lesions within Broca's area, insula, the STG, and Heschl's gyrus were associated with overall aphasia severity, and difficulties within repetition, naming, and reading aloud.

Paper II

Paper II, *Associations between stroke severity, aphasia severity, lesion location, and lesion size in acute stroke, and aphasia severity one year post stroke,* was a follow-up study of the patients with aphasia. The patients were assessed with the NBAA at three time points, the acute stage, three-, and twelve-months post-stroke. The results showed that initial lesion size and aphasia severity were associated with aphasia severity at T2. However, we did not find initial lesion size, stroke severity, nor aphasia severity at T1 to be associated with aphasia severity at T3. Aphasia severity at T2 was however found to be strongly associated with aphasia severity at T3. As in Paper I, we also performed VLSM to investigate the relationships between lesioned areas of the brain and aphasia severity. Our results showed that lesions within the left postcentral gyrus and left inferior parietal gyrus were associated with the patients' aphasia severity at T3.

Paper III

The main findings of Paper III, *Self-reported symptoms of anxiety and depression in chronic stroke patients with and without aphasia*, were that there were no significant differences in symptoms of anxiety and depression between the patients with aphasia and the patients without aphasia. However, we did find that aphasia severity was associated with more symptoms of depression, thus indicating that the patients with more severe aphasia also experienced more depressive symptoms. Moreover, we found that difficulties within the subtests repetition and reading comprehension were associated with the overall HADS score, indicating that deficits within these language domains was associated with more symptoms of anxiety and depression.

5. Discussion

The papers in the present thesis aimed to investigate the relationships between lesion location, lesion size, initial stroke, and aphasia severity and symptoms in the acute, subacute, and chronic post-stroke. Furthermore, quality of life and emotional difficulties in persons with aphasia in the chronic stages post-stroke were investigated. To sum up the results, aphasia severity in the acute stages post-stroke was associated with lesion size. Further, specific regions within the left hemisphere were associated with specific aphasic symptoms. Aphasia in the subacute stage was also associated with initial lesion size and aphasia severity. However, this was not the case for aphasia severity at twelve-months post-stroke. Only aphasia severity at three months post-stroke was associated with aphasia severity at twelve months post-stroke. Lesions within the postcentral gyrus and inferior parietal gyrus were associated with aphasia severity at twelve months post-stroke. Finally, we found that at twelve months post-stroke patients with aphasia did not exhibit more symptoms of anxiety and depression than patients without aphasia. However, the patients with aphasia reported on average, more symptoms of anxiety and depression that were related to specific language tasks.

5.1 Aphasia in the acute stages

Paper I concluded that the patients' overall aphasia severity was associated with lesion size in the acute stages post-stroke. The patients' performance on all subtests from the NBAA, auditory comprehension, naming, repetition, reading comprehension and writing, were associated with the patients' lesion size.

5.1.1 Lesion size

As reported earlier (c.f. 1.8.2.), studies have reported that lesion size is a predictor of aphasia outcome in the acute stages post-stroke (Plowman et al., 2012; Thye & Mirman, 2018). The results from Paper I support earlier findings of lesion size as being important when investigating aphasia severity and aphasia symptoms within the acute stages post-stroke.

5.1.2 Lesion location

Lesion analysis of the whole group showed that lesions within the RO were associated with the patients' performance on the naming and repetition tasks. Lesions within the STG were also associated with performance on the repetition subtest. The specific regions of our analyses differ from those of Baldo, Katseff, et al. (2012), who reported repetition and auditory-verbal short-term memory deficits in aphasia to be associated with lesions within the posterior temporoparietal cortex. However, looking past the specific regions in Paper I, both studies support that performance in naming and repetition involve regions within the ventral and dorsal streams as proposed by (Hickok & Poeppel, 2007).

To investigate the patients' further, we divided the patients into two groups based on their scores on the auditory comprehension subtest. The division of the groups was based on the notion that we would find more damage to dorsal regions within the low auditory comprehension group, than the high comprehension group. For patients with milder auditory comprehension deficits, lesions within Broca's area, the insula, the STG, and Heschl's gyrus were associated with overall aphasia severity, and more severe deficits on the subtests repetition, naming, and reading aloud. For all subtests, except naming, lesions within the SMG, postcentral gyrus, angular gyrus, inferior parietal lobule and superior parietal lobule were significant regions. Despite different lesion patterns, the findings support current views that these language functions, as measured by clinical language tests, are related to both speech production and comprehension, thus dependent of interaction of both the ventral and dorsal streams

(Fridriksson et al., 2016). Also, these findings also support the research that has been published the past two decades on challenging the role of Broca's and Wernicke's as the two main language areas in the brain (Bates et al., 2003; Dronkers et al., 2004). Finally, we observed a different lesion pattern for naming deficits. As we argue in Paper I, naming deficits was associated with lesions within the pars triangularis, pars opercularis, the insula, the STG and Heschl's gyrus. Clearly, naming deficits are highly related to lesions within regions in the dorsal stream, which is in line with current views of the dual-stream pathways in speech processing (Hickok & Poeppel, 2007).

Another interesting finding from Paper I was that the group of patients with more severe auditory comprehension deficits, did not yield any statistical relationships between their lesions and aphasia severity and symptoms. We hypothesized that one reason was that the patients with more severe auditory comprehension deficits also had a wider spread in lesion patterns than in the high comprehension group, thus decreasing the statistical power and diminishing statistical relationships when performing the statistical corrections. Finally, the result is interesting as it highlights that severe auditory comprehension deficits can occur from lesions at various places within the language network. Our findings are supported by the notion that large lesions affecting both streams alter the whole language network, thus causing long-lasting deficits across language modalities (Fridriksson et al., 2016).

5.2 Long-term outcome of aphasia

Paper II concluded that initial lesion size and aphasia severity were associated with aphasia severity at three months post-stroke, but the findings diminished when investigating their associations to aphasia severity at twelve months post-stroke. Aphasia severity at three months post-stroke was however strongly associated with aphasia severity at twelve months post-stroke. Initial stroke severity was not associated with aphasia severity at three- or twelve-months post-stroke.

5.2.1 Initial severity and lesion size

The results from Paper II differ from earlier studies that report initial aphasia severity as a predictor of long-term aphasia outcome post-stroke (El Hachioui et al., 2013; Plowman et al., 2012). In Paper II we argued that one significant difference between Paper II and El Hachioui et al. (2013) study was the outcome measures at twelve-months. El Hachioui et al. (2013) used a dichotome functional outcome measure to investigate recovery after one year, and not the same measures as they used as baseline predictors. The results from Paper II are however consistent with Benghanem et al. (2019) who reported lesion size as a predictor of aphasia outcome at three months post-stroke. Time of assessment is clearly of relevance when aiming to predict aphasia recovery and outcome after stroke. This was also confirmed in Paper II, where there was a significant improvement in overall aphasia severity from T1 to T2, and from T1 to T3. There were no statistically significant changes in aphasia severity from T2 to T3. Also, as I will discuss in chapter 5.6, one major limitation of all three papers is the lack of information about the therapy the patients' received between the test points, thus limiting the interpretation of the results.

5.2.2 Lesion analysis and long-term aphasia outcome

Lesions within the left post-central gyrus and the left inferior parietal gyrus were associated with the patients' overall aphasia severity at twelve months. Our initial hypothesis, that we would find lesions within the temporoparietal regions of the left hemisphere to be associated with aphasia severity was therefore partially confirmed. The findings from Paper II indicate that lesions within the left inferior and postcentral parietal regions are crucial when investigating long-term overall language performance. Especially the long-term outcome of language comprehension seems to be associated with lesions within the parietal lobe. Lesions within temporoparietal regions have been shown to cause a disconnection of the dorsal and ventral language pathways, thus causing both language comprehension and production deficits (Benghanem et al., 2019). Our results suggest that lesions along the anterior and

inferior parietal gyrus also causes a disconnection of the streams, causing long-lasting aphasic difficulties.

Auditory comprehension and reading comprehension deficits at twelve months post-stroke were both associated to lesions within the postcentral gyrus, indicating a significant role of the postcentral gyrus in comprehension tasks. This finding was surprising, as both comprehension tasks were associated with damage within the dorsal stream, and not the ventral stream. This finding is also contradictive of what Fridriksson et al. (2018) reported, where the postcentral gyrus was primarily associated with language functions related to speech production. On the other hand, Sul et al. (2019) also reported the parietal cortex as significant in comprehension tasks. The research literature is not equivocal.

As in Paper I, lesions within the RO were associated with repetition deficits. The RO is located on the borders of the precentral and postcentral gyri (Triarhou, 2021). As repetition is a speech production task, the findings line up with the notion of repetition being localized within the dorsal stream.

Finally, deficits in reading aloud were associated with lesions within the RO, the insula, the STG, and the SMG. These results are somewhat consistent with the structural patterns of the visual word form area. This also confirms the notion of reading being dependent of the structural integrity of the visual word form area, which comprises the parietal, temporal, and frontal areas, including the insula (Dehaene, 2009). These specific lesion patterns were also found to be associated with the patients' performance on the reading subtest in Paper I, thus suggesting that the relationship between this language task and initial lesion location remains unaltered throughout the first-year post-stroke. One possible explanation for this is that since reading is dependent of a large network across different brain regions, it is more likely to be a long-lasting impairment than language functions that are associated with more specified and concentrated brain structures.

5.3 Quality of life and emotional difficulties in aphasia

Paper III differed from Paper I and II and focused on the emotional and psychosocial impact of acquiring aphasia. In Paper III we sought to investigate the consequences of living with aphasia, compared to a group of patients living with stroke, but without aphasia.

5.3.1 Group differences

Differences in self-reported symptoms of anxiety and depression and quality of life in individuals with and without aphasia were investigated. We also included a measure of daily living, self-perceived communication difficulties, as well as cognitive functioning to investigate possible group differences. There were no differences between the groups regarding their self-reported symptoms of anxiety and depression, but there was a non-significant descriptive difference between the groups, whereas the patients with aphasia reported slightly more symptoms of anxiety and depression. Our findings differ from previous studies reporting a high incidence of emotional difficulties in patients with aphasia after stroke (Hilari, 2011; Shehata et al., 2015; Starkstein & Robinson, 1988). The reason for this finding is uncertain, but the small sample size and the number of dropouts might be plausible explanations. It is also likely that persons with aphasia suffering from depression and anxiety are more unlikely to attend the follow-up assessments in clinical research.

As we expected, the patients with aphasia experienced more communication problems and had a lower level of cognitive functioning than the patients without aphasia. This is in line with previous studies showing that persons with aphasia have lower scores on tasks within cognitive domains (Fonseca et al., 2019). The patients without aphasia reported more difficulties in daily activities. In retrospect, one might assume that the large differences in group sizes might have contributed to this finding, as one might expect that the group without aphasia, on average, were more varied in their physical outcomes than the patients with aphasia.

5.3.2 Aphasia and symptoms of anxiety and depression

By investigating the patients with aphasia closer, we found that patients with more severe aphasic symptoms reported more symptoms of depression. This is in line with Worrall, Hudson, et al. (2017) who found that milder aphasia severity was a predictor for successfully living with aphasia in the chronic stages post-stroke. In our study, we found that patients with more difficulties within repetition and reading comprehension had more self-reported symptoms of both anxiety and depression. We also found that patients that had difficulties with repetition, reading comprehension and reading aloud reported more symptoms of depression, but not anxiety. As we discuss in Paper III, one possible explanation for this finding might be that the experience of difficulties within everyday communication, such as reading the newspaper, or a text message, might increase the symptoms of anxiety and depression in one's life.

5.4 Clinical implications

The present thesis has a biopsychosocial approach to aphasia. This includes a medical, social, and psychological perspective on aphasia. The thesis is also carried out within a cognitive neuroscientific framework. As discussed in chapter 1.6, these perspectives on aphasia are not mutually exclusive, but rather complement each other. As mentioned in chapter 1.9.4, the goal of every clinician working with aphasia should be improving the language impairment as well as the quality of life of the person with aphasia. Having a holistic and broad perspective will benefit all persons with aphasia.

The findings from Paper I and II support the theory of dual-stream pathways for speech and language processing as proposed by Hickok and Poeppel (2007). According to Fridriksson et al. (2018) there has been relatively limited efforts on explaining aphasic symptoms within the model. Paper I and II can provide valuable

information about lesion patterns and prognostic variables in aphasia in the acute and chronic stages post-stroke.

Communicating information about recovery is an important part of aphasia treatment and care (Plowman et al., 2012). According to a recent study by Cheng et al. (2022), patients with aphasia experience mistrust and misinformation in the process of receiving prognostic information. The authors suggest that the neurological basis of aphasia, as well as the underlying mechanisms of rehabilitation, should receive more attention, and clinicians should formulate this information in an aphasia-friendly manner to establish a good patient-clinician relationship and trust. The authors emphasize the importance of giving this information without undermining the importance of hope.

Until recently, therapy for aphasia has shown little or no effect (Brady et al., 2016). However, the development of individually tailored aphasia therapies, along with systematic research with sufficient power, has shown that therapy has an effect in improving language functions (Brady et al., 2016). Aphasia therapy is more informed by understanding the neurobiology of language, and by incorporating models of neuroscience with linguistic and social models of understanding aphasia.

Newer experimental techniques, such as cortical brain stimulation that can modulate cortical excitability, are in the starting pit (Tippett et al., 2014), and results from lesion studies in aphasia might contribute in the tailoring of neuroscience-based interventions for individuals with aphasia. A recent study by Iyer et al. (2020) sought to predict aphasia recovery based on changes in cortical connectivity pathways during a therapy program. The authors found that bilateral cortical responses in patients with aphasia predicted treatment-induced improvements in naming. Targeting the language functions associated with the dorsal and ventral stream while investigating the neural correlates of recovery due to therapy, is a promising way to further develop and enhance aphasia interventions.

However, to ensure good therapy outcomes in aphasia, an integrated approach must be provided. As stated above, one goal is to improve the aphasia recovery through

targeted therapy. Another equally important goal is to facilitate good quality of life for the patients with aphasia and their surroundings. As we suggested in Paper III, patients with aphasia should be screened for anxiety and depression with proper assessment tools during their rehabilitation course to prevent and adequately treat emotional difficulties. A holistic perspective on aphasia will therefore serve as the most prominent aphasia management.

5.5 Ethical considerations

Ensuring ethical standards within research is essential to take care of patient interests, as well as research interests. Including patients with aphasia in research introduces some considerations. In the following section I will discuss informed consent in the present studies.

5.5.1 Informed consent in patients with aphasia

An important question when conducting research is if the informed consent is handed out in an accessible format (Kagan & Kimelman, 1995). Persons with aphasia benefit from getting information in different modalities; this can be verbal information, written information, and information through pictures (pictographs are frequently used). Persons with aphasia need to be communicated to in a simplified way. Examples of this can be the use of simple grammar, repetition of important concepts, diagrams, and models to explain, and to avoid open-ended questions. A common feature in aphasia is that patients might mask the lack of understanding, or even the other way around, mask their competence. The pragmatics of language may be adequate; they nod or shake their head at the right places. Of course, some patients with aphasia will acknowledge that they do not comprehend, but others may not realize that they do not understand (Kagan & Kimelman, 1995).

In the present thesis, data were collected from two larger studies conducted at HUS. In the ESD-study all patients that met inclusion were asked to participate (see table 1). Severe auditory comprehension deficits were not exclusion criteria. If the patient was unable to understand the information and make a decision, a designated nurse working in the Stroke Unit informed the patients about the study. If the patient was unable to sign an informed consent, a next-of-kin was asked to sign. These specific issues were approved by the Western Norway Regional Committee for Medical Research Ethics (Hofstad, 2015).

Naturally, the patients could withdraw from the study at any time. We experienced a large drop-out rate within the project period. In Paper III we addressed this finding by performing a drop-out analysis. We did not find any differences regarding age, nor aphasia severity at admission between the patients who attended the retesting and those who did not. Other explanations might also be possible, but our data were limited. From a clinical point of view, we reflected upon the possibility that some of the patients did not understand the informed consent and the written information they got when they were summoned for retesting at T2 and T3. In the aftermath of the project, the patients with aphasia clearly should have been given aphasia-friendly consent-forms such as proposed by Penn et al. (2009).

5.6 Limitations

There are several limitations in the present thesis that should be discussed. One important limitation is the considerable number of dropouts from T1, to T2, and to T3, resulting in a low n, especially in the twelve-month assessment. One possible explanation for this, as mentioned above, was the lack of aphasia-friendly consent forms, and aphasia-friendly information when the patients were summoned at three- and twelve-months post-stroke. One might speculate that other causes could be the commute to the hospital for retesting, or other issues related to planning and organization. Unfortunately, dropouts seem to be a common challenge within aphasia

research (Pollock et al., 1993). In retrospect, one way to avoid dropouts could be to do the follow-up assessments in the patients' homes or elsewhere if the patient is hospitalized. However, this would be very time-consuming for the clinicians involved in the follow-up assessments, but it would increase the overall power of the studies.

In Paper II the final selection of patients was reduced by almost 50%. This was due to missing data from the language assessments at T2 and T3. Also, some of the patients who met for retesting did not have adequate MRI scans from T1. They were therefore also excluded from the analyses. To account for this in Paper II, we did not predict aphasia outcome, but we sought to investigate the associations between variables at the different time-points. Lorca-Puls et al. (2018) argue that studies with low power due to a small sample size produce heterogeneous results, hence our results should be interpreted with caution. Lorca-Puls et al. (2018) argue that larger studies using multivariate methods should be pursued, including information about time post-stroke, education, and age to provide sufficient information to predict language outcome and recovery.

Another critical issue in the present thesis was related to the lesion mapping method in Paper I and II. As explained in chapter 3.4.1, lesions are traced manually directly onto the patients' DWI-images in MRIcron. VLSM is a time-consuming and subjective procedure. In Papers I and II, the tracing was performed under the supervision of an experienced neuroscientist. Supervision was given especially in tracing lesions adequately, and in distinguishing different types of damage, such as gliosis, atrophy, and ventricular changes. Finally, uncertain, or unclear cases were always discussed. If they still were unclear after further inspection, the patient was excluded from the study. Another issue related to the VLSM-method was the statistical corrections that were carried out to control for false positive results. When performing VLSM a large number of voxels are being sampled, thus resulting in multiple comparisons. To control for this, we performed permutation testing and corrections before interpeting the results. However, this also creates a pitfall as the power to detect actual differences is reduced because of the small sample size (Baldo, Wilson, et al., 2012). In retrospect, we should have carried out a power analysis prior

to the VLSM-analysis to decide whether the analysis was able to detect statistical differences across the different voxels (Kimberg et al., 2007).

A third challenge relates to the clinical assessments used in all three papers, especially Paper III. As mentioned in chapter 3.3.1, the clinical experience using the NBAA shows that the test has a ceiling effect for patients with mild aphasias. Clinical observation was therefore necessary to determine the diagnosis of aphasia. Also, the NBAA was standardized for 40 years ago, an update of the test would be appropriate. The NBAA has until recently been the only standardized aphasia assessment in Norway. In 2021 the Norwegian version of the Comprehensive Aphasia Test was published (Swinburn et al., 2021), which might have been an alternative or supplement to the NBAA. At the same time, the subtests in the NBAA are similar to the subtests in the Boston Naming test and the WAB, thus making comparisons across studies transparent.

As described in Paper III, and in chapters 3.3.5 and 3.3.6 the HADS and the SIS are not specifically developed for individuals with aphasia. The HADS was primarily developed for use in patients with somatic comorbidity. However, the scale has been validated and was found to be suitable for the stroke population (Aben et al., 2002). However, in the validation of the HADS, Aben et al. (2002) excluded patients with severe aphasia and dementia. As mentioned in Paper III, we consider this a limitation of our study, but as the patients in Paper III had moderate to mild aphasic symptoms, we might assume they understood questions that were asked. The SIS was developed for the overall stroke population, thus including patients with aphasia. To my knowledge, the Norwegian translation of the SIS has not been validated. This decreases the overall validity of the study. However, when comparing groups it is of essence that we use the same measurements to investigate group differences.

Finally, one important limitation of the present project, which has been mentioned earlier, was the lack of information on speech and language therapy that the patients received throughout their first-year post-stroke. Information about dosage, intensity, frequency, and type of speech and language therapy would have enhanced the

methodological quality of Paper II and III substantially. As mentioned in Paper III, therapy might have had a substantial effect on therapy between the test-points. Longitudinal studies in aphasia should clearly strive to report information regarding therapy.

5.7 Future directions

There are several potential future directions that would be interesting to pursue in the aftermath of the present thesis. First, it would be interesting to continue investigating the relationships between the neural correlates and emotional difficulties in persons with aphasia, as the neural localization of aphasia and depression has been suggested to be associated in earlier studies (Starkstein & Robinson, 1988).

Secondly, the rapid development of technology and methods to investigate the brain, gives new insights and possibilities in the future of cognitive neuroscience. A clearer understanding of speech and language regions and pathways in the brain can enhance and inform aphasia therapy, prognostication, and recovery.

Finally, as mentioned earlier, larger longitudinal studies using multivariate analyses, including information about therapy, time post-stroke, education, age, and personal factors, such as social support, motivation, quality of life, and emotional status would be interesting to pursue in the future. In order to obtain this, I agree with the researchers working with the PLORAS database (Price et al., 2010), who emphasize that international databases should be prioritized to enhance the predictions of language outcome and recovery after stroke.

6. Conclusions

To summarize, this thesis has provided insights into the associations between lesion size, lesion location, and stroke and aphasia severity and symptoms, in acute, subacute, and chronic stroke. The thesis provides an understanding of the emotional consequences of living with aphasia in the chronic stages post-stroke.

The three main findings are that lesion size is highly associated with aphasia severity in the acute and subacute stages post-stroke, but not after twelve months post-stroke. In the acute stage lesions within dorsal and ventral pathways were associated with aphasia outcome, while lesions within the dorsal stream were primarily associated with aphasia outcome after one year. Finally, we did not find differences in self-reported symptoms of anxiety and depression between patients with and without aphasia at one-year post-stroke.

From a theoretical perspective, the holistic framework of the ICF should be emphasized within neuroscience to encompass all aspects of living with aphasia post-stroke. Further, the findings from the present thesis support the notion of a dual stream pathway of speech and language processing, which is dependent on the integrity of the entire network, comprising cortical structures and their interconnecting fibre tracts. As Fridriksson et al. (2018) so nicely put it, it is the harmony of the entire network that makes communication possible. I suggest that, as well as language networks in the brain, it is the harmony of the entire life of the person with aphasia that makes communication possible.

Source of data

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Associations between lesion size, lesion location and aphasia in acute stroke

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Associations between lesion size, lesion location and aphasia in acute stroke

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ABSTRACT

Background: The localization and organization of language has been an ongoing research interest ever since the early findings of Paul Broca. The emergence of neuroimaging the past 20 years has given us new insights on the anatomical and structural organization of the brain. Lesion studies on patients with aphasia can provide knowledge on where and how specific language functions are organized in the brain.

Aims: The primary objective of the study was to investigate the relationships between aphasia severity, aphasic symptoms, lesion location and lesion volume in patients with left hemispheric stroke in the acute phase (within one week post-stroke). Using a voxel-based lesion-symptom mapping method (VLSM), we hypothesized that lesions associated with speech comprehension deficits mainly would involve regions within the posterior superior and middle temporal lobe, and lesions associated with speech production deficits would mainly be associated to the inferior frontal areas of the left hemisphere.

Methods & procedures: Findings from diffusion-weighted magnetic resonance imaging (DWI-MRI) and patients' scores from the Norwegian Basic Aphasia Assessment (NBAA) were used to investigate our research questions. We did a whole group analysis of descriptive statistics, lesion localization and lesion volume. We thereafter divided the patients into two groups based on their median scores on the NBAA, one high comprehension group and one low comprehension group. We used VLSM to investigate the associations between the patients' lesions and the results from the NBAA.

Outcomes & Results: Lesion volume was significantly associated with all subtest from the NBAA. Our initial analysis of the whole group showed that difficulties in naming was associated with lesions within the rolandic operculum. We also found that difficulties in repetition was associated with lesions within the rolandic operculum, and in addition, the superior temporal gyrus. In the group of patients with high comprehension scores lesions within Broca's area, insula, the superior temporal gyrus (STG) and Heschl's gyrus were found to be associated with difficulties with overall aphasia severity,

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repetition, naming, and reading out loud from the NBAA. **Conclusions:** Lesion volume is strongly associated with aphasia severity in the acute stages of stroke. Further, lesions within Broca's area, the insula, the STG and Heschl's gyrus were found to be crucial areas in language comprehension and production. This confirms current views that speech and language processes depend on the integrity of the entire network comprising both cortical structures and their interconnected fibre tracts.

Introduction

The neurobiology of language

Aphasia can be defined as an acquired communication disorder, and can cause impairments in verbal comprehension and production, and in reading and writing. The most common cause of aphasia is left hemispheric stroke (Hallowell & Chapey, 2008). The neurobiological localization of language functions has been an ongoing research interest ever since the clinical findings of Paul Broca and Carl Wernicke in the late 19th century. The research on the neurobiological basis for language has mainly focused on lesion studies, but the past twenty years research on healthy language processing using functional magnetic resonance imaging (fMRI) has sought to understand how language is organized and processed in the brain (Friederici, 2011; Price, 2000; Price & Crinion, 2005). Language processing is now considered a complex system dependent of several neural sites and connections within the brain (Damasio, 2008).

Lesion size or lesion location?

Several studies have investigated the role of lesion size and lesion location in patients with aphasia (Cherney & Robey, 2008; Crinion, Holland, Copland, Thompson, & Hillis, 2013a; Plowman, Hentz, & Ellis, 2012). However, the quantification of lesion volume differs across studies depending on MRI-sequence and variability in quantification methods that makes it difficult to compare results across studies. Crinion et al. (2013a) requested a gold standard for quantifying lesion volume and concluded that until the standard is clear researchers should thoroughly explain and define cut offs and quantification procedures when reporting findings from lesion quantification studies. Using diffusion tractography Forkel et al. (2014) found that lesion volume was a predictor of aphasia recovery six months post-stroke. Plowman et al. (2012) investigated stroke related factors in post-stroke recovery, and found that both lesion volume and lesion site was associated with aphasia severity six months post-stroke, however initial aphasia severity was found to be the most predictive factor of aphasia recovery. However, there seems to be an agreement that lesion location might be more important to consider than lesion size when investigating initial aphasia outcome post-stroke (Cherney & Robey, 2008; Crinion, Holland, Copland, Thompson, & Hillis, 2013b).

This view has been supported by recent neuroimaging studies, indicating that focal lesions of certain cortical areas or fibre tracts can have a substantial impact on recovery and therapy outcome (Abel, Weiller, Huber, Willmes, & Specht, 2015; Specht et al., 2009). In

addition, there is growing evidence that lesions also have remote effects through disinhibition (Price & Crinion, 2005; Saur et al., 2006) or altered perfusion (Robson et al., 2017).

Towards a new model of language processing

The Classic Model of the neurobiology of language was developed by Geschwind (1965) and is based on the functional view upon language that emerged after the findings of Broca and Wernicke (Geschwind, 1965a, 1965b). To simplify, the Classic Model focuses on the associations between language functions and brain structures. Within the Classic Model, language processing is considered to be dependent on activation of the posterior temporal area (referred to as Wernicke's area) which is responsible for auditory comprehension, storage, synthesis and overall language comprehension. In the Classic Model, the location of Wernicke's area is assumed to comprise the posterior third of the superior temporal gyrus (STG), on the border between the temporal and parietal lobe. Further, Broca's area is postulated to be within the anterior inferior frontal area and is thought to be crucial for the production of oral and written language. According to the Classic Model, a fiber tract, the arcuate fasciculus, is essential for the flow of information from the posterior language areas to the anterior language areas making language processing possible (Geschwind, 1965a, 1965b).

The Classic Model of language has dominated the view on language processing since it emerged in the 1960s. However, newer neuroimaging studies using functional neuroimaging and voxel-based lesion symptom mapping (VLSM) have facilitated several new theories on the neurobiology of language. Tremblay and Dick (2016) argue that the Classic Model of language is outdated, and more precise anatomical definitions should be used in the neurobiological descriptions of language processes. Further, the authors argue that there is no precise anatomical definition of Broca's and Wernicke's area; therefore, the field of the neurobiology of language should be updated with new evidence from research on language processing. Poeppel and Hickok (2004) also argue that the Classic Model is empirically incorrect as it does not account for the aphasic syndromes and is underspecified in its neuroanatomical descriptions.

In recent years, several functional neuroimaging and meta-analysis studies have investigated the neuroanatomical basis of language processing and proposed new models of language comprehension and language production (Ardila, Bernal, & Rosselli, 2016a; Dronkers, Wilkins, et al. 2004; Hickok & Poeppel, 2007; Specht, 2014). Based on earlier findings from lesion analysis (Dronkers, Wilkins, et al. 2004), fiber tractography and functional connectivity analysis, Turken and Dronkers (2011) suggested a language comprehension network including the left middle temporal gyrus (MTG), the anterior superior temporal gyrus (STG/BA22), the pars orbitalis (IFGpOrb/BA47) and the superior temporal sulcus (STS/BA39). Further, Turken and Dronkers found that the inferior occipito-frontal fasciculus, the arcuate fasciculus, and the middle and inferior longitudinal fasciculi, and transcallosal projections via the tapetum were found to be the most significant white matter pathways bridging the areas crucial in language comprehension. Finally, the MTG was found to be a core region in the language comprehension network.

In a meta-analysis of the Brodmann areas (BA) involved in language by Ardila et al. (2016a) the authors suggested an extended Wernickes' area for auditory comprehension. This included the traditional core areas as the planum temporale, the posterior thirds of the

STG (BA22), the posterior part of the MTG (BA21) and the auditory cortex (BA41/42), and further including corresponding areas as the inferior temporal gyrus (BA20), the fusiform gyrus (BA37), the angular gyrus (BA39) and the supramarginal gyrus (SMG/BA40) (Ardila et al., 2016a). Accordingly, Ardila and colleagues refer to the Brocas' complex and suggest extending the borders of Brocas' area, which traditionally includes the pars opercularis (IFGpOp/BA44) and the pars triangularis (IFGpTri/BA45), to also include the dorsolateral prefrontal cortex (BA46), IFGpOrb, supplementary motor area (SMA/BA6), and extending subcortically towards the basal ganglia. Finally, in their view, the insula (BA13) has a crucial coordinating role in language production and comprehension (Ardila et al., 2016a).

These results have been confirmed and extended by studies investigating the relationship between the patients' lesioned areas in the brain and their language specific deficits by using voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003). VLSM has become a commonly used lesion mapping method in aphasia research (Baldo, Arevalo, Wilkins, & Dronkers, 2009; Dronkers, Wilkins, Van Valin Jr., Redfern, & Jaeger, 2004; Harvey & Schnur, 2015). VLSM calculates the statistical relationship between performance on a given task and the status, i.e. lesioned or not, for each voxel of the brain (Crinion et al., 2013b; Schwartz et al., 2009).

Bates et al. (2003) were one of the first using VLSM. They conducted a study investigating speech fluency and auditory comprehension deficits in patients with aphasia. Bates and colleagues found that lesions within the anterior insula were an important contributor to fluency deficits in aphasia, and the middle temporal areas were associated with auditory comprehension deficits. Interestingly, they also found that lesions limited to Broca's area was not the area that explained fluency deficits in patients with aphasia. Furthermore, their results showed that lesions within the MTG had a strong association to the patients' auditory comprehension difficulties, especially when the contribution of Wernicke's area was factored out. Finally, Bates et al. found that the peri-Sylvian areas contributed to both fluency and comprehension difficulties in patients with aphasia suggesting that the peri-Sylvian areas account for core language functions. Accordingly, Dronkers, Wilkins, Van Valin Jr., et al. (2004) found in their lesion study on language comprehension that the most distinct areas within the left hemisphere were the posterior MTG and underlying white matter, the anterior STG, the superior temporal sulcus (STS) and the angular gyrus. This is in line with the results by Baldo et al. (2009), who investigated the associations between brain lesions and difficulties with category-specific naming. They found that lesions within the left MTG and STG were associated with naming difficulties, and that lesioned areas overlapped across naming categories (Baldo et al., 2009). Finally, Dronkers et al. (2004a) did not find that lesions within either Broca's or Wernicke's area were significant contributors to the language comprehension difficulties on the given tasks in the study.

The findings from Bates et al. and Dronkers and her colleagues raise important questions that challenge the traditional assumption about the contribution of Broca's and Wernicke's area in language production and comprehension. However, Bonilha and Fridriksson (2009) suggest a more pragmatic approach by acknowledging that Broca's area is crucial for speech production, but damage and disconnection from surrounding language areas might also result in fluency disorders (Bonilha & Fridriksson, 2009).

Based on these converging evidences from both functional neuroimaging and lesion studies, Hickok and Poeppel published in 2007 the dual-stream theory on the cortical

organization of speech processing (Hickok & Poeppel, 2007). In short, the concept of the model is that a ventral stream processes signals for auditory comprehension, which involves structures within the superior and middle temporal lobe. The ventral stream interacts with a dorsal stream which maps acoustic speech signals to the frontal lobe articulatory networks. The dorsal stream involves structures in the posterior frontal lobe and the posterior dorsal region of the temporal lobe, and also the parietal operculum. Further, both streams share neural tissue in the left posterior STG. While the dorsal stream is left-hemisphere dominant, the ventral stream is assumed to be bilaterally organized (Hickok & Poeppel, 2007), or may even represent two separated streams, one for phonological and sub-lexical processing and one for prosody and voice recognition (Specht, 2014). The precise anatomical areas which comprise the ventral and dorsal stream, and where the two streams diverge is still a debate (Specht, 2014).

Assessment and classification of aphasia

The assessment of aphasia varies across research, languages, and theoretical traditions. One common way to define aphasia is to conceptualize aphasia dichotomously, such as fluent versus non-fluent aphasia, or Broca's versus Wernicke's aphasia and so forth (Hallowell & Chapey, 2008). In the present study we used a standardized test of aphasia severity which is based on the Boston classification of aphasia. The Boston Diagnostic Aphasia Examination (Goodglass, 2001), and the Norwegian Basic Aphasia Assessment (NBAA) (Reinvang & Engvik, 1980) are designed to classify patients into localization-based classifications of aphasia; Broca's, Wernicke's, anomic, conduction, transcortical motor, transcortical sensory and global aphasia syndromes. According to the Boston-classification of aphasia, the different aphasia syndromes have certain hallmark symptoms dependent on lesion location (Hallowell & Chapey, 2008). The Boston-classification of aphasia is based on the Classic Model of the neurobiology of language. Even though newer classifications and theories on language processing and aphasia have emerged, the Classic Model of language neurobiology is still commonly used as a theoretical framework in aphasia assessment, and the NBAA is the most frequently used aphasia assessment in Norway.

The primary objective of the present study was to investigate the relationship between symptoms of aphasia, lesion location and lesion volume in patients with left ischemic stroke in the acute phase (within one-week post-stroke). We used findings from diffusion-weighted magnetic resonance imaging (DWI-MRI) and the patients' scores from the Norwegian Basic Aphasia Assessment (Reinvang & Engvik, 1980) to investigate our research questions.

Using VLSM, we hypothesized that lesions associated with speech comprehension deficits mainly would involve regions within the posterior superior and middle temporal lobe, and lesions associated with speech production deficits would mainly be associated to the inferior frontal areas of the left hemisphere.

Methods

Participants

The present study is a part of two larger projects at Haukeland University Hospital (HUS); the Early Supported Discharge after stroke in Bergen-study (ESD) (Hofstad, Naess, Moe-Nilssen, & Skouen, 2013) and the Bergen NORSTROKE study. From January 2008 throughout

December 2012 a total of 347 patients were included in the ESD-study. The patients were recruited from the Stroke Unit of the Department of Neurology at HUS. Of 347 patients included in the ESD-study a total of 114 (33%) patients with aphasia-like symptoms caused by stroke were asked to participate in the present study. The patients underwent diffusion-weighted magnetic resonance imaging within 24 hours post-onset of first symptoms. Aphasia was diagnosed based on the convergence of clinical consensus and the results from the NBAA (Reinvang & Engvik, 1980). The patients were tested with the NBAA within seven days post-onset of initial symptoms. Fifty-three patients were excluded from the study because they did not have aphasia when diagnosed by the speech and language pathologist. Of the remaining 66, eight were excluded because DWI-MRI was not performed. Thereafter, six patients were excluded because of inconclusive MRI findings, three patients had earlier episodes of stroke, four patients were excluded because of cerebral haemorrhage, and finally three patients were excluded because of right hemispheric lesions (see Figure 1 for an overview). Patients with apraxia of speech and dysarthria were not excluded from the study.

Finally, 42 patients (mean age 72.9, SD: 11.8, range: 27–89) were included in the present study. All patients had first time episode of ischemic stroke and all patients were native Norwegian speakers. Twenty-four men and 18 women were included, 36

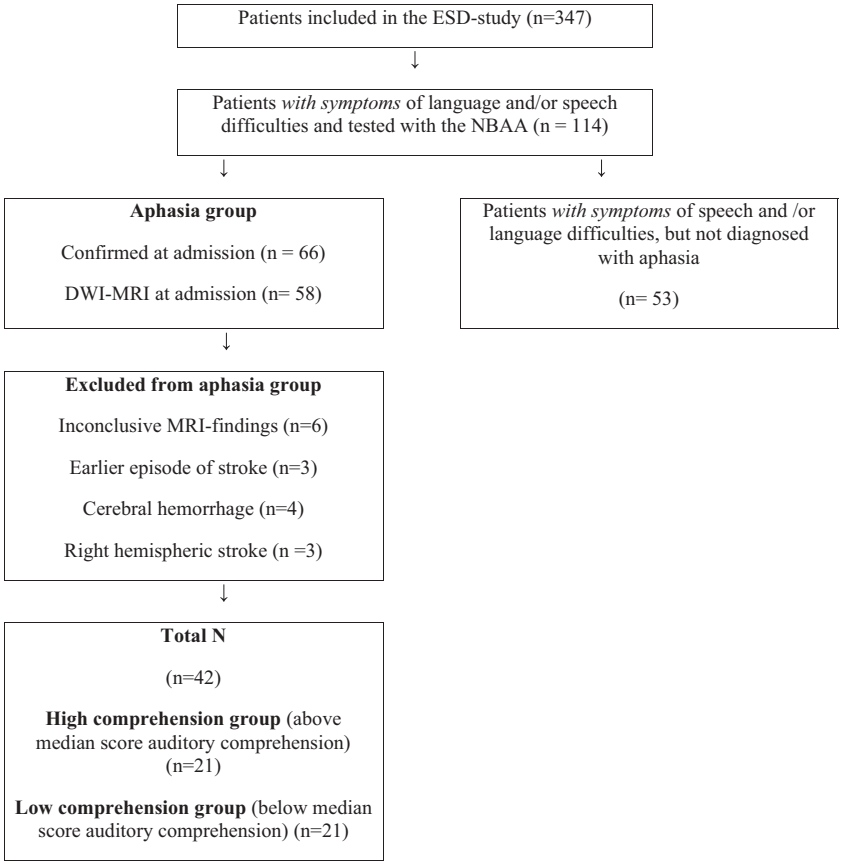

Figure 1. Flow-chart of patients included in the study.

were right-handed, one left-handed and five were uncertain. Four patients had lesions in both hemispheres, and the remaining 38 patients had lesions in the left hemisphere.

Materials and procedures

The Norwegian Basic Aphasia Assessment (NBAA). The NBAA is a standardized Norwegian test for assessment of aphasia. The test was developed by Reinvang and Engvik (1980) and is based on the Boston model of aphasia. The score ranges from 0–217 where 217 is the maximum of correct responses. The NBAA consists of seven subtests measuring auditory comprehension, repetition, naming, reading comprehension, reading out loud, syntax, and writing. The overall aphasia score gives an aphasia profile indicating aphasia severity and what type of aphasia the patient has acquired. However, in the present study we did not divide the patients' into aphasia subgroups based on the aphasia types suggested in the NBAA. This was due to the clinical routines at the hospital where subgrouping the patients based on their results from the NBAA is not part of the clinical diagnosis of aphasia. The aphasia assessment was administered to all patients as part of the existing research protocol of the ESD-Bergen project.

Diffusion-weighted magnetic resonance imaging

DWI-MRI is a magnetic resonance imaging technique increasingly used in acute stroke (Neumann-Haefelin et al., 1999). DWI-MRI gives *in vivo* images and allows a rapid characterization of stroke pathophysiology (Lee, Kidwell, Alger, Starkman, & Saver, 2000). By using the DWI-sequences one can easily differentiate between old and new lesions by looking at the white matter hyperintensities which are white when new, and black when old (Crinion et al., 2013b).

MRI specifications

All patients underwent diffusion-weighted magnetic resonance imaging within 24 hours post-onset of stroke symptoms. The DWI-MRI data were collected on a Siemens 1.5 Tesla Symphony using a DWI-sequence with TR 3200 ms, TE 94 ms, field of view 230mm, 128 × 128 matrix, in-plane voxel size 1.8 × 1.8 mm^2, slice thickness 5mm, as specification parameters.

Data pre-processing for voxel-based lesion-symptom mapping

Lesions were traced manually slice-by-slice on patients DWI-images in MRIcron (Rorden, Karnath, & Bonilha, 2007). Uncertain or unclear cases were excluded because of inconclusive MRI-findings. Both the DWI images as well as the lesion maps were thereafter normalised into standard Montreal Neurological Institute (MNI) stereotactic space, using the "old normalisation" procedure of the SPM12 software. First, DWI images were normalised into the MNI space using an EPI template, as provided by SPM12. In order to achieve the most optimal normalisation, the transformation was based on the non-lesioned tissue by masking the individual DWI images with the respective lesion maps. Thereafter, the transformation was applied to the lesion map, and images were resampled to a voxel size of $2mm^3$.

Data analysis

For the VLSM data analysis we used the non-parametric mapping (NPM) software package in MRIcron (Rorden et al., 2007). In order to correct for multiple comparisons, we added the non-parametric permutation test to determine the critical *t* cut-off score ($p < 0.05$) which was based on 1,000 random permutations of the data. In order to control for false positives, Family Wise Error (FWE) control was carried out on the primary, whole group analysis, and False Discovery Rate (FDR) control was carried out on all subsequent sub-group analyses. For statistical analysis, the lesion detection threshold was set to 5% prior the analysis, thus meaning that tests were not run for voxels with less than 5% of the subjects having damage there. We used a two-sample t-test where the predictor variable was the two patient groups (if a voxel was lesioned or not). The outcome variable was the raw scores from the overall aphasia severity score and each subtest from the NBAA. The colorized maps are based on the resulting *t*-value of each voxel. To determine anatomical structures, the Automated Anatomical Labelled map in MRIcron was used. Lesion volume was quantified using an in-house Matlab script that extracts the number of voxels of a lesion and estimates its volume, based on the respective voxel size. Finally, we carried out independent samples t-test to investigate differences in lesion volume between the high and low comprehension group. All t-tests on lesion volume data, descriptive statistics and frequencies of the behavioral data were calculated using IBM SPSS v20.

Results

The mean score on the Norwegian Basic Aphasia Assessment was 130.7 (max: 215, min: 0, SD: 66.5 range: 0–217). A high score on the aphasia test indicates mild aphasia, and a low score indicates severe aphasia. Descriptive statistics from the patients' scores on the subtests from the NBAA are presented in Table 1.

Whole group lesion analysis

Our primary analysis with the whole group of patients showed, using a FWE-corrected threshold of $p < 0.05$, that the patients' performance on the subtests repetition and naming were found to be associated to lesions within two specific areas. On the subtest repetition, we found that lesions within the rolandic operculum, and the STG were significantly associated with the patients' performance on the repetition subtest.

Table 1. Descriptive statistics of the patients scores on the Norwegian Basic Aphasia Assessment (n = 42).

NBAA	Min/max	Mean	Median	Standard Deviation
Total score	0-215	130.7	152.5	66.5
Auditory comprehension	0-70	47.4	55.5	21.8
Repetition	0-40	22.9	27.5	15.6
Naming	0-41	21.8	25.0	15.6
Reading comprehension	0-23	15.8	20.0	8.2
Reading out loud	0-26	16.0	21.0	10.0
Writing	0-10	4.4	4.5	3.5

Note. NBAA = the Norwegian Basic Aphasia Assessment.

Table 2. VLSM-analysis of lesions associated with patients scores on the subtests repetition and naming, MNI-coordinates in parenthesis (n = 42).

	Repetition	Naming
	Z score	Z score
Frontal lobe		
RO	4.03 (−58 − 3 10)	4.09 (−54 − 1 7)
Temporal lobe		
STG	3.98 (−54 − 27 19)	

Note. All scores FWE-corrected Z score with permutations, $p < .05$. T-test range repetition: −1.336–4.037, FWE corrected Z score with permutations = 3.88. Naming: t-test range: −0.902–4.146, FWE corrected Z score with permutations = 3.76. RO = Rolandic operculum, STG = Superior temporal gyrus

Further, on the subtest naming we also found that the patients' results were significantly associated with lesions within the rolandic operculum (see Table 2).

Group differences based on auditory comprehension scores

In order to disentangle the differential effect of a lesion on comprehension and production further, the patients were divided into two groups based on the median score on the subtest auditory comprehension from the NBAA. This was done for several reasons. Firstly, impaired auditory comprehension is a key symptom of aphasia. Secondly, the division was based on the descriptive statistics of the patients, when comparing the two groups, auditory comprehension had the greatest effect size, measured with Cohen's d (see Table 3). Thus, indicating that the greatest difference in language performance between the groups was on their performance on the auditory comprehension subtest from the NBAA.

The high comprehension group performed significantly better on all NBAA subtests than the low comprehension group. To specify, the high comprehension group consists of patients with mild aphasic symptoms, whereas the low comprehension group consists of patients with moderate to severe aphasic symptoms. An overview of the results of the independent samples t-tests are presented in Table 3.

Table 3. Independent samples t-test of all subtests from the NBAA between the patients who scored above the median and the group who scored below the median (55.5) on the auditory comprehension subtest from the NBAA.

			High comprehension group (above median score)		Low comprehension group (below median score)			
	Range	*n*	M (SD)	*n*	M (SD)	*t*	Cohen's *d*	p
Age		21	72.9 (10.0)	21	72.9 (13.6)	0.0		1.000
NBAA total score	0-217	21	179.1 (33.5)	21	82.2 (54.9)	6.9	2.13	.001
Auditory comprehension	0-71	21	64.3 (4.7)	21	30.5 (18.8)	7.9	2.48	.001
Repetition	0-40	21	30.0 (12.2)	21	15.8 (15.7)	3.3	1.01	.002
Naming	0-41	21	32.7 (10.7)	21	11.0 (11.8)	6.2	1.92	.001
Reading comprehension	0-23	21	21.5 (1.5)	21	10.1 (8.2)	6.3	1.94	.001
Reading out loud	0-26	21	20.8 (7.5)	21	11.2 (10.0)	3.5	1.08	.001
Syntax	0-6	21	3.6 (2.0)	21	0.9 (1.8)	4.6	1.42	.001
Writing	0-10	21	6.4 (2.9)	21	2.3 (2.8)	4.6	1.41	.001

Note. *$p < .05$, **$p < .001$. *Range* = range of possible scores on the NBAA. M = Mean. SD = Standard Deviation. *n* = total participants. NBAA = Norwegian Basic Aphasia Assessment

Median score on the subtest was 55.5 (max: 70, min: 0) and the groups consisted of 21 patients in each group. Mean age was 72.9 in both groups, and each group consisted equally of 12 men and 9 women. The groups differed significantly on all subtests on the NBAA as indicated by independent samples t-tests. On the overall aphasia score the high comprehension group had a mean score of 179.1 (SD: 33.5), and the low comprehension group had a mean score of 82.2 (SD: 54.9), $t = 6.9$, $p < .001$.

Lesion volume

The group specific lesion localizations are illustrated in Figure 2. By visual inspection of the images, the patients in the high comprehension group had lesions mostly in the inferior frontal and posterior temporal areas, while the lesions of the patients in the low comprehension group had a more heterogeneous and widely spread pattern. Independent samples t-test was performed to investigate the differences in lesion volume between the groups. Mean lesion volume in the high comprehension group was 19,019.43mm^3 (SD: 22,040.46 mm^3), and 43,443.81 mm^3 (SD: 39,382.34 mm^3) in the low comprehension group, $t = 2.48$, $p = .017$. The mean lesion volume was larger in the low comprehension group.

Pearson's product moment correlation was performed on the whole group (n = 42) to investigate the associations between lesion volume and aphasia severity and aphasic symptoms. The results yielded a significant association between the patients' lesion volume and aphasia severity, as measured by the NBAA ($r = -.59$, $p < .001$), and the subtests auditory comprehension ($r = -.40$, $p < .009$), repetition ($r = -.49$, $p < .001$), naming ($r = -.51$, $p < .001$), reading comprehension ($r = -.47$, $p < .002$), and reading out loud ($r = -.50$, $p < .001$). The results indicate that greater lesion volume was associated with greater aphasia severity within the subtests.

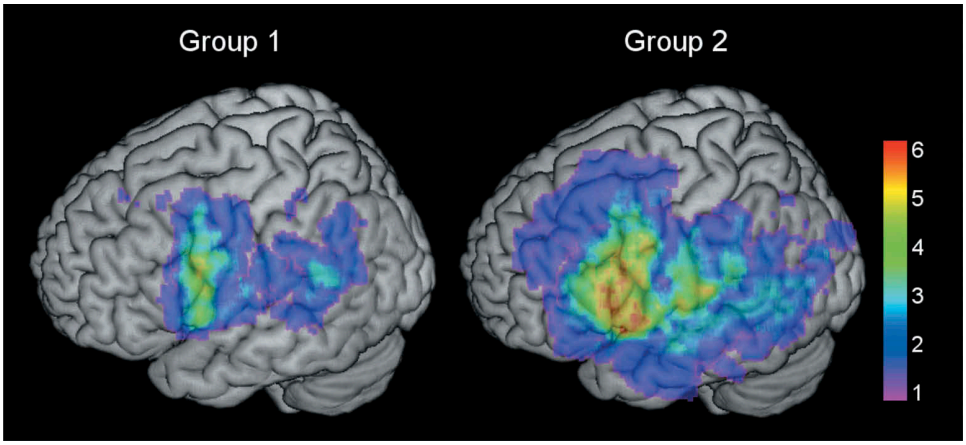

Figure 2. Colorized maps depicting lesion overlaps in the left hemisphere in the high comprehension group (left, group 1) and the low comprehension group (right, group 2) (n = 21 each group). Warmer areas (red) illustrate a greater lesion overlap than colder areas (purple/blue). Maximum overlap in individual voxels in the high comprehension group was 6, and 11 in the low comprehension group. Mean lesion was 19,019.43mm^3 in the high comprehension group, and 43,443.81mm^3 in the low comprehension group.

Associations between lesions and overall aphasia severity

We investigated the patients' overall aphasia severity scores from the NBAA and the patients' lesions in both groups. We found a significant association between the overall aphasia severity score and lesioned areas of the brain in the high comprehension group, but not in the low comprehension group.

Our results showed that within the frontal lobe, lesions within the rolandic operculum (RO) the IFGpTri and IFGpOrb, the insula and the IFGpOp were associated with aphasia severity. Within the temporal lobe, lesions within the STG and Heschl's gyrus were significantly associated with aphasia severity. Finally, lesions within the parietal lobe, specifically the SMG, the angular gyrus, the superior parietal lobule (SPL), the postcentral gyrus (postCG), and the inferior parietal lobule (IPL) were associated with aphasia severity.

Associations between lesions and difficulties with word, non-word and sentence repetition

We investigated the association between lesion site and the patients' performances on the subtest repetition from the NBAA. The subtest was treated as one subtest, and not divided into word, non-word and sentence repetition because there are too few items in each category (8 non-words, and 32 words and sentences).

Within the frontal lobe, we found that lesions of the insula, the IFGpTri, the IFGpOrb, the IFGpOp, and the RO were associated with repetition difficulties. For the temporal lobe, lesions of the Heschls' gyrus and STG showed this association, as well. For the parietal lobe lesions within the IPL, the angular gyrus, the postCG, and the SMG were associated with repetition difficulties in aphasia.

Associations between lesions and naming

Significant results were found for the associations between the patients' lesions and the patients' performance on the subtest naming.

In the high comprehension group, lesions within the frontal lobe that were associated with naming difficulties included the insula, the IFGpOrb, the IFGpTri, and the IFGpOp. Finally, within the temporal lobe, we found associations between the patients' lesions in Heschl's gyrus and the STG and their performance on the naming subtest.

Associations between lesions and difficulties reading words and sentences out loud

We found a significant association between the patients' lesioned areas of the brain and the patients' performance on the subtest reading out loud from the NBAA in the high comprehension group.

Lesions within the frontal lobe associated with difficulties reading out loud included the insula, the IFGpOp, the IFGpOrb, the IFGpTri, and the RO. Furthermore, in the temporal lobe, lesions within the STG, and Heschls' gyrus were

Table 4. VLSM-analysis of lesions associated with overall aphasia severity, repetition, naming and reading out loud in the high comprehension group, MNI-coordinates in parenthesis (n = 21).

	Aphasia severity	Repetition	Naming	Reading out loud
	Z score	Z score	Z score	Z score
Frontal lobe				
RO	2.95 (−38 − 25 20)	3.12 (−38 − 25 20)	3.52 (−61 9 5)	4.02 (−38 − 25 20)
Insula	2.92 (−36 2 7)	3.12 (−36 2 7)	3.52 (−34 9 − 8)	3.84 (−36 2 7)
IFGpTri	2.92 (−49 17 1)	3.12 (−49 17 1)	3.52 (−48 23 10)	3.84 (−49 17 1)
IFGpOrb	2.92 (−49 20 − 2)	3.12 (−49 20 − 2)	3.52 (−49 20 3)	3.84 (−49 20 − 2)
IFGpOp	2.92 (−49 16 5)	3.12 (−49 16 5)	3.52 (−62 9 5)	3.84 (−49 16 5)
Temporal lobe				
STG	2.95 (−50 − 35 20)	3.12 (−50 − 35 20)	3.52 (−61 − 6 3)	2.70 (−50 − 35 20)
Heschls' gyrus	2.65 (−41 − 25 12)	2.65 (−41 − 25 12)	2.58 (−41 − 25 12)	2.70 (−41 − 25 12)
Parietal lobe				
SMG	2.95 (−47 − 35 33)	3.12 (−47 − 35 33)		4.02 (−47 − 35 33)
postCG	2.65 (−37 − 39 59)	2.65 (−37 − 39 59)		2.70 (−37 − 39 59)
Angular gyrus	2.65 (−39 − 59 42)	2.65 (−39 − 59 42)		2.70 (−39 − 59 42)
IPL	2.65 (−39 − 51 53)	2.65 (−39 − 51 53)		2.70 (−39 − 51 53)
SPL	2.65 (−39 − 48 64)	2.65 (−39 − 48 64)		2.70 (−39 − 48 64)

Note. All scores FDR-corrected Z scores with permutations. T-test range aphasia severity: −1.593–2.949, FDR-corrected Z score with permutations = 2.50, $p < .05$, repetition: −1.475–3.119, FDR-corrected Z score with permutations = 2.44, $p < .05$, naming: −1.240–3.524, FDR-corrected Z score with permutations = 2.58, $p < .05$, reading out loud: −1.195–4.016, FDR-corrected Z score with permutations = 2.44, $p < .05$. RO = Rolandic operculum, IFGpTri = pars triangularis, IFGpOrb = pars orbitalis, IFGpOp = Inferior frontal operculum, STG = Superior temporal gyrus, SMG = Supramarginal gyrus, postCG = Postcentral gyrus, IPL = Inferior parietal lobule, SPL = Superior parietal lobule.

associated with the patients' difficulties with the subtest reading out loud from the NBAA. Finally, lesions in the parietal lobe included areas within the SPL, the postCG, the SMG, the IPL, and the angular gyrus. All results are presented in Table 4.

Discussion

The aim of the present study was to investigate the associations between lesion location, lesion volume, aphasia severity, and aphasic symptoms in the acute phase in a group of patients with left hemispheric stroke. We hypothesized that lesions that were associated with speech comprehension deficits would mainly affect regions within the temporal lobe, and lesions associated with speech production deficits would mainly affect the areas comprising the frontal areas of the left hemisphere.

Greater lesion volume was associated with patients' performance on the overall aphasia score, and the subtests auditory comprehension, repetition, naming, reading comprehension and reading out loud. Thus indicating that lesion volume has an adverse effect on initial aphasia severity. This is in line with findings from several studies showing that lesion volume is an important factor in aphasia outcome and recovery (Forkel et al., 2014; Plowman et al., 2012). One important consideration in the interpretation of the results of the current study is that the results are derived from the acute stage. A more differential outcome could be expected, if the results were from the subchronic and chronic stages after the stroke, hence ruling out the possible influence of spontaneous recovery and cerebral blood flow in the acute stages of a stroke.

Our initial analysis of the whole group showed that difficulties in naming was associated with lesions within the rolandic operculum. Likewise, we also found that difficulties in repetition was associated with lesions within the rolandic operculum, and in addition,

the STG. In a case study by Tonkonogy and Goodglass (1981) the rolandic operculum was found to be associated with articulatory difficulties in a patient with aphasia. However, Baldo et al. (2009) show that naming difficulties are a result of lesions within several areas along the left hemisphere. Friederici and Gierhan (2013) emphasize that speech repetition is a complex language process. This involves several regions along the parietal, temporal and frontal cortex, which are connected by several white matter tracts such as the superior longitudinal fascile and the arcuate fasciculus. Baldo, Katseff, and Dronkers (2012) also did a VLSM analysis of brain lesions related to performance on a repetition task and found that lesions along the left posterior temporo-parietal cortex were associated with repetition difficulties in aphasia. Our findings from the whole group lesion analysis are therefore not consistent with the theory of language processing as a system dependent of several neural sites and connections within the brain (Damasio, 2008).

In order to investigate the lesion data further, we divided the patients into two groups, based on the notion that auditory comprehension deficits is a key symptom in aphasia, and based on the patients' descriptive results on the subtest auditory comprehension. One group consisted of patients with low auditory comprehension scores and the other of patients with high auditory comprehension scores. As one would expect, we found that in the high comprehension group the patients also scored significantly better on all subtests from the NBAA compared to the patients in the low comprehension group. Further, we found that in the high auditory comprehension group the patients' performance on the overall aphasia severity score, the subtests repetition, naming and reading out loud were associated to lesions within specific regions within the frontal, temporal and posterior areas of the brain. Surprisingly, the group of patients with more severe auditory comprehension deficits did not have any significant associations between lesion localizations and their results on the NBAA subtests. One possible explanation of this finding is that the localization of lesions in the low auditory comprehension group is much more heterogeneous. As shown in the group differences in lesion volume it is likely that the patients in the low comprehension group have more cortical and subcortical areas that are affected.

Aphasia severity, repetition and reading out loud

The overall aphasia severity score and the patients' performance on both the repetition and reading out loud subtests were all associated with the same lesion patterns within the inferior frontal (RO, insula, IFGpTri, IFGpOrb and the IFGpOp), temporal (STG), and parietal areas (SMG, SPL, IPL, angular gyrus, postCG) of the left hemisphere (see Table 4).

The results indicate that patients with extending lesions within the frontal, temporal and parietal areas of the left hemisphere have difficulties with more than repetition and reading out loud as indicated by the association to the overall aphasia score. This is in line with the notion that language is a complex process involving the activity of several brain regions, that all contribute to the processing of language (Damasio, 2008; Turken & Dronkers, 2011). As Turken and Dronkers (2011) point out in their study on the structural and functional connectivity of regions associated with auditory sentence comprehension, the language comprehension network consists of several regions and pathways extending beyond the traditionally recognized language areas. It involves a large-scale network including several white-matter pathways such as the arcuate fasciculus, the inferior occipito-frontal fasciculus, the middle and inferior

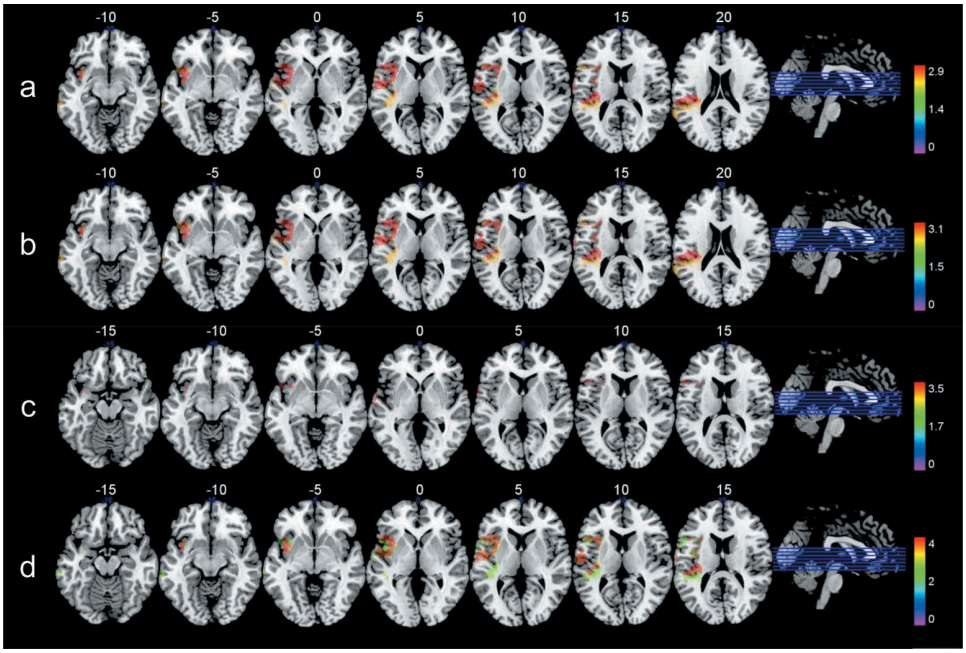

Figure 3. Colorized multislice maps of lesions associated with A: aphasia severity, B: repetition, C: naming, D: reading out loud in the high comprehension group (n = 21). All maps include FDR-corrections with permutations, $p < .05$. Warmer areas (red) indicate a greater lesion overlap than colder areas (purple/blue). Color bars indicate Z scores.

longitudinal fasciculi, the uncinate fasciculus and the tapetum. However, Turken and Dronkers (2011) emphasize that the left MTG is a significant area in language comprehension. Our results do not confirm the left MTG to be significant, but the STG and Heschl's gyrus were found to be associated with several subtests and the overall aphasia score.

As seen in Table 4 and illustrated in Figure 3 the test statistic values share the same numbers across brain regions. By visual inspection in Figure 3, one can see that the lesion patterns in all analysis are similar, except for the naming subtest. This indicates that the same subgroup of patients share the same lesion patterns across the analysis.

Our results show that several regions within the frontal, temporal and parietal areas are related to aphasia severity in the acute stage, but some regions overlap to a greater extent indicating that certain areas are more crucial in aphasia in the acute stages post-stroke. Furthermore, our findings are consistent with previous VLSM studies investigating aphasia and lesion location suggesting that certain areas are more involved in speech production, and certain areas are more involved in speech comprehension (Buchsbaum, Hickok, & Humphries, 2001).

Naming difficulties associated with a different lesion pattern

We found that focal lesions within the IFGpTri, IFGpOp, the insula, the STG and Heschl's gyrus were associated with naming difficulties in the high comprehension group. These

findings are to a certain degree consistent with Baldo et al. (2009) who investigated the effect of lesion site on category-specific naming in patients with aphasia. Their results showed that lesions within the left MTG, STG and the insula were associated with difficulties in naming. Further, Baldo and colleagues found that smaller regions, such as the lFGpTri, the lFGpOrb, the SMG and the angular gyrus were also significantly associated with difficulties in naming tools and animals. However, the latter results could only be partly replicated by our study, since we did not find lesions within the parietal lobe to be associated with naming difficulties. One possible explanation might be the assessment of naming difficulties. While Baldo and colleagues used category-specific tests and investigated differences in lesion sites based on the categories, we did not divide the subtest naming based on categorical properties.

General discussion

Five lesioned areas appeared to be more significant in aphasia severity post-stroke, since they all were consistently associated with several subtests (see Table 4). These areas were the lFGpTri, lFGpOp, insula, STG and Heschl's gyrus.

The lFGpOp and lFGpTri correspond to the classical Broca's area. These areas have been related to a range of language functions; from language production, grammar, and verbal fluency (Ardila, Bernal, & Rosselli, 2016b), to motor sequencing in speech and morphosyntax (Ardila & Bernal, 2007), and to a broader role in the unification of semantic, syntactic and phonological language processing (Hagoort, 2005). Our results confirm the traditional assumption that Broca's area is a crucial region in speech production; however, it does not confirm that lesions within Broca's area necessarily lead to Broca's aphasia.

The insula has also been suggested to be important for the coordination of both language comprehension and production (Ardila et al., 2016a). Oh, Duerden, and Pang (2014) did a meta-analysis of fMRI-studies investigating the insula in both speech and language tasks. They found that speech perception activated the left dorsal mid-insula, and expressive language tasks activated the more ventral parts of the mid-insula. Their findings suggest that the mid-insula is crucial in both speech and language processing. Further, they suggest that the insula has a role in the coordination of higher-order cognitive functions in speech and language processing (Oh et al., 2014). Further, a lesion within the insula may also affect nearby language-related fiber tracts, like the arcuate fasciculus or the tracts through the extreme capsule (Weiller, Bormann, Saur, Musso, & Rijntjes, 2011).

The STG was suggested to have a central role in the dual-stream model of speech processing, since it is active both during speech perception tasks, and speech recognition tasks (Hickok and Poeppel (2007). Further, Buchsbaum et al. (2001) suggested that the dorsal stream involves the posterior STG and that it projects to Broca's area. The authors suggest that the function of these areas is to connect speech sounds with speech motor functions. In a study by Butler, Lambon Ralph, and Woollams (2014) it was found that phonological processing involved the left posterior perisylvian region, including Heschl's gyrus, the posterior middle STG and STS, and also white matter underlying the posterior STG. In accordance with Butler et al. (2014) our results confirm that lesions of the STG and Heschl's gyrus and the perisylvian region may contribute to deficits in both language comprehension and language production.

Limitations

Drawing lesions and determining lesions in VLSM is a time consuming, and subjective procedure. MRI in the acute stage might also show distortion due to gliosis, atrophy and ventricular changes which may be misinterpreted as the core lesion (Geva, Baron, Jones, Price, & Warburton, 2012). However, the inter-rater reliability in the present study was enhanced by a close cooperation between the authors by discussing and excluding uncertain or unclear cases. Furthermore, distinguishing whether aphasic difficulties arise from the lesioned area or from disconnection of undamaged areas of the brain might be impossible to infer (Price, 2000). One cannot draw a causal relationship between lesions and language functions based on the results of lesion studies. Lesion studies merely tells us that the neuronal systems and the connections within a specific lesioned area of the brain are associated or necessary for the lost function (Price, 2000).

Conclusions

To summarize, initial aphasia severity is clearly associated with lesion volume in the acute stage. A further investigation to see if lesion volume still is associated with aphasia severity in the more subchronic and chronic stages of aphasia would be interesting. Furthermore, our results show that lesions within Broca's area, insula, the STG and Heschl's gyrus seem to be part of a network that all are associated with difficulties with overall aphasia severity, repetition, naming and reading out loud. These areas therefore seem to be crucial in both language comprehension and production. This confirms current views that speech and language processes depend on the integrity of the entire network comprising both cortical structures and their interconnecting fiber tracts in the left hemisphere.

The results further confirm that a much cleaner picture can be obtained when patients are categorized by specific deficits and not by their "classical" subtypes. One should further emphasize that the patient group with low comprehension scores represented a very heterogonous group in terms of lesion patterns. This is an interesting aspect in its own, as it highlights that severely disturbed language comprehension can occur from lesions at various places within the network.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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II

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Associations between stroke severity, aphasia severity, lesion location, and lesion size in acute stroke, and aphasia severity one year post stroke

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Associations between stroke severity, aphasia severity, lesion location, and lesion size in acute stroke, and aphasia severity one year post stroke

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ABSTRACT

Background: The aim of the present study was to investigate the associations stroke severity, aphasia severity, lesion location and lesion size in acute stroke, and aphasia severity in the subacute and chronic stages post stroke. We hypothesized that initial stroke severity and aphasia severity were associated with the patient's aphasia severity in the subacute and chronic stages of stroke. We expected to find that lesions within the left frontotemporal regions of the brain were associated with aphasia severity post-stroke.

Methods: Thirty-three patients with aphasia were included in the study. They were assessed with a standardized aphasia test at admission to the hospital (T1), after 3 months (T2) and finally after 12 months (T3). Stroke severity, initial physical impairment, and initial functional independence were also assessed at T1. Diffusion-weighted magnetic resonance imaging was performed as clinical-routine at admission. Voxel-based lesion symptom mapping and a region of interest analysis (ROI) was performed to analyze MRI-findings.

Results & Outcomes: Initial lesion size and aphasia severity were associated with aphasia severity at T2. Initial stroke severity, aphasia severity, and lesion size were not associated with aphasia severity at T3, but the patients' aphasia severity at T2 predicted aphasia severity at T3. Lesion analysis showed that lesions within the left postcentral gyrus and the left inferior parietal gyrus were significantly associated with aphasia severity at T3. The ROI-analysis did not yield any significant regions of interest to explain the total variance of the patients' change in scores on the aphasia test from T1 to T3.

Conclusion: Lesions within the postcentral gyrus and the inferior parietal gyrus are associated with aphasia severity at T3. Lesion size in the acute stages of stroke is associated with aphasia severity at T1 and T2, but not T3. However, neither initial aphasia severity nor

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stroke severity was associated with aphasia severity at T3. Aphasia severity in T2 is however strongly associated with aphasia severity in T3.

Introduction

It is estimated that approximately 24% of all stroke patients will experience aphasia post-stroke (Gronberg et al., 2020). The long-term prognosis of aphasia is influenced by a range of factors. There is no clear consensus on what the most important predictors of post-stroke aphasia are, and there is great variability in the factors that are found to be associated with aphasia recovery (Forkel et al., 2014; El Hachioui et al., 2013; Plowman et al., 2012; Price et al., 2010). Knowledge about the course of aphasia recovery and understanding the variables associated with aphasia recovery is an important topic for patients, caregivers, health care providers and an important question for researchers within the field of aphasia.

There is no clear consensus on the definition of acute, subacute, and chronic stroke. However, Wittler (2009) suggests that the functional recovery of aphasia can be divided into three stages based on the underlying neural mechanisms taking place post stroke. The acute stage is the first month post stroke (4–6 weeks), the subacute stage continues for weeks or months after the stroke (1–12 months), and finally, the chronic stage of recovery is defined from 12 months post onset (Wittler, 2009).

Predictors of aphasia severity

A vast number of studies have investigated possible predictors of aphasia post-stroke, such as lesion size, lesion location, initial stroke, and aphasia severity (Ali et al., 2021; Benghanem et al., 2019; Forkel & Catani, 2018; Forkel et al., 2014; El Hachioui et al., 2013; Pedersen et al., 2004; Plowman et al., 2012; Watila & Balarabe, 2015). Clearly, aphasia recovery must be considered a complex course influenced by a multitude of variables, and an interaction between these variables.

Initial stroke and aphasia severity

There is a broad consensus that initial aphasia severity is a predictor of aphasia outcome post-stroke (El Hachioui et al., 2013; Laska et al., 2001; Lazar et al., 2010; Pedersen et al., 2004). Other variables, such as age, education, and other patient-related factors are more debated in the research literature (Plowman et al., 2012; Watila & Balarabe, 2015). In a literature review by Plowman et al. (2012), the authors investigated factors associated with the long-term prognosis of post-stroke aphasia. They reported that initial stroke and aphasia severity, lesion site, and lesion size were found to be the most influential variables in aphasia recovery. More specifically, initial aphasia severity was found to be the most predictive variable of post-stroke aphasia. In a recent systematic review and meta-analysis of aphasia recovery, Ali et al. (2021) (The Rehabilitation and recovery of people with Aphasia after StrokE Collaborators – RELEASE) investigated individual participant data in a large dataset including overall

language ability, auditory comprehension, naming, and functional communication. The study showed that improvements in language scores from baseline assessments diminished with patients increasing age and aphasia chronicity. A greater change in all the language datasets was seen in younger patients (<55 years). Further, Ali et al. (2021) reported that enrollment within 1 month post stroke was associated with greater change in overall-language ability. Also, the findings from the study shows that earlier language intervention was associated with the greatest improvement across language domains.

Lesion size and lesion location

Several studies have investigated the role of lesion size and lesion location in aphasia recovery (Benghanem et al., 2019; Forkel & Catani, 2018; Hillis et al., 2018; Lazar et al., 2010; Plowman et al., 2012; Seghier et al., 2016; Sul et al., 2019; Thye & Mirman, 2018; Watila & Balarabe, 2015). Benghanem et al. (2019) investigated aphasia outcome in the subacute stages of aphasia three months post stroke. The authors found that in patients with severe aphasia at admission, lesion size, or critical damage to the left temporoparietal junction was associated with poor language outcome at three months post stroke. Forkel et al. (2014) investigated the anatomical predictors of aphasia recovery six months post-stroke by performing tractography in both hemispheres. The authors found that the volume of the long segment of the arcuate fasciculus in the right hemisphere (contralateral to the lesion) was a predictor of aphasia recovery. They hypothesize that a larger right long segment might facilitate direct communication between the right hemisphere homologues of Broca's and Wernicke's area. Further, Forkel et al. (2014) did not find the volume of other segments in either the right or left hemisphere to be significant factors in aphasia recovery. In their study the strongest predictor of aphasia recovery six months post-stroke was lesion size. Other factors such as age and sex were also found to be predictive of aphasia recovery, with lower age and female sex being good predictors of recovery. The findings of Forkel et al. (2014) results suggest that the right hemisphere language network also plays an important role in the functional compensation of aphasia recovery after left hemispheric stroke.

The PLORAS database (Predicting Language Outcome and Recovery after Stroke) has generated several studies aiming to predict aphasia recovery based on brain scans (Price et al., 2010; Seghier et al., 2016). In their literature review Price et al. (2010) reported on language functions that were impaired after damage to specific brain regions. The authors found that auditory speech comprehension deficits were strongly associated with lesions within the left posterior superior temporal and/or left middle temporal regions (Wernickes' area). Further, non-fluent speech production was found to be associated with damage to the left inferior and/or middle frontal gyri and underlying white matter.

Thye and Mirman (2018) investigated the relative predictive role of lesion size and lesion location. Their results showed that speech production and speech recognition deficits could be predicted by lesion size and lesion location. Further, aphasia severity and naming deficits were predicted by lesion size, but not lesion location. Based on their findings, Thye and Mirman (2018) suggested that lesion-symptom prediction is more suitable for deficits that have specific neural localizations than for broad functional deficits which were found to be better predicted by overall lesion size. Lazar et al. (2010)

investigated variables that were predictive of aphasia recovery three months post stroke. In their study they found initial impairment to be predictive of aphasia recovery at three months, but lesion size was not found to be predictive of aphasia recovery.

Sul et al. (2019) investigated the relationship between lesion location and recovery of fluency, comprehension, naming, and repetition in patients with aphasia one-year post stroke. The authors found that specific lesion locations were associated with long-term outcomes for the different language measures. Further, the authors reported that lesions within the Rolandic cortex, Heschl's gyrus, posterior corona radiata, supramarginal cortex, superior longitudinal fasciculus, superior temporal gyrus, and insula were associated with overall poor language outcomes (Sul et al., 2019). Hillis et al. (2018) found that lesion load in the posterior parts of the left superior temporal gyrus, and the superior longitudinal fasciculus/arcuate fasciculus in the acute stages post stroke predicted difficulties in naming performance six months post stroke. In addition, their findings showed that patients that used selective serotonin reuptake inhibitors (SSRI) the following three months post stroke had greater improvements in naming. The use of SSRIs in stroke recovery is an ongoing investigation, and studies have shown promising effects on the functional recovery in non-depressive patients the first three months post stroke (Chollet et al., 2018), and improvements in naming outcome in patients with aphasia three months post stroke (Hillis et al., 2018). However, a more recent randomized, double-blind, placebo-controlled trial by Lundström et al. (2020) showed that functional outcome after stroke did not improve with the intake of fluoxetine 20 mg daily for six months.

Baldo et al. (2006) investigated the role of frontal versus temporal cortex in verbal fluency using voxel-based lesion symptom mapping (VLSM) in patients with chronic aphasia (at least nine months post-stroke). The authors found that reduced letter fluency was associated with damage to anterior regions (left frontal cortex), while reduced category fluency was associated with lesions in more posterior regions (left temporal cortex). However, as their findings suggest, fluency tasks also are affected by lesions within the insula, putamen, and the inferior parietal cortex.

Aphasia recovery

The recovery of aphasia has also been suggested to follow to specific patterns as in the principles of proportional recovery (Krakauer & Marshall, 2015; Marchi et al., 2017). The principles of proportional recovery were initially used to characterize motor recovery after stroke, suggesting that most patients recover approximately 70% of their initial impairment. However, some patients with initial severe deficits show little or no improvement (Krakauer & Marshall, 2015). The principles of recovery have also been debated in Hope et al. (2019) where the authors argued that the empirical support for the proportional rule of recovery is weak.

Stroke is a risk factor for developing post-stroke dementia (Leys et al., 2005; Mijajlović et al., 2017; Pendlebury & Rothwell, 2009). It has been found to affect 30% of stroke survivors (Leys et al., 2005; Mijajlović et al., 2017). However, the mechanisms and causes underlying cognitive decline, besides the obvious tissue damage, remains unclear (Mijajlović et al., 2017). The most common determinants of post stroke-dementia are demographic and clinical characteristics such as increasing age, low education level, pre-stroke dependency, and pre-stroke cognitive decline (Leys et al., 2005; Rasquin et al., 2004). Studies have also shown that left hemispheric lesions and multiple stroke lesions

are associated with post-stroke dementia (Zhou et al., 2004). Zhou et al. (2004) also found that patients with aphasia were more likely to develop post-stroke dementia. Fonseca et al. (2017) on the other hand states that it is not known whether aphasia enhances the risk of post-stroke dementia, but in their review, they found that patients with aphasia tend to score lower on non-verbal neurobehavioral tools assessing cognitive functions than those with left hemisphere stroke without aphasia.

Even though there is no clear consensus on all the factors that might predict and influence aphasia outcome post stroke, there seems to be a tendency in the research literature that initial stroke and aphasia severity, lesion size, and specific lesion locations are strongly associated with aphasia severity in the chronic stages post stroke. Also, it is important to point out that therapy has been found to have a substantial effect on aphasia recovery. In a Cochrane-review by Brady et al. (2016) they assessed the effects of speech and language therapy for aphasia post stroke. Therapy was found to be associated with improved functional communication, reading, writing, and expressive language compared to no therapy in aphasia (Brady et al., 2016). Even though type and intensity of treatment are relevant for aphasia recovery we do not provide information regarding type or amount of therapy in the present study.

Assessment of aphasia

In the present study we used the Norwegian Basic Aphasia Assessment (NBAA) (Reinvang & Engvik, 1980) which is based on the Boston classification of aphasia to assess the patients' aphasia symptoms. The Boston Diagnostic Aphasia Examination (Goodglass et al., 2001) and the NBAA (Reinvang & Engvik, 1980) classify patients into localization-based classifications of aphasia; Broca's, Wernicke's, anomic, conduction, transcortical motor, transcortical sensory, and global aphasia syndromes. This classification of aphasia is based on the Classic Model of the neurobiology of language (Geschwind, 1965). Even though newer classifications and theories on language processing and aphasia have emerged, the Classic Model of language neurobiology is still commonly used as a theoretical framework in aphasia assessment, and the NBAA is the most frequently used aphasia assessment in Norway (Døli et al., 2021; Lind & Haaland-Johansen, 2013).

Aim of the study

The aim of the present study was to investigate the associations between stroke severity, aphasia severity, lesion location and lesion size in acute stroke, and aphasia severity in the subacute and chronic stages of stroke. We hypothesized that initial stroke severity, aphasia severity, and lesion size in the acute stages are associated with aphasia severity in the subacute and chronic stages of aphasia post stroke. Further, we expected to find that lesions within the frontal inferior and temporal regions of the left hemisphere would be associated with aphasia severity in the subacute and chronic stages of aphasia.

Methods

Participants

The data in the study were collected through two research projects at Haukeland University Hospital (HUS). The Early Supported Discharge after Stroke in Bergen – study (ESD) (Hofstad et al., 2013) and the Norwegian Stroke Research Registry (NORSTROKE) (n = 3500). The patients were included in both studies at admission to the Stroke Unit at HUS. A total of 347 patients with stroke were included in the ESD-study. A total of 114 patients were referred to a speech and language therapist based on initial suspicion of aphasia. Of the 114 patients, 66 patients were confirmed to have aphasia by a speech and language therapist at the Stroke Unit. Aphasia was diagnosed based on the convergence of clinical symptoms and by assessment with the NBAA within seven days post-admission (T1). The patients were thereafter summoned for a follow-up with the NBAA after 3 (T2) and 12 months (T3). All patients underwent diffusion-weighted magnetic resonance imaging (DWI-MRI) within 24 hours post-onset of initial symptoms as clinical routine at the Stroke Unit. The present study is a follow-up study of the same patients as in Døli et al. (2021).

Of the initial 66 patients with aphasia, 45 met at T2 and 33 patients attended the assessments at T3. The mean assessment time post-stroke for the T3 follow-up was 12.2 months (Min: 10.0, Max: 15.0, SD: 1.2). The present study contains all the 33 patients with aphasia after ischemic stroke that attended the T3 assessments. Of these 33 patients, 32 patients were also assessed with the NIHSS at T1, and 29 met for retesting with the NBAA at T2 and we had Siemens MRI-scans from admission available in 30 of the 33 patients. However, seven of the 30 patients were excluded from the VLSM-analysis because of unclear findings, and three patients lacked MRI-scans. The total amount of available MRI-scans was 23. See Figure 1 for a flow-chart over the assessments at each time point.

Materials and procedures

The patients underwent several assessments in the acute stage in the Stroke Unit. Thereafter they were summoned for retesting three- (T2) and twelve-months (T3) post stroke. In the present study we report the patients results from the NBAA at T1, T2, and T3.

The Norwegian Basic Aphasia Assessment (NBAA)

(Reinvang & Engvik, 1980). The NBAA is a standardized Norwegian basic test for the assessment of aphasia. The test is based on the Boston model of aphasia (Goodglass & Kaplan, 1972), and consists of seven subtests measuring auditory comprehension, repetition, naming, reading comprehension, reading out loud, syntax, and writing. The overall aphasia score suggests an aphasia profile indicating both aphasia severity and aphasia type. In the present study we used their raw scores from the aphasia subtests and the overall aphasia severity score from the NBAA. The score on the NBAA ranges from 0–217 where 217 is the maximum of correct responses. In the ROI-analysis we used the patients change in scores from T1 to T3 as the predictor variable.

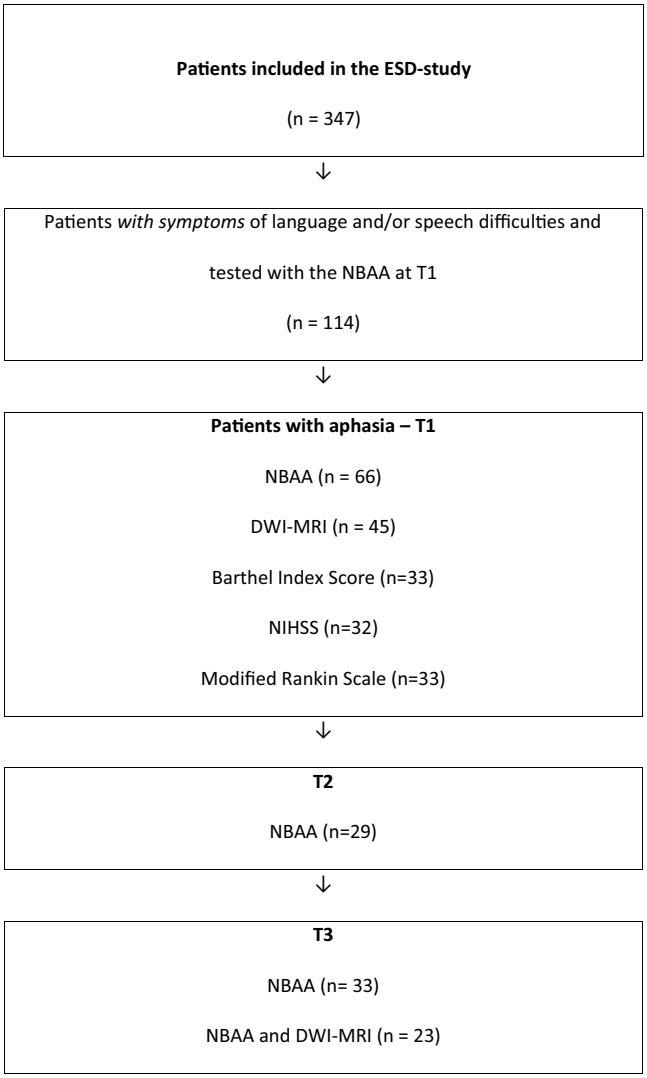

Figure 1. Flow-chart of participants in the study and tests performed at each time point.

National Institute of Health Stroke Scale (NIHSS)

(Brott et al., 1989). The NIHSS is an assessment tool that measures neurological deficits common in acute stroke. The modified version (P. D. Lyden et al., 2001), used in the present study, consists of 11 subtests investigating level of consciousness, gaze, visual fields, facial palsy, left motor arm, right motor arm, left motor leg, right motor leg, ataxia, sensory, language, dysarthria, and neglect. Only results from the affected side (left/right) were reported in the study. The NIHSS was conducted at several time points from admission to the hospital and until seven days post-onset of symptoms or earlier if the patients were discharged. In the present study we used the NIHSS score from admission to the Stroke Unit. The score ranges from 0 to 34 points, where a higher score indicates more severe stroke symptoms.

Barthel Index (BI)

Mahoney & Barthel, (1965) measure a patients' performance in activities of daily life. The BI consists of 10 items that can be divided into self-care tasks (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and items related to mobility (ambulation, transfers, and stair climbing). The maximal score is 100, indicating that the patient has no difficulties in daily activities, and the lowest score is 0, indicating that the patient is dependent on constant nursing care and attention. In the present study we used the BI as a measure for functional status at seven days post stroke or at discharge (if discharged earlier).

The Modified Rankin Scale (mRS)

Rankin, (1957) is a widely used global disability measure (Banks & Marotta, 2007) aiming to measure functional independence by incorporating the World Health Organization components of body function, activity, and participation (Kasner, 2006). The mRS is shown to have high validity, however the reliability of the measure is debated due to the few items (Kasner, 2006). The score ranges from 0–6, where 0 indicates no symptoms at all, and 6 represents the patient being dead. We used the mRS scores from day seven post stroke, or on discharge if the patient was discharged earlier.

MRI specifications

According to clinical routine at the Stroke Unit all patients were referred to diffusion-weighted magnetic resonance imaging (DWI) within 24 hours post-onset of stroke symptoms. The imaging data were collected on a Siemens 1.5 Tesla Symphony using a DWI-sequence with TR 3200 ms, TE 94 ms, field of view 230 mm, 128 × 128 matrix, in-plane voxel size 1.8 × 1.8 mm^2, slice thickness 5 mm, as specification parameters.

Data pre-processing for voxel-based lesion-symptom mapping

We traced lesions manually slice-by-slice directly onto patients DWI-images in MRIcron (Rorden et al., 2007). Uncertain or unclear cases were excluded. Both the DWI images and the lesion maps were thereafter normalised into standard Montreal Neurological Institute (MNI) stereotactic space, using the "old normalisation" procedure of the SPM12 software. First, DWI images were normalised into the MNI space using an EPI template, as provided by SPM12. To achieve the most optimal normalisation, the transformation was based on the non-lesioned tissue by masking the individual DWI images with the respective lesion maps (Brett et al., 2001). Thereafter, the transformation was applied to the lesion map, and images were resampled to a voxel size of 2mm^3.

Data analysis

For the VLSM data analysis we used the non-parametric mapping (NPM) software package in MRIcron (Rorden et al., 2007). To correct for multiple comparisons, we added the non-parametric permutation test to determine the critical *t* cut-off score ($p < 0.05$) which was based on 1,000 random permutations of the data, False Discovery Rate (FDR) control was carried out on all analyses. For statistical analysis, the lesion detection threshold was set to 5% prior to the analysis, thus meaning that tests were not run for voxels with less than 5%

of the subjects having damage there. We used a general linear model (GLM) where the predictor variable was the lesion (whether a voxel was lesioned or not). The outcome variables were the patients scores from the NBAA. The colorized maps are based on the resulting *t*-value of each voxel. To determine anatomical structures, the Automated Anatomical Labelled map in MRIcron was used. For the power map of aphasia severity at T3 and lesions at T1 (Figure 3) the lesion detection threshold was set to 20% prior to the analysis, indicating that at least five persons had a damage within the voxel, and the Family wise error-correction (FWE) was carried out on the analysis. Lesion size was quantified using an in-house Matlab script that extracts the number of voxels of a lesion and estimates its volume, based on the respective voxel size.

We carried out post-hoc ROI-analysis to explore our data further, including the insula, the IFG triangularis, IFG opercularis, and the posterior and anterior divisions of the STG. The ROIs were created using the 3D-bubble tool in MRIcron. All individual ROIs were extracted from the Harvard-Oxford-Atlas in MRICron including cortical and subcortical structures with a threshold of .25, in other words there was a 75% chance of the ROIs being grey matter only. The patients mean lesions (mm^3) in each region of interest, as well as total lesion size were entered into a stepwise regression analysis to investigate associations to aphasia recovery (change in scores from T1-T3). Descriptive statistics, frequencies, t-tests, correlations, and regression analysis were calculated using IBM SPSS v25.

Results

The patient's mean score on the NBAA at T1 was 139.7 (SD: 61.4, min: 0, max: 215, $n = 33$), at T2 188.2 (SD: 27.8, min: 112, max: 217, $n = 29$) and at T3 197.2 (SD: 22.1, min: 112, max: 216, $n = 33$). The patients had an improvement in their aphasia score from T1, to T2 and to T3. The patient's descriptive results from the NBAA, their scores from the mRS, the BI, the NIHSS, and mean lesion size are presented in Table 1.

A drop-out analysis was conducted to investigate whether the patients that attended the T3 follow-up differed significantly from the patients who did not attend the T3 follow-up. A Levene's t-test for equality of means was performed investigating the patients scores on the NBAA at admission. There were no significant differences in the initial aphasia severity scores for the patients who did not attend the T3 follow-up (M = 150.7,

Table 1. Descriptive statistics of patients scores on the NBAA at T1, at T2 and T3, mRS, Barthel, NIHSS and lesion size.

	n	Min	Max	Mean	SD
Age	33	27	89	68.4	11.8
NBAA T1	33	0	215	139.7	61.4
NBAA T2	29	112	217	188.2	27.8
NBAA T3	33	112	216	197.2	22.1
mRS	33	0	5	2.6	1.2
BI	33	5	100	81.8	25.8
NIHSS	32	0	22	7.0	5.4
Lesion size (mm^3)	23	696	88,016	31,291.1	29,365.6

Note. NBAA = Norwegian Basic Aphasia Assessment, mRS = Modified Rankin Scale, BI = Barthel Index, NIHSS = National Institute of Health Stroke Scale.

SD = 75.3, N = 52) and the patients who attended the T3 follow-up (M = 137.8, SD = 63.4, N = 33, t (83) = −.82, p = .41, two-tailed). The magnitude of the difference in the means (mean difference = −12.95, 95% CI: −44.37–18.46) was small (Cohen's d = .01).

Initial stroke severity and aphasia severity, lesion size, and their associations to aphasia severity at three- and twelve-months post stroke

Pearson's correlation was performed to investigate the associations between the patients' lesion size, age, scores from the NBAA, the mRS, the BI and the NIHSS at T1 and the patients scores on the NBAA at T2 and T3. Lesion size was significantly associated with aphasia severity at T2. However, none of the variables included in the analysis were associated with the NBAA total score at T3, except the NBAA at T2 (r = .75, p < .001).

Interestingly, only lesion size and the patients' results from the mRS were significantly associated with the patients' aphasia severity at admission. Further, as seen in Table 2 the associations between lesion size and aphasia severity decrease throughout the time course of aphasia recovery.

Change in aphasia severity over time

A one-way repeated measures analysis ANOVA was conducted to compare the patients change in scores on the NBAA at the three time points, T1, T2, and T3. The results of the ANOVA indicated a significant effect of time, Wilks' Lambda = .51, F(2, 27) = 13.0, p < .001, η^2 = .49. We added post-hoc pairwise comparisons to investigate the differences in the patients scores on the NBAA at each time point, which showed a significant change in scores between the patients NBAA scores at T1 and T2 (Mean = −54.4, Std: 11.4, p < .001) and from T1 to T3 (Mean = −61.5, Std: 11.9, p < .001). We did not find a significant change in the patients scores from T2 to T3 (Mean: 7.1, Std: 3.4, p < .144).

To investigate the patient group further, we divided the patients into three groups based on their change in scores from the T2-assessment to the T3-assessment to see whether the groups differed in age and lesion volume. We divided the patients into three groups based on their change in scores. Group 1 (n = 9) consists of patients with

Table 2. Pearson's correlation between patients' age, and scores on the NBAA, mRS, BI and NIHSS at T1, NBAA at T2 and NBAA at T3.

Measure	Age	NBAA T1	NBAA T2	NBAA T3
NBAA T1	−.17	1	.26	.15
NBAA T2	−.17	.26	1	.75**
NBAA T3	−.24	.15	.75**	1
mRS T1	−.02	−.54**	−.33	−.30
BI T1	−.12	.55	.24	.12
NIHSS T1	−.21	−.29	−.12	−.10
Lesion size T1	−.40	−.58**	−.47*	−.11

Note. *p < .05, **p < .001. NBAA = Norwegian Basic Aphasia Assessment, T1 = Acute stage, T2 = 3 months post stroke, T3 = 12 months post stroke, mRS = Modified Rankin Scale, BI = Barthel Index, NIHSS = National Institutes of Health Stroke Scale.

Table 3. Descriptive statistics of the patients divided into three groups based on their change in scores on the NBAA from T2-T3; age, lesion volume, and change in scores are reported in the three groups.

	Group 1		Group 2		Group 3	
	n	M (SD)	*n*	M (SD)	*n*	M (SD)
Age	9	69.4 (10.3)	11	69.4 (9.6)	9	66.2 (16.6)
Change NBAA T2-T3	9	−7.8 (4.2)	11	2.2 (2.4)	9	28.0 (19.9)
Lesion volume (mm^3)	3	12,378.7 (16,321.8)	9	26,268.4 (25,766.7)	3	58,556.6 (27,402.8)

Note. NBAA = Norwegian Basic Aphasia Assessment. Group 1: patients with negative change in scores on the NBAA from T2-T3, group 2: patients with no or minimal change in scores from T2-T3, group 3: patients with greater change in scores from T2-T3.

a negative change in scores from T2 to T3. Group 2 (n = 11) consists of patients with minimal or no change in scores from T2 to T3 (0–10 points), and group 3 (n = 9) consists of patients with improvement in scores from 10 and above. We had missing data of lesion volume in 10 patients. With such a low n in each group we did not compare means between groups, but a descriptive presentation of group differences is provided in Table 3.

Associations to aphasia severity in the chronic stages of aphasia

As shown in Table 2 none of the variables in T1 was associated with aphasia severity at twelve-months post-stroke. To investigate the results further, we investigated how well initial stroke severity, measured by patients' scores on the NIHSS, and initial aphasia severity, measured by the NBAA at T1, and aphasia severity at T2 could explain the patients' variance in scores from the NBAA at T3. We performed a standard multiple regression with the aphasia total score at T3 as the predictor variable and the patients scores on the NIHSS, and the NBAA at T1 and at T2 as independent variables. The results from the multiple regression analysis showed that R squared = .56 (adjusted R Square = .51), thus indicating that 56% of the variance of the patients' total aphasia score can be explained by their initial stroke and aphasia severity and their aphasia score at T2. The patients' total aphasia severity score at T2 had the largest Beta coefficient (β = .76, Sig. = .001), thus indicating a strong contribution to explaining the patients scores on the NBAA at T3. The Beta coefficients of the scores on the NIHSS (β = −.06) and the NBAA (β = −.03) at T1 showed non-significant unique contributions in explaining the total variance.

Lesion location and aphasia severity

We investigated the associations between the patients' lesions at admission and the patients' overall aphasia severity score on the NBAA at T3. We found significant associations between specific lesioned areas and the patients' performance on the total aphasia severity score on the NBAA. More specifically, lesions within the postcentral gyrus (MNI = −31x-35x54, Z score = 3.681) and the inferior parietal gyrus (MNI = −31x-35x4,

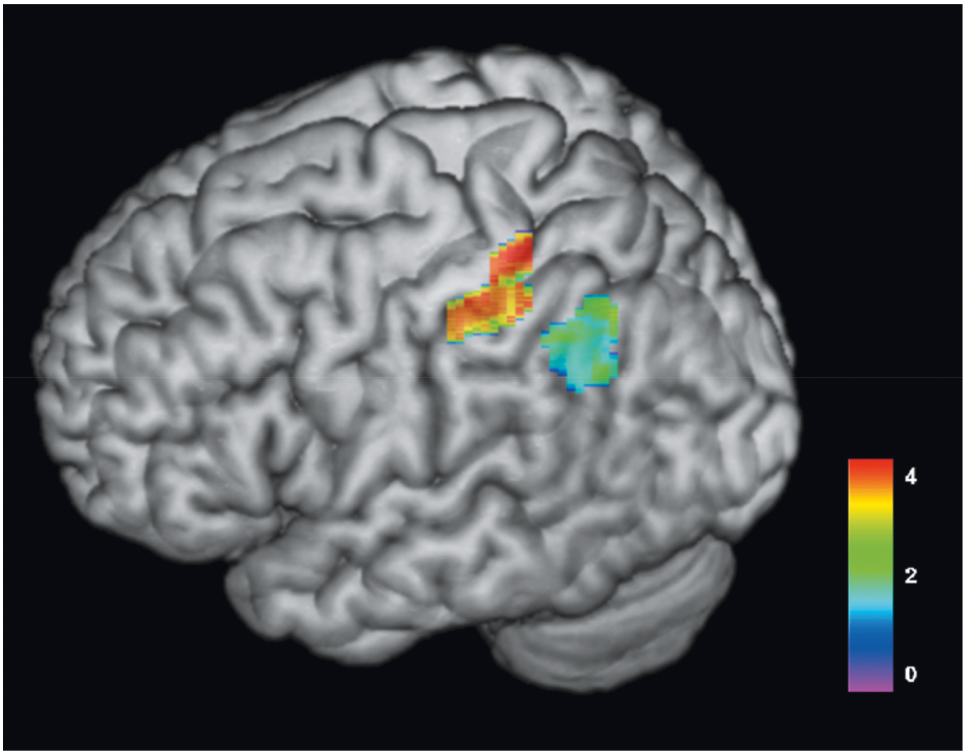

Figure 2. Colorized 3D render map of results from VLSM-analysis of associations between lesioned areas at T1 and aphasia severity at T3 (n = 23). The map illustrates that warmer areas (red) have a strong association to aphasia severity in patients with aphasia. T-test range = −1.263–4.336, FDR-corrected Z score with permutations = 3.61, $p < .05$. Areas significantly associated with aphasia severity at 12 months post-stroke included the postcentral gyrus (MNI = −31x-35x54, Z score = 3.681) and the inferior parietal gyrus (MNI −31x-35x44 Z score = 3.681).

Z score = 3.681) were significantly associated with aphasia severity at T3. Figure 2 illustrates the results from the VLSM-analysis of the patients' lesioned areas at T1 and aphasia severity at T3.

We carried out a power analysis of aphasia severity at T3 and the patients' lesions at T1 in VLSM in order to investigate the regions that have sufficient power to detect an effect of maximum effect size of $p < .05$. The lesion detection threshold was set to 20% prior to the analysis, thus indicating that at least five persons had a damage in the specific voxels. The analysis showed that regions within the frontal lobe; the insula (MNI-42-1x5) Z = 4.27, the inferior frontal operculum (IFGpOp) (MNI-50x13x16) Z = 4.02 and the precentral gyrus (preCG) (MNI-49x11x32) Z = 4.02 were associated with the patients' aphasia severity at T3. In the temporal lobe we found that lesions within the superior temporal gyrus (STG) (MNI-54x-31x20) Z = 4.27, and Heschl's gyrus (MNI-39x-23x10) Z = 4.27 were associated with the patients' aphasia severity at T3. Finally, in the

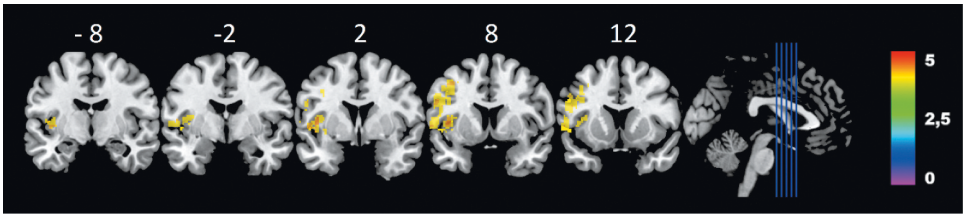

Figure 3. Colorized multi-slice power-map of the patients' lesions at T1 and performance on the NBAA at T3 (n = 23). Warmer areas (red) indicate a greater lesion overlap than colder areas (yellow). FWE-corrected Z-score, with 1000 permutations Z = 3.33, $p < .05$. Only voxels tested in a minimum of 20% of patients were calculated (at least 5 persons had damage to the voxel). Color bars indicate Z-score.

parietal lobe, lesions within the supramarginal gyrus (MNI-57x-26x20) Z = 4.02, was found to be associated with the patients' aphasia severity at T3. A power-map of the analysis is shown in Figure 3.

To investigate the aphasia scores in more detail, we also investigated the patients' performance on the subtests' auditory comprehension, repetition, naming, reading comprehension and reading out loud from the NBAA at T3, and the relationship to their initial lesion locations at T1. In line with the overall aphasia severity score, the patients' auditory comprehension scores from T1 were also associated with lesions within the postcentral gyrus. We also found the patients' scores on the reading comprehension task to be associated with lesions within the postcentral gyrus.

The patients' performance on the repetition task was only associated with lesions within the rolandic operculum (RO). Finally, the patients' scores on the reading out loud subtest at T1 were associated with lesions within the RO, the insula, the superior temporal gyrus (STG), and the supramarginal gyrus (SMG). Table 4 shows the results from the VLSM-

Table 4. VLSM-analysis of lesions associated with overall aphasia severity, repetition, naming, reading comprehension, and reading out loud, MNI-coordinates in parenthesis (n = 23).

	Aphasia severity	Auditory comprehension	Repetition	Reading comprehension	Reading out loud
	Z score	Z score	Z score	Z score	Z score
Frontal lobe					
RO			2.43 (−35x-34x17)		4.06 (−34x-33x19)
INS					3.32 (−33x-15x19)
Temporal lobe					
STG					2.76 (−42x-34x19)
SMG					3.32 (−63x-29x27)
Parietal lobe					
InfPG	3.68 (−31x-35x44)				
postCG	3.68 (−31x-35x54)	6.51 (−27x-39x54)		4.54 (−30x-38x57)	

Note. All scores FDR-corrected Z scores with 1000 permutations. T-test range aphasia severity: −1.263–4.336, FDR-corrected Z score with permutations = 3.61, $p < .05$, auditory comprehension: −0.984–6.513, FDR-corrected Z score with permutations = 3.59, $p < .05$, repetition: −2.015–3.359, FDR-corrected Z score with permutations = 2.43, $p < .05$, reading comprehension: −1.183–5.635, FDR-corrected Z score with permutations = 4.39, $p < .05$, reading out loud: −1.219–4.630, FDR-corrected Z score with permutations = 2.67, $p < .05$. RO = Rolandic operculum, INS = Insula, STG = Superior temporal gyrus, SMG = Supramarginal gyrus, postCG = Postcentral gyrus, InfPG = Inferior parietal gyrus.

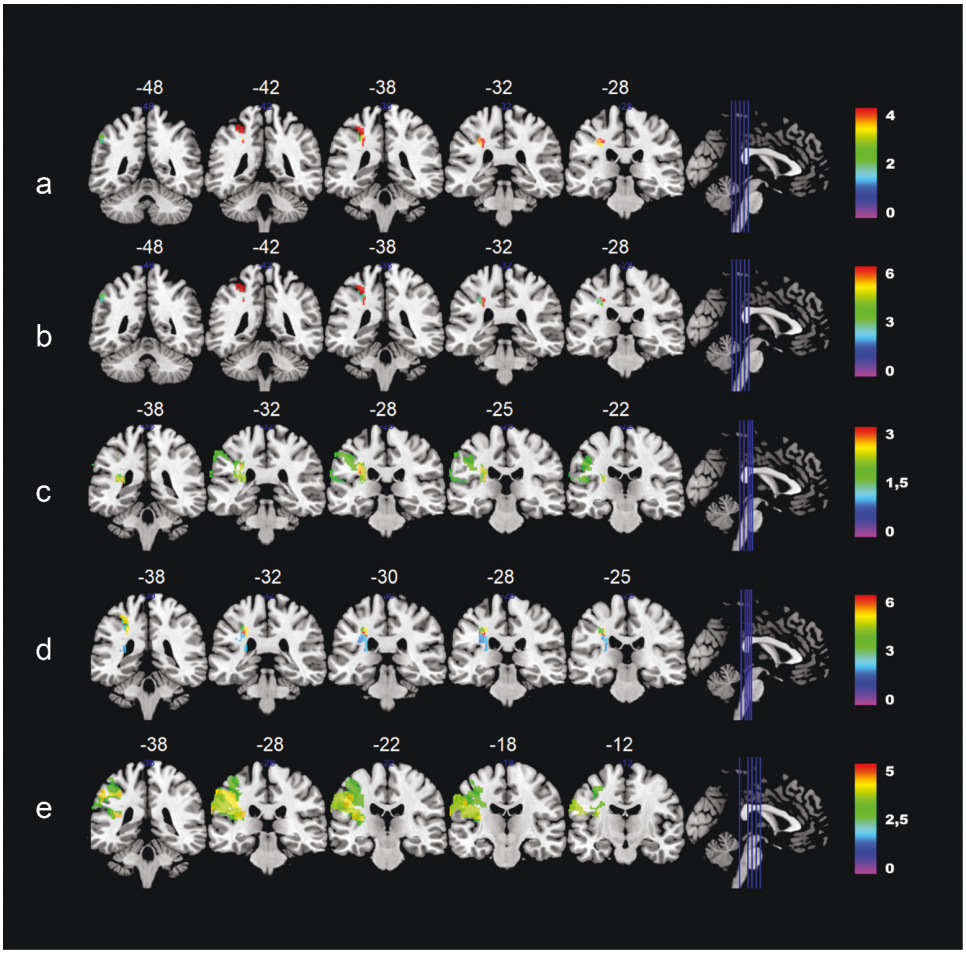

Figure 4. Colorized multi-slice maps of left hemispheric lesions at T1 and associated performance on the overall aphasia severity score (A) and subtests at T3. A: Aphasia severity, B: Auditory comprehension, C: Repetition, D: Reading comprehension, E: Reading out loud at T3 (n = 23). All maps include FDR-corrections with permutations, $p < .05$. Warmer areas (red) indicate a greater lesion overlap than colder areas (purple/blue). Color bars indicate Z scores.

analysis, while Figure 4 illustrates the results in colorized multislice maps of the associations between patients' lesions at T1 and associations to performance on the subtests from the NBAA.

Region of interest-analysis

A *post-hoc* region of interest (ROI) analysis was carried out to investigate lesion size within each specific region. Based on previous studies we included three areas of interest; the insula (Price, 2000; Sul et al., 2019), the IFGpOp (Richardson et al., 2012), and the posterior divisions of the STG (Hillis et al., 2018) as ROIs. We performed

a standard multiple regression analysis with the patients changes in their aphasia scores from T1 to T3 as the predictor variable, and their total lesion volume (mm3), and lesion volume within each ROI as independent variables. The results from the analysis showed that R squared = .38 (adjusted R square = .25), thus indicating that 38% of the variance of the patients' change in aphasia severity scores from T1-T3 can be explained by lesions within the insula, IFGpOp, the posterior portions of the STG, and the patients total lesion volume. The patients total lesion volume had the largest Beta coefficient (β = .46, Sig. = .07), thus indicating a small non-significant contribution to explaining the patients change in scores from T1-T3. The Beta coefficients of the insula (β = .06), the IFGpOp (β = −.13) and the posterior STG (β = .23) also showed non-significant unique contributions in explaining the total variance of the patients recovery from T1-T3.

Discussion

The aim of the present study was to investigate the associations between stroke severity, aphasia severity, lesion location and lesion size in acute stroke, and aphasia severity in the subacute and chronic stages post-stroke. We hypothesized that initial stroke severity, aphasia severity, and lesion location in the acute stages were associated with aphasia severity in the subacute and chronic stages of aphasia post stroke.

Our results showed that lesion size is associated with aphasia severity at admission and in the subacute stages of aphasia. However, initial lesion size was not associated with aphasia severity at one-year post stroke. Surprisingly, we did not find initial stroke severity, measured by the NIHSS, the mRS and the BI, and initial aphasia severity, as measured with the NBAA, to be associated with aphasia severity one-year post stroke. However, we found aphasia severity in the subacute stages post stroke to be highly associated with the patients' aphasia severity one-year post stroke.

Lesion analysis showed that lesions within the postcentral gyrus (postCG) and the inferior parietal gyrus (IPG) were associated with the patients' overall aphasia severity one-year post stroke. The power-analysis yielded that several lesioned areas within the frontal lobe; the insula, the IFGpOp, the preCG were associated with aphasia severity at T3, and the temporal lobe; the STG and Heschl's gyrus, and the SMG located within the parietal lobe were associated with aphasia severity at T3.

By investigating the subtests from the NBAA from T3 and the patients lesions at admission we also found that lesions within the postcentral gyrus were associated with the patients' auditory comprehension score and their scores on the reading comprehension subtest. Further, lesions within the RO were associated with the patients' scores on the repetition subtest. Finally, lesions within the RO, the insula, the STG, and the SMG were associated with the patients scores on the reading out loud subtest.

In order to investigate the contribution of a lesion within a specific region, we conducted an ROI-analysis investigating three brain regions reported in lesion studies (Baldo et al., 2006; Price, 2000; Sul et al., 2019), as well as overall lesion size. The findings from our *post-hoc* ROI-analysis showed that neither lesion size, lesions within the insula, the IFGpOP, or the posterior divisions of the STG could explain the patients changes in aphasia severity scores from T1 to T3.

Initial stroke and aphasia severity

Notably, our results were not consistent with earlier studies showing that initial stroke severity and aphasia severity are considered predictors of aphasia severity in the subacute and chronic stages post stroke (Benghanem et al., 2019; El Hachioui et al., 2013; Lazar et al., 2010; Pedersen et al., 2004; Plowman et al., 2012). Our initial hypothesis was therefore not confirmed.

Studies vary in their definitions of acute, subacute, and chronic stroke. The time of assessment post stroke might play a crucial role when investigating the relationships between initial aphasia severity and long-term outcomes. It is well documented that stroke-patients might experience great improvement in the first days after their initial symptoms (Toni et al., 1997). Our T1 aphasia assessment was carried out within the first seven days post-stroke. As reported earlier, El Hachioui et al. (2013) found that the phonology score in the ScreeLing were significant predictors aphasia one-year post stroke. The time of baseline assessment was administered at one-week post stroke, thus differing slightly from the time of T1-assessment in the present study. In the study by Laska et al. (2001) the Swedish translation of the Norwegian Basic Aphasia Assessment was carried out at a median of 5 days (range 0–30) post stroke, and at their follow-up assessments at 3, 6 and 18 months post stroke. The authors also used the Amsterdam-Nijmegen-Everyday-Language-Test (ANELT) (Blomert et al., 1994) to assess verbal communicative language, and a subjective measure ranked by the speech and language therapist. The authors specify that ninety per cent of all subjects in the study were assessed within 11 days. Laska et al. (2001) report that great improvements were seen in almost all patients. This is mainly based on their findings from the ANELT. In their study the Swedish version of the NBAA was used to assess aphasia subtype. Whereas the present study used the total score of the test, and the raw scores from the subtests to investigate recovery. Further, in Lazar et al. (2010) the baseline assessment was carried within 24–72 hours post stroke. However, patients with severe comprehension deficits were not included in the study because of their inability to sign an informed consent. Flowers et al. (2016) conducted a systematic review and meta-analysis to investigate the frequency, recovery, and associated long-term outcomes for post-stroke aphasia. The authors thoroughly reported on the methodological qualities of the studies included in the analysis. The authors point out that few studies provide data of the exact timing of the baseline evaluations from stroke onset. Clearly, different methodological and statistical approaches differ across studies, and this might be misleading when comparing studies on the long-term recovery of aphasia.

Another important consideration when interpreting the results are the assessment tools included in the present study. The NIHSS, the BI and the mRS are commonly used in the functional assessment of stroke (Harrison et al., 2013). Even though the validity of the NIHSS has been well documented (Adams et al., 1999), it has also been questioned (Peters et al., 2015). Peters et al. (2015) argue in their study that the NIHSS lacks associations between measures of impairment and functional limitations. They concluded that the NIHSS had poor validity in distinguishing long-term poststroke outcomes. Even though the NIHSS is commonly used to predict outcome, the tool was originally designed to measure stroke severity in clinical trials (P. Lyden et al., 1994). Therefore, a different measure, which had been designed to predict stroke long-term stroke outcome, might

have been more appropriate in the present study. The mRS has been found to lack specificity (Kasner, 2006). It does not assess difficulties within cognition, language, visual function, emotional impairment, and pain which are factors that might be more associated with post-stroke aphasia.

The use of the NBAA in acute stroke has shown high validity (Reinvang & Engvik, 1980). However, the validation of the NBAA was carried out on a group of patients primarily in the subacute stages post-stroke. Also, in the validation of the NBAA patients with a range of brain diseases were included, whereas ischemic stroke accounted for 60%.

Therefore, naturally, our results should be interpreted with caution, hence not ruling out the possibility of inadequate measures, nor time of assessment of aphasia and stroke severity as possible explanations for the lack of associations within the measurements used in the present study.

Lesion size

Lesion size was associated with aphasia severity at T1 and at T2. This is consistent with earlier findings investigating the role of lesion size in acute and subacute post-stroke aphasia (Benghanem et al., 2019; Døli et al., 2021). However, we did not find any associations between initial lesion size and aphasia severity at T3. This finding is contradictory to other studies investigating predictors of aphasia recovery post-stroke (Forkel et al., 2014; Plowman et al., 2012). The time of assessment might be crucial when investigating possible predictors of aphasia. It is generally agreed upon that the greatest spontaneous recovery occurs within the first three months post stroke (Laska et al., 2001). In a study by Saur et al. (2006) they investigated patients with aphasia using functional magnetic resonance imaging (fMRI) at three time points, in the acute stage (within the first days post stroke), subacute (2 weeks) and chronic stages (one year post stroke) post stroke. They suggest that brain reorganization post stroke follows three phases, from a reduced activation of the remaining left language areas in the acute phase, to an upregulation with recruitment of contralateral language areas in the subacute stages, and finally, a normalization of activation in the chronic phases post stroke. The results from the present study indicate that the greatest improvement in aphasia occurs within the first month's post-stroke, and that this improvement is associated with the patients' initial lesion size. The patients' aphasia scores improve throughout the first-year post stroke, and the greatest improvement is seen the first three months. Our results suggest that lesion size is highly associated with the subacute aphasia recovery, but it is not associated with aphasia recovery in the chronic stages post stroke.

Lesion location

Lesions within the parietal regions of the left hemisphere were found to be associated with the patients' overall aphasia severity at T3. In the power analysis we also found the SMG to be associated with the patients' aphasia severity at T3. Several studies have emphasized the role of the temporoparietal regions of the brain in the recovery of aphasia (Benghanem et al., 2019), and damage to parietal regions has been found to be associated with fluency deficits in aphasia (Baldo et al., 2006). Our power-analysis yielded that

temporal regions, such as the STG and Heschl's gyrus also were associated with aphasia severity at T3. Our findings underline the importance of the temporoparietal lobe in speech and language processing(Bates et al., 2003; Dronkers et al., 2004).

Our power-analysis also showed associations between specific frontal inferior and frontal posterior regions (IFGpOP, PreCG and the insula) and the patients' aphasia severity at T3. Regions within the left frontal lobe have also been found to be associated with aphasia in previous studies (Baldo et al., 2006; Price et al., 2010). The insula has been suggested to have an important role in both language production and comprehension (Ardila et al., 2016). Our findings are therefore in line with previous studies on both the role of the specific areas in speech and language processing, and the role of lesions within these specific regions in aphasia recovery.

When we investigated the associations between initial lesions and the NBAA subtests at T3 we found that several specific brain regions in the left hemisphere were associated with the different subtests from the NBAA. First, lesions within the InfPG and PostCG were found to be associated with overall aphasia severity. Also, the patients' performance on the auditory comprehension and the reading comprehension subtest were associated with lesions within the postCG, indicating that lesions within the parietal lobe might be crucial in language comprehension. Dronkers et al. (2004) suggested an extensive left-lateralization for language comprehension based on findings from lesion-symptom mapping and functional magnetic imaging studies on the healthy brain. The network was proposed to include areas throughout the left peri-sylvian cortex and close-by regions, including parts of the middle temporal gyrus, inferior temporal regions, the inferior parietal lobule, the Inferior frontal gyrus, and in addition other frontal regions associated with working memory and cognitive control operations.

Limitations

The present study is based on data acquired during routine care as well as the ESD-study (Hofstad et al., 2013). The missing data from the MRI scans of several patients, and especially the data from the language assessments at three and twelve months reduced the final selection of patients by almost 50%. This is consistent with other longitudinal studies investigating patients with aphasia, where large numbers of dropouts are reported (Benghanem et al., 2019; Flowers et al., 2016). Lorca-Puls et al. (2018) investigated the impact of sample size on the reproducibility of voxel-based lesion-deficit mappings. The authors found that studies with low-power due to small sample sizes, produced heterogeneous results. The authors argue that this might over- or underestimate the populations true effect-size. The low sample size in the present study might therefore underestimate the associations between the patients lesions and aphasia severity. Therefore, based on the sample size, we cannot predict aphasia severity at T3 based on our available data at T1 and T2, and our results should be interpreted with caution.

Further, we did not control or collect any information regarding the amount and type of speech and language therapy given between the test points. It is likely to assume that the majority of patients included in the study received speech and language therapy while hospitalized and after discharge from the hospital, as it is a statutory right financed by the Norwegian government. Therefore, we cannot rule out the effect of treatment in

the present study, which might be substantial (Ali et al., 2021). The scope of the study is therefore observational, and information about type and amount of therapy would have enhanced the quality of the study.

Drawing and determining lesions in VLSM is a time-consuming and subjective procedure. To enhance the inter-rater reliability in the study, a close cooperation between the authors was ensured. However, it is important to point out that VLSM-analysis does not give a causal relationship between the lesioned regions of the brain and aphasia. The results from the VLSM-analysis merely show us that the neuronal systems and the connections within a specific lesioned area of the brain are associated with or necessary for the language function which is affected (Price, 2000). Furthermore, it is also important to point out that the lack of statistical relationships between damaged regions and language functions does not rule out the regions importance in language processing (Price et al., 2010).

As discussed earlier, studies investigating aphasia post stroke differ in the time of the assessment. Our study showed that one should distinguish between subacute and more chronic stages of aphasia recovery when aiming to investigate associations because the relationships between variables seem to change over time. Therefore, a follow-up study of patients in an even longer perspective, such as two years or longer, would be of interest.

Conclusions

In the present study initial stroke and aphasia severity were not associated with aphasia severity in the chronic stages post stroke. However, aphasia severity in the subacute stage is associated with aphasia severity in the chronic stages post stroke. Lesion size is associated with initial and subacute aphasia severity. Finally, lesions within the IFGpOp, the insula, the left STG, Heschl's gyrus, and left inferior parietal and postcentral gyrus were found to be associated with aphasia severity in the chronic stages post stroke.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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III

Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
1981	Myhrer, Trond, Dr. philos.	Behavioral Studies after selective disruption of hippocampal inputs in albino rats.
1982	Svebak, Sven, Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, Rolf, Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, Ragnar J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, Arnulf, Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, Tor, Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, Tore, Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, Wenche, Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, Knut A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, Finn K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
1987	Aarø, Leif E., Dr. philos.	Health behaviour and sosioeconomic Status. A survey among the adult population in Norway.
	Underlid, Kjell, Dr. philos.	Arbeidsløyse i psykososialt perspektiv.
	Laberg, Jon C., Dr. philos.	Expectancy and classical conditioning in alcoholics' craving.
	Vollmer, Fred, Dr. philos.	Essays on explanation in psychology.
	Ellertsen, Bjørn, Dr. philos.	Migraine and tension headache: Psychophysiology, personality and therapy.
1988	Kaufmann, Astrid, Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.

	Mykletun, Reidar J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, Magne A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, Mary E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, Svein, Dr. philos.	Cultural background and problem drinking.
	Nordhus, Inger Hilde, Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, Frode, Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, Ragnar, Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.
	Johnsen, Bjørn Helge, Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, Finn E., Dr. philos.	The etiology of Dyslexia.
	Kvale, Gerd, Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.
	Asbjørnsen, Arve E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.

	Bru, Edvin, Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, Eli T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, Birte F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, David L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, Inger-Kristin, Dr. philos.	Component processes in word recognition.
	Martinsen, Øyvind, Dr. philos.	Cognitive style and insight.
	Nordby, Helge, Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, Arild, Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, Wencke J., Dr. philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, Wibecke, Dr. philos.	Subjective conceptions of uncertainty and risk.
	Aas, Henrik N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, Stål, Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, Norman, Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.
	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.
	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.

1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998 V	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.
H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999 V	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.
H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.

	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.
2000 V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.
H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.
2001 V	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.
H	Fekadu, Zelalem W., Dr. philos.	Predicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.
2002 V	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.
	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.

	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 V	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 V	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.
	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.

	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 H	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.
	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.

	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints
	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work

	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skoleledereres og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
	Johansen, Venke Frederike	Når det intime blir offentlig. Om kvinners åpenhet om brystkreft og om markedsføring av brystkreftsaken.
	Herheim, Rune	Pupils collaborating in pairs at a computer in mathematics learning: investigating verbal communication patterns and qualities
	Vie, Tina Løkke	Cognitive appraisal, emotions and subjective health complaints among victims of workplace bullying: A stress-theoretical approach
	Jones, Lise Øen	Effects of reading skills, spelling skills and accompanying efficacy beliefs on participation in education. A study in Norwegian prisons.

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