Subjective disease burden due to cognitive and behavioural impairment in amyotrophic lateral sclerosis, frontotemporal dementia and Parkinson’s disease – a comparison
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Abbreviations

ALS  Amyotrophic lateral sclerosis
ALS-FRS  Amyotrophic lateral sclerosis functional rating scale
ALS-FTD  Amyotrophic lateral sclerosis and frontotemporal dementia
bvFTD  Behavioural variant FTD
CNS  Central nervous system
cTBS  Caregiver-estimated Total Burden Scale
DSM IV  Diagnostic and Statistical Manual of Mental Diseases IV
ECAS  Edinburgh cognitive and behavioural ALS Screen
ECASbq  ECAS behavioural questionnaire estimated by a primary caregiver
H&Y  Hoehn and Yahr
IPS  Idiopathic Parkinson Syndrome
ISCED  International Standard Classification of Education
MDD  Major depressive disorder
MDS  Movement Disorder Society
MMST  Mini-Mental State Examination
MND  Motor neuron disease
NIV  Non-invasive ventilation
PEG  Percutaneous endoscopic gastrostomy
PET  Positron emission tomography
PNFA  Primary non-fluent aphasia
QoL  Quality of life
SF 12 MCS  Short Form 12 Questionnaire Mental Component Summary
SF 12 PCS  Short Form 12 Questionnaire Physical Component Summary
SF 36  Short Form 36 Questionnaire
SPECT  Single photon emission computed tomography
sTBS  Subjective Total Burden Scale
TBS - DS  Total Burden Scales calculated Differential Score
ToM  Theory of Mind
UPDRS  Unified Parkinson’s Disease Rating Scale
1 Introduction
The chronic neurodegenerative diseases amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and idiopathic Parkinson’s syndrome (IPS) are progressive diseases that can cause impairment in behaviour and cognition. The worldwide incidence of neurodegenerative diseases increases and with it mortality and morbidity. In the following, a summary about each disease, and their behavioural and cognitive impairments will be given.

1.1 Overview of amyotrophic lateral sclerosis

Epidemiology
The incidence rate in southwestern Germany is 3.1 per 100,000 person-years in 2016 and is thought to be rising [210]. Within three years of onset, 50% of patients die mainly because of respiratory insufficiency. In most cases the disease is sporadic; 5-10% of patients have a positive family history with an autosomal dominant inheritance (familial ALS). The main onset of the disease is between 50 and 70 years, however also younger and older patients can be affected; especially in the familial ALS onset tends to be earlier.

Pathogenesis
The pathogenesis of this motor neuron disease (MND) is multifactorial, leading to progressive degeneration of Betz cells in the motor cortex (first motor neurons) and anterior horn cells (second motor neurons). The glutamate transport is decreased leading to toxic effects on first and second neurons [161, 212]. In 2013, Brettschneider et al. defined four stages of ALS post-mortem, based on a sequential regional spread of phosphorylated 43-kDa transactive response DNA-binding proteins (pTDP43) [23]. The pTDP43 is a primarily intranuclear located protein, the mutation of which is involved in ALS or FTD pathology. In 2014, Kassubek et al. found that the specific pattern of spread can be identified with diffusion tensor imaging analysis. This enables determination of the disease stage in ALS in vivo [100]. The distinct pattern of pathological spread [21, 23] and diffusion tensor MRI based staging [100] in ALS is consistent with the occurrence of cognitive and behavioral deficits [131]. The occurrence of cognitive deficits is specific to one of the four defined MRI stages by Kassubek et al. [100, 131].
Symptoms
Degeneration of upper and lower motor neurons lead to typical physical signs; however, the initial clinical picture varies depending on the onset type: Bulbar onset type or spinal onset type. Spinal involvement can be further divided by the affected neurological level: Cervical, thoracic or lumbar. The spinal onset type initially presents with muscle cramps or fasciculations, increased fatigue and exercise intolerance, followed by paresis and atrophies. Paresis often starts focally in the hand or foot and spreads to a neighbouring region. Difficulties in writing, getting dressed or cutting with a knife are frequent complaints as well as problems walking stairs or a tendency to fall. Severe wasting of skeletal muscles is often visible. Swallowing difficulties (dysphagia), pseudo-hypersalivation or speech difficulties (dysarthria) with stuttering or slurred speech are typical for bulbar onset patients. Often symptoms are accompanied by fasciculations and atrophy of the tongue, palate and throat muscles and hyperactive palmomental reflex. Patients with bulbar onset have a worse prognosis than those with a spinal onset. The disease progresses and eventually results in "locked-in" syndrome, a complete tetraparesis. Only eye movement is spared because motor nuclei of extrinsic eye muscles, are not affected as the cranial nerves III, IV and VI, which regulate those muscles, come from fiber tracts within medial longitudinal fascicle [87, 103, 161].

Diagnosis
No diagnostic test or biomarker exists, so neurologists diagnose ALS by using El Escorial criteria, revised by Ludolph et al. in 2015, defining the characteristic picture of ALS by the involvement of first and second motor neuron [24, 127]. Symptoms should be progressive and other diseases should be excluded [103]. Strong et al. introduced new guidelines in 2009 to classify cognitive alterations of FTD in ALS in extension to the El Escorial criteria [24, 127, 230]. The guidelines allow the classification of ALS patients according to their behavioural and cognitive symptoms into five stages along a continuum. 1) ALS patients cognitively and behaviourally intact; 2) ALSci: ALS patients with mild cognitive impairment 3) ALSbi: ALS patients with mild behavioural impairment 4) ALS - FTD (amyotrophic lateral sclerosis-frontotemporal dementia) 5) ALS non-FTD dementia: With other non-FTD-forms of dementia [230].
Treatment
Symptomatic treatment may improve quality of life (QoL). Pseudo-hypersalivation is treated with anticholinergics, orthopedic interventions to support neck musculature or in some cases botulin toxin. To control dysphagia, change of food consistency or special swallowing techniques can help. If choking is severe and occurs together with weight loss and dehydration, QoL can be improved with a percutaneous endoscopic gastrostomy (PEG). High caloric fatty diet was found to decrease mortality in the fast-progressing ALS group [125]. Early visits to the speech therapist and early introduction of modern computer technology communication aids can replace the language in case of anarthria [118]. Noninvasive ventilation may ameliorate symptoms of daytime sleepiness, sleep disturbances and improves survival and QoL [125]. Invasive ventilation is used to secure survival in advanced stages. N-acetylcysteine or assisted coughing techniques can relieve thick mucus secretions. Physiotherapy and early support by physical aids such as a wheelchair or peroneus splint are recommended. Muscle cramps and fasciculations can be relieved with magnesium, vitamin E, or, if severe, with carbamazepine. Spasticity can be improved with baclofen, memantine or tetrazepam. For drooling, amitriptyline, atropine or transdermal hyoscine patches, and in severe cases, botulinum toxin injections give relieve.

Depression should be treated with selective serotonin reuptake inhibitors (SSRIs), or tricyclic antidepressants (TCAs), as amitriptyline for example, has the advantage of not only improving emotional lability, but also sleep disturbance and drooling. The severe anxiety, often accompanying bouts of dyspnea, can be managed with short-acting benzodiazepines. Increased affective lability and pathological laughing or crying can be controlled with amitriptyline, lithium or levodopa.

The disease-modifying drug riluzole was approved in the USA in 1995. This glutamate antagonist shows neuroprotective effects by slowing the progression of the disease with a mean lifespan prolongation of three months. Early start of the drug shows better results, as these patients remain longer in the earlier phases of the disease. Uptake of the oral drug riluzole into the brain was highly variable due to a pharmacokinetics which depend on many factors such as gastrointestinal motility. Twenty-two years later, after investigation of many possible treatments for ALS, edaravone was approved 2015 in Japan.
This antioxidant is thought to decrease oxidative injury mainly in central nervous system (CNS) motor neurons and therefore slows disease progression. To decrease hospital-stay costs and improve patients’ compliance, the goal is to introduce an oral form of edaravone [47, 105, 211]. Further, rasagiline may provide a disease-modifying effect but further studies are needed to confirm [126].

1.2 Overview of frontotemporal dementia

Frontotemporal lobar degeneration, originally known as Pick’s disease, is a term that describes a spectrum of impairments: Behavioral variant frontotemporal dementia (bvFTD), primary non-fluent aphasia (PNFA) and semantic dementia (SD) [170, 172].

Epidemiology

FTD is the third most common dementia after Alzheimer disease and Lewy body dementia and the most common cause of midlife dementia with a median onset of 56 years (range from 21-75). Men and women are equally affected. Median survival after onset is eight years (range 2-20 years). Prevalence is between 0.01 – 4.6 per 1000 persons and incidence 0.0-0.3 per 1000 person-years [86]. However, to name exact numbers of median survival and incidence is difficult as universally accepted diagnostic criteria are recognized only since 2011 [201] and initial symptoms such as personality changes remain often unrecognized [77].

Pathophysiology

Macroscopically, frontal and/or temporal lobe atrophy and hypometabolism are the main pathologic feature in FTLD, associated with the clinical representation [249]. Microscopically, there may be neuronal loss, loss of myelin, spongiform degeneration and possible development of abnormal intraneural silver-stained inclusion bodies, “Pick Bodies”, named after neurologist Arnold Pick [77]. Early loss of spindle neurons, also called von Economo neurons, are often affected by C9orf72 expansion mutation in bvFTD [60, 117, 220]. These bipolar projecting neurons are found in the anterior cingulate cortex and fronto - insula cortex. Gami-Patel et al. found that von Economo neurons are part of neurons expressing gamma-
aminobutyric acid receptor subunit theta, which are involved in social and emotional functioning [60].

**Symptoms**
With respect to behavioural variant FTD, insidious onset of disease and progressive worsening with early personality changes, altered social conduct, emotional blunting, loss of personal hygiene and loss of insight are typical. In language variant FTD, early cognitive deficits are language changes such as decreased talkativeness, naming deficits or increased urge to talk, mutism or stereotypies. The initial clinical picture varies between patients, however in final stages most patients present with mutism, incontinence and require total nursing care [77, 172, 255]. Other physical findings are primitive reflexes such as grasp or palmomental reflex, hypotension, signs of motor neuron disease in ALS-FTD or parkinsonism with tremors, akinesia or rigidity [77, 188].

**Diagnosis**
The Rascovksky Criteria were established in 2011 to have universally accepted criteria for bvFTD [201]. By history or observation, deterioration of behaviour and/or cognition should be present. In early disease stages of bvFTD, which are usually only personality changes, caregiver reports are the main tool to detect bvFTD [95]. No reliable biomarkers, but MRI criteria are available for diagnosis of bvFTD. For possible bvFTD at least three clinical criteria, namely disinhibition, apathy, loss of empathy, preservative and stereotypical behaviour and hyperorality or changing in eating behaviour should be present.

1) **Disinhibition** includes socially inappropriate behaviour and vocabulary, impulsivity, hypersexuality or aggressiveness [254].
2) **Early Apathy or Inertia** which may present as lack of personal hygiene and inactivity.
3) **Loss of empathy or sympathy** may present with a decline in social behaviour, problems in emotion recognition or blunting of emotions.
4) **Preservative and stereotypical behaviour** present with utilization behaviour, echolalia, preservations or other ritualistic, complex behaviours.
5) **Hyperorality or changes in eating behaviour** present as binging, increased consumption of sweets, alcohol, cigarettes or consumption of inedible objects.
For diagnosis of probable bvFTD the criteria for possible bvFTD together with decreased ability to manage daily activities plus atrophy in prefrontal or anterior temporal lobe or hypoperfusion or hypometabolism in single photon emission computed tomography (SPECT) and positron emission tomography (PET) are needed [201]. Definitive FTLD pathology is confirmed with biopsy or post-mortem proof or known mutation. Other neurological diseases such as Alzheimer’s disease or psychiatric diagnoses such as schizophrenia, depression or mania that might explain the illness better should be excluded clinically and with biomarkers for other neurodegenerative diseases.

The Neary diagnostic criteria were established in 1998 and include five core diagnostic criteria and several supportive diagnostic criteria. The core criteria focus on personality changes and include, in contrast to the Rascovksky criteria, loss of insight as a core diagnostic criterion. The following are the five core Neary diagnostic criteria: 1) Insidious onset and gradual progression, 2) early decline in social interpersonal conduct, 3) early impairment in regulation of personal conduct, 4) early emotional blunting and 5) early loss of insight [172].

Treatment

Both pharmacological and behavioural interventions may relieve symptoms. Selective Serotonin reuptake Inhibitors (SSRIs) have been shown to decrease depression, lethargy, disinhibition and hyperorality. Dopaminergic medication such as bromocriptine, amphetamines and methylphenidate improve apathy and lethargy. Aggressive symptoms and irritability can be treated with antipsychotics such as quetiapine and olanzapine [77].
1.3 Overview of idiopathic Parkinson’s syndrome

Epidemiology

IPS, defined in 1817 by James Parkinson, is one of the most common neurodegenerative movement disorders worldwide. Incidence peaks between 60-70 years, with early onset being in the 40s. In the United States at least 1.5 million people are affected. Initial symptoms are mild but usually progress to a severe disability over 10-20 years. About 15% of IPS patients have a positive family history. Deficits in the degradation of specific proteins lead to accumulation, deposition and spread, thereby theorized to cause IPS. Currently, several proteins are identified, such as the synaptic protein alpha-synuclein. Examples of genes which are thought to play a role in pathogenesis of IPS are Parkin (ubiquitin ligase), UCHL1, PINK1 or CHCHD2 [91, 181].

Pathophysiology

The basal ganglia are an important part of the extrapyramidal system, regulating and suppressing movements. The basal ganglia consist of seven distinct structures: The striatum, caudate nucleus, lenticular nucleus (putamen and globus pallidus), substantia nigra, subthalamic nuclei, nucleus accumbens and the olfactory tubercle. In the substantia nigra, dopamine is synthesized. Several dopaminergic loops lead to the striatum, where mainly dopamine is released. In IPS, degeneration of dopamine depletes the pigmented dopaminergic neurons of dopamine and in the residual dopaminergic neurons, alpha-synuclein positive neuronal inclusions (Lewy Bodies) deposit [91].

Braak et al. proposed a model that predicts the "prion-like" scheme of spread of misfolded alpha-synuclein deposits: It ascends and spreads from the lower brainstem through regions of the midbrain and forebrain into the cerebral cortex [20, 181, 243]. Overexpression and spread of misfolded alpha-synuclein protein deposits aggregate in neuronal processes (Lewy neurites) and neuronal cell bodies (Lewy bodies) and in other parts of the peripheral and central nervous system [64, 181]. Additionally, the deficiency of noradrenalin and serotonin is hypothesized leading to symptoms such as depression. Lastly, acetylcholine seems to contribute to the problem as well; deficiency leads to dementia, while excess manifests as tremors and vegetative symptoms.
Symptoms
Motor symptoms usually start unilaterally and later progress to both sides. The four primary motor signs are 1) rigidity, 2) tremor, 3) bradykinesia and 4) gait disturbance or postural instability.

Three phenotypes are differentiated: Hypokinetic-rigid type, Tremor-dominant type and Equivalent type where hypokinesia, rigidity and tremor are dominant.

Parkinson disease rating scales classify IPS according to the Unified Parkinson disease rating scale (UPDRS) and Hoehn and Yahr (H&Y) scale. These two scales assess most of the following symptoms: Bradykinesia, the decreased ability to initiate movements, which also present with micrographia and mask-like face (decreased blinking, loss of expression). Glabellar tap sign is usually positive. Rigidity is a muscular dystonia, presenting as resistance during passive movement. The classic cogwheel phenomenon is also tested in UPDRS motor scale. Initially, patients feel limitations when exercising and experience earlier fatigue. Tremor is classically prominent at rest. Gait disturbance and postural instability are often present later with retropulsion and propulsion, a stooped posture, a shuffling gait with small steps and lack of supplementary arm movements.

After years of dopamine replacement therapy, many patients start fluctuating with their symptoms between ON states when there is better motor functioning, and OFF states when the motor abilities worsen. During ON states, some patients develop involuntary chorea-like movements. During both states, albeit, more pronounced during OFF states, rigidity and bradykinesia occur.

Prodromal nonmotor symptoms involve olfaction, with less than 80% of IPS patients having hyposmia [181] and sleep disorders such as insomnia or rapid eye movement sleep behavior disorder [225]. Autonomic dysfunction may manifest as orthostatic hypotension, bladder dysfunction, erectile dysfunction, impaired gastrointestinal motility or reduced heart rate variability [181].

Diagnosis
IPS is mainly a clinical diagnosis presenting with typical motor symptoms bradykinesia, rigor and tremor. Other etiologies and atypical Parkinson syndromes should be excluded. A good response to dopaminergic therapy supports the diagnosis. Although the diagnosis is mainly clinical, there are additional tests. Striatal dopamine transporter scintigraphy (DaTSCAN) is a specific type of SPECT
imaging, which depicts nigrostriatal pathways by visualizing dopamine transporter. Fluorodeoxyglucose positron emission tomography (FDG-PET) and Dopamine D2 receptor scintigraphy (IBZM-SPECT) may aid discriminating IPS from other parkinsonian syndromes. Olfactory testing may determine the nonmotor symptom hyposmia.

**Treatment**
There is no neuroprotective therapy available preventing further progression, but symptomatic treatment may ameliorate complaints. However, those medications may have a number of side effects which might mimic behavioural deficits.

Levodopa, especially, might induce psychotic symptoms such as hallucinations, but also somnolence, confusion, pathological gambling and hypersexuality [59, 181]. This drug is frequently prescribed to older, multimorbid patients with significant motor disabilities, where other medications have failed. With progressed disease, effective symptom control becomes more challenging, as response to drugs presents with delayed onset and shorter duration of action. Some patients might receive bolus doses of levodopa via a continuous battery-driven pump [38]. To increase bioavailability, drugs such as dopamine decarboxylase Inhibitors (e.g. benserazide or carbidopa) might be added to levodopa. Still, side effects such as dyskinesia, choreiform-like movements, nightmares, confusion and psychosis might occur. Dopaminergic agonists, monoamine oxidase B inhibitors (e.g. selegiline) or N-methyl-D-aspartate receptor antagonists (e.g. amantadine) have similar side effects to levodopa, but usually milder. The benefit of catechyl-O-methyltransferase inhibitors (e.g. entecapone) is controversial. In younger patients without cognitive dysfunction a non-ergot dopamine agonist can be used such as ropinirole, which might have similar side effects to a therapy with levodopa, but less frequently. Anticholinergics, such as biperiden, and deep brain stimulation of the subthalamic nucleus are mainly used to treat tremor dominant types in younger patients [181]. Anticholinergics might present with side effects such as dry mouth, narrow-angle glaucoma, constipation, urinary retention, memory impairment and hallucinations. In our study, some patients were part of a double-blind study receiving alpha synuclein antibodies [214].
1.4 Genetics of the three diseases

It is suggested that there is a shared genetic susceptibility in ALS and also IPS, as these two were found more often in families. There are also significant genetic overlaps in ALS and FTD. The most common example of this genetical overlap is C9orf72 repeat expansion on chromosome nine. This mutation can lead to familial ALS, familial FTD, or both, amyotrophic lateral sclerosis – frontotemporal dementia (ALS-FTD) [18, 177]. Furthermore, mutations of TBK1, VCP and neuronal inclusions of TDP-43 and CHCHD10 can be found in both, ALS and FTD [177]. Often, in families affected by either disease, there is a family history of ALS, FTD or ALS-FTD [103, 171]. Brundin et al. describe the phosphorylated 43-kDA TAR DNA binding protein (pTDP-43) to aggregate and spread in a characteristic “prion-like fashion” to specific neurons and CNS glial cells. This spread is hypothesized to play a major role in the pathogenesis of FTD and ALS, reminiscent of that of alpha synuclein in IPS or phosphorylated tau protein in Alzheimer’s disease [27]. The special pattern of dissemination could explain the executive deficits in ALS, as pTDP-43 is predominantly found in the prefrontal cortex [23]. In a subgroup of FTD patients without motor symptoms, ubiquitin aggregates in bulbar and spinal motor neurons could be found [231].

C9orf72 repeat expansions alone or together with SOD 1 (copper/zinc superoxide dismutase) or FUS (encodes fusion in sarcoma), ANG (angiogenin) and OPTN (optineurin) [177] may result in ALS; while C9orf72 combined with GRN (progranulin) mutation may cause FTD [195]. Lastly, C9orf72 combined with a mutation in NEK1 may present as either ALS or ALS-FTD [177]. MAPT is a gene on chromosome 17, that similarly to C9orf72 can result in different diseases; in this case, however for IPS or FTD [77].
1.5 Cognitive impairments

Detection of cognitive dysfunction in patients with motor neuron diseases has become more important as for these patients an increased mortality was found [52, 185].

Cognitive changes are high level brain functions which can be divided into different cognitive domains. The domains encompass among others language, executive function, verbal fluency, learning and memory, complex attention, perceptual motor and social cognition [1-3, 92, 235]. Five of these domains, including visuospatial functions, have been extensively tested and assessed with the Edinburgh cognitive and behavioural ALS screen (ECAS) questionnaire [1, 78, 133]. Abrahams et al. published several works about cognitive changes, verbal fluency and executive dysfunction in ALS. They found that verbal fluency deficits are not a result of linguistic or phonological disabilities but rather due to higher order dysfunctions such as the central executive component of the working memory [2, 3]. According to the study by Taylor et al., executive impairments explained 44% of the language impairment variance and many non-demented ALS patients have executive deficits and mild language deficits [235]. Similarly, Lomen-Hoerth et al. found that half of ALS patients have executive deficits [121]. A comparative study by Machts et al. showed that ALS patients have a distinct type of memory deficit when compared to patients with amnestic mild cognitive impairment [142].

Language impairments include impaired communication and deficits in understanding of metaphors and humour or the incorrect usage of words. Executive functions help to plan and initiate goal-directed behaviour and aid in adapting to new situations by changing behaviour. Executive dysfunctions are also associated with lack of attention and impaired problem solving. Verbal fluency impairment may be recognized by asking the patient to name words that start with a certain letter or when giving a specific category. Visuospatial deficits refer to impaired identification of visual and spatial relationships, for example correctly estimating distances. Memory includes three subdomains: Semantic, working and procedural memory. Semantic memory stores knowledge about names, meanings and about the usage of things around us. Working memory collects verbal and nonverbal information to complete goal-directed actions. Lastly, procedural memory is responsible for correct
performance of certain tasks, without conscious knowledge about the correct execution [150].

Cognitive impairments, for instance difficulties in recalling and generating words/names, are to a certain extent, non-pathological in aging [72]. Cognitive impairments may also increase the burden. Thus, we assessed the affected cognitive domains.

**Amyotrophic lateral sclerosis**

Cognitive impairments are found in 30% of ALS patients in at least one domain. These are mainly executive function, language and less often memory function [74, 235]. Caga et al. describe cognitive deficits in 30 - 50% of ALS patients additionally in the domain’s social cognition, verbal fluency (which share cognitive substrates of executive function) and memory function [32]. Imaging showed that prefrontal and temporal areas are responsible for early executive and memory dysfunctions in ALS patients [99]. Usually, after impairment of one domain, an additional domain becomes affected in progressed disease [46]. However, about 50% of ALS patients have no or only mild cognitive impairments. One reason for this might be that these patients show such rapid physical decline, that they die before cognitive and behavioural symptoms arise [185, 254, 255]. ALS patients presenting with severe, mainly executive cognitive and behavioral symptoms, may meet FTD diagnostic criteria and are therefore assigned the diagnosis of ALS-FTD [122, 161, 206, 254].

**Frontotemporal dementia**

Similar to ALS patients who present with additional cognitive and behavioral symptoms, some FTD patients may also show symptoms of motor neuron disease, in which case, they fall under the umbrella of ALS-FTD [31]. In patients with ALS-FTD and bvFTD, even major cognitive impairments can be expected compared to patients with only ALS [129].

FTD patients’ cognitive deficits, especially executive ones, are prominent from the start, which may worsen with progressed disease. Besides executive dysfunctions, loss of verbal fluency may occur [201]. Impairments in working and semantic memory as well as visuospatial functions are only mild or occur in progressed diseases. Speech and language disorders such as echolalia, lack of speech or preservation are frequently reported [255]. There is no deficit in spatial memory;
however, autobiographical memory, imagination and future thinking can be affected in bvFTD [193].

Social cognitive dysfunction is common in FTD patients presenting with *loss of empathy, social disinhibition and lack of social skills* [51], but to some extent, social cognitive dysfunction has also been observed in IPS and ALS [17, 240, 246]. Social cognition refers to the cognitive processes that are involved in interpersonal interactions, which are necessary for successful communication and social interaction [42]. These include the interpretation and recognition of facial expressions, body language and meanings. *Social cognition* is a complex construct, containing several individual subdomains, one of which is Theory of Mind (ToM). ToM can further be subdivided into *cognitive and affective ToM*. ToM is the ability to understand other peoples’ mental states, such as intentions, desires and beliefs [17, 144]. Empathy refers to the understanding and appropriate response to emotions of others [240]. In longterm, ALS and FTD patients having difficulties to recognize feelings and thoughts of others, may contribute to behavioural manifestations of apathy and loss of insight [240].

**Idiopathic Parkinson’s syndrome**

IPS patients' cognitive impairment may range from mild to severe, leading to disruption of daily living. About 25 - 30% of IPS patients with mild cognitive impairment are without functional decline, however, as the cognitive impairment progresses, up to 80% develop dementia [119]. Memory is the most frequently affected domain, involving mainly working and procedural memory [150]. Cognitive changes in advanced IPS disease are 1) bradyphrenia (slowed thinking), 2) preservation, 3) executive deficits including impaired planning and temporal sequencing, 4) verbal fluency impairment and language deficits [108].

Especially in early stages of disease, IPS patients are reported to have executive deficits [115, 155, 251] which may be accompanied by visuospatial deficits [155]. Furthermore, studies showed that IPS patients have impairments in understanding meanings of narratives but also using correct language [80, 164].
Previous studies researched cognitive and behavioural symptoms either in ALS alone or in comparison to either FTD or IPS individually [32, 50, 129]. A study by Lewis et al. used event-related-functional magnetic resonance imaging which identified that IPS patients with executive cognitive impairments had reduced activity in striatum and frontal cortex during working-memory tasks [115]. Kassubek et al. confirmed the specific pattern of spread including the involvement frontotemporal parts with diffusion tensor imaging analysis in ALS patients [100]. Lulé et al. reviewed that frontal cortical involvement in MRI is visible also in ALS patients with only subclinical cognitive impairment [137]. Mendez et al. found by SPECT imaging in FTD patients typical behavioural impairments depending on the affected area. Patients with right frontal hypoperfusion may present with alterations such as a prolonged gaze, abnormal posture or physical behaviour inconsistent with social context [159]. These findings suggest a similar pathogenesis of some cognitive and behavioural deficits across our three investigated diseases [5, 104, 115, 188, 190, 215, 234, 252]. Further, all three pathologies may present with language deficits including word-finding difficulties, verbal fluency deficits and naming deficits [9, 164, 228].

1.6 Affective and behavioural changes

Behavioural impairments involve neuropsychiatric deficits such as apathy, anxiety, loss of personal hygiene, loss of empathy or affective changes like depression which might occur before the onset of cognitive impairment [233]. Affective disorders are an umbrella term for psychiatric disorders, such as uni- and bipolar depression, the former of which is often of reactive nature, meaning an affective response to a traumatic life event, and concomitant with chronic disease. A reactive depression is often a result of inappropriate adjustment to said event, which is why it is sometimes considered an adjustment disorder with depressive mood.

Depression is characterized by depressed mood, loss of interest or pleasure in activities which formerly were pleasurable (anhedonia) and fatigue or loss of energy, present for at least two weeks. Further symptoms may include lethargy, irritability, difficulties concentrating, insomnia or hypersomnia, change in appetite, psychomotor agitation or retardation, feeling of guilt and suicidality.
Rabkin et al. found that depressive symptoms increase distress in ALS patients [198]. Depressive symptoms may negatively affect psychosocial adaptation and therefore increase disease burden. However, Lulé et al. showed in a study comparing 30 ALS and 29 cancer patients that both have a good psychosocial adjustment and only mild depressive symptoms without any patient having severe depressive symptoms [136]. Furthermore, other works supported, that ALS patients have a good affective state [135, 139].

In IPS patients, usually depression or sleeping disorders precede motor symptoms [225]. Depressive symptoms may also occur later in disease in reaction to worsening complications such as motor fluctuations and progressed physical impairment [26]. Many behavioural symptoms in IPS may be side effects of medication which were presented in the introduction part (Chapter 1.3 Overview of IPS, Treatment). However, some studies also report other behavioural symptoms such as social disinhibition [155].

In ALS patients, in contrast, depressive symptoms are frequently reactive and a result of the diagnosis of terminal illness [136, 139]. The depression being of reactive nature, tends to subside, or lessen with disease progression; nonetheless, studies show depression among ALS patients may be as common as nine percent [62, 178, 198, 199].

For FTD, behavioural changes are part of the core diagnostic criteria and are divided into five groups: 1) Disinhibition, 2) apathy, 3) early loss of empathy, 4) preservative behaviour or ritualistic behaviour and 5) hyperorality [201].

In IPS and ALS these are not part of the core diagnostic criteria but might be present in a milder form. One of the most common behavioural symptoms in all three groups is apathy, which is reported in more than half of IPS patients and as the most dominant in ALS patients [33].

In FTD, the above mentioned behavioural changes might be accompanied by an increase in self-centeredness, irritability, personality changes such as obsessions with new hobbies (which are often spiritual or religious) and lack of insight. Furthermore, early psychotic features such as hallucinations and delusions may appear [245].

In both FTD and ALS, affective instability can occur presenting with pathological laughing or crying. Pathological laughing or crying are defined by the inability to
control emotions. They are often provoked by stimuli that may be nonsentimental or sentimental, followed by an excessive emotional response [88].

1.7 Subjective burden

To understand subjective burden, initially, subjective well-being is defined. Subjective well-being is a complex construct based on individual's affect and cognition. Affect describes the perception of emotions. Happiness, for example is an emotion, leading to a mainly positive affect. There is a large cognitive aspect to well-being, as it necessitates the capacity for reflection about the overall satisfaction with life. Life satisfaction belongs to mental health which is one of few important parts of subjective well-being.

The second part of subjective well-being is ego identity. Ego identity describes the degree of satisfaction with the own overall achievements, as well as the confidence about these. Social support might help in this case, to keep thoughts and emotions mostly positive, increase self-esteem and prevent depression and greater distress, thereby ultimately strengthening ego identity [25]. Well-being does not only depend on the severity of physical impairment [175], but also on the availability of existential needs such as social support, interdisciplinary treatment and affordability of medical supervision or availability of health insurance, financial security and a disability-friendly home [130]. The fact, that a severe physical impairment and impending death do not necessarily decrease subjective well-being, seems paradoxical [83].

The subjective burden indicates, to which extent the disease is subjectively perceived as a burden including all its symptoms and drug-related side effects. Cognitive, behavioural and physical impairment, as well as depressive symptoms may increase the burden. Literature showed, that cognitive impairment negatively influences the level of burden [237]. Burden is a measure, independent of the diagnosis [237]. Unfortunately, burden is frequently perceived higher, than the impairment is objectively measured.

Every patient may cope different with their individual impairments, depending on their capacity for psychosocial adaptation, this ultimately dictates their burden. For instance, a stroke-patient with hemiparesis, may objectively have a lower physical impairment than a bedridden ALS patient. However, if the hemiparesis is
accompanied by depressive symptoms, whereas the ALS patient enjoys good mental health, the subjective burden of the stroke-patient might be higher. Psychosocial adaptation may be measured by assessing QoL and affective state. In case, adaptation is insufficient, it might be indicated by depressive symptoms and low QoL. Therefore, depression and QoL serve as indicators for psychosocial adaptation. The cognitive, behavioural and physical impairments pose limitations on daily life and may contribute to disease burden [166, 218]. The subjective burden may increase in case of behavioural and cognitive deficits which lead to conflicts with friends and family or to problems at work [32]. Cognitive dysfunctions, such as language impairments, interfere with communication and therefore might further increase the burden on the patient.

Behavioural and cognitive impairments are most severe in the FTD group, as indicated by the Rascovisky criteria for diagnosis of FTD, which require the presence of at least three behavioural deficits together with executive cognitive deficits (Diagnostic criteria are presented in chapter 1.2 FTD Diagnosis) [201]. Although cognitive and behavioural impairments are rare in early stages of ALS, they increase with progression of disease. Therefore, Crockford et al. appeal to include them in the diagnostic criteria for ALS [46]. Recognizing cognitive and behavioural impairments early, may help develop and implement more successful non-pharmacological treatments, decrease the subjective burden and improve survival time [32, 153]. Often, the behavioural and cognitive deficits are associated with nonadherence to treatment and decreased autonomy, which further increase morbidity and mortality [42, 254]. However, with factors such as interdisciplinary care, coping strategies and family support, a good QoL can be maintained in ALS [41, 62, 75, 130, 152, 207].

In contrast to ALS, IPS patients generally have a longer disease duration, with various medication options, making them vulnerable to treatment-specific side effects [98, 218] and motor fluctuations [56]. Therefore, in IPS, disease burden is not due to a sudden instance of physical impairment such as in ALS [145], but rather, a slow but steady increase of physical (motor) and cognitive (nonmotor) deficits and medication side effects [226].
1.8 Quality of life

Quality of life is the individuals' perception of their well-being. These perceptions depend on individuals' expectations of a good QoL, influenced by culture, values and goals. Health related QoL (HRQoL) evaluates QoL in relation to individuals’ health.

With subjective well-being, satisfaction with life and good QoL, the burden may be decreased. These three terms are strongly related and frequently used synonymously reflecting the subjective self-assessment of patients’ own health [83]. Global QoL indicates, that this QoL questionnaire may be used for everyone, despite culture, sex or health status. QoL can be evaluated subjectively, meaning in a self-assessment, or objectively which involves an external evaluation for instance by a caregiver or physician. The subjective measure of QoL seeks to achieve an individual QoL score, where the patient may choose each individual area that is important for a good QoL.

We assessed QoL with three different questionnaires: Anamnestic comparative self-assessment (ACSA), the Schedule for the Evaluation of Quality of Life (SEIQoL) and the Short Form 12 (SF-12). ACSA and SEIQoL evaluate QoL and do not focus on medical aspects but rather patients' subjective well-being [44]. The third questionnaire, SF-12, evaluated HRQoL, which focuses on patients' physical impairment and patients' attitude and coping behaviors towards its health state [41]. The ACSA questionnaires might be influenced by certain life-events, positive or negative (e.g. diagnosis, hospitalization, death of a loved one), as it asks about general well-being within the last two weeks compared to the happiest and most sad time in life. To avoid this bias, we also used the SEIQoL questionnaire, which is usually not as heavily influenced by recent events.

In the healthy general population, QoL was measured in a pilot study with 7,220 participants as “well” or “very well” [241]. In the three diseases, QoL has been assessed before in other studies, but for the FTD group, studies on this topic are less common [41, 89, 107, 112, 207]. Most studies found, that in ALS, QoL was surprisingly good, even in progressed stages, which is the phenomenon, previously described (chapter 1.7, subjective burden), the “well-being paradox” [83]. Many studies with IPS patients, describe that all three, affective, cognitive and physical impairments decrease QoL [112, 141, 218, 250]. FTD patients' QoL decreases, as
their daily functioning is impaired due to behavioural symptoms [50], however, due to lack of disease insight, this is often not recognized by themselves [95, 183], especially in case of severe cognitive deficits [200].

**Coping mechanisms**

Independent of the burden, a patient might have a good QoL as it depends on patients’ individuals’ coping and adaptation abilities. Satisfaction with life and QoL depend on each individual attitude and might yield different results. Depressive symptoms shortly after diagnosis are a sign of impaired adaptation. A depressed patient might feel a high burden, due to lack of pleasure and *apathy*. Someone who focuses on physical decline and the limitations such as inability to walk, might have a lower QoL than one who changes its determinants for a good QoL. Flexible adaptation to life situations might help retain a satisfactory QoL and demonstrates good psychosocial adaptation.

The subjective burden can be perceived less with good coping strategies and adaptation mechanisms. In case of stressful, lifechanging situations, coping mechanisms help to overcome the feeling of losing control [25]. Nowadays, in Germany it has been recommended that fatal diagnoses are openly and honestly communicated by the treating doctor, in order to avoid wrong expectations and to clear up misunderstandings from the patient [205]. With a good education about the disease, the patient can adapt to the situation yielding improved QoL and decreased mortality [163]. In ALS patients, coping strategies have been studied extensively. These coping strategies may change over time and include information seeking, followed by understanding gained knowledge, expressing emotions and being supported by friends and family [82, 94, 151, 163], which might eventually result in acceptance.

To our knowledge, this is the first study which compares these three neurodegenerative diseases and determines disease burden and its possible distortion in case of lacking disease insight.

Previous studies assessed disease burden mostly in caregivers of ALS, FTD and IPS [16, 40, 97, 147], but rarely in the patients themselves.
An example for a study, which addressed disease burden in patients themselves, measured burden in children with rheumatic disease and found that several socioeconomic factors such as finances, relationships with friends and family, participation in extracurricular activities and psychological factors like depression, insomnia and fatigue affected burden [184].

There is a lack of studies assessing burden from patient’s perspective and, at the time of our study, there was no validated test available, which measures subjective burden in the patient. Caga et al. addressed this point that there is lack of research focusing on patients with behavioural or cognitive impairments and their influence on patients’ well-being [32]. We hereby address this gap.
1.9 Disease insight

The subjective burden largely depends on disease insight, as a patient with low insight might not recognize impairments as such or misjudge their extent. This results in a disease burden which is disproportionate to the actual impairments present.

The lack of disease insight includes decreased self-awareness about ones’ condition and under- or overestimation of abilities. This might have a serious impact, as overestimation of abilities may occur in daily functioning which can lead to misbehaviour at work or relationships, provoking severe consequences [209], but also delayed diagnosis due to late referral to a doctor and incomppliance with treatment [113]. Lack of disease insight might have positive or negative effects on QoL. Partial or complete lack of insight most commonly occurs in patients with cognitive impairments, due to their inability to remember situations where they failed [209]. In IPS patients and in ALS patients with dementia, lack of disease insight was found [101, 113, 253], as well as in those with at least mild cognitive impairment (Mini Mental Status Test >20) [90, 186]. Hvidsten et al. report that self-awareness in FTD patients is good, especially when compared to Alzheimer patients [89].

Contrary, Maier et al. report about a possible lack thereof in nondemented, nondepressed IPS patients [143] in line with the majority of literature which agrees on a lack of disease insight [95, 209]. Lack of disease insight is one of the five core features of the Neary diagnostic criteria for bvFTD [172], however, curiously, does not appear in the Rascovksy criteria. There are limited reports about disease insight in nondemented ALS patients. However, in literature, the question has been brought up of whether their low subjective burden is due to good coping mechanisms or low disease awareness [152]. We suspected, that disease awareness is low in both FTD and ALS, potentially leading to underestimation of own impairments, ultimately resulting in lower disease burden in comparison to IPS.
1.10 Aim and Hypothesis

Aim
This study aims to assess and compare the influence of cognitive and behavioural impairments on the subjective burden of ALS, IPS and FTD patients. The study investigates this by evaluating QoL and affective state as measures of psychosocial adaptation to cognitive and behavioural impairments, while taking the patients’ disease insight into account. The influence of cognitive and behavioural changes and disease insight on the subjective burden of patients with ALS, IPS and FTD has never been compared before in one collective study.

Hypothesis 1
Cognitive and behavioural deficits in ALS and IPS patients are similarly low, compared to FTD. Regardless, subjective disease burden is relatively low in FTD and ALS patients, while that of IPS patients is comparatively greater. We suspect a comparatively higher number of cognitive and behavioural deficits in the FTD group, but, as we simultaneously assume a lower disease insight, we expect a lower subjective disease burden. We anticipate, that IPS patients have a greater disease burden compared to ALS and FTD patients, due to their long disease duration with slowly increasing physical, cognitive and behavioural impairments.

Hypothesis 2
FTD and ALS patients have a lower disease insight, thus decreasing subjective burden in comparison to IPS.
Low disease insight is a phenomenon, commonly described in literature. Additionally, however, we assume that ALS patients may have an impaired disease awareness, since, in literature, they are often described to have a high QoL, despite their severe limitations and terminal diagnosis. If a patient group lacks disease insight, it is plausible to assume, that they might underestimate their disease burden. We hypothesize, that this is the reason, why IPS patients will have the highest subjective burden of our three patient groups.
2 Material and Methods

2.1 Study Design

The clinical, prospective cross-sectional study compared three neurodegenerative diseases: ALS, IPS and FTD patients. Patients were examined once at home or in the hospital with tests to assess cognition, affect and QoL. Behaviour was evaluated by a primary caregiver who could be a close family member, a close friend or someone who is in close contact with the patient.

2.2 Patients

In total, 137 patients were recruited: 50 ALS, 51 IPS and 36 FTD patients from the Department of Neurology, University Ulm, Germany. Due to exclusion criteria, the cohort included 97 patients: 40 ALS patients from the in- and outpatient clinic of University hospital in Ulm diagnosed with definite ALS by neurologists according to El Escorial revised criteria [24, 127]. The control group included two patient groups: 40 IPS patients diagnosed by neurologists and 17 FTD patients with either probable or definite bvFTD (n=13) according to International Consensus Rascovsky criteria [201] or ALS – FTD (n=4) patients.

Patients were recruited from 02. September until 26. November 2019. The patients either presented for the first time, second opinion or follow-ups; others were contacted because they were in- or outpatients in the past or part of the Swabian ALS-registry [168]. In case patients were not in- or outpatients of the clinic, but have been patients in the past, we contacted them by phone call and agreed on a date for a home visit. Usually, FTD patients do not come for follow-ups frequently and not many were hospitalized in that period. All patients were first educated about the study and data protection declaration. Patients or their authorized representatives signed a written consent form. All patients completed all tests, except one IPS patient (n=39), who did not complete ADI12.
Inclusion and exclusion criteria

Inclusion criteria were good German knowledge and the ability to either write or speak, whereas severe CNS comorbidity (other than ALS, IPS or FTD) was an exclusion criterion.

In the ALS group, ten patients were excluded for the following reasons: 1) Denied participation (n=1), 2) diagnosis was changed during hospitalization (n=7) and 3) insufficient German knowledge (n=2). From the IPS group eleven patients were excluded due to: 1) Insufficient German knowledge (n=2), 2) severe Parkinson dementia and unresponsiveness (n=2), 3) acute psychotic decompensation (n=1), 4) denial of participation (n=2), 5) severe stroke (n=2) 6) changed diagnosis from IPS to PSP (n=1). Nineteen patients from the FTD group were excluded for the following reasons: 1) Death (n=1), 2) denial of participation (n=2), 3) diagnosis was changed during hospitalization (n=4), 4) severe CNS diseases like major hemispheric stroke (n=4) or 5) severe progression of disease so that examination was not possible (n=6). From these six patients with progressed disease, four were unable to speak and unable to concentrate on the given tasks, one could not speak or understand German anymore and one was too aggressive, wherefore caregivers denied participation.

Questionnaires for the primary caregivers

Two questionnaires, ECASbq (ECAS behavioural questionnaire) and cTBS (primary caregivers estimated total burden score) were assessed by the primary caregivers. Primary caregivers could be close friends, a close family member or another close person who visits the patient regularly. Primary caregivers were reminded to complete the questionnaires by phone or mail. In the ALS group, nine declined participation in both questionnaires. Therefore, 31 primary caregivers participated (77.5%) in the ALS group. In the IPS group, nine ECAS behavioural questionnaires and ten cTBS questionnaires were not returned. Therefore, in the IPS group, 31 primary caregivers participated (77.5%), and 30 participated in the burden questionnaire (75%). In the FTD group, one patient did not have anyone who could complete these questionnaires. Therefore, in the FTD group, 16 primary caregivers participated (94.11%). To screen for any significant differences between the groups that returned the cTBS questionnaires and those that were declined, we compared
the main variables in the entire test group including all completed questionnaires to their whole group (ALS/FTD or IPS).

2.3 Setting

Patients were examined at home or in the hospital. The setting was under controlled conditions. Most patients were interviewed in a special, closed examination room or alone in their hospital room seated at a table or in their bed. In some cases, a second interviewer attended the examination or a primary caregiver who helped with anamnesis report. For the cognitive tests and ADI12, the primary caregiver, if possible, left the room for privacy. The setting might vary depending on patient’s health: In severe physical disability, the examination was performed while in bed in the hospital room. The interview duration was 40 - 90 minutes and was interrupted upon patient’s wish (e.g. due to exhaustion). The interview could be interrupted at any time, except for during the cognitive test (ECAS and MMST) examination. The duration depended mostly on the patients’ cognitive abilities and speed. The ECAS behavioural questionnaire (ECASbq) and the burden questionnaire (cTBS) were both completed by a primary caregiver, close relative or close friend. If caregivers could be met in person, the questionnaires were answered in a personal, structured interview under controlled conditions; if the primary caregiver was not available, the questionnaires were completed at home and sent back to us. Primary caregivers were reminded after several weeks with a phone call or a postal letter, in case they did not return the questionnaires.

2.4 Demographic Data

First, the patients were assessed for demographic data about age, gender, education, occupation, marital status, family history of ALS, IPS, FTD and psychiatric diseases. Subsequently, a detailed anamnesis was made, including symptoms, onset, most affected body part, medication, time of onset and date of diagnosis and lastly whether they had received NIV or PEG and since when. In the case of language or speech difficulties, primary caregivers were asked to complete anamnestic information or anamnesis was completed in written form.
Education level was assessed by the International Standard Classification of Education (ISCED 2011) [217], which organizes qualifications and educations in an international framework according to the highest degree completed, with the highest number 844 being a doctorate and the lowest being ten which is equivalent to the children’s group. This classification helps to differentiate between patients with higher or lower education. Levels of education are organized according to following scheme: >200 lower secondary education, > 300 upper secondary education, > 400 post-secondary education, > 500 short cycle tertiary education, > 600 bachelor or equivalent, > 700 master or equivalent, > 800 doctorate or equivalent. Further, we assessed whether the patients have or had a history of major depressive disorder (MDD) diagnosis, following Diagnostic and Statistical Manual of Mental Diseases IV (DSM IV) criteria.

2.5 Instruments

2.5.1 Physical impairment

The severity of physical impairment was assessed by a trained physician, with amyotrophic lateral sclerosis – functional rating scale (ALS-FRS) test being specific for ALS and FTD patients and unified Parkinson’s disease rating scale (UPDRS) and Hoehn and Yahr (H&Y) for IPS patients.

Amyotrophic lateral sclerosis - functional rating scale
The revised ALS functional rating scale, developed by Cedarbaum et al. for ALS and ALS-FTD patients [36], assesses physical functioning in twelve activities of daily living. Spinal symptoms such as walking stairs, getting dressed, hygiene and using cutlery are assessed. Furthermore, bulbar symptoms such as speaking, swallowing problems, hypersalivation, dyspnea, orthopnea and need for NIV are asked. Each item is rated from 4 (no impairment) to 0 (unable to attempt); the sum of all earned points results in a total score ranging from 0 to 48. Lower scores mean greater functional impairment, so a score of 0 corresponds to locked-in state and 48 points to no impairments at all. Total scores reflect the severity of physical impairment. A score above 15 points is considered mild to moderate physical impairment and a
score below 15 points corresponds to a severe physical impairment [139]. ALS-FRS was measured for all three patient groups.

**Progression rate**
Kollewe et al. introduced a factor to calculate progression rate. Progression rate was calculated by the quotient of the total sum of ALS-FRS (48 points) subtracted by ALS-FRS score of the patient; both divided by disease duration in months (months since symptom onset). The PR helps to show what effect a faster or slower disease progression might have on other factors [106].

**Unified Parkinson's Disease Rating Scale**
The Movement Disorder Society – Unified Parkinson's Disease Rating scale (MDS-UPDRS) is the third motor part of the UPDRS [71]. It is used to evaluate the extent of motor symptoms and complications of physical functioning in different body parts. It was evaluated by a neurologist or a doctor to assess speech, facial expression, postural stability, gait, brady-/hypokinesia, tremor, rigidity, agility, dysdiadochokinesia in upper and lower extremities and axial symptoms. It includes thirteen questions with points from zero to four (zero is normal, one slight symptom, two mild to moderate, three severe, four marked symptoms or inability to fulfil the task). The total score is the sum of all individual points earned in parts of the test, with the maximum score being 52 points, indicating the most severe form of physical impairment. For classification into mild, moderate and severe physical impairment, we used the cut-off scores by Martinez et al.: “Mild/moderate” 32/33 points and 58/59 for “Moderate/severe” [146].

**Hoehn and Yahr Scale**
The modified Hoehn and Yahr Scale (H&Y) [85] is a fast and straightforward assessment done by a neurologist or doctor to describe the severity of symptoms in Parkinson’s disease. The scale has five stages from 0 to 5 and two intermediate stages (1.5 and 2.5) which differentiate by uni- or bilateral, axial symptoms, severity and postural instability. In stage 0, there are no signs of disease and stage 1 has only unilateral, mild signs. Stage 5 is the most severe stage, describing a bedridden or wheelchair-bound patient. H&Y is classified into mild severity in stage 1-2,
moderate in stage 3 and severe in stage 4-5 according to Martinez-Martin et al. [146].

2.5.2 Cognitive impairments

Mini-Mental state examination
The Mini-Mental state examination (MMST) is a quick bedside examination with eleven questions to screen for general cognitive impairment and to define dementia. The MMST tests orientation to time, place, person; repeating, attention and calculation, recall information, language, complex commands, copying a geographical figure and writing a sentence. In case a patient had (fine) motor impairments and was not able to draw or write, the score was adjusted accordingly to receive comparable results. Total maximum points are 30, which indicate normal cognitive function. The MMST score can be used to classify the severity of cognitive impairment: Normal cognitive function 27-30 points, mild cognitive impairment 21-26 points, moderate cognitive impairment 11-20 points and severe cognitive impairment 0-10 points [58].

Edinburgh Cognitive and Behavioral ALS Screen
The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) was developed by Sharon Abrahams and Thomas Bak to test for cognitive and behavioural impairments in patients with prominent motor symptoms such as ALS patients [1]. The test has been validated and showed good sensitivity and specificity to detect cognitive impairment in ALS patients [1, 133]. Even in patients with moderate to severe physical disability, cognitive and behavioural changes can be assessed with this scale as it is validated for verbal and written performance. The ECAS screens for ALS-specific (executive, verbal fluency, language) and ALS non-specific functions (memory, visuospatial functions tests) in 16 tasks [133]. The ECAS has shown to be also sensitive in detecting different cognitive impairments in IPS patients [57] and also detects verbal fluency deficits in contrast to MMST test. The German version is available since 2014 [133].

In the language part, the patient was asked to name what he/she sees on the picture, to point out the picture that was described in the sentence that was read aloud by the examiner and to spell or write down twelve words. The memory part
tests the immediate recall memory, where the examiner reads a text in the beginning of the test aloud, and the patient should name everything, he/she remembers. The delayed memory is tested by asking the patient to remember details from that story at the end of the test, after completing twelve tasks.

To test delayed recognition, eight sentences will be read aloud by the examiner which refer to the story in the beginning of the test and the patient should recognize, which statements are false or true. Verbal fluency was tested by asking the patient to name as many words as possible in a limited time with a given initial letter. The next task requires a higher cognitive demand, as an initial letter is given by the examiner and the words should have four letters. Executive function is tested with four tasks. The examiner reads aloud twelve numerical sequences, which gradually increase in length and the patient is asked to repeat them in reversed sequence. In another task, the patient should connect letters from the alphabet with the number of their position in the alphabet. Further, twelve sentences will be read aloud, and a missing word should be added that does not fit to the meaning of the sentence. Social cognition will be tested by assessing whether the patient acts egocentrically when seeing a smiling face that looks at different objects. The visuospatial functions are assessed by counting points, cubes and localizing numbers.

All tasks are summed up to give a total score. Cut-off scores were calculated according to the age and years of education [123]. The cut-offs are derived from four different groups. 1) Under 60 years and with either education longer or 2) shorter than 12 years and 3) older than 60 years with education years more or 4) less than 12 years.

Patients with severe dysarthria or mutism completed the tasks in written form (n=1). Two tasks for verbal fluency assess time for completion. Accordingly, the given points are adjusted depending on oral or written completion of the task. We assessed the total ECAS score and the number of specific cognitive ECAS parts (memory, visuospatial function, language, verbal fluency, executive functions). The ECAS has three versions: A, B and C [45]. The B and C versions were consecutively used if a previous examination with ECAS A was done more than 6 months ago in ALS patients. In FTD patients the ECAS B or C test was performed already after less than 3 months because of presumed rapid decline of cognitive functions in these patients.
The total sums of ECAS and MMST score were calculated and compared in percentages, as some tasks were excluded due to severe physical disabilities preventing completion of specific tasks. Nine from the ALS group could not fulfil tasks in MMST (two or five tasks were excluded, due to fine-motor skill impairments in writing and drawing). In the ECAS test, three patients could not fulfil all tasks due to language difficulties. One patient did not know the alphabet (spelling task was excluded) and two patients had problems with the language and fluency tasks.

2.5.3 Behavioural and language deficits and psychotic symptoms

Edinburgh Cognitive and Behavioral scale - Behavioral questionnaire
Behavioral impairments and psychotic symptoms were assessed through a primary caregiver. The behavioral questionnaire assesses five behavioral symptoms plus language deficits and psychotic symptoms. Answer possibilities are “yes”, “no” and “I do not know” with the possibility to describe symptoms further and date the onset of these symptoms. The first behavioral symptom disinhibition is subdivided in three subcategories: Socially inappropriate behavior, loss of social manners, impulsive or risky behavior. The second symptom apathy is shown by loss of interest and motivation. The third symptom early loss of empathy includes loss of reaction to emotions of other persons or decreased interest in social contacts or closeness. The fourth symptom preservative, stereotypical or ritualistic behaviour” includes repetitive movements, collecting things or other stereotypies. The fifth symptom askses about changed eating behaviours such as craving for sweets or other hyperoraity symptoms like putting inedible things into one’s mouth.

In addition, primary caregivers estimated language deficits in patients, which may present with word finding difficulties, impaired repetition of words or wandering of speech.

Additionally, the primary caregivers evaluated psychotic symptoms with three questions. The first question asks, if the patient has bizarre ideas or behaviours, the second question assesses if the patient feels the presence of non-existent things or persons and lastly, whether the patients shows increased mistrust or paranoia. All symptoms are assessed as categorical variables of either being present or absent and a total sum of behavioural impairments are calculated.
2.5.4 Depressive symptoms

**Amyotrophic lateral sclerosis depression inventory 12**
The ALS depression inventory is a screening tool to identify patients with increased risk for depressive disorders specifically developed for ALS patients by Kübler et al. [81, 110]. It is based on the Beck's depression inventory with reduced items to confound with the physical symptoms of ALS. For instance, questions about insomnia were excluded as these can be part of ALS symptoms [81]. It includes 12 statements with four possibilities ranging from "totally agree", "agree", "not agree", "not agree at all" within the last two weeks including the day of the interview. Each question gives points from 1 to 4 with a maximum score of 48 points. According to Hammer et al., more than 28 points indicate a clinically relevant depression, 22-28 points a mild depression and below 22 points no depression [81].

2.5.5 Quality of Life

**Health-related quality of life: Short form health status survey 12**
The Short Form Health status survey 12 (SF 12) [61] reports patients’ health-related quality of life in 12 questions. It is a shorter version of Short Form Health status survey 36 (SF 36) reflecting the mean values of the eight subscales of the SF-36. It tests whether patients are able to do their usual work and daily activities. The survey is divided into two scores. The physical component summary (SF 12 PCS) tests health perception, physical functioning, physical role functioning and pain. The mental component summary (SF 12 MCS) investigates emotional role functioning, mental well-being, negative affect and social functioning. Some questions have dichotomous answers (yes/no), some use a Likert scale (excellent, very good, good, less good). By using regression coefficients, the values from the physical and mental scores can be standardized, resulting in the same mean values of SF 36. The standardized values allow comparing the data with the same age group, same gender or other groups such as patients with chronic diseases. Results were compared to the sum-scale from the German population with chronic diseases (n=2805): Mean PCS 39.5 ± 10.43 and mean MCS of 47.5 ± 9.82 [165].
Individual quality of life: Schedule for individual quality of life

The schedule for the evaluation of individual Quality of Life (direct weighting, SEIQoL-DW) [182] focuses on individual areas of life from the patients’ perspective and investigates which of those are most important to patients’ overall QoL. QoL is determined in three steps: In part A the patient is asked to name five areas (cues), which they consider the most important determinants for a good QoL. Those patients who had difficulties received some suggestive examples. The named cues were classified according to Neudert et al. into the following: Family, social contacts (neighbors, friends), sport, hobby, mobility (driving a car or motorcycle), profession, autonomy (being independent), home (having good food and drinks, having a home), travelling and holidays, nature (going for a walk, being outside, hiking), spare time (watch TV, shopping), health, interests (music, chopping wood), mental agility (sudoku, quizzes, reading), garden (gardening, being in the garden), pets (having a dog, cat), volunteering (being part of a volunteer project, club, society), well-being of the family, education (going to a good school, education from parental home) [176]. In part B, each area is weighted in percentages according to their importance in influencing QoL. The total sum for all cues should be 100%, and each cue should be included with a chosen percentage. In part C, the individual satisfaction of each part of life at this current time on a vertical visual analogue scale is given ranging from "as bad as possible" to "as good as possible". As bad as possible is rated 0%, as good as possible 100%. Each cue rating and weight is multiplied, then all products are summed up for the overall QoL Score [96].

Subjective quality of life: Anamnestic comparative self-assessment

Global subjective QoL is measured with amnestic comparative self-assessment (ACSA) after J. Bernheim [12]. In part A of the test, the patient is instructed to rate his/her happiest time in life and his/her saddest time in life. In part B, the current life quality is evaluated by asking the patient to compare the last two weeks on a scale to the happiest (+5) and saddest (-5) time in life. The scale has a center at 0 being neutral and offers eleven options to choose from. Each patient can use this scale by considering their own culture and values, therefore making this test reliable and valid to assess individual QoL [11].
2.5.6 Burden

Subjective and caregiver-estimated burden questionnaire

The burden questionnaire was established by our team to assess the subjective burden on private and occupational life. The test is not validated, but its usability was tested on n=5 people and adjustments were made accordingly to improve usability. The behavioural part of the test is inspired by ECASbq [1]. The questionnaire has one version for the patient, a self-rated burden questionnaire, the subjective total burden score (sTBS), and a version for a primary caregiver, a caregiver-rated burden score (cTBS), to estimate patients’ burden from each perspective. The test is divided into three parts. In the first part, the severity of burden due to disease on private (question one) and occupational life (question two) is evaluated. The questions are rated on a Likert scale from “totally not agree”, “do not agree”, “do agree”, “totally agree”. In part two, the cognitive impairments are assessed: Memory, orientation, concentration, word-finding and fluency. The last two questions of part two assess whether these changes pose a burden on private and work life. The third part investigates behavioural changes: Impulsivity, apathy, loss of empathy, ritualistic behaviour and hyperorality. The last two questions of part three assess whether these changes pose a burden on private and work life. Each question was rated with one to three points, with three points indicating severe burden (totally agree). For each private and occupational burden, a sum score between zero (low burden) and nine (high burden) points can be reached.

For cognitive and behavioural burden, a score between 0 and 15 points can be reached. Patients who had to go into an early pension because of their disease, automatically receive three points for all three of the occupational questions, equating to a total of nine points. By summing the parts occupational, private, cognitive and behavioural subjective burden, we calculated the total subjective burden score (sTBS). The same parts were also summed for the caregiver-rated burden questionnaire to yield the caregiver-estimated burden (cTBS).
Severity of disease burden

We calculated the mean of all groups (the whole cohort) and the mean of each group (ALS, IPS, FTD). A z-score was calculated to represent the relationship between ALS (n=40), FTD (n=17) and IPS (n=40) groups’ subjective burden (sTBS) and the mean of the whole cohorts’ TBS (n=97). The same relationship was also calculated for the relationship between ALS (n=31), FTD (n=16) and IPS (n=30) caregiver-estimated burden (cTBS) to the mean of the whole cohorts’ cTBS (n=77). Therefore, a z-Score of 1 SD above the mean of the whole cohort was set as a mild burden, 2 SD above as moderate burden and 3 SD above as severe burden.

Disease insight

The primary caregiver received the same burden questionnaire to estimate the burden of the patient. A discrepancy score (DS-TBS) was generated to obtain an index of patients’ insight. The caregiver-estimated burden (cTBS) was subtracted from the self-rated burden (sTBS). In case of a significant positive result, the patient overestimated him-/herself, in case of a significant negative result the patient underestimated him-/herself. The higher the differences between both values, the more the estimations differed [227].

2.6 Databases

Pub Med, Medline, Embase, Cochrane Library and Ovid data were used for literature research and all sources were collected and managed with RefWorks citation manager. Microsoft Word (Office 365) was used to write the text.
2.7 Statistics

First, data was pseudonymized and included in an excel table. All data was managed in SPSS (version 25.0; IBM Corporation) for Windows and Mac. Absolute and relative frequencies, sums, means, standard deviations (±), medians and ranges were given for demographic data, total scores and subtests. The threshold for significance was set at p < .05 and highly significant results at the level p < .01. Tests were two-tailed. Cases were split into the three disease groups except if the significance of difference between groups was tested.

For the significance of tests, we used for categorical variables the chi-square test (goodness of fit test). We tested for normality gender, age, disease type, family history and genetic mutation, marital status, place of examination, NIV, PEG, medications, ECAS cognitive and behavioural symptoms. All interval scaled data were tested with one-sample Kolmogorov Smirnov test for normality (Lilliefors Significance Correction) first with the whole group (n=97) and also for each separate disease group (n=40, n=40, n=17). Parametric tests were used for all normally distributed data and nonparametric tests for all abnormally distributed data. We determined significance within confidence interval of 95% for physical impairment and disease severity (ALS-FRS, UPDRS, H&Y, PR, NIV, PEG), medication, cognition (ECAS, MMST, cognitive parts ECAS), affective state (ADF 12, MDD), TBS (all parts of TBS and DS - TBS), QoL (SF12, SEIQoL, ACSA). The binominal test was used for dichotomous variable marital status for the significance of variables.

All results were compared between groups and the significance of differences was tested with one-way analysis of variance (F) and post-hoc-test Tamhane in normally distributed variables or group size >25. Differences were assessed in the three groups in age, age at onset of disease, disease duration, cognitive impairments (ECAS total score in %, MMST total score in %); affective state (ADF12); QoL (SF12 MCS, SEIQoL). Post-hoc-test Tamhane was conducted to detect which groups significantly differed. Levene test was done before one-way ANOVA for homogeneity of variances; all variables given above were homogenous (not significant result).
ANOVA could also be used for MMST and ECAS as these were normally distributed in the group (FTD) or the groups had >25 probands (ALS, IPS).

The nonparametric test Kruskal Wallis (H Test) and post-hoc-test Bonferroni were used for ordinal scaled dependent variables to determine significant difference between groups. Following variables were tested: Education (ISCED), ACSA, SF12 PCS, diagnosis delay, PR, the sum of cognitive deficits, cTBS, sTBS, DS-TBS. Post-hoc-test Bonferroni was done for SF12 PCS, PR and sum of cognitive deficits, cTBS, DS-TBS.

For interval scaled, normally distributed variables we used paired samples T – Test to test significance of difference between the mean of two dependent variables: cTBS and sTBS as well as SF12 MCS and SF12 PCS within each group.

The following interval scaled, normally distributed variables were compared with T-Test for independent samples: Disease insight difference in depressed and non-depressed groups.

Significance of association between two categorical variables was determined with Pearson chi-square test (crosstabs). The effect strength was given with Cramers V for significance of association of the following variables: Cognitive deficits, behavioural deficits, MMST below 24 points, higher education (ISCED >400) and lower education (ISCED <400), depressive symptoms (ADF12 >28) severe physical impairment (ALS FRS >30) and sTBS, each behavioural symptom and ALS-FRS, each cognitive deficit and each behavioural deficit with diagnosis, NIV and PEG with sTBS, cTBS, QoL (SEIQol, ACSA, SF12) and depressive symptoms (ADI12), as well as L-Dopa and sTBS and cTBS. Also, we determined association of the behavioural symptom apathy and age, MMST, ADI12 and UPDRS. Fisher’s exact test was used if the expected count of cells was less than five.

Linear bivariate correlation between interval scaled variables was determined with the Bravais Pearson test between two normally distributed variables. To determine the impact of the correlation, the correlation coefficient after Pearson \( r \) was given. Strength of effect was interpreted after Cohen (1992) where a weak effect was at \( r=.1 \), a moderate effect at \( r=.3 \) and a strong effect at \( r=.5 \). Correlation of depressive
symptoms (ADF12) and sTBS/ cTBS was determined with Bravais Pearson correlation.

The nonparametric test Spearman’s rho was used for correlation between ordinal scaled and not normally distributed variables. We determined correlations of sTBS with UPDRS; H&Y, ALS-FRS, Disease duration, ADI12, QoL (ACSA; SF12, SEIQoL), the sum of cognitive deficits and the sum of behavioural deficits. Furthermore, correlations between ADI12 and disease duration, UPDRS, H&Y, ALS-FRS, ECAS, ACSA, SF12, SEIQoL and cTBS was assessed. Also, Physical impairment (UPDRS; H&Y, ALS-FRS) and QoL (SF12, SEIQoL; ACSA), disease duration; disease duration and SF12; SEIQol, and cTBS. The correlation between the sum of behavioural deficits and cTBS, sTBS and ECAS, as well as cognition (ECAS, MMST) and ADF12, SF12, sTBS, physical impairment (ALS-FRS, UPDRS, Hoehn and Yahr) and disease duration.

Linear regression determined significance between UPDRS, H&Y, ALS-FRS and sTBS, SF12.

Multiple regression analysis determined influencer on sTBS by finding variances and weight (in %) of its influence in each group. Adjusted R2 was given if more than one independent variable was used, for one independent variable we used R. Significance level was set at p < .05. Unstandardized B regression coefficient was given. We tested the influence of marital status, affective state (ADF12), cognition (total score of ECAS and MMST, sum of cognitive impairments), QoL (SF12, ACSA, SEIQoL), cues from SEIQoL (Family and Social SQL), behavioural impairment (sum of ECASbq), behavioural symptoms (apathy, impulsivity, loss of empathy), disease duration and physical impairment (ALS FRS, PR, UPDRS, H&Y), on subjective burden (sTBS).

A variable for ADI12 below/ equal or above 28 points was made to compare within groups differences in burden, cognitive and behavioural deficits (sums, MMST, ECAS), QoL (SF12, ACSA, SEIQoL), marital status, physical impairment (ALS-FRS, UPDRS, H&Y, mild disease, severe disease), higher education (>400 points) and lower education (<400 points).
Results of SF12 were also compared with a standard sample of German population with a chronic disease. The results are presented in tables, boxplots, bar charts, error bars and line charts.

2.8 Ethic Vote

The study was approved by the ethics committee of the University of Ulm (Number 381/19 additionally to 19/12, motor neuron disease net project; MND-Net) and has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.
3 Results

3.1 Normality of distribution

All categorical data were not normally distributed except: Medication riluzole ($X^2(1, n=97)= 2.98, p= .0084$), Apathy ($X^2(1, n=97)=.821, p=.365$) and Language difficulties (ECASbq) ($X^2(1, n=97) = .462, p=.497$) were normally distributed. Most interval scaled variables (nonparametric test, Kolmogorov Smirnov) for the whole group ($n=97$) were normally distributed, except Education (ISCED), H&Y, ALS-FRS, MMST sum %, ECAS sum %, SF12 MCS, ACSA, disease duration, PR, the sum of behavioural deficits and sum of cognitive deficits. As the normality of variables in each group differed, we also assessed normality for each group (ALS, FTD, IPS). Following interval scaled variables were not normally distributed in the FTD group: ISCED, ACSA, SF12 PCS, diagnosis delay, PR, the sum of cognitive deficits. In the ALS group, the following variables were not normally distributed: ISCED, ALS-FRS, MMST, ACSA, SEIQoL, diagnosis delay, disease duration, PR, the sum of cognitive and behavioural deficits. In IPS group ISCED, H&Y, ALS-FRS, MMST%, ACSA, diagnosis delay, PR, the sum of behavioural deficits, the sum of cognitive deficits variables were not normally distributed.
3.2 Comparison for any group differences

For assessment of significant differences, we compared the disease group who returned the primary caregiver-estimated questionnaires ("entire ALS/IPS/FTD test group"), to their whole group ("whole group"). The "whole group" also included those patients, that declined the primary caregiver questionnaires (ALS n=40, IPS n=40, FTD n=17). In descriptive statistics, we found that in the "entire ALS test group" (n=31) more were married or lived with a partner (93.5%) than in the "whole ALS group" (87.5%, n=40); however, the difference of marital status was not significant ($X^2(1)=4.61$, p=.065). In the IPS group we compared the entire test group (n=30) to the whole IPS group (n=40). In the entire test group, median disease duration was 12 months shorter (87 months) than in the whole IPS group (99 months); however, disease duration did not significantly differ (Fishers Exact Test (26)=22.74, p=.858). In the entire IPS test group significantly more were married (93.3%) than in the whole IPS group (82.5% married) ($X^2(1)=9.76$, p=.006).

In the FTD group, only one test was declined, and we did not detect significant differences between the entire group (n=16) and the whole FTD group (n=17).

3.3 Clinical presentation

Figure 1 shows counts of clinical presentation of the disease. The ALS group included 75% (n=30) with spinal onset, 22.5% (n=9) with bulbar onset and 2.5% with flail arm syndrome (n=1). In IPS group were 55% (n=22) hypokinetic-rigid type, 20% (n=8) tremor dominant type and 25% (n=10) equivalent type. In the FTD group 76.47% (n=13) were bvFTD and 23.53% (n=4) ALS-FTD (spinal onset type). One patient from the bvFTD group had a mixed type of bvFTD and PNFA, another patient is suspected to have FTD Phenocopy variant. The disease types were not normally distributed in IPS and ALS groups: IPS group ($X^2 (2, n=40)=8.6$, p=.014), in ALS group ($X^2 (2, n=40)=33.65$, p<.001), but in FTD group ($X^2 (1, n=17)=4.77$, p=.29).
Figure 1: Clinical presentation in the three disease groups. Amyotrophic lateral sclerosis (ALS, n=40): Spinal onset (light blue, n=30), Bulbar onset (dark blue, n=9), Flail arm syndrome (red, n=1); frontotemporal dementia (FTD, n=17): ALS-FTD (light grey, n=4), behavioral variant FTD (dark grey, n=13); idiopathic Parkinson’s syndrome (IPS, n=40): Hypokinetic-rigid type (light green, n=22), Tremor-dominant type (yellow, n=8), Equivalent type (brown, n=10), University Ulm, 2019-2020.

3.4 Sociodemographic data

Descriptive statistics of ages in the three disease groups are shown in Table 1. The median age was 66.5 years in ALS and IPS groups and 63 years in the FTD group. Ages are comparable, as they did not significantly differ between groups (F(2;94) = .497), p=.61).
Table 1: Age of patients in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD) groups given in minimum (min.), maximum (max.), median, mean and standard deviation (SD), University Ulm, 2019-2020. Significance of difference with one-way analysis of variance testing was not significant (n.s.), indicating comparable ages.

<table>
<thead>
<tr>
<th></th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td>One-way ANOVA</td>
</tr>
<tr>
<td>Min - Max</td>
<td>43 - 87</td>
<td>31 - 80</td>
<td>39 - 81</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66.5</td>
<td>66.5</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Mean, SD</td>
<td>65.05 ± 1.67</td>
<td>66.05 ± 1.63</td>
<td>63 ± 2.75</td>
<td></td>
</tr>
</tbody>
</table>

The groups’ gender distribution is depicted in the bar chart in figure 2. ALS group included 30% (n=12) female and 70% (n=28) male patients, the IPS group 60% male (n=24) and 40% female (N=16) and all FTD patients (100%, n=17) were male. The groups’ gender distribution significantly differed ($X^2$(7,n=97)=52.69, $p<.001$).

Figure 2: Gender distribution in percentage among amyotrophic lateral sclerosis, idiopathic Parkinson’s syndrome and frontotemporal dementia, University Ulm, 2019-2020. Female are shown in blue colour, male in grey.

Table 2 shows frequencies of patients living without a partner. In FTD group 23.53%, in IPS group 17.5% and in ALS 12.5% lived alone. All groups significantly more often lived with a partner than without (Binominal test, $p<.001$, ALS: n=40, IPS: n=40, FTD: n=17).
Marital status distribution did significantly differ between groups ($X^2 (1; n=97) = 51.97, p < .001$).

Education (ISCED 2011) in both ALS and FTD groups’ median indicated a level of education in accordance with “vocational upper secondary education” and IPS group a level of education complying with “post-secondary non-tertiary education”. In all groups, the education ranged from lower (244 in ALS and PD group) or upper secondary education (344 in FTD group) to master or diploma studies (747 or 748). Education did not significantly differ between groups ($H(2)=3.766, p=.152$). Additionally, there was no significant association between higher (ISCED >400) or lower education (ISCED <400) and subjective burden (sTBS).

Table 2. Marital status and education in amyotrophic lateral sclerosis, idiopathic Parkinson’s syndrome and frontotemporal dementia, University Ulm, 2019-2020. Marital status was assessed in those who lived without a partner (w/o) and education with minimum (min.), maximum (max.), median, mean and standard deviation (SD). Significance for the difference was tested: Significant in marital status (*), not significant in education (n.s).

<table>
<thead>
<tr>
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<th>ALS</th>
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<th>FTD</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
<td></td>
<td>$X^2$</td>
</tr>
<tr>
<td>w/o Partner</td>
<td>5/40 (12.5%)</td>
<td>7/40 (17.5%)</td>
<td>4/17 (23.53%)</td>
<td>p &lt; .001*</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td>$H$ Test</td>
</tr>
<tr>
<td>Min - Max</td>
<td>244 - 747</td>
<td>244 - 748</td>
<td>344 - 748</td>
<td>p = .152 n.s.</td>
</tr>
<tr>
<td>Median</td>
<td>354</td>
<td>454</td>
<td>354</td>
<td></td>
</tr>
<tr>
<td>Mean, SD</td>
<td>413.5 ± 22.17</td>
<td>497.65 ± 27.74</td>
<td>475.24 ± 39.32</td>
<td></td>
</tr>
</tbody>
</table>

Places of examination for this study differed significantly between groups ($X^2 (2, n=97)= 31.32, p < .001^*$) (Figure 3). Majority of inpatients were from ALS group (85%, n=34) and only 15% (n=6) came for follow up to the outpatient clinic. From FTD group, 52.9% (n=9) were visited at home, 23.5% (n=4) were inpatients and 23.5% (n=4) were outpatients. From IPS group 55% (n=22) were outpatients, 42.5% (n=17) inpatients and 2.5% (n=1) visited at home.
3.5 Family history and genetics

Family history is listed in Table 3 and were significantly different between groups ($X^2 (1, n=97)=64.34, p<.001$). In IPS group 12.5% (n=5) had a positive family history of Parkinson’s disease, in FTD group 23.5% (n=4) had a positive family history of FTD or ALS/MND. Whereas in the ALS group no family history of ALS was known. Only for the FTD group, genetic testing results were available. From the FTD group, 17.6% (n=3) had an expanded hexanucleotide repeat on gene C9orf72 ($X^2 (1, n=97)=85.37, p<.001$).
Table 3. Family history and Mutation C9orf72 in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. Chi-Square Test with significant results (*) indicated a significant difference between groups.

<table>
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<th>ALS</th>
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<th>FTD</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Family History</td>
<td>0</td>
<td>5/40</td>
<td>4/17</td>
<td>p &lt; .001*</td>
</tr>
<tr>
<td>C9orf72</td>
<td>-</td>
<td>-</td>
<td>3/17</td>
<td>p &lt; .001*</td>
</tr>
</tbody>
</table>

### 3.6 Clinical characteristics

Age at onset of disease significantly differed between groups (F (2;94) = 3.68, p = .029) (Table 4). ALS group was significantly older at diagnosis than IPS group (M=6.550, p= .019, mean 62.5 ± 1.63 years). IPS group was youngest at onset with a mean of 55.95 ± 1.68 years, followed by FTD group (57.65 ± 3.24 years).

The diagnosis delay (time from the first manifestation of symptoms until diagnosis) median of FTD group was 24 months, being twice as long as in IPS and ALS group, even though we found no significant difference between groups (H(2)=4.18, p=.124). Disease duration (time since first manifestation of symptoms) significantly differed between groups F (2;94) =22.11, p < .001). IPS group had a disease duration of 121.33 ± 13.8 months, being significantly longer than FTD (M=58.619, p= .004, mean 62.71 ± 10.62 months) and ALS groups (M=92.475, P < .001, mean 28.85 ± 5.08 months).
Table 4. Descriptive statistics of age at onset of disease (in years), diagnosis delay (in months) and disease duration (in months) in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD) giving minimum (min.), maximum (max.), median, mean and standard deviation (SD), University Ulm, 2019-2020. In a one-way analysis of variance both results were significant (*), indicating a significant difference. In Kruskal Wallis test (H-Test), the result was not significant (n.s), indicating no significant difference between groups.

<table>
<thead>
<tr>
<th></th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Anova</td>
</tr>
<tr>
<td>Min - Max</td>
<td>43 - 84</td>
<td>28 - 75</td>
<td>31 - 80</td>
<td>p &lt; .029*</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td><strong>63</strong></td>
<td><strong>56.5</strong></td>
<td><strong>59.0</strong></td>
<td></td>
</tr>
<tr>
<td>Mean, SD</td>
<td>62.5 ± 1.63</td>
<td>55.95 ± 1.68</td>
<td>57.65 ± 3.24</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis delay (m.)</strong></td>
<td></td>
<td></td>
<td></td>
<td>H Test</td>
</tr>
<tr>
<td>Min - Max</td>
<td>1 - 64</td>
<td>0 - 168</td>
<td>5 - 119</td>
<td>p=.124 n.s.</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td><strong>11.5</strong></td>
<td><strong>12</strong></td>
<td><strong>24</strong></td>
<td></td>
</tr>
<tr>
<td>Mean, SD</td>
<td>16.4 ± 2.42</td>
<td>30.05 ± 6.82</td>
<td>34.47 ± 7.88</td>
<td></td>
</tr>
<tr>
<td><strong>Disease duration (m.)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Anova</td>
</tr>
<tr>
<td>Min - Max</td>
<td>6 - 189</td>
<td>9 - 321</td>
<td>5 - 146</td>
<td>p &lt; .001*</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td><strong>18.5</strong></td>
<td><strong>99</strong></td>
<td><strong>57</strong></td>
<td></td>
</tr>
<tr>
<td>Mean, SD</td>
<td>28.9 ± 5.08</td>
<td>121.3 +13.8</td>
<td>62.71 ± 10.62</td>
<td></td>
</tr>
</tbody>
</table>

**Disease severity**

Physical impairment measured by ALS-FRS in the ALS group was a median of 37 points (Range: 15 – 44) indicating mild to moderate physical disability. ALS-FTD group had a median of 40 points (Range: 28 – 48) indicating mild physical disability (Figure 4). An ALS-FRS score of fewer than 28 points had 20% (n=8) from ALS group, which indicates a significant limitation of strength and physical function. Physical impairment significantly differed (F (2,94) = 6.642), p = .002), as ALS group had a significant higher physical impairment than the ALS-FTD group (M=-5.063, p=.025). IPS was not compared to ALS and ALS-FTD with ALS-FRS (mean 39.45 ± 1.4) as we have more specific tests for this group (UPDRS and H&Y).
Mean progression rate (PR) of physical impairment significantly differed between ALS and FTD groups ($H(1) = 9.48$, $p = .002$) (Figure 5). We excluded the IPS group because PR includes ALS-FRS, which is not specific for the assessment of physical impairment IPS group (Figure 5). PR of ALS group (Median .714; Range .074 – 2.7) was significantly faster than in FTD group (Median .133; Range 0 - 2.4) ($z = 3.225$, $p = .004$).
Figure 5. Progression rate in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) to show the speed of physical impairment over time, University Ulm, 2019-2020.

Physical impairment in IPS was mild to moderate with a mean UPDRS of 25.95 ± 1.84 points (Median: 26 points, Range: 4 - 47) and H&Y mean stage was 2.59 ± .17 (Median stage 2.5, Range: 1-4) both indicating a mild to moderate physical impairment. In contrast to ALS-FRS, a higher value in UPDRS and H&Y indicates a severer physical impairment (Figure 6.1 and 6.2). ALS-FRS yielded a mean of 39.45 ± .952 points, indicating a mild-moderate physical impairment; however, this test is not IPS specific. Linear regression showed a significant association between UPDRS and H&Y Test (F(1,38) =113.99, p < .001), thereby both results are related. UPDRS and H&Y positively correlated with disease duration highly significant (r=.666, p<.001, n=40) suggesting, that a longer disease duration is related to a higher physical impairment.
Figure 6.1 and Figure 6.2: Physical impairment of idiopathic Parkinson’s syndrome (IPS) group assessed by the Unified Parkinson disease rating scale (UPDRS) Motor part III in Figure 6.1 and Hoehn & Yahr scale in Figure 6.2. A higher number in UPDRS and H&Y indicates a more severe physical impairment, University Ulm, 2019-2020.

We divided patients into three groups according to their severity of physical impairment with ALS-FRS in ALS and FTD groups and H&Y in IPS group. Following patients had mild physical impairment: 22.5% (n=9) from ALS group, 47.1% (n=8) from FTD group, 42.5% from IPS group (n=17). Moderate physical impairment had 52.5% (n=21) from ALS group, 47.1% (n=8) from FTD group and 30% (n=12) from IPS group. Severe physical impairment had 25% (n=10) from ALS group, 5.9% (n=1) from FTD group and 27.5% (n=11) from IPS group.

Table 5 shows that 12.5% (n=5) from ALS group had a PEG ($X^2(1, n=97)=78.03, p < .001$) and 37.5% (n=15) a NIV ($X^2(1, n=97)=43.56, p < .001$) and one from FTD group (5.9%) received a NIV because of sleep apnea. No patient from IPS group had a NIV or PEG. We found no significant association between NIV or PEG usage and QoL (SEIQoL, ACAS, SF12), depressive symptoms (ADI12) and subjective or caregiver-estimated burden (sTBS, cTBS).
Table 5. Total sum of noninvasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) users in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. Chi-Square test results ($X^2$) were both significant (*), indicating a significant difference between groups.

<table>
<thead>
<tr>
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<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
<th>Significance</th>
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<tbody>
<tr>
<td>NIV</td>
<td>15/40 (37.5%)</td>
<td>0</td>
<td>1 (5.9%)</td>
<td>$p &lt; .001^*$ ($X^2$ Test)</td>
</tr>
<tr>
<td>PEG</td>
<td>5/40 (12.5%)</td>
<td>0</td>
<td>0</td>
<td>$p &lt; .001^*$ ($X^2$ Test)</td>
</tr>
</tbody>
</table>

Medication

The majority from the ALS group received riluzole (92.5%), followed by edaravone (15%). Furthermore, ALS patients received additional medication such as antipsychotics (lithium, 2.5%), antidepressants (7.5%) and 12.5% rasagilin (12.5%). From the IPS group, 12.5% used quetiapine as antipsychotic and 12.5% an antidepressant. Opioid class drug (tramadol, fentanyl) received 5% and 2.5% rivastigmine. From the FTD group only few received medication: 17.6% used riluzole, 5.9% risperidone, 23.5% antidepressants, 17.6% antipsychotics, 5.9% benzerazide. In the IPS group, 12.5% had deep brain stimulation and 5% a dopamine pump. Other Parkinson specific drugs are listed in table 6.
Table 6. Medication in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. Dopamine ag.: Dopamine agonist, DOPA dec. Inh.: Dopamine decarboxylase Inhibitor, COMT Inhibitor: Catechol-O-methyl-transferase Inhibitor, MAO B Inhibitor: Monoamine Oxidase B Inhibitor, Pramiprexol/Rasagiline/Placebo: Pramiprexol + Rasagiline or Pramiprexol + Placebo or Rasagiline + Placebo. Significance was tested with the Chi-square test ($X^2$); all significant results are labelled (*) and all non-significant (n.s.).

<table>
<thead>
<tr>
<th>Medication</th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riluzole</td>
<td>37/40 (92.5%)</td>
<td>0</td>
<td>3/17 (17.6%)</td>
</tr>
<tr>
<td>Edaravone</td>
<td>15/40 (15%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>1/40 (2.5%)</td>
<td>5/40 (12.5%)</td>
<td>2/17 (17.6%)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>3/40 (7.5%)</td>
<td>5/40 (12.5%)</td>
<td>4/17 (23.5%)</td>
</tr>
<tr>
<td>Benserazide</td>
<td>0</td>
<td>0</td>
<td>1/17 (5.9%)</td>
</tr>
<tr>
<td>Levodopa</td>
<td>0</td>
<td>18/40 (45%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Dopamine ag.

<table>
<thead>
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<th>ALS</th>
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<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>0</td>
<td>10/40 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Piripedit</td>
<td>0</td>
<td>3/40 (7.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pramiprexol</td>
<td>0</td>
<td>1/40(2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Apomorphin</td>
<td>0</td>
<td>2/40 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

DOPA dec. Inh.

<table>
<thead>
<tr>
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<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbidopa</td>
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<td>8/40 (20%)</td>
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</tr>
<tr>
<td>Benserazide</td>
<td>0</td>
<td>17/40 (42.5%)</td>
<td>0</td>
</tr>
<tr>
<td>COMT Inhibitor</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opicapone</td>
<td>6/40 (15%)</td>
<td></td>
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</table>

MAO B Inhibitor

<table>
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<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasaglin</td>
<td>5/40 (12.5%)</td>
<td>9/40 (22.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Safinamide</td>
<td>0</td>
<td>4/40 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>0</td>
<td>7/40 (17.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Alpha Synuclein/Placebo

<table>
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<tr>
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<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramiprexol/Rasagline/Placebo</td>
<td>0</td>
<td>1/40 (2.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramiprexol/Rasagline/Placebo</td>
<td>0</td>
<td>2/40 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>
3.7 Cognitive impairments

Figure 7 compares cognitive performance between groups: Median MMST of ALS group was 93.3% (Range: 63.3 – 100%; mean 91.63 ± 1.28%) and median ECAS 75.73% (Range 41.17 - 93.38%; mean 72.643 ± 2.14 points). FTD group had a median MMST of 86.67% (Range 36.67 – 100; mean 79.21 ± 4,68 %) and an ECAS median of 48.53% (Range 12.5 – 86.03; mean 49.95 ± 5.72 %). IPS group had a median MMST of 96.67% (Range (76,67 – 100; mean 94.4 ± .92 %) and ECAS median of 74.64% (Range: 30.88 – 94.85; mean 73.27 ± 2.22 %). Those from the IPS group with a clinically relevant depression performed worse in ECAS with a mean of 70.47 ± 4.52 %. In the FTD group, 58.8% performed in ECAS below age and education adjusted cut-off, whereas in ALS and IPS only 30%.

Figure 7: Comparison of total mini mental state examination (MMST: blue) and Edinburg cognitive and behavioural screen (ECAS: grey) scores in percentage between amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. A higher percentage indicates a better result in the cognitive test.
Performance in the cognitive tests significantly differed between groups in MMST (F (2;94) = 13.49, p< .001) and ECAS (F (2;94) =14.74, p < .001). FTD group had a significantly lower cognitive performance in MMST score compared to ALS (post-hoc Tamhane, M=-12.42, p<.001) and IPS group (M=-15.19, p < .001). ALS and IPS groups did not significantly (p= 0.45, -2.77) differ in their cognitive performance (MMST and ECAS). There was a significant difference (p<.001) of ECAS scores between FTD and ALS group (post-hoc Tamhane, M=-22.69, p=.004) as well as FTD and IPS group (M=-23.32, p=.003), but not IPS and ALS group (p=.996). The ECAS and MMST score performance in contrast to ALS and IPS groups strongly suggests, that the FTD group had a significantly lower performance in both cognitive tests.

The number cognitive impairments for each domain in ECAS were counted per patient, with maximum points of five domains in case a patient performed below age- and education adjusted cut-off in all cognitive parts of ECAS. In the ALS group, the mean was 1.35 ± .225 cognitive deficits (Median 1, Range 0-5). FTD group had most cognitive deficits with a mean of 3.12 ± .41 (Median 4, Range: 0-5). IPS group mean 1.2 ± .2 cognitive deficits (Median 1, Range: 0-4). FTD group had a significantly higher total number of cognitive deficits below age and education adjusted cut-off (F (2;94)=11.93, p <.001) compared to the other groups. The confidence interval (95%) of cognitive deficit sums in each group are depicted in Figure 8, showing that the FTD group had a significantly higher total number of cognitive deficits (ECAS) than ALS (z=-3.473, p=.002) and IPS (z=3.78, p<.001) groups.
Physical impairment in relation to the cognition
A worse physical impairment was related to a lower cognitive function in ALS and IPS group: ECAS sum and ALS-FRS ($r=.331$, $p=.371$, $n=40$) positively statistically significant correlated in the ALS group. MMST and UPDRS ($r=-.425$, $p=.006$, $n=40$) and H&Y ($r=-.362$, $p=.022$, $n=40$) negatively statistically significantly correlated in IPS group. In IPS group, a longer disease duration correlated negatively with MMST ($r=-.425$, $p=.006$, $n=40$) and ECAS ($r=-.334$, $p=.035$, $n=40$).

Table 7 compares the frequency of patients with cognitive deficits between patients with mild, moderate to severe cognitive impairment and those who performed below ECAS age- and education adjusted cut-off. Most patients from the FTD group had lower cognitive performance in ECAS and MMST.
Table 7: Frequency of patients performing below age and education adjusted cut-off in Edinburgh cognitive and behavioural screen (ECAS < cut-off), with a mild cognitive impairment assessed by mini mental state Examination (MMST 19-24) and with moderate to severe cognitive impairment (MMST <19). Comparison is between amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020.

<table>
<thead>
<tr>
<th></th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMST 19-24</td>
<td>7.5% (n=3)</td>
<td>2.5% (n=1)</td>
<td>35.3% (n=6)</td>
</tr>
<tr>
<td>MMST &lt;19</td>
<td>0</td>
<td>0</td>
<td>17.6% (n=3)</td>
</tr>
<tr>
<td>ECAS &lt; cut-off</td>
<td>30% (n=12)</td>
<td>30% (n=12)</td>
<td>58.8% (n=10)</td>
</tr>
</tbody>
</table>

For each of the five tested cognitive parts in ECAS, we assessed the frequency of patients who performed below age- and education adjusted cut-off (Figure 9). Most frequent symptoms in the ALS group were visuospatial deficits (32%) and memory deficits (27.5%), in IPS group language deficits (35%) and verbal fluency deficits (25%) and in FTD group memory deficits (70.6%) and verbal fluency deficits (70.6%). A significant difference between the groups was found in memory deficits ($X^2(2)= 13.41, p < .001$) with a medium strength of association (Cramers V effect size .372) as well as in verbal fluency ($X^2(2)=13.18, p < .001$, Cramers V effect size .369), in visuospatial functions ($X^2 (2)= 6.14, p = .046$) and in executive functions (Fishers Exact Test 10.39, $p = .004$, Cramers V .349, $p=.003$).

All three groups had deficits in the language part, so these did not significantly differ between groups ($p =.112$). In the ALS group, 30 cases (75%) were below cut-off in ALS-specific impairment (language, fluency, executive Functions) and ALS unspecific impairment (memory, visuospatial function) in 24 cases (60%).
Figure 9: Bar chart comparing frequencies of cognitive deficits in the three groups in percentage. Cognitive deficits were five domains (memory, visuospatial function, language, verbal fluency, executive function) tested with the Edinburgh cognitive and behavioural screen (ECAS). The deficits were counted if results were below age- and education adjusted cut-off. Comparison was between amyotrophic lateral sclerosis (ALS: blue), idiopathic Parkinson’s syndrome (IPS: green) and frontotemporal dementia (FTD: red), University Ulm, 2019-2020.

Table 8 shows the counts and frequencies of the total number of cognitive deficits per patient assessed by ECAS. From ALS group 22.5% patients had one or two cognitive deficits, from IPS group 25% had one cognitive deficit, but in FTD group majority had four cognitive deficits (35.3%) or even five (23.5%). Differences were significant between groups (H (2) =15.6, p<.001), hence proving, that the FTD group had significantly more cognitive deficits than the IPS (z=3.77, p <.001) and the ALS groups (z=-3.473, p=.002).
Table 8. Counts and percentages of number of deficits in the five cognitive domains assessed by Edinburgh cognitive and behavioural screen (ECAS) including memory, visuospatial function, language, verbal fluency and executive function in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020.

<table>
<thead>
<tr>
<th>Cognitive deficits</th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 cognitive domains</td>
<td>15/40 (37.5%)</td>
<td>16/40 (40%)</td>
<td>1/17 (5.9%)</td>
</tr>
<tr>
<td>1 cognitive domain</td>
<td>9/40 (22.5%)</td>
<td>10/40 (25%)</td>
<td>3/17 (17.6%)</td>
</tr>
<tr>
<td>2 cognitive domains</td>
<td>9/40 (22.5%)</td>
<td>7/40 (17.5%)</td>
<td>3/17 (17.6%)</td>
</tr>
<tr>
<td>3 cognitive domains</td>
<td>2/40 (5%)</td>
<td>4/40 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>4 cognitive domains</td>
<td>4/40 (10%)</td>
<td>3/40 (7.5%)</td>
<td>6/17 (35.3%)</td>
</tr>
<tr>
<td>5 cognitive domains</td>
<td>1/40 (2.5%)</td>
<td>0</td>
<td>4/17 (23.5%)</td>
</tr>
</tbody>
</table>

3.8 Behavioural and language deficits and psychotic symptoms

Primary caregivers estimated behavioural impairments, language deficits and psychotic symptoms in the patients with ECAS and their sum was calculated within groups. In the ALS group, the mean number of behavioural impairments, language deficits and psychotic symptoms was $1.19 \pm 0.26$ and a median of 1 deficit (Range: 0 - 5). In FTD group, the mean was $5.06 \pm 0.37$ and median 5 (Range: 2 - 7). In IPS group, the mean was $1.52 \pm 3.5$ behavioural impairments, language deficits and psychotic symptoms and median 1 (Range: 0 – 7). The FTD group had a significantly higher sum of total behavioural impairments, language deficits and psychotic symptoms ($H (2;78)=29.34$, $p <.001$) than the ALS ($z=-5.11$, $p<.001$) and the IPS ($z=4.72$, $p<.001$) groups.

Behavioural deficits were reported by caregivers in 41.9% (13/31) of ALS patients, in 45.2% (14/31) of IPS patients and in 100% (16/16) of FTD patients.

In the FTD group, 35.3% (6/16) of caregivers reported psychotic symptoms in contrast to 9.7% (3/31) of IPS patients. No caregiver of an ALS patient reported psychotic symptoms.

Caregivers of ALS patients reported language impairments in 41.9% (13/31), in the IPS group 41.9% (13/31) and in the FTD group 100% (16/16). Language impairment was the most common caregiver-reported impairment in all groups (Table 9).
A significant difference between groups with a high association was found in impulsivity (Fishers exact(2)=25.09, p.<.001) (Cramers V= .616, p.<.001); hyperorality (Fishers Exact Test(2)=18.87, p.<.001) (V= .516, p.<.001) and loss of empathy (X^2(2)=23.56, p.<.001) (V =.55, p.<.001).

There were no significant correlations between each behavioural impairment, language deficits, psychotic symptoms (ECASbq) and sTBS.

Table 9: Behavioral impairments, language deficits and psychotic symptoms estimated by a primary caregiver with the caregiver-evaluation part in Edinburgh Cognitive and behavioural screen (ECASbq) in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. “Number > 1 symptom” shows the number of patients with at least one behavioural impairment symptom, language deficit or psychotic symptom.

<table>
<thead>
<tr>
<th>ECASbq</th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number &gt; 1 symptom</td>
<td>13/31 (41.9%)</td>
<td>14/31 (45.2%)</td>
<td>16/16 (100%)</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>1/31 (3.2%)</td>
<td>4/31(12.9%)</td>
<td>11/16 (68.8%)</td>
</tr>
<tr>
<td>Apathy</td>
<td>12/31 (38.7%)</td>
<td>9/31 (29%)</td>
<td>14/16 (87.5%)</td>
</tr>
<tr>
<td>Loss of empathy</td>
<td>4/31 (12.9%)</td>
<td>8/31 (25.8%)</td>
<td>13/16 (81.3%)</td>
</tr>
<tr>
<td>Ritualistic behaviour</td>
<td>3/31 (9.7%)</td>
<td>3/31 (9.7%)</td>
<td>9/16 (56.3%)</td>
</tr>
<tr>
<td>Hyperorality</td>
<td>4/31 (12.9%)</td>
<td>7/31 (22.6%)</td>
<td>12/16 (75%)</td>
</tr>
<tr>
<td>Other Impairments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Language deficits</td>
<td>13/31 (41.9%)</td>
<td>13/31 (41.9%)</td>
<td>15/16 (94.1%)</td>
</tr>
<tr>
<td>Psychotic Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One psychotic symptom</td>
<td>0</td>
<td>2/31 (6.5%)</td>
<td>6/16 (37.5%)</td>
</tr>
<tr>
<td>Three psychotic symptoms</td>
<td>0</td>
<td>1/31 (3.2%)</td>
<td>0</td>
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</tbody>
</table>

From the FTD group, 17.6% had four and 35.3% five behavioural impairments, language deficits and psychotic symptoms, in contrast, 7.5% from each the ALS and IPS group had two behavioural symptoms and 2.5% three behavioural symptoms (Table 10).
Table 10: Number of behavioural deficits per patient were counted and frequencies were assessed in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. Behavioural deficits were estimated by a primary caregiver with the behavioural questionnaire part in Edinburgh Cognitive and Behavioural screen (ECASbq).

<table>
<thead>
<tr>
<th>Behavioral deficits</th>
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<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Symptoms</td>
<td>18/31 (45%)</td>
<td>12/31 (38.7%)</td>
<td>0</td>
</tr>
<tr>
<td>1 Symptom</td>
<td>7/31 (17.5%)</td>
<td>7/31 (17.5%)</td>
<td>1/16 (5.9%)</td>
</tr>
<tr>
<td>2 Symptom</td>
<td>3/31 (7.5%)</td>
<td>3/31 (7.5%)</td>
<td>2/16 (11.8%)</td>
</tr>
<tr>
<td>3 Symptom</td>
<td>1/31 (2.5%)</td>
<td>1/31 (2.5%)</td>
<td>4/16 (23.5%)</td>
</tr>
<tr>
<td>4 Symptom</td>
<td>2/31 (5%)</td>
<td>0</td>
<td>3/16 (17.6%)</td>
</tr>
<tr>
<td>5 Symptom</td>
<td>0</td>
<td>3/31 (7.5%)</td>
<td>6/16 (35.3%)</td>
</tr>
</tbody>
</table>

3.9 Affective state

The affective state was assessed by ADI 12 and patients with a diagnosis of MDD ($X^2(1,n=97)=43.557$, $p <.001$). As seen in Figure 10, groups did not significantly differ in ADI12 means ($F, p=.98$): The median was in all groups 22 points, which can be interpreted as a (clinically) non-depressed affect as the median was below cut-off (< 28 points) for a clinically relevant depression. The mean of ADI12 in the ALS group was 22.28 points ± .82 (Range: 14-36). In the FTD group, mean ADI12 was 22.06 ± 1.66 points (range: 12 -35), and IPS groups' mean ADI12 was 22.46 ±1.15 points (Range 12- 44). Clinically relevant depression (>28 Points) according to ADI 12 had 12.5% (n=5) from ALS group (mean 31.4 ± 3.05, Range 29 to 36 points). From these five patients above cut-off, two were previously diagnosed with MDD. In ALS group, 7.5% (n=3) had MDD, in IPS group 25% (n=10) and in FTD group 17.6% (n=3) ($p <.001$). When excluding all patients with major depressive symptoms assessed by a total ADI 12 score above 28 or MDD, the difference was not significant ($p=.58$).
Figure 10: Amyotrophic lateral sclerosis depression inventory questionnaire (ADI 12) score in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. The red line is at cut-off 28 points, above indicating a clinically relevant depressive disorder.
3.10 Health related quality of life and quality of life

Health related quality of life
SF12 PCS and SF12 MCS are compared between groups in Figure 11. ALS group had an SF12 PCS mean of 34.35 ± 1.48 points (Median 32.49, Range: 18.2 – 55.3). The median of the ALS group was above 25th percentile of the German population with a chronic disease (28.58 points). In comparison, the IPS group had a mean SF12 PCS of 40.67 points ± 1.77 (Median 40.18, Range: 20.84 – 58.16), resembling the mean of German population with chronic diseases (39.5). FTD group had the highest mean SF12 PCS of 45.77 ± 2.4 points (Median 49, Range: 24.25 – 65.47) which resembled the German population with chronic diseases in 75th percentile (47.62 points). There were significant differences in SF12 PCS between the groups (H (2;97) = 15.0, p < 0.001). The post-hoc-test Bonferroni showed significant difference between ALS and IPS group (z=-2.59, p<.028) and between ALS and FTD group (z=-3.654, p<.001), hence proving, that the ALS group had the lowest physical HRQoL.

In contrast, the ALS group had a high mean SF12 MCS of 51.5 ± 1.74 points (Median 53.2, Range: 25 – 70.53). FTD group had a mean SF12 MCS of 49.65 ± 2.96 points (Median 52.15 Range: 24.25 – 65,47) and IPS group a mean SF12 MCS of 48.42 ± 1.62 (Median 50.43, Range: 17.38 – 64.15). Difference between groups was not significant (F, p=.411). The groups’ mental HRQoL as compared to the German population with chronic diseases was between 50th and 75th percentile (49.32 – 53.59 points). Figure 11 illustrates, that SF12 MCS and SF12 PCS means within ALS group (t=-7,288, p <.001, n=40) and within IPS group (t=-3.6, p <.001, n=40) highly significantly differed. However, the SF12 MCS and PCS did not significantly differ in the FTD group (t=-.98, p= .34, n=17), demonstrating, that although physical HRQoL is very low, ALS and IPS maintain a comparatively good mental HRQoL.
Figure 11: Short Form 12 Physical component summary (SF12 PCS in red) and Short form 12 Mental component summary (SF12 MCS in blue) comparisons of means in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. ALS group had a good SF 12 MCS when compared to the significantly low SF 12 PCS.

In the IPS group, disease duration and SF12 PCS negatively statistically significantly correlated ($r=-.429$, $p=.006$, $n=40$), strongly suggesting a relation between longer disease duration and a lower physical HRQoL. In the ALS group, a higher physical impairment and lower SF12 PCS were related, as we found a significant positive correlation between ALS-FRS and SF12 PCS ($r=.331$, $p=.037$, $n=40$).

In the IPS group ALS-FRS and SF12 PCS highly significantly correlated ($r=.778$, $p<.01$) and significant in the ALS ($r=.331$, $p=.037$) and FTD group ($r=.484$, $p=.049$).
Quality of life

The mean of ACSA in the ALS group was 1.2 points ± .362 (Median 2, range (-5) – (+5) indicating a slightly to pretty good QoL (Figure 12). ALS-bulbar onset group indicated a slightly good QoL (1 ± .91). The FTD group had a mean of 1.24 ± .55 points (Median 2, Range: -5 – 4) and the IPS group a mean of .68 ± .41 points which was between neutral (0) and feeling positive QoL (Median 1, Range: -5 – 5). Difference of ACSA means between groups was not significant (H (2) =1.03, p = .598).

Figure 12: Global Quality of Life results measured by Amnestic comparative self-assessment (ACSA) in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020. ACSA points (number) range from -5 to +5. A more positive number indicates a better global QoL.

Similarly, to the ACSA score, difference between groups in mean SEIQoL was not significant (Figure 13) (F, p = .15): ALS group mean was 67.39 ± 2.43% (Median 72.08, Range: 26.67 – 91.83). FTD group mean was 73.51 ± 4.48% (Median 73.33, Range 40 -100). IPS group mean SEIQoL was 73.71 ± 2.22% (Median 72.5, Range: 43.3 – 100).
Figure 13: Boxplot chart with mean scores of SEIQoL in percentages (Schedule for Evaluation of individual Quality of life) for amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and idiopathic Parkinson’s syndrome (IPS) group, University Ulm, 2019-2020. A higher score in percentage indicates a better QoL.

Most commonly named cues in the whole cohort were 1) family (88.7%), 2) social contacts (70.1%), 3) sport (39.6%), 4) hobby (33%) and 5) profession (30.9%). Frequency in percentage of named cues per group is shown in Table 11. The ALS group most commonly named family (92.5%), followed by social contacts (72.5%), sport (42.5%), home, travelling and hobby (30%). Similarly, the IPS group most commonly named family (92.5%), social contacts (75%), profession (37.5%), sport (32.5%), home (30%) and travelling (30%). The FTD group most frequently named family (70.6%), social contacts (52.9%), sport (50%), hobby (35.3%), being outside (35.3%) and home (35.3%).
Table 11: Frequencies in the percentage of most commonly named cues in SEIQoL (Schedule for evaluation of individual Quality of life) in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and idiopathic Parkinson’s syndrome (IPS) group, University Ulm, 2019-2020.

<table>
<thead>
<tr>
<th>SEIQoL named cues</th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>92.5%</td>
<td>92.5%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Social contacts</td>
<td>72.5%</td>
<td>75%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Sport</td>
<td>42.5%</td>
<td>42.5%</td>
<td>50%</td>
</tr>
<tr>
<td>Hobby</td>
<td>30%</td>
<td>37.5%</td>
<td>35.3%</td>
</tr>
<tr>
<td>Profession</td>
<td>27.5%</td>
<td>37.5%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Having a home, good food</td>
<td>30%</td>
<td>30%</td>
<td>35.3%</td>
</tr>
</tbody>
</table>

In all three groups highest importance and satisfaction yielded family, profession and travelling (Table 12).

Table 12: Mean rating of importance multiplied by satisfaction of the most commonly named cues in SEIQoL (Schedule for evaluation of individual Quality of life) given in percentages in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and idiopathic Parkinson’s syndrome (IPS) group, University Ulm, 2019-2020.

<table>
<thead>
<tr>
<th>SEIQoL (importance x satisfaction)</th>
<th>ALS</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>31.8 ± 17.14</td>
<td>30.52 ± 18.28</td>
<td>19.11 ± 19.38</td>
</tr>
<tr>
<td>Social contacts</td>
<td>8.43 ± 8.23</td>
<td>10.6 ± 10.52</td>
<td>5.13 ± 6.28</td>
</tr>
<tr>
<td>Sport</td>
<td>2.83 ± 5.15</td>
<td>2.9 ± 5.4</td>
<td>6.07 ± 10.17</td>
</tr>
<tr>
<td>Hobby</td>
<td>1.67 ± 3.85</td>
<td>2.77 ± 4.6</td>
<td>4.79 ± 6.77</td>
</tr>
<tr>
<td>Profession</td>
<td>11.67 ± 25.1</td>
<td>26.67 ± 36.36</td>
<td>19.61 ± 36.91</td>
</tr>
<tr>
<td>Having a home, good food</td>
<td>2.73 ± 5.33</td>
<td>2.74 ± 6.08</td>
<td>5.69 ± 8.8</td>
</tr>
<tr>
<td>Travelling</td>
<td>16.67 ± 28.25</td>
<td>15.83 ± 31.57</td>
<td>18.63 ± 35.3</td>
</tr>
<tr>
<td>Nature, going for a walk</td>
<td>1.62 ± 4.4</td>
<td>1.63 ± 4.16</td>
<td>2.6 ± 5.17</td>
</tr>
</tbody>
</table>
3.11 Disease burden

To describe the severity of burden, the burden of the entire cohort (n=97, all groups) was assessed (Table 13). Mean sTBS of all groups (n=97) was 15.59 ± 0.8 points (Median 16, range 0-33). Mean cTBS was 18.71 ± 1.37 points (Median 18, range 0-43). Mean of differential score by subtracting mean sTBS and mean cTBS was -3.42 ± 1.2 points (Median -4, Range -25 – 23). A z-score of the observed group with an SD of +1 above mean of the whole cohort was set as a mild burden, +2 SD a moderate burden and +3 SD severe burden.

Table 13: Description of the whole cohorts’ burden divided into subjective total burden score (sTBS) and caregiver-estimated total burden score (cTBS). By subtracting these two, we calculated the differential score of the total burden (DS-TBS). The cohort included three groups: Amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and idiopathic Parkinson’s syndrome (IPS), University Ulm, 2019-2020. The sTBS included all 97 patients and cTBS 77 patients, as 20 questionnaires were declined. For each variable, median, minimum (min), maximum (max.), means and standard deviation (SD) are given. The z score compares the subjective total burden score (sTBS) and caregiver-estimated total burden score (cTBS) between the groups by subtracting mean burden of the group to the whole cohorts’ mean burden divided by the standard deviation of the whole cohorts mean.

<table>
<thead>
<tr>
<th>Burden of the entire cohort</th>
<th>ALS, FTD and IPS groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTBS</td>
<td>n = 97</td>
</tr>
<tr>
<td><strong>Median</strong> (min – max)</td>
<td>16 (0 – 33)</td>
</tr>
<tr>
<td>Mean, SD</td>
<td>15.59 ± 0.8 points</td>
</tr>
<tr>
<td>cTBS</td>
<td>n = 77</td>
</tr>
<tr>
<td><strong>Median</strong> (min – max)</td>
<td>18 (0 – 43)</td>
</tr>
<tr>
<td>Mean, SD</td>
<td>18.71 ± 1.37 points</td>
</tr>
<tr>
<td>DS – TBS</td>
<td></td>
</tr>
<tr>
<td><strong>Median</strong> (min – max)</td>
<td>- 4 (- 25 – 23)</td>
</tr>
<tr>
<td>Mean, SD</td>
<td>-3.42 ± 1.2 points</td>
</tr>
<tr>
<td>Burden</td>
<td>ALS</td>
</tr>
<tr>
<td>sTBS z score</td>
<td>-.5</td>
</tr>
<tr>
<td>cTBS z score</td>
<td>- 2.52</td>
</tr>
<tr>
<td>DS-TBS z score</td>
<td>+ 2.79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Burden</th>
<th>IPS</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTBS z score</td>
<td>- 1.7</td>
<td>+ 3.09</td>
</tr>
<tr>
<td>cTBS z score</td>
<td>- 2.54</td>
<td>+ 9.66</td>
</tr>
<tr>
<td>DS-TBS z score</td>
<td>+ 1.77</td>
<td>- 8.72</td>
</tr>
</tbody>
</table>
In ALS group, the sTBS mean was 15.19 ± 1.24 points (Median 16.5, Range: 2 -30) and the cTBS mean was 15.26 ± 1.9 points (Median 13, Range: 0-39) (Figure 14). The DS-TBS mean of the ALS group was -.07 ± 1.85 (Median 1 point, Range: -22 – 23). The FTD groups’ sTBS mean was 18.06 ± 1.8 points (Median 19, Range: 0-33), cTBS mean 31.94 ± 1.75 points (Median 33, Range: 15 – 43) and DS-TBS mean -13.88 ± 2.02 points (Median -16, Range -25 – 4).

In the IPS group sTBS mean was 14.23 ± 1.31 points (Median 14, Range: 0-32), cTBS mean 15.23 ± 1.96 points (Median 16, Range: 0-38) and DS-TBS mean was -1.3 ± 1.52 points (Median -1, Range: -15 -20).

The sTBS did not significantly differ between groups (H(2)=2.87, p=.24). According to the z score, the FTD group had a severe burden in comparison to the whole cohort (z score = +3.09) (Table 13). In contrast, ALS (z score = -.41) and IPS group (z score= -1.7) had no burden in comparison to the whole cohort. Caregivers of the FTD group estimated a severe burden in the FTD group (z score=9.66). The cTBS did significantly differ between the groups (H(2)= 23.15,p<.001). The FTD group had a significantly higher cTBS compared to the ALS group (Post-hoc-Bonferroni, z=-4.39 p < .001) and the IPS group (z=4.37, p <0.001).
Figure 14: Comparison of the subjective burden (sTBS in blue) and the caregiver-estimated burden (cTBS in red) between amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and idiopathic Parkinson’s syndrome (IPS) groups, University Ulm, 2019-2020. The differential score (DS-TBS in grey) was calculated by subtracting the subjective burden and caregiver-estimated burden to evaluate over- or underestimation of the patient. The FTD group had a higher mean cTBS compared to the other groups and a lack of insight, due to significant underestimation in DS-TBS. Means are given in total numbers.

3.12 Disease insight

Figure 14 shows a significant difference between caregivers’ (cTBS) and FTD patients’ subjective estimation of burden (sTBS). There was no significant difference in the ALS group (t = .035, p=.972, n=31) and the IPS group (t=.851, p=.402, n=30), indicating a good insight. ALS patients’ (r= .382, p < .034, n=31) and IPS groups’ (r=.598, p<.01, n=30) sTBS highly significantly, as well as cTBS, significantly positively correlated. Hence, the burden was similarly estimated by the caregivers (cTBS) and the patients themselves (sTBS), resulting in a low DS-TBS score. Therefore, we assume a good insight in ALS and IPS groups.
In contrast, there was a significant difference within the FTD group between cTBS and sTBS ($t= 6.86$, $p<.001$, $n=16$) and effect strength after Cohen’s ($d=-3.542$) ($r= .871$) showed a strong association. This significant discrepancy between sTBS and cTBS in FTD group strongly suggests a lack of insight. Therefore, we compared the insight between the three groups, ALS, FTD and IPS. The three groups significantly differed in their disease insight ($H(2)=19.36$, $p<.001$). The total DS-TBS significantly differed between FTD and ALS groups ($z=4.24$, $p < .001$) as well as FTD and IPS groups ($z=-3.66$, $p < .001$), thereby proving, that the FTD group significantly underestimated their burden compared to ALS and IPS groups. The IPS and ALS groups did not significantly differ ($z=.678$, $p=1.0$). Furthermore, when comparing the differential score of burden (DS-TBS) from FTD group (-13.87 ± 2.02 points) with the total cohort (-3.42 points), they severely underestimated themselves ($z$ score = -8.77).

3.13 Comparison of depressed patients to their whole group

We divided all three groups into patients with depressive symptoms (ADI 12 above 28 points) and those without depressive symptoms (ADI 12 below 28 points). From the IPS group, 15% ($n=6$) had a clinically relevant depression with an ADI12 above 28 points (mean 34.76 points ± 2.28). The mean education was higher, with 451.33 ± 81.71 points, than in the whole IPS group ($n=40$). The age at onset was later (mean 59.5 years ± 3.53); however, disease duration was longer with a mean time of 137 months ± 33.32. Physical impairment measured by UPDRS (29 points ± 4.23) and H&Y (3.08 ± 0.32) was severer compared to the whole IPS group. The SF12 PCS (35.27 ± 2.03 points) was comparable, but SF12 MCS (36.39 ± 4.76 points, $H(1)=6.56$, $p=.01$) and ACSA (-1.86 ± .8 points, $H(1)=7.28$, $p=.007$) indicated a significantly lower QoL. The SEIQoL (64.4 ± 6.13%) was comparable. Both sTBS (22.14 ± 2.64 points) and cTBS (16.6 ± 5.95 points) were higher in the depressed group.
In the ALS group, 12.5% (n=5) had a clinically relevant depression with an ADI12 above 28 points. The mean education was higher than in the whole ALS group (n=40) with 470.4 ± 86.03 points. Age at onset of disease was also higher with 68.6 ± 4.05 years, and disease duration was longer with 71.03 ± 7.22 months. Physical impairment was higher compared to the whole ALS group, with 32.2 ± 1.69 points. SF12 MCS was lower with 40.61 ± 6.42 points and SF12 PCS as well, being 30.33 ± 3.97 points. ACSA was significantly lower with -2.2 ± .58 points (H(1)=4.38, p=.036), but SEIQoL 71.03 ± 7.22% was slightly higher. The subjective burden was higher, with 21 ± 3.65 points (sTBS), however, cTBS with 12.5 ± .5 points lower.

In the FTD group, 17.6% (n=3) had a clinically relevant depression with an ADI12 above 28 points. The mean education was 481 ± 87.93 points and age at onset of disease (58.3 ± 5.9 years) were similar to the whole FTD group. Disease duration was longer with 77 ± 22.27 months. Physical impairment (ALS-FRS) was comparable (41.67 ± 3.38 points). SF12 MCS was with 33.29 ± 5.6 points significantly lower in the depressed group (H(1)=5.14, p=023), but SF12 PCS (47.35 ± 5.6 points) was similar. ACSA was more neutral with 0 ± 1.53 points, but SEIQoL was slightly better (79.44 ± 7.22) in the depressed group. The burden was higher in the depressed group. The sTBS was 22 ± 6.1 points and cTBS 35 ± 4.0. The difference in disease insight was not significant between depressed and non-depressed groups in ALS and FTD groups (T-Test for independent samples). The difference in subjective burden (sTBS) between depressed and non-depressed groups was only significant in the IPS group (t=3.014 (37), p=.005).

3.14 Variables correlating with burden

Correlation between behavioural impairments and burden

In the IPS group the sum of behavioral deficits highly significantly correlated with cTBS (r=.690, p<.001, n=30). In none of the groups subjective burden correlated with the behavioural impairments significantly.
Association of cognitive deficits, subjective burden and depressive symptoms
The sum of cognitive deficits ($r=0.424$, $p=0.006$, $n=40$) highly significantly and total ECAS sum ($r=-0.326$, $p=0.04$) significantly correlated with sTBS in the ALS group, thus proving, that more cognitive deficits were related to a higher subjective burden (Figure 15). Significant correlation in ALS group between verbal fluency (cognitive part ECAS) and sTBS (Fishers Exact (21)=25.19, $p=0.021$, $n=40$) with a high strength of association (Cramers V =.882, $p=.022$). Similarly, in IPS group, total ECAS score correlated with sTBS ($r= -0.375$, $p=.017$). In FTD group, cognitive function and subjective burden did not correlate.

Figure 15: Simple scatter depicting a significant negative linear correlation between cognitive function measured by Edinburgh cognitive and behavioral screen total score in percentage (ECAS) and subjective total burden score (sTBS) in amyotrophic lateral sclerosis (ALS) group ($n=40$), University Ulm, 2019-2020. A similar negative linear correlation can be seen in idiopathic Parkinson’s disease group.
Within the IPS group, the total ECAS score correlated with ADI12 (r=-.382, p=.016), SF12 PCS (r=.403, p=.01), SF12 MCS (r=.352, p=.026), SEIQoL (r=.405, p=.01) and ACSA (.382, p=.015). Therefore, in the IPS group, the cognitive function was related to depression, QoL and HRQoL. However, in the FTD and ALS groups, none of these correlated significantly.

Multiple regression analysis determined a similar influence of cognitive impairment in ALS group and non-depressed IPS group on sTBS. In the ALS group cognitive impairment significantly predicted 17.6% of sTBS variance (F (3;39) = 3.772, p= .019, adjusted R2=.176). However, in the IPS group (p=.117) and the FTD (p = .606) groups, these did not significantly predict variance of sTBS. When excluding IPS participants with ADI 12 above 28 points (excluding patients with clinically major depression), total ECAS significantly explained 17.7% of sTBS variance (R= 0.177, p = .034). In the ALS and FTD group, there was no significant variance when excluding the depressed group.

There was no significant association within groups between language difficulties and sTBS, cTBS or DS-TBS (assessed by ECAS language deficits and language impairments estimated by a caregiver in the behavioural part of ECAS).

**Family and subjective burden in sTBS**

Satisfaction and high importance of family (cue in SEIQoL) highly significantly negatively correlated with sTBS in the IPS group (r=-4.07, p=.009, n=40). This was not a significant correlation in the other groups.

**Physical impairment and disease duration correlated with depression in IPS group**

Significant correlation of disease duration (r= .381, p=.017, n=39), H&Y (r=.609, p<.001, n=39) and UPDRS (r=.579, p<.001, n=39) with ADI 12 in IPS group. Thus, only in the IPS group a longer disease duration and higher physical impairment were associated with a higher risk for depressive symptoms, as this association was not significant in other groups or specific disease types.
Physical impairment and QoL in IPS group
A higher physical impairment (H&Y, UPDRS) was related to a lower QoL (SF12, ACSA, SEIQoL) in the IPS group: H&Y and SF12 PCS highly significant negatively correlated \((r=-.708, p <.001, n=40)\) as well as UPDRS and SF12 PCS highly significant \((r=-.610, p <.001, n=40)\). H&Y and UPDRS also significantly correlated with SF12 MCS \((r= -.356, p=.024, n=40)\), \((UPDRS: r=-.392, p =.012)\). H&Y as well as UPDRS and ACSA negatively correlated significant \((r=-.378, p=.016, n=40)\), \((UPDRS: r=-.435, p=.005)\). Also, UPDRS and SEIQoL significant negatively correlated \((r=-.364, p=.021, n=40)\).

Physical impairment and disease duration were related to sTBS in IPS
Physical impairment (NIV, PEG, ALS-FRS) and PR did not significantly predict sTBS variance in the FTD \((p= .791)\) and the ALS group (multiple regression, adjusted R2: .006, p=.393). The type of onset in the ALS group (bulbar onset and spinal onset) did not explain the total sum burden \((p = .795)\). In contrast, physical impairment in the IPS group was assessed with H&Y and UPDRS, which did explain 37.1% of sTBS variance with a high significance (Adjusted R2 =.371, p <.01). In the IPS group, UPDRS \((r=.653, p<.001, n=40)\) and H&Y \((r=.652, p<.001, n=40)\) highly significant and positively correlated with a higher sTBS (Figure 16). Additionally, a longer disease duration \((r=.357, p=.024, n=40)\) significantly and positively correlated with a higher sTBS. When using these variables or ALS-FRS and PR, we found no significant correlation in the other groups. UPDRS explained 38.4% of sTBS variance \((R \text{ square: } .384, p<.001)\) and H&Y 37.4% of sTBS variance \((p<.001)\). H&Y explained 51.5% of SF12 variance in IPS group \((p<.001)\). Both were not significant in ALS and FTD groups with ALS-FRS.
Depressive symptoms were related to QoL and sTBS in IPS and ALS groups

Furthermore, a higher depressive risk in IPS group was related to a lower HRQoL and QoL. The ADI12 highly significantly negatively correlated with SF12 MCS (r=-.687, p<.001), SF12 PCS (r=-.513, p<.001, n=39), ACSA (r=-.575, p<.001) and SEIQoL (r=-.539, p<.001). ADI12 also highly significantly positively correlated with sTBS (r=.735, p=.000, n=39), thereby proving, that depressive symptoms were related to a higher subjective burden (Figure 17). In the IPS group, sTBS significantly correlated with SF12 PCS (r=-.227, p=.017, n=30) and SF12 MCS (r=-.501, p=.001, n=40). Thus, a better HRQoL was related to a lower subjective burden. Similarly, in the ALS group, higher depressive symptoms were related to a lower HRQoL and global QoL as well as an increased subjective burden. We found a significant negative correlation between ADI12 and ACSA (r=-.555, p < .001, n=40) and SF12 MCS (r=-.225, p=.001, n=40) and positive significant correlation with sTBS (r=-.369, p=.019, n=40).
Similarly, to the IPS group, a better QoL was related to a lower subjective burden. SEIQoL highly significantly \((r=-0.479, p=.002, n=40)\) and SF12 MCS significantly \((r=-.365, p=.021, n=40)\) negative correlated with sTBS \((r=-0.479, p=.002, n=40)\) in the ALS group. In the FTD group, only ADI12 and cTBS positively statistically significant correlated \((r=.526, p=.036, n=16)\) as well as SEIQol and cTBS negatively statistically significant correlated, therefore a better QoL and lower depressive symptoms did relate to a lower burden of caregivers. There was no correlation between depression and lack of insight within all groups.

Figure 17: Simple Scatter depicting the significant positive linear correlation between depressive symptoms assessed by amyotrophic lateral sclerosis depression inventory questionnaire (ADI12) and subjective total burden score (sTBS) in idiopathic Parkinson’s disease (IPS) group, University Ulm, 2019-2020. A similar positive linear correlation can be seen in amyotrophic lateral sclerosis group.
Affect, Cognition and QoL influenced subjective burden in ALS

Multiple regression analysis determined the influence of affect, cognition and QoL on sTBS. In the ALS group, ADI 12, the sum of cognitive deficits, behavioural deficits and SEIQoL highly significantly explained 44.6% of sTBS variance (Adjusted R2 = .446, p <.001). However, behavioural deficits were not significant and did not significantly correlate with sTBS in previous tests. Therefore, we tested the model without behavioural deficits. The model was significant without behavioural deficits in the ALS group and all three parameters were significant influencers (Adjusted R2=.428, p <.001) (Table 14).

This model, with and without behavioural deficits was not significant in the FTD and IPS groups. After adding physical impairment and disease duration, the model was not significant. There was no significant increase of variance in FTD and ALS group when adding ALS-FRS, disease duration or SF12 MCS.

In the IPS group, 57.5% of sTBS variance could be explained by sum of cognitive deficits, depressive symptoms (ADI 12), SF 12 PCS (physical HRQoL), disease duration and physical impairment (H&Y) (Table 14).

Behavioural symptoms and family influenced sTBS in the FTD group

The variance models for ALS and IPS (including QoL, ADI12, cognition) (p = .151) as well as HRQoL (adjusted R2= .003, p=.44) did not significantly predict sTBS variance in FTD group.

In the FTD group 45% of sTBS variance could be explained significantly (F(4,11)=4.1, p=.029) by behavioural symptoms including *loss of empathy, apathy, impulsivity* and high importance and satisfaction with *family* (cue in SEIQoL) (Table 14). This model was not significant in the ALS and IPS groups.
Table 14: Effect of different variables on subjective burden (sTBS) assessed by multiple regression analysis in amyotrophic lateral sclerosis (ALS), idiopathic Parkinson’s syndrome (IPS) and frontotemporal dementia (FTD), University Ulm, 2019-2020.

<table>
<thead>
<tr>
<th>Effect on sTBS</th>
<th>ALS (B)</th>
<th>IPS (B)</th>
<th>FTD (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>17.862*</td>
<td>-21.82*</td>
<td>12.14*</td>
</tr>
<tr>
<td>Sum of cognitive deficits</td>
<td>1.87 (.01)*</td>
<td>.326 (.666)</td>
<td>-</td>
</tr>
<tr>
<td>SF 12 PCS</td>
<td>-</td>
<td>.261 (.031)*</td>
<td>-</td>
</tr>
<tr>
<td>SEIQoL</td>
<td>-.204 (.003)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADI 12</td>
<td>.415 (.032)*</td>
<td>.625 (.000)*</td>
<td>-</td>
</tr>
<tr>
<td>Family SQL</td>
<td>-</td>
<td>-</td>
<td>-.204 (.027)*</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr</td>
<td>-</td>
<td>5.24 (.003)*</td>
<td>-</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-</td>
<td>-.02 (.177)</td>
<td>-</td>
</tr>
<tr>
<td>Loss of empathy</td>
<td>-</td>
<td>-</td>
<td>-1.16 (.79)</td>
</tr>
<tr>
<td>Apathy</td>
<td>-</td>
<td>-</td>
<td>7.8 (.116)</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>-</td>
<td>-</td>
<td>6.09 (0.92)</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>.428</td>
<td>.575</td>
<td>.45</td>
</tr>
</tbody>
</table>
4 Discussion

4.1 Summary of the results

Physical impairment, as well as cognitive and behavioural impairments, were in similar range in both ALS and IPS groups. In contrast, the FTD group had better physical function, however more cognitive and behavioural deficits. Deficits in language were the only cognitive domain with comparable prevalence in all groups. Prevalence of all other cognitive domains was significantly higher in FTD.

The affective state, mental HRQoL and QoL were comparable between groups. The ALS group had the significantly lowest physical HRQoL. Both ALS and IPS groups had a very good mental HRQoL, despite their low physical HRQoL. All groups named family, social contacts, sport and hobbies as essential determinants for their QoL. Patients rated family, profession and travelling as the most important cues. Incidentally, these were also the cues the patients were most satisfied with.

Our hypothesis was, that the subjective burden of ALS and FTD will be similarly low, while that of IPS will be relatively higher. Even though all groups had a comparable affective state and QoL, the burden differed. In our study, FTD patients had the highest sTBS, partially disproving our hypothesis. Further, ALS and IPS patients had a similar sTBS, which was comparatively lower than that of FTD. Despite already estimating their sTBS quite high, we have to assume, that FTD patients underestimated their burden, as their cTBS was even greater. Our results further support the idea, that FTD patients suffer of low disease insight, as their sTBS did not correlate with their cTBS. The sTBS of our IPS and ALS groups correlated and had low discrepancy with their respective cTBS, translating to a good disease insight, further partially disproving our second hypothesis.

In both ALS and IPS groups, higher cognitive impairments were associated with a more severe sTBS. Depressive symptoms in both groups negatively correlated with QoL. Exclusively in the IPS group, cognitive impairments also correlated with depressive symptoms and QoL. Furthermore, only in the IPS group, physical impairment and disease duration significantly influenced depressive symptoms, sTBS and QoL. Family satisfaction and importance negatively correlated with sTBS in the IPS group. In the ALS group, QoL and mental HRQoL significantly correlated
with sTBS, whereas in the IPS group, additionally QoL, physical and mental HRQoL significantly correlated with the sTBS. In the FTD group, however, these factors did not correlate with the sTBS, but the SEIQoL correlated with the caregiver-estimated total burden score. In the FTD group, the three behavioural deficits *loss of empathy, apathy, impulsivity* and the *family* explained 45% of sTBS variance. The ALS group had a sTBS variance of 42.8% when including cognitive deficits, SEIQoL and ADI12. When adding physical impairment, disease duration and SF12 PCS instead of SEIQoL to this model, the sTBS variance in the IPS group was 57.5%.

4.2 Discussion of the results

This cross-sectional study investigates the disease burden of ALS, IPS and FTD patients by evaluating QoL and affective state as measures of psychosocial adaptation to cognitive and behavioural impairments, while taking disease insight into account.

The main finding was, that FTD patients, despite having a high subjective burden, had a limited disease insight. In contrast, ALS and IPS patients had good disease insight and a lower burden compared to the FTD group. Although the FTD group had the highest subjective burden, the QoL and depressive symptoms were comparable between the three groups.

In both ALS and IPS groups, cognitive impairments were associated with a higher subjective burden. ALS patients showed a good QoL, despite that cognitive deficits influenced subjective burden, indicating a very good psychosocial adaptation. IPS patients showed a comparatively insufficient psychosocial adaptation, as cognitive deficits, physical impairment and long disease duration were associated with a low QoL and depressive symptoms.

Even though, the ALS group had the worst physical HRQoL compared to the FTD and IPS groups, they had the most significant discrepancy between mental and physical HRQoL. The IPS group had also a very good mental HRQoL, despite the low physical HRQoL.
4.2.1 General data of the cohort

In literature, ALS is described to have a gender distribution of approximately 30% female and 70% male and a peak age of onset of 58-63 years of age [103]. Our data, with a gender distribution of 40% female and 60% male and mean age at onset of 62.5 years, corresponds to these findings. The distribution of onset types in our study was in line with other studies. Spinal onset had 75% (n=30) of ALS patients, 22.5% (n=9) had bulbar onset and one had a flail arm syndrome (2.5%) [222].

The age of IPS patients, with a mean of 66 years and a mean age at onset of 55.95 years, is comparable to other studies, describing a wide range from the third decade to old age [181]. Gender distribution of 60% male and 40% female IPS patients also corresponds to distributions in another study [162]. IPS patients were grouped according to their clinical type; 55% (n=22) corresponded to the hypokinetic-rigid type, 20% (n=8) to the tremor dominant type and 25% (n=10) to the equivalent type.

The mean age at onset of our FTD group of 57.65 years is in line with the mean age of 56 years, reported by Greck et al. [77]. In our sample group, all patients were male; this is not in line with literature findings, which describe gender distribution to be roughly equal [86]. We examined female patients, however all had to be excluded from the study. In our study, 23.5% of patients had a positive family history, and 17.6% of which had a C9orf72 mutation, which does not deviate far from the findings by Goldman et al., who reported 15% of FTD patients with a positive family history [73]. It should be noted, that our small FTD cohort only included patients with either a proven diagnosis due to the mutation being detected in genetical testing or a fulfilment of all Rascovksy diagnostic criteria. Among our patients, bvFTD predominated with 76.5%, this is in accordance with literature findings, reporting bvFTD to be the predominant type [86]. The remainder of our FTD cohort were ALS-FTD patients (23.53%).
4.2.2 Physical impairment

Our results of a moderate physical impairment (ALS-FRS: 34.53 ± 1.18) in the ALS group are in line with measurements by Vieregge et al. [242]. From the ALS group 20% had a significant limitation of strength and physical function indicated by an ALS-FRS score below 28 points.

FTD patients’ physical impairment was mild to moderate, as motor symptoms usually occur only in ALS-FTD forms or more progressed bvFTD patients. The mild to moderate physical impairment results (ALS-FRS score) of our FTD group might be explained by the fact, that ¾ of our FTD group consisted of bvFTD patients.

As discussed in the Materials and Methods chapter, while physical impairment in ALS and FTD was measured using the ALS-FRS score, in IPS, the H&Y and UPDRS scores were utilized. Physical impairment in the IPS group was mild to moderate when assessed by H&Y (.59 ± .17) and UPDRS (29.95 ± 1.84) [146].

The diagnostic delay describes the time elapsed from the time of symptom onset, until the time of diagnosis. Its median value in the ALS group of 11.5 months is in agreement with literature [210]. The median diagnostic delay in the IPS group of twelve months agrees with findings in the literature; this is presumably due to a delay between symptom onset and presentation to the diagnosing physician [22]. The median diagnostic delay in the FTD group of 24 months does not conflict with Besser et al., who states that diagnosis might take more than a year [13].

4.2.3 Cognitive impairments

The FTD group had the highest cognitive impairments, as they yielded lower results of 49.95% in the ECAS and 79.21% in the MMST tests. In contrast, the ALS group (MMST: 91.63%, ECAS: 72.64%) and IPS group (MMST: 94.4%, ECAS: 73.27%) yielded higher results in both cognitive tests, translating to better cognitive function. The cognitive performances of ALS and IPS groups were comparable.

Cognitive impairments in the FTD group

More than half of the FTD group (64.7%) performed below age- and education-adjusted cut-off in the ECAS test, indicating cognitive impairment. In the ECAS test, five cognitive domains were assessed. The FTD patients had a mean of 3.12 impaired cognitive domains. The most frequently impaired cognitive domains in the
FTD group were memory (71%), verbal fluency (71%), followed by impairments in executive functions (59%), language (59%) and visuospatial functions (53%). According to the Rascovksy criteria, FTD patients typically show executive deficits and mostly retain visuospatial and memory function [201]; however, with more progressed disease, other deficits might occur. The prevalence of verbal fluency impairments, executive impairments, and language impairments in our FTD cohort, fulfills the Rascovksy criteria [201]. Accordingly, our findings support, that the FTD group had more severe cognitive deficits and a significant higher number of affected cognitive domains, compared to ALS and IPS patients [32]. There was one patient in the FTD group without any cognitive deficit in one domain, who was thought to have a bvFTD phenocopy variant as the patient presented with typical fronto-temporal behavioural symptoms. It is arguable, whether we should exclude this patient, however, as this patient fulfilled Rascovksy criteria, we decided against exclusion.

In the IPS and ALS groups, 30% performed below the ECAS age- and education-adjusted cut-off, which is comparable to results of other studies in the ALS group [1, 28, 123, 208] and in the IPS group [57].

Cognitive impairments in the ALS group
In our study, 22.5% of ALS patients had a deficit in only one single cognitive domain [128, 129] and 62.5% had deficits in at least one cognitive domain, which is comparable to findings in literature, ranging from 40% - 55% [78, 129, 131, 191].
In our study, 75% of the ALS group had deficits in ALS-specific cognitive domains, namely language, verbal fluency and executive functions. Further 60% presented with deficits in ALS-nonspecific cognitive domains, which are visuospatial functions and memory. The ALS-specific cognitive deficit [1] verbal fluency was assessed in 25% and executive deficit in 20% of ALS patients in our study. Our measured prevalence of verbal fluency deficits agrees with that reported in a study by Loose et al.. However, this domain was our second most common reported deficit, whereas in the study by Loose et al. it was on fourth place [123]. Another ALS-specific cognitive deficit was language deficit in 12% of ALS patients. Executive functions frequently co-occur with verbal fluency and language deficits [1-3, 28, 46, 74, 79, 158, 187, 191, 197, 219].
The majority of our ALS group had visuospatial deficits (32%) and memory deficits (27.5%). Although both classify as ALS non-specific impairments [1], memory impairment was frequently reported in other studies [10, 219] and Elamin et al. declared the increase of visuospatial deficits with the progression of disease [52]. Executive functions include the ability to shift the attention in response to changing circumstances, to maintain concentration, problem solving and mental flexibility. The relative high frequency of executive deficits in the ALS group, led to the assumption that these negatively affected the ALS non-specific deficits visuospatial and memory functions [1].

Cognitive impairments in the IPS group
Language impairment was the most commonly reported cognitive deficit domain within the IPS group (35%), which complies with the result by Foley et al., who announced ECAS as a sensitive tool to detect cognitive deficits in IPS patients [57]. The second most frequent impairments in our IPS group were verbal fluency (25%) and visuospatial deficit (25%), which are both reported to occur in early disease stages [155, 251]. The third most frequent impairment was memory deficit (22.5%) [57]. IPS patients without dementia are reported to have executive deficits in early stages of disease [115, 155, 251], which are accompanied by attentional dysfunction and disinhibition [155]. In our study, only 17.5% of the IPS group had executive deficits, although, in the study by Foley et al., these were reported to be more common [57]. The different results might be explained by the smaller cohort, and the shorter disease duration in their IPS cohort.

Language impairment
The language impairment was assessed by two tests in our study: 1) As a cognitive deficit in objective testing with ECAS and 2) as a deficit with the ECAS behavioural questionnaire completed by a primary caregiver. In each group, language impairment was the most frequently reported symptom by primary caregivers. In the FTD group, 94.1% caregivers reported language impairments and, in each ALS and IPS group 41.9%. There are several reasons for language impairment in the ALS and IPS groups. One is the disruption of motor speech [70], which presents in IPS patients frequently by a decrease in tone or slowing of speech and in ALS as well
as ALS-FTD patients with bulbar symptoms. Our high frequency of language deficits in the groups agrees with literature [52, 164, 191, 235].

The ALS [9], IPS [164] and FTD [228] patients may all present with pragmatic language impairments, characterized by word-finding difficulties, verbal fluency deficits and naming deficits [114, 192, 235]. In ALS and FTD, naming and verbal fluency deficits are thought to be predominantly caused by executive deficits [48, 192, 235]; however, they may also present in the absence of it [191, 235].

Verbal fluency deficits strongly positively correlated with an increased subjective burden in the ALS group from our study, presumably as verbal fluency is essential to social communication, which has been shown to correlate with well-being [82, 118]. Additionally, verbal fluency is also described to decline even further with progression of ALS [2]. Studies suggest that technological aids which help anarthric ALS patients to speak, improves their well-being, thereby preventing depressive symptoms and decreasing the burden [82, 84, 118].

Studies examining social cognition discovered that ALS patients recognized fewer facial emotions [4], identification of socially tactless acts was impaired [158] and patients had deficits in interpreting intentions [68]. Gibbons et al. found that ALS-FTD patients were poor in interpreting mental states of others in cartoons and stories [66]. Selmer et al. proposed social and emotional cognition deficits in ALS and FTD patients, compared to healthy controls, as both had deficits in judging specific situations as morally or ethically right or wrong [221].

With progressed IPS disease, interpretation of meanings is impaired and sustaining conversations becomes challenging [17, 144]. Montemurro et al. found that IPS patients had problems understanding narrative and humorous stories, sustaining a conversation and interpreting facial expressions [9, 164].

Behavioural deficits such as loss of empathy and apathy may further complicate the interpretation of other feelings and thoughts [140]. We assume that deficits in identifying and interpreting emotions, beliefs and intentions in social interactions may impair relationships and participation in social activities and thus increase the risk of social withdrawal [68, 158].
The importance of social contacts

All patients in this study, regardless of their disease, valued social contacts very highly, as can be seen in the frequency with which they named family as a cue in SEIQoL. All of the patient groups in this study, present with their own type of language impairment, which, over the course of disease, is a key factor in the patients’ social withdrawal. As many of these diseases predispose for depressive symptoms, understandably, the loss of social contacts may make matters worse. The cue family was most commonly named and also yielded the highest importance and satisfaction ratings. This is supported by other studies [41, 55, 75, 82, 94, 139, 151, 152, 174, 175]. In our study, the cue family also determined subjective burden, which agrees with Simmons et al. [224]. In the IPS and FTD groups, family significantly influenced the subjective burden. In the ALS group, family was frequently named and highly rated, however was not a significant influencer of sTBS. In the IPS group, the cue family highly significantly correlated with sTBS. In the FTD group, the three behavioural deficits loss of empathy, apathy, impulsivity and the family explained 45% of sTBS variance. The three behavioural symptoms loss of empathy, apathy and impulsivity may impair social interaction. That impaired social participation may have negative consequences has been extensively studied, as it may be associated with higher depression, anxiety, reduced functional ability [65], decreased HRQoL [17, 57] and decreased QoL [42] in ALS and IPS patients [7, 17, 72, 218, 239].

Physical impairment and cognitive function

Physical impairment in the ALS and IPS groups was significantly related to a lower cognitive function in ECAS or MMST. Accordingly, higher cognitive deficits in the ALS and IPS groups tend to be related to a more progressed disease, whereas this correlation did not exist in the FTD group. Cardinal symptoms in both IPS and ALS are motor impairments, which reflect disease progression. These are frequently accompanied by nonmotor symptoms in ALS [46] and IPS [39, 143, 164]. In FTD, motor symptoms are not part of the diagnostic criteria, except in ALS-FTD. In IPS, motor impairments may frequently be accompanied by cognitive impairments and in some cases, dementia might even present before onset of motor symptoms [196].
Correspondingly, Elamin et al. found in a large ALS cohort of 244 patients, that cognitive impairments tend to be associated with a faster physical decline in contrast to ALS patients with normal cognition [52]. Crockford et al. observed that ALS patients in more advanced stages had a higher number of cognitive and behavioural impairments [46]. Similarly, Phukan et al. researched in a population-based study that ALS patients with executive impairments tend to be older-aged and have a more rapid disease progression [191]. Bock et al. reported, in contrast to our findings, a lower number of ALS patients who developed cognitive impairments. However, the longitudinal design and the usage of a short cognitive screening tool and verbal fluency test which lack, to our knowledge, assessment of visuospatial and language impairments may explain the different findings. Besides, we must note that other confounders influence the patient cohorts, such as the level of education. Patients with a higher cognitive reserve may be protected from the early development of cognitive and behavioural deficits [164]. Cognitive reserve postulates that patients with a higher reserve, influenced by environmental and genetic factors, have a higher threshold of developing cognitive and behavioural deficits [19, 189].

4.2.4 Behavioral impairments

All patients of the FTD group in our study had at least one behavioural impairment; which is in contrast to 45.2% of the IPS group and 41.9% of the ALS group. These prevalences of behavioural symptoms in our study correspond to findings in other studies [28, 158, 167]. Our reported percentage, that 41.9% of the ALS group had at least one behavioural deficit, is in line with the reported numbers by Goldstein et al. [74]. An epidemiologic study in southern Germany reported lower prevalences of behavioural symptoms (29%) [210]. This different prevalence of behavioural symptoms in the epidemiologic study might be explained by the larger cohort (n=699), of which 110 patients agreed to a home interview. In contrast, the majority of our ALS cohort was examined in the hospital. Another difference was the higher frequency of bulbar onset patients, than in our cohort.

Similar to the ALS group, 45.2% in the IPS group had at least one behavioural symptom. Most commonly reported behavioural impairments were apathy and loss of empathy in our study which were also reported in other studies [1, 5, 9, 15, 33, 78,
79, 104, 114, 164, 235, 252, 254]. These behavioural deficits were reported in a large observational study of 161 ALS patients [46, 210].

FTD patients had the significantly highest frequency of behavioural deficits compared to the other two groups. According to Rascovksy criteria, three behavioural or cognitive symptoms should be present to diagnose bvFTD [201]. Three patients presented two or less behavioural symptoms assessed by ECASbq, however two of them were diagnosed with ALS-FTD. The third patient showed psychological symptoms and deficits in executive tasks and therefore also fulfilled Rascovksky criteria.

**Behavioural symptom: Apathy**
The high prevalence of the behavioural symptom *apathy* in our study was observed in other studies as well [1, 33, 79, 129, 210, 242]. *Apathy* was prevalent in 86.7% of the FTD group, in 38.7% of ALS patients and 29% of IPS patients. In the ALS and the IPS groups, *apathy* was the second most common behavioural symptom, being in line with other studies [28, 49, 66, 104, 181]. A meta-analysis by den Brok determined an even higher prevalence of *apathy* in IPS (39.8%), which was related to more severe disability [49] and a lower QoL [8]. The prevalence of the behavioural symptom *apathy*, did not significantly differ between our ALS spinal and bulbar onset groups, in contrast to studies, where those with bulbar onset had more often *apathy* symptoms [79]. Similarly, Rosenbohm et al. reported most frequently *apathy* in their cohort, whose majority included bulbar onset patients [210]. Lulé et al. suggested that in the ALS group, *apathy* is partly a reaction to the terminal diagnosis of their illness [129], which might explain the high occurrence [33]. In the FTD and IPS groups, *apathy* may even precede motor symptoms [39].

**Behavioural symptom: Loss of empathy**
Similar to *apathy*, *loss of empathy* was detected in the ECASbq frequently. The measured prevalence was 86.7% in the FTD group, 25.8% in the IPS group and 12.9% in the ALS group. The prevalence of *loss of empathy* in the ALS group is in agreement with other studies [28, 66].

Even though, this behavioural symptom has been most prevalent in the FTD group, this group did not have a lower QoL compared to the ALS and IPS groups, but a higher subjective burden. We think that the self-rating of QoL requires good
cognitive function for abstract thinking to estimate subjective QoL. Furthermore, the lack of insight in the FTD group might have distorted QoL results. In the QoL questionnaires, we asked about cues that are important for the patient. Many patients had difficulties freely thinking about their own cues. Most patients from the FTD group (37.5%), followed by the IPS group (9.7%) had reported psychotic symptoms. Frequently, side effects from dopaminergic medication are responsible for psychotic symptoms, pathological gambling or hypersexuality in the IPS group [59, 181]. FTD patients may show psychotic symptoms and which frequently leads to misdiagnosis.

**Behavioural impairments and burden**

The prevalence of each individual domain of behavioural impairments was assessed, as well as the total sum of behavioural impairments. In the IPS group, the caregiver-estimated burden highly significantly positively correlated with the caregiver-reported behavioural deficits. This correlation may be explained by the caregiver expecting a high patient burden after reporting a high number of behavioural deficits. Behavioral impairments did not significantly correlate with the subjective burden in any of the groups.

**4.2.5 Affective state**

The affective state reflects the psychosocial adaptation to motor and nonmotor impairments. The psychosocial adaptation to these changes might lead to depressive symptoms [30, 75, 104, 181] and may even influence subjective burden and QoL [120, 146].

We assessed patients for depression according to 1) history of MDD diagnosis, following DSM IV criteria and 2) self-reported depression questionnaire (ADI12). Depressive symptoms assessed by ADI12 did not significantly differ between the groups, and the mean result of each group indicates no clinically significant depressive symptoms. Previously diagnosed patients with MDD, as well as an ADI12 above 28 points, were not excluded. The cut-off above 28 points in the depression questionnaire ADI12 indicates a higher risk for a clinically relevant depressive disorder.
In the IPS group, 25% were clinically diagnosed with MDD, and 15% were above the cut-off in ADI12, which lies within prevalence rates of a systematic review that measured the prevalence of MDD in 17% of IPS patients and minor depression in 22% of IPS patients [203]. Other studies results ranged from 15 - 50% [181, 203] depending on the assessment methods.

In the FTD group, 17.5% were diagnosed with MDD, and 17.6% were above the cut-off in ADI12. Previous studies assessed depression in FTD with a caregiver interview yielding a prevalence of up to 50% which varied, depending on the type of assessment. Assessment types could be a self-rating, a caregiver-rating or a clinical diagnosis by a physician [37, 223]. We assessed depressive symptoms with a self-anamnestic report (ADI12) and clinical diagnosis of MDD. Similarly, Lopez et al. conducted a personal and structured interview by using the Hamilton depression rating scale based on 17 questions, and both results are comparable (24% of FTLD patients with MDD) [124].

In the ALS group, 7.5% had a clinical diagnosis of MDD and 12.5% according to ADI12. The results might differ, as those who showed depressive symptoms on that day, were not yet assessed by a physician as a large part of this group has been recently diagnosed and depressive symptoms might be a reaction to this fatal diagnosis. Those studies, which used DSM-IV criteria for clinical diagnosis of MDD in ALS patients, yielded comparable results ranging from 9-11% [62, 81, 139, 198, 199]. The depression rates in the ALS group were higher than in the general population (4-5%) [169]. Nonetheless, it matters at which time the depression symptoms were assessed, as many patients might develop a reactive depression shortly after diagnosis, which commonly resolves after a few months [84, 134]. Still, depression can occur at any time [75]. The studies, which used self-reported questionnaires, had very different prevalences of clinically relevant depression [65, 236]. For instance, the Becks Depression Inventory, a self-reported multiple-choice depression questionnaire, also includes somatic items, which might lead to an overestimation of depressive symptoms in physically impaired ALS patients [107, 110]. For this reason, Körner et al. excluded these somatic items, which resulted in a lower depressive prevalence [107]. Kübler et al. developed the ADI12 and yielded much higher prevalences which might be explained by their selection bias, as they recruited all patients via an ALS magazine, likely leading to the participation of many patients with a lower affect [110].
Disease severity and depression

In the ALS and FTD groups, we found no association between disease severity and depressive symptoms. Disease severity was measured by assessing the physical impairment with the ALS-FRS and the disease progression as well as duration of disease. This finding is similar to other studies and presents that depressive symptoms did not solely depend on the severity of physical impairment and duration of disease [43, 76, 84, 139, 178, 199, 207, 224]. Contrarily, Kübler et al. found that the severity of depressive symptoms increased moderately with physical impairment [110]. The different assessments may explain these conflicting results as Kübler et al. used two questionnaires for evaluation of depressive symptoms, one for the patients and one for the caregivers (Becks Depression Inventory, ADI12). The caregivers might have overestimated patient’s depression and rated it higher, similarly to the phenomenon that caregivers seemed to underestimate ALS patients’ QoL [135, 224]. Moreover, Körner et al. reported a correlation between physical impairment (ALS-FRS) and depressive symptoms [107]. Both Körner et al. and Kübler et al. used the Becks Depression Inventory, a self-reported questionnaire that includes somatic symptoms, which might have inflated the severity of depressive symptoms and biased the correlation. To avoid this inflation of depressive symptoms, we used the depression questionnaire ADI12, which does not include somatic items.

Similar to our finding, depression and disease duration did not correlate in another study [107] but some even suggest that depressive symptoms decreased with longer duration of disease [110].

To prove this, we recommend longitudinal studies, as our cross-sectional findings do not prove a possible relationship between depressive symptoms and a longer disease duration. Some studies outline that especially patients with bulbar symptoms should be screened for depression, as essential functions such as speech impairment, as well as impaired breathing and swallowing correlated with depression [84]. However, in our study, we could not find a correlation between ALS with bulbar symptom onset, language or fluency impairment, NIV, PEG usage and depressive symptoms. This might be explained by the relatively small number of patients with bulbar symptoms.
4.2.6 Quality of Life

The parameter QoL generally assesses how satisfied one feels with life. Factors which might modify QoL are aspects that may increase patients burden, including physical impairment, mental, social and cognitive burden. The coping mechanisms with these burdens determine QoL and depend on their intensity and individuals’ attitude to life [247]. Weis stated, that burden can be experienced differently per individual and just receiving a fatal diagnosis can be a considerable stressor [248]. The increased burden is associated with a decline of QoL [147]. However, a high burden must not in all cases imply a low QoL, as with good psychosocial adaptation, the QoL might remain relatively satisfying.

ACSA and SEIQoL
All three groups had a good QoL measured by ACSA and SEIQoL, and variation between the groups was relatively low. The SEIQoL means from our study (67% in ALS, 72% in IPS and FTD group) are better than those of cancer patients (57/59%) [35, 54] and only slightly below scores of the healthy population (80/82%) [116], indicating a general sense of contentment with life despite the terminal diagnosis. Lulé et al. even found, that the QoL of ALS patients was comparable to the healthy population [139].

SF12
Similar to the assessed affective state with the ADI12, all groups had no significant differences in the mental HRQoL evaluated by SF12 MCS. Compared to the chronically ill German population, the IPS group was below the 50th percentile, indicating a better mental health than 50% of the chronically ill German population. Further, ALS and FTD patients were in the 50th to 75th percentile, demonstrating a better mental HRQoL than 50% to 75% of the chronically ill German population. The physical HRQoL (SF12 PCS) significantly differed between the three groups. The ALS group had the significant lowest physical HRQoL contrary to the other two groups. The physical HRQoL of the ALS group was below the mean of the chronically ill German population, whereas IPS and FTD patients were between the 50th and 75th percentile, with FTD patients being closer to the 75th percentile. Thus, FTD patients had a better physical HRQoL than almost 75% of the chronically ill
German population; which is in contrast to the ALS group, whose physical HRQoL was less than 50% of the chronically ill German population.

The result of physical HRQoL and ALS-FRS did correlate in all groups, which showed the significant worst physical function in the ALS group. The major difference between these two questionnaires is that the ALS-FRS focuses on the physical functions, whereas the physical HRQoL assesses subjectively, which activities the patient thinks, he/she can physically attempt. Once the ALS-FRS indicated severe physical impairment, in most cases, except in severe lack of insight, the physical HRQoL also reflected severer physical health. For instance, physical HRQoL assesses whether there is severe, moderate or no impairment when climbing stairs and the ALS-FRS assesses on a Likert scale, how limited the patient is and whether support is needed when climbing stairs. As seen, the questions are similar and might yield a comparable result, provided that the patient does not lack insight, because the physical HRQoL questionnaire evaluated patients’ subjective estimation. In contrast, the ALS-FRS should be assessed more objectively, despite being based on questions and not a physical examination.

Caregiver’s estimation and physician’s perspective may be included to yield a more objective answer in ALS-FRS.

The ALS group had the highest discrepancy between physical and mental HRQoL. The discrepancy in physical and mental HRQoL shows that the ALS group, despite physical impairment, had an excellent mental HRQoL and a good QoL [134]. Additionally, the IPS group also had a good mental HRQoL, despite their low physical HRQoL, which also shows a relatively good maintenance of their mental HRQoL.

**Depression as a determinant for quality of life and subjective burden**

In our ALS cohort, depressive symptoms significantly correlated with a higher subjective burden and a lower QoL. The correlation between depressive symptoms and QoL in ALS is in line with many other studies [16, 32, 41, 43, 76, 93, 109, 110, 139]. Depressive symptoms may be a sign of insufficient psychosocial adaptation to other impairments, such as physical, cognitive or behavioural deficits. Insufficient coping may increase the subjective burden and may also have a negative effect on QoL.
All QoL questionnaires used in this study were based on patients’ own reports. Interestingly, only the ACSA and SF12 score, but not SEIQoL correlated with depressive symptoms. We might argue, that the SEIQoL allows more individual assessment of QoL, whereas the ACSA focuses on events within the past two weeks. As 85% of the patients in the ALS group were hospitalized recently, we assume the hospitalization, involving a change of a familiar environment, might have caused higher distress than being at home. Such events within the past two weeks might lead to a lower QoL score. In contrast to the IPS group, the SEIQoL did not correlate with depressive symptoms, which indicates maintenance of a satisfactory QoL in the ALS group. It is frequently argued, that ALS patients use coping factors, which improve their adaptation helping them retain a good QoL [135, 138]. Lastly, Matuz et al. outlined the importance of social support in coping with the disease to prevent depression [152].

In contrast, in the FTD group, depressive symptoms, SEIQoL and caregiver-reported burden significantly correlated. In this group, depression might not be reactive but rather a consequence of subcortical structural damage involving the right temporal lobe [124, 159]. Further, we assume, that FTD patients lack disease insight, including the ability to recognize impairments to estimate their QoL. More FTD patients than those from the IPS and ALS groups needed suggestions to name cues in SEIQoL, which might have biased the results. Many FTD patients do show symptoms of depression but do still have a lack of insight. Often, symptoms such as apathy, are recognized by caregivers. Apathy may be so pronounced in an FTD patient, that the disinterest in their environment might be misdiagnosed as MDD [14]. This might be amplified by the fact that frequently, apathy and other behavioural and cognitive deficits are not recognized in FTD patients [53]. We assume, that primary caregivers of FTD patients estimated a higher burden, as patients seem burdened due to a high prevalence of apathy and depressive symptoms.

In ALS and FTD, physical function was not associated with QoL and sTBS. QoL can be assessed with questionnaires not focusing on medical aspects, such as SEIQoL and ACSA, which rather reflect patients’ well-being [44, 224]. Whereas HRQoL is determined with questionnaires like SF12 that focus on patients’ physical impairment and patients’ reaction to this health status [41].
In our ALS and FTD groups, subjective burden and QoL were not associated with
the severity of physical impairment. Interestingly, the ALS group had the significantly
lowest physical HRQoL compared to the other groups. Many studies agree that QoL
in the ALS and FTD groups does not decrease with the severity of physical
impairment [55, 62, 81, 93, 139, 175, 207, 224]. However, it should be noted, that FTD
patients had not such severe physical impairment compared to the other groups.

Several studies reported in ALS patients a good QoL, which is mostly retained
throughout the progression of the disease [76, 110, 139, 174, 207, 224]. Neudert et al.
examined 42 ALS patients three times over four months, and although physical
functions declined, QoL assessed by SEIQoL remained stable [175]. A large
prospective study in ALS patients showed a positive life-sustaining attitude, and QoL
remained stable over a time of 12 months with two measurement points [134]. This
phenomenon of a satisfactory well-being, despite the fatality of the ALS diagnosis,
is called the well-being paradox [136, 138, 139]. Similarly, in our study, we can speak
of this phenomenon, as the ALS group had the most severe physical impairment but
a comparatively satisfied QoL.

Adaptation mechanisms and determinants for a good QoL
Throughout the course of disease, patients who initially declined the use of NIV or
PEG changed their mind and started using them, hence indicating adaptation
processes to better cope with their disease [134]. In terminal diseases, decisions
might radically change, from the wish for assisted suicide [232], to fear of death and
deciding in favor of supportive, palliative treatments [134]. Trust in their coping
strategies and psychosocial adaptation, particularly social support, are one of the
reasons for a relatively good QoL [41, 62, 75, 82, 94, 134, 139, 152, 163, 174, 175].
Patients with terminal diseases tend to focus on the most important things they
retain and on optimizing their remaining time [43, 244]. Life areas, which previously
determined a good QoL, may be shifted to different ones. For instance, health may
be replaced by other determinants like communication and interdisciplinary
treatment, or patients might decrease their expectations regarding health [96, 111,
178, 179, 244].

Similar to other studies, family was most commonly named, and the three groups
rated this cue as being most important and most satisfied with [41, 75, 82, 94, 130,
A supporting family or partner might decrease the burden [151]. A longitudinal study by Goldstein et al. determined the social factors to be essential predictors for well-being in early stages in ALS, which increase self-esteem and lower depression rates. However, as our examination of cognition was in the early stages, most patients did not have cognitive deficits, including executive deficits or verbal fluency deficits which might have impaired social interaction [75]. Nelson et al. split 100 ALS patients into two groups. The first group included patients with a more positive self-reported QoL, and the second group with a more negative self-reported QoL. More than ¾ of patients in both groups named family and other social contacts which helped them cope with their diagnosis [174]. Lulé et al. compared ALS patients with carcinoma patients and found that ALS patients named social contacts as an important determinant for QoL significantly more frequently [136]. A prospective, longitudinal study by Larsson et al. assessed newly diagnosed ALS patients five times within 24 months. Over the whole period, family and friends were rated as essential and weighted highly in SEiQoL [93].

Other crucial factors are a thorough education about the diagnosis as well as an excellent medical treatment by an interdisciplinary team [130, 139, 151, 178] together with early interventions for depressive symptoms [75, 94, 139, 152] and implementation of technological aid devices [41, 75, 157]. Positive thinking is a fundamental part of a good QoL as well [94]. Furthermore, in other studies including ours, the profession was rated as very important with a high satisfaction [175, 176]. Correspondingly, other studies outlined the importance of acceptable socioeconomic status to afford medical appliances, insurance, relaxation activities, as a buffer, and for a disability-friendly home [130, 139, 175, 176]. In our study, travelling and holidays were named as relaxation activities and in all three groups, holidays were rated as very important and with high satisfaction. Albertini et al. found that ALS patients used more coping strategies such as humour, acceptance and positive reframing, the longer the disease lasted [163]. Negative predictors for adjustment were the severity of disease and fast progression rate [134, 151] and a low self-esteem [70].
4.2.7 Subjective burden

Our first hypothesis was, that the subjective burden of ALS and FTD will be similarly low, while that of IPS will be relatively higher. Even though all groups had a comparable affective state and QoL, the burden differed. In our study, FTD patients had the highest subjective burden, partially disproving our hypothesis. Further, ALS and IPS patients had a similar subjective burden, which was comparatively lower than that of FTD patients.

The burden might occur if a patient perceives anxiety or distress when recognizing impairments. The burden might be modified by physical, cognitive or behavioural impairments, as well as other social and mental factors including depressive symptoms. Therefore, we assessed self-reported depressive symptoms in the patient with the ADI12 and with two versions of the burden questionnaire, a self-reported and a caregiver-reported questionnaire, cognitive and behavioural impairments and if those led to a burden in private and occupational life.

Among our FTD cohort, self-reported burden was most severe, and caregiver-reported burden was even higher (+13SD). Still, the self-reported burden between the three groups did not significantly differ. However, the FTD caregiver-reported burden was significantly higher compared to the ALS and IPS caregiver-reported burden. We have to reject our hypothesis, that the IPS group had the highest burden, and that the self-reported burden is low in FTD. When comparing self-reported burden to the mean of all groups (15.59 points), FTD groups’ self-reported burden was moderate to severe with +2.47 SD above the group mean, and ALS (15.09 points) and IPS (14.23 points) groups’ burden was similar to the mean of all groups.

In contrast to the ALS and IPS groups, QoL did not significantly correlate with the self-reported burden in the FTD group. We found that in the FTD group, only SEIQoL and caregiver-estimated burden significantly correlated, which might indicate that the FTD group was not able to reflect on their burden and probably underestimated the burden due to a lack of disease insight. Whereas the caregivers seemed to accurately estimate the burden according to FTD patients’ QoL.
We did not find another study that researched the burden in the FTD group compared to other neurodegenerative diseases, albeit one that compared QoL. Hvidsten et al. found that QoL in early-onset Alzheimer patients was better than in FTD, as FTD patients’ QoL worsened with progressive disease as awareness increased [89]. This study gives a hint to the possibility of FTD patients gaining increased insight of their disabilities and limitations. For further investigations we suggest a longitudinal study about disease burden in FTD and characterization of their change of insight over time.

Determinants for subjective burden in idiopathic Parkinson’s diseases
Ensuring a good QoL is crucial in chronic diseases. Improvement of determinants of QoL can enhance QoL even though the condition itself is not curable [145].

Physical impairment determined depressive symptoms
In our IPS group, physical impairment did significantly determine depressive symptoms which is in line with other studies [149, 202]. During motor fluctuations and off periods, when effectivity of medication decreases, there is a higher level of distress, depression and anxiety. Studies found, that distress increased as the day progressed, due to frustration about motor fluctuations [29, 56]. Similarly, Burn et al. state that depressive symptoms are related to a higher physical impairment, which might indicate that depressive symptoms occur with a more progressed clinical picture [29].

Depressive symptoms determined subjective burden and QoL
In the IPS group, we found a relationship between depressive symptoms and a higher self-reported burden as well as a lower QoL. The SF12, ACSA and SEIQoL significantly negatively correlated with depressive symptoms, indicating that more depressive symptoms were related to a decreased QoL. Other studies agree that depressive symptoms are related to a higher distress and a lower QoL [5, 8, 149, 204]. In the IPS group, the SEIQoL questionnaire correlated with depressive symptoms, whereas in the ALS group, it did not. Therefore, we assume that the IPS group was not able to change determinants to retain a good QoL. A prospective longitudinal study during twelve months in 145 IPS patients researched that depression was one of the strongest predictors of HRQoL [204]. A negative affect
might lead to a high burden and a low QoL, due to deficient dopamine production and release, as well as deficiency of serotonin and noradrenaline, increasing the risk of developing motor and cognitive impairments [6].

In our study, the IPS group had a significantly longer disease duration (mean 121.33 months) compared to the other two groups. We suspect that this longer exposure to and witnessing of the own physical and mental decline, might be a major culprit for the comparatively more significant depressive symptoms in the IPS group. The nature of neurodegenerative diseases with prolonged courses such as IPS, is that symptoms progress, which may be accompanied by progressed frustration about the impairments accompanied by an increased burden and a decline in QoL [141]. All of this, however, presumes intact disease insight. The correlation between a longer disease duration and a lower physical HRQoL (SF12 PCS) is in line with a study by Lyons et al. [141].

Physical impairment and disease duration correlated with subjective burden

Furthermore, physical impairment and disease duration significantly positively correlated with subjective burden. These factors did not correlate in the ALS and FTD groups. In the IPS group, physical impairment highly significantly explained 37.1% of the subjective burden variance. Physical impairment evaluated by H&Y even explained HRQoL (SF12) variability by 51.5%. Thus, a higher subjective burden was related to a longer disease duration and severe physical impairment, especially when measured by H&Y. This relationship complies with Lyons et al., who found that physical impairment and disease duration influenced QoL with a variance of 45% [141]. In an international survey on factors impacting QoL, the physical impairment and medication influenced HRQoL variability, however only by 17.3% [69]. In a prospective, longitudinal study over four years, IPS patients showed increased distress with worsening physical health measured by H&Y and UPDRS [98].

Similarly, Schrag et al. defined physical impairment as one of the determinants of HRQoL in the IPS group [218]. Martinez-Martin et al. argue, that severe symptoms in IPS groups increase the burden and also influence HRQoL [147].

Over time, the risk of treatment specific side effects and complications increases as controlling motor symptoms becomes more challenging. Due to increased resistance to drugs after years of treatment, dosages need to be increased [173].
Besides that, also nonmotor symptoms may fluctuate [148]. The progression of fatigue, apathy, depression, sleep disturbances [39, 218] and autonomic disorders [98, 204, 218] has a substantial impact on the burden and HRQoL [56, 147, 218]. Some studies state, these have an even greater impact on HRQoL than motor symptoms, as nonmotor symptoms often occur before the onset of motor symptoms [148, 226]. This demonstrates the strong influence of disease duration, physical impairment and other nonmotor symptoms on QoL. Skorvanek et al. explored in a cohort of 3206 IPS patients, that both, physical impairment and nonmotor symptoms influenced HRQoL [226]. Still, a shorter disease course in ALS and FTD does not imply milder physical symptoms since their progression can be fast [238]. Comparing other chronic diseases with a long disease course might reveal whether they similarly focus more on physical health and if the physical symptoms and disease duration are related to a higher burden and lower QoL. So far, studies have shown that most patients with fatal diseases such as cancer and ALS, learn to adapt and cope with the situation in their short remaining time [152, 244].

**Physical impairment and disease duration correlated with QoL**

In contrast to the other two groups, in the IPS group, physical impairment and disease duration determined depressive symptoms, subjective burden and QoL. Our finding of a relationship between physical impairment and QoL is in line with other studies [29, 141, 156, 204]. The two tests which objectively assessed physical impairment in IPS, H&Y and UPDRS, correlated with ACSA (QoL) and SF12 (HRQoL). Only the UPDRS correlated with SEIQoL (QoL). Our finding shows, that physical impairment, assessed by UPDRS and H&Y is related to QoL in the IPS group. In contrast to Schrags' findings, in our study, the UPDRS was also sensitive in evaluating the impact of disease severity on QoL [218].

This correlation was not significant in the ALS and FTD group. Matuz et al. agree, that depressive symptoms and low QoL in ALS are not related to the degree of physical impairment but rather a consequence of insufficient psychosocial adaptation to these changes [152].
Correlation of subjective burden and QoL in the ALS and IPS groups

In the ALS and IPS groups, subjective burden and QoL negatively correlated. While in both, ALS and IPS, a higher burden was associated with a lower QoL (SEIQoL for ALS and ACSA for IPS), in ALS it was also associated with a lower mental HRQoL (SF12 MCS) and in IPS with HRQoL (SF12 MCS and PCS).

In the IPS group, the variance of subjective burden was explained by 18.2% from mental HRQoL (SF12 MSC). These correlations show that a lower HRQoL was related to a higher subjective burden in the IPS group, whereas, in the ALS group, only mental HRQoL influenced subjective burden.

In the IPS group, the subjective burden was related to the Global QoL questionnaire ACSA, which assesses how well the patient felt during the last two weeks. In the ALS group, a lower SEIQoL was related to a higher subjective burden, which measures individual QoL and therefore focuses more on individual adaptation abilities. Therefore, a recent negative event does not have a big impact on the burden in the ALS group, as the SEIQoL is not limited to a certain time frame. In contrast, ACSA assesses QoL within the last two weeks and might be negatively influenced by certain events. As only in the IPS group physical HRQoL influenced subjective burden, we might argue that IPS patients focus more on their physical health, in contrast to ALS patients, who seem to prioritize non-physical determinants, resulting in a low burden and a good QoL. However, in all groups, we found no significant association between NIV or PEG usage and depressive symptoms, subjective burden or QoL. This might be explained by the low prevalence of patients using NIV or PEG.

Cognition as a determinant for depression, subjective burden and quality of life

In both ALS and IPS groups, cognitive impairments were related to an increased subjective burden, but not in the FTD group. In contrast to FTD patients, ALS and IPS patients recognized cognitive deficits restricting them in activities of daily living [104, 160, 213]. Noticing limitations may, in case of insufficient psychosocial adaptation, lead to frustration, negative mood and a higher subjective burden. Cognitive decline might lead to an impairment of daily activities and hobbies, thereby contributing to a reactive depression, ultimately increasing their burden. However,
one could also argue, that cognitive impairment is not an uncommon symptom of depression, hence raising the question of which one of these two syndromes, is the culprit, causing the other.

Although, seemingly paradoxical, in ALS patients, cognitive deficits usually accompanied higher burden scores, whilst not affecting QoL and depressive symptoms. However, this can be explained, once we start accounting for psychosocial adaptation. Even with a high burden, good psychosocial adaptation can negate its effects on QoL, resulting in a scenario, where decreased cognition, high burden and yet a good QoL coexist. In a longitudinal study over three years, Sandstedt et al. assessed limitations in activities of daily living in an ALS cohort and found that restrictions in social and lifestyle activities were characteristic, which may increase burden [213]. Still, ALS patients may retain a good QoL, by focusing on other determinants for a good QoL [96, 178]. A slower decline of cognitive deficits, compared to physical function in ALS patients, probably helps their adaptation processes to maintain a good QoL [24, 219, 252].

In IPS patients, we can see the opposite of this phenomenon happening. While in IPS patients, cognitive impairment also positively correlated with subjective burden, the psychosocial adaptation seems to be lacking here, as this increase in burden also manifests itself in a decreased QoL and higher depression scores. This is in line with other studies, which support that nonmotor symptoms [204], including cognitive deficits and depression, cause limitations in activities of daily living [218, 226] and a lower QoL. Cognitive impairments may increase burden and with insufficient psychosocial adaptation, reactive depressive symptoms may arise, which often result in a lower QoL. Correspondingly, studies report a relationship between cognitive impairment and depressive symptoms [180, 218] and between increased burden and a lower QoL in IPS patients [112, 156, 218, 250]. Lawson et al. researched the association between QoL and cognitive deficits in 212 IPS patients over three years at 1.5-year intervals, supporting that cognitive impairment may decrease QoL.
Lack of disease insight was evaluated with a burden questionnaire version for the patient and the primary caregiver, which assesses cognitive and behavioural impairments in private and occupational life. Similar to methods in other studies, we quantified the insight by comparing patients' self-report of burden to the caregiver-report [53, 113, 253].

Our second hypothesis was, that ALS and FTD patients have a lack of disease insight. Despite that the FTD group already estimated their subjective burden quite high, we have to assume, that FTD patients underestimated their subjective burden, as the caregiver-estimated burden was significantly higher. The discrepancy score of the FTD group significantly differed from that of the other two groups, showing that the FTD group underestimated their burden in contrast to the ALS and IPS groups. Our results further support the idea, that FTD patients have a low disease insight, as their subjective burden did not correlate with the caregiver-estimated burden. The subjective burden of our IPS and ALS groups correlated and had low discrepancy with their respective caregiver-estimated burden, translating to a good disease insight, further partially disproving our second hypothesis. Furthermore, depressive symptoms and QoL did not correlate with a higher subjective burden in the FTD group, but only in the ALS and IPS groups.

Loss of disease insight in the FTD group is one of the core criteria in Neary diagnostic criteria for FTD [171]. The significant lower disease insight of FTD patients in contrast to ALS and IPS patients, is in agreement with other studies [53, 253]. Similarly, Woolley et al. found a lack of disease insight in a smaller cohort of ALS-FTD patients [253]. Scherling et al. studied behaviour and reactions to errors in a two-alternative choice button press task in bvFTD, Alzheimer and healthy controls by studying facial emotional response. The bvFTD patients did not produce self-conscious emotions, and skin conductance did not increase. However, they showed a negative emotional response in the face, similar to healthy participants [216]. The partial reaction to the mistake in the FTD patients might be due to limited awareness of mistakes, indicating a lack of disease insight.
Our result, that ALS patients have a good insight, complies with Woolley et al., who found that ALS patients without dementia have a good insight [253]. Only those patients with at least a mild cognitive impairment were associated with a decreased disease insight [113, 253]. Only patients impaired in social cognition were found to have a poor insight [240]. In our study, only 7.5% from the ALS group, and 2.5% from the IPS group, had a mild cognitive impairment (MMST between 19 and 24 points). The majority from the ALS and IPS group had no cognitive impairment, which might explain their good insight. Slight discrepancies between self-report and caregiver-report are normal in self-critical patients and especially in those with depressive symptoms where a patient might underestimate their qualities [200]. Additionally, Ichikawa et al. showed that ALS patients with dementia underestimated their errors in writing and identifying physical impairment. Regardless it must be noted, that from their cohort of 121 ALS patients, only seven had dementia [90].

Similar to our hypothesis, Rankin et al. agree that FTD patients, including those with depressive symptoms, underestimated their subjective burden [200]. We assume that FTD patients with depressive symptoms might differ from the rest of the FTD cohort in disease insight, as we cannot know whether the depression is reactive or not, and reactive depression would necessitate some form of disease insight. To test this hypothesis, we excluded FTD patients with depressive symptoms and found, that in the nondepressed FTD group, cognitive impairments positively correlated with the subjective burden significantly. Therefore, patients without depressive symptoms may actually better recognize their impairments and therefore have a better insight. This contradicts our initial hypothesis.

In the FTD group, 35.3% had mild cognitive impairments and 17.6% even moderate to severe cognitive impairments. We assume that the severe cognitive impairments in the FTD patients are one of the reasons for the lack of disease insight. Eslinger et al. found that FTD patients had less disease insight than the patients with probable Alzheimer disease. The FTD patients with prominent social and dysexecutive impairments had no insight that most behavioural domains were impaired [53]. Furthermore, FTD patients were found to have impaired self-assessment of abilities such as driving a car safe or doing a particular job conscientiously, which indicates a lack of insight [216, 227].
4.3 Strengths and Limitations

In this study, we compared the disease burden in three different neurodegenerative diseases at one time point. Data might be different, depending on an examination closer to the onset of disease or after the disease has progressed.

4.3.1 Strengths

First comparative study among ALS, FTD and IPS patients, to our knowledge
ALS, FTD and IPS have all been plentifully investigated individually. However, to our knowledge there is no study taking the findings for each disease and comparing them in an effort to be able to better estimate QoL and burden in affected patients. Furthermore, along the way of assessing QoL and burden, we carried out a whole array of different tests, which might provide useful comparative data for future studies.

Evaluation of a new variable
To our knowledge, the subjective burden of patients affected by ALS, FTD and IPS has not been investigated, as a variable, before. Not only did we create a new questionnaire in an attempt to record this new data, but we compared it to the burden estimated by a caregiver. However, as discussed in the limitations below, creating a new questionnaire does have its own set of challenges, which might be seen as drawbacks.

Size and characteristics of cohort
Our cohort measures a relatively high number of participants. This, along with a homogenous age group and the presence of neurodegenerative diagnoses in all patients, makes for a uniform cohort, which aids in comparison of patient groups. Our measured mean physical impairment in the ALS group (ALS-FRS 37 points) lies in between the comparatively milder physical impairment documented in other studies by Lulé et al. in 2018 (ALS-FRS 40 points) [132] and the relatively higher physical impairment found by Lulé et al. in 2013 (32.8 points) and Burkhardt et al. (ALS-FRS 32.4 points) [28, 135].
Randomized patient selection
All patients who consented to the study and fulfilled inclusion criteria, in absence of any exclusion criteria, were included in the study. For the FTD group, this proved to be a challenge due to the sparsity of patients. To circumvent this, we not only used patients that were in treatment at the time of recruitment, but we also reached out to former patients, who were still scheduled to future follow-ups. In case the patients consented, we either invited them to the clinic, or scheduled a date for home examinations.

High patient questionnaire-completion rate
All patients, except for one, completed the full battery of self-reported questionnaires. As mentioned in the materials and methods chapter, in both ALS and IPS groups, a similar number of caregiver-reported questionnaires were not returned and in the FTD group, one was declined. Upon comparison of sociodemographic factors in groups with completed caregiver questionnaires and those without, no significant differences were found, aside from the IPS group. In the IPS group significantly more patients were married, with higher caregiver-reported questionnaire completion rate.

Quality and quantity of tests
The standardized, neuropsychologic test battery aided to screen for cognitive, behavioural and physical impairments and depressive symptoms. Furthermore, the questionnaires were used to compare the caregiver and subjective rating, which is a well-recognized method to assess disease insight. The ECAS is a validated, reliable and repeatable instrument to screen for cognitive impairments in ALS, FTD and showed to be sensitive and specific in the IPS group as well [57, 133, 194]. The ADI12 questionnaire is a short, validated test to screen for the most critical depressive symptoms specifically developed for ALS patients [81]. As the IPS group has, to our knowledge, no specific test to screen for depression, we used this test for all three groups. This test is well suitable for neurodegenerative diseases, as it is based on the Becks Depression Inventory, but excludes somatic items.
In contrast to other studies, we used an extensive battery of QoL questionnaires, including HRQoL and QoL questionnaires. SEIQoL evaluates patients' selected cues which determine its QoL, so each can be evaluated individually and summed
together to one score. Each cue can be individually evaluated according to their satisfaction and weighing of importance. SEIQoL is a non-distressing test to assess QoL as it does not focus on disease symptoms. It can help to understand if the patient adjusts to the disease [41]. SEIQoL has been evaluated and considered as a valid tool for ALS [41, 43, 55, 76, 93, 110, 136, 175, 176, 178] and other diseases [96, 154, 229]. The test has the advantage over HRQoL questionnaires, that patients can nominate cues not related to health. These cues might be areas that patients may still retain such as family, hobbies, profession and gardening [43]. The HRQoL questionnaire used in our study focused on other aspects of QoL, namely the mental and physical health-related domains.

4.3.2 Limitations

Unequal gender distribution in the FTD group
We had a small number of FTD patients, and all of them were male, so a study including an equal distribution of gender and disease groups is suggested. Our FTD cohort had a good size comparable to other studies, with a smaller FTD cohort [220, 223] or the same number [216]. There are studies with a few more FTD patients [124, 227] and some with larger cohorts including 74-191 patients [159, 188, 215].

Time and place of examination
A significant criticism is that the place of examination differed and also the time since diagnosis.
Some ALS patients were interviewed shortly after receiving their diagnosis, or while still being uncertain about their diagnosis. This group often experienced increased anxiety and depressive symptoms. A patient who just received its diagnosis might feel a higher burden than one who learnt to adapt to its diagnosis. Additionally, the place of examination differed between patients, as some were examined at home and others in the clinic. The different places of examination might have influenced performance in tests, as a patient being examined in a familial environment might feel more comfortable and secure. Those patients in the hospital might be more depressed, which decreases cognitive performance [34] and also may influence QoL assessments.
Confounding factors
Comparisons are challenging as not all factors can be the same such as living conditions, disease duration and family members. Especially questions on QoL and disease burden might be influenced by the interviewer, place, time, weather, and one’s mood. It should be highlighted, that this is a cross-sectional study, which determined all measured variables at only one certain point in time and therefore results might be negatively influenced by side effects of medication, pain or mood [67]. Especially in IPS, physical impairment scores might be influenced by how well the symptoms were controlled with medication or if the effect already decreased.

Exclusion of patients with severe cognitive impairment
Only a limited number of patients in the ALS and IPS group were available with mild, moderate and severe cognitive impairment, as the line between mild cognitive impairment and being too impaired to answer all questions, is thin. This led to the exclusion of a small amount of ALS, IPS and FTD patients. Due to this preselection of patients, based on cognitive capacity, the meaningfulness of the results about cognitive performance is somewhat limited.

Difficulties with questionnaires
It must be noted, that especially patients from the FTD group had difficulties freely thinking about cues in the self-report questionnaire SEIQoL. In such cases, we presented some examples. Most patients from the ALS and IPS group, however, never saw these examples and thought of their own cues. Therefore, one could argue, that some cues such as profession, were forgotten in pensioners or those on sick leave, although this cue might have been essential for them. Thinking of own cues is preferable, as this self-report questionnaire is designed to measure individual QoL and its determinants. Presenting examples to the cognitively impaired cohort, who had difficulties thinking abstract or understanding the visual analogue scale, might bias results as they might choose the cue, that catches their attention first, without appropriately reassuring, which cues are actually most important to them in life.
Medication

Majority of the patients included in this study were medicated. Of the ALS group 92.6% received riluzole. Other drugs taken by this group were edaravone (15%), rasagiline (12.5%), antidepressant (7.5%) and antipsychotic (2.5%). IPS patients were predominantly taking levodopa (45%). All medication used by the group can be found in the table in chapter 3.6. Four drugs mentioned in the table, were taken by IPS patients (n=5) who participated in a double-blind medication study. In the FTD group the majority received antidepressants (23.5%). However, some ALS-FTD/bvFTD patients additionally took riluzole (17.6%), antipsychotic (17.6%) or benserazide (5.9%). Whether these medications alter the results in any way, is up for debate and could be investigated in a future research.

Criticism of caregiver questionnaires

Many caregivers completed the ECASbg and cTBS with a personal and structured interview, being able to ask questions. Those caregivers, who were not available for a personal and structured interview, had to complete the questionnaires alone at home. We offered this group to contact us in case of any questions. Still, this could bias some results, as the caregivers might interpret some of the symptoms wrong. For instance, it might be challenging to differentiate between behaviour that is a trait of one's personality or a pathologic symptom, such as impulsive behaviour or unemphatic behaviour. Furthermore, the caregiver-estimated questionnaire can be biased by caregivers’ own over- or underestimation of behavioural deviations and burden due to different coping abilities, perspectives and changing mood [252]. An older patient might become more apathetic over time or start to collect things, but this must not be pathologic. We suggest, to rate these symptoms on a continuous scale and not with a dichotomous possibility of either yes or no.

Furthermore, some caregivers spend every day with the patient and therefore might have a different picture and knowledge of the patients' burden than someone, who just visited the patient a few times per week [113].

Additionally, not all primary caregivers' questionnaires were returned. Patients declined the questionnaires due to three main reasons: 1) The caregivers had no time, 2) the patient did not want to put more burden on the caregiver, 3) no close caregiver was available. Some did not return the questionnaires even after being reminded by phone or mail, and one questionnaire was returned empty. More
questionnaires are missing in the ALS and IPS groups, compared to the FTD group. In the ALS and IPS groups, ten caregivers did not estimate behavioural symptoms and to exclude selection bias; we compared the group from which we received the primary caregivers questionnaires to the whole group for any differences in age, duration of disease, physical symptoms, cognitive and behavioural symptoms, QoL and burden. We recommend improvement of caregiver support, to prevent them from being overwhelmed which may also result in an increase of patients’ feeling of being a burden.

Criticism of the amyotrophic lateral sclerosis-functional rating scale
The ALS-FRS has some weaknesses, as the questionnaire does not evaluate increased sputum production, which many patients have. Question twelve asks for respiratory insufficiency; however, in the case of some patients, noninvasive ventilation is indicated and planned, but not yet given. These unprecise questions might bias real physical impairment. For this reason, we also evaluated usage of noninvasive impairment, if it was indicated.

Physical impairment assessment methods differed
Furthermore, it must be noted that physical impairment was assessed with different methods, as each disease has specific physical characteristics. The parameter of physical impairment, was assessed in IPS utilizing the H&Y and UPDRS scores, while in ALS and FTD, the ALS-FRS score was used; hence, the results of the ALS and FTD groups, are fully comparable with each other, but only partially so to the scores of the IPS group. This limitation is unfortunate, but difficult to avoid, as the ALS-FRS score is ALS-specific, and its results for IPS would be meaningless, as IPS and ALS patients differ not only in quantity, but also in quality of impairments. In FTD patients the ALS-FRS score was used due to the ALS-FTD patients and because there is no FTD-specific test for physical impairment. Another limitation is that the physical impairment assessment methods in the IPS group included a physical examination, whereas in ALS and FTD groups are based on questions.
**Anamnestic comparative self-assessment**

In contrast to the SEIQoL, the QoL test ACSA assesses the global happiness within the past two weeks. This can, however, be influenced by one incidental positive event and result in increased global well-being. For instance, some patients just returned from a holiday and still felt happy about it, whereas others were just recently diagnosed, which was one of their worst life events and therefore led to lower global QoL results.

**Short form 12**

In some patients, the SF12 induced feelings of sadness, frustration or anger in the patients, as these focus on aspects of their mental and physical health. During the HRQoL questionnaire, many patients realized the amount of activities they cannot attempt due to physical health, or in other, patients are asked about how they felt mentally in certain situations.

**Assessment of anxiety**

We did not assess the effect of anxiety on disease burden. In many studies, anxiety and depressive symptoms often co-occurred in ALS and IPS groups [173, 178]; however, depression was found to influence cognitive symptoms in ALS, but anxiety was not [34]. Therefore, we decided to focus on depressive symptoms only.

**Burden questionnaire**

The burden questionnaire might yield different results in other countries with different socioeconomic status, culture and countries' health care system as this questionnaire is non-validated; however, to our knowledge, there is no questionnaire available which focuses on the subjective burden of patients.

**Anticipation bias**

There might have been anticipation bias as the interviewer knew about the (suspected) diagnosis. To avoid this, in future studies, a second person could do the interview, who does not know about the diagnosis.
4.4 Conclusion and Outlook

Overall, although all three groups maintained a relatively good QoL and affective state. The burden significantly differed between groups. FTD patients had the highest subjective burden, despite an increased lack of disease insight compared to the other groups. Thus, our first hypothesis has to be partially rejected. Further, ALS patients were found to have a good disease insight similar to the IPS group and thus our second hypothesis has to be partially rejected, too.

ALS patients showed a good QoL, despite that cognitive deficits influenced subjective burden, indicating a very good psychosocial adaptation. IPS patients showed a comparatively insufficient psychosocial adaptation, as cognitive deficits were associated with a low QoL and depressive symptoms. As to be expected from lower levels of disease insight, in FTD patients, these parameters did not influence the subjective burden and QoL as strongly. Additionally, in the IPS group, physical impairment and disease duration played an essential role in determining subjective burden. Depressive symptoms did not correlate with SEIQoL and SEIQoL highly significantly negatively correlated with subjective burden in the ALS group, both suggesting good adaptation and coping.

Therefore, we advocate early diagnosis and management of depressive symptoms and cognitive changes [32]. Changes in cognition might interfere with compliance [92] and may thus lead to increased exposure to hazardous behaviour in case of lack of disease insight. A holistic approach, such as it is promoted by Nelson et al., may influence good well-being [174].

Especially in IPS and FTD patients, family was related to a lower subjective burden. Due to the cross-sectional design, deriving causalities is limited; in order to conclude more reliable cause-effect relationships, further research on disease burden and disease insight in ALS, IPS and FTD patients, and especially longitudinal studies may further promote our understanding of interacting factors and causalities. For this, special emphasis is to be put on testing patients with severe physical impairment. The application of motor adjusted questionnaires can ensure inclusion of patients with an inability to write and speak [82]. Test appliances with eye tracking and brain-computer interfaces are already under development [102, 111, 118, 132].
Only this allows a comprehensive understanding of how disease burden changes in the course of disease trajectories.

Concluding from our results, educating caregivers about lack of disease insight in FTD patients, may increase empathy and thereby also social support from friends and family. Finally, support groups for caregivers and patients may decrease the patients' feeling of being a burden to their caregivers with positive impact for all family members [4, 63, 151, 152, 199].
Abstract

Objective
The influence of cognitive and behavioural impairments and disease insight on subjective burden [sTBS] in amyotrophic lateral sclerosis [ALS], idiopathic Parkinson’s disease [IPS] and frontotemporal dementia [FTD] has never been compared before in one collective study.

Aim
This cross-sectional study investigates the disease burden of ALS, IPS and FTD patients by evaluating the Quality of Life [QoL] and affective state as measures of psychosocial adaptation to cognitive and behavioural impairments, while taking disease insight into account.

Methods
In a prospective design, cognitive and behavioral impairments of 40 ALS, 40 IPS and 17 FTD patients and the ratings of 31 ALS-, 30 IPS- and 16 FTD-caregivers were assessed to compare disease burden and disease insight. Cognition was measured with the Edinburgh cognitive and behavioral screen [ECAS] and mini mental state examination [MMST]. Behavioural impairments were estimated by a caregiver with the ECAS behavioural questionnaire. QoL was evaluated with the schedule for the evaluation of individual QoL [SEIQoL], anamnestic comparative self-assessment [ACSA] and health related QoL with short form 12 [SF 12]. Affect was measured with ALS depression inventory 12 [ADI 12]. The disease burden questionnaire had a self-assessed [sTBS] and a caregiver-assessed [cTBS] version for the patients’ burden. To determine disease insight, we evaluated the discrepancy between sTBS and cTBS.
Results
All three groups maintained a relatively good QoL and affective state. The ALS group had the lowest physical HRQoL but still a good mental QoL, followed by the IPS group. In both, the IPS and ALS groups, cognitive impairments significantly positively correlated with the sTBS. Solely in the IPS group, cognitive impairments, physical impairment and longer disease duration significantly correlated with increased depressive symptoms and a lower QoL. Physical impairment and disease duration also significantly positively correlated with sTBS in the IPS group.
Despite the FTD group scoring the highest burden in sTBS and cTBS, their discrepancy between these two scores was the greatest. The caregiver estimated scores, usually rated the FTD patients’ burden even higher, than their self-assessed questionnaire. Apart from indicating an unexpectedly high burden for the FTD patients, this also indicates a significantly lower level of disease insight, compared to the ALS and IPS groups. In IPS and FTD, family significantly influenced sTBS.

Conclusion
The FTD group displayed the highest sTBS, whereas in the ALS and IPS groups it was in a similar range. The FTD group had the lowest level of disease insight, whereas the ALS and IPS groups had a good disease insight. ALS patients showed good QoL, despite that cognitive deficits influenced the sTBS, indicating a good psychosocial adaptation. IPS patients showed a comparatively insufficient psychosocial adaptation, as cognitive deficits, physical impairment and long disease duration were associated with a low QoL and more depressive symptoms. Social support positively influenced burden especially in IPS and FTD groups and thus should be promoted in a holistic therapy approach. Caregivers should be educated about the lack of insight in FTD patients, in an attempt to raise empathy and increase social support.

Outlook
Research on disease burden and disease insight, especially longitudinal studies may further promote our understanding of interacting factors and causalities.
6 Bibliography


Behavioural Amyotrophic Lateral Sclerosis Screen: A cross-sectional comparison of established screening tools in a German-Swiss population. Amyotroph Lateral Scler Frontotemporal Degener, 16: 16-23(2014)


criterion to reconcile 2 surveys' estimates. Arch Gen Psychiatry, 59: 115-123(2002)


### Psychische Belastung: Selbsteinschätzung des Patienten

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<tr>
<th>Name</th>
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<tr>
<th>Fragen zu generellen Änderungen durch Ihre Erkrankung</th>
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<td>1 Sind die Änderungen durch die Erkrankung belastend in Ihrem Privatleben?</td>
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<th>Fragen zu Änderungen Ihres Denkens (Kognition)</th>
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<td>3 Haben Sie Probleme, sich Dinge zu merken?</td>
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<td>4 Haben Sie Probleme, sich zu orientieren?</td>
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<td>5 Lässt Ihre Aufmerksamkeit schnell nach oder haben Sie Schwierigkeiten Probleme zu lösen?</td>
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<td>7 Haben Sie das Gefühl, dass Sie Probleme haben, flüssig zu sprechen?</td>
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Psychische Belastung aus der Sicht des Angehörigen

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Fragen zu Änderungen seines/ihres Verhaltens

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8 Danksagung

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9 Lebenslauf

Die Inhalte der Seite wurden aus Datenschutzgründen entfernt.