Aus der Klinik und Poliklinik für Nuklearmedizin

der Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. med. Peter Bartenstein

Einsatz der Positronen-Emissions-Tomographie mit [^{18}F]FDG für die Diagnostik von neurodegenerativen Erkrankungen aus dem frontotemporalen Formenkreis

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von

Johanna Meyer-Wilmes

aus

Münster

Jahr

2022

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	PD. Dr. Matthias Brendel
Mitberichterstatter:	PD. Dr. Janusch Peter Blautzik
	Prof. Dr. Dieter Edbauer
Mitbetreuung durch den promovierten Mitarbeiter:	Dr. Leonie Beyer
Dekan:	Prof. Dr. med Thomas Gudermann
Tag der mündlichen Prüfung:	14.07.2022

Affidavit

Eidesstattliche Versicherung

Meyer-Willmes, Johanna

Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Einsatz der Positronen-Emissions-Tomographie mit [^{18}F]FDG für die Diagnostik von neurodegenerativen Erkrankungen aus dem frontotemporalen Formenkreis

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 18.07.2022
Ort, Datum

Johanna Meyer-Wilmes
Unterschrift Doktorandin

Inhaltsverzeichnis

Affidavit **3**

Inhaltsverzeichnis **4**

Abkürzungsverzeichnis **5**

Publikationsliste **7**

Beitrag zu den Veröffentlichungen **8**

1.1 Beitrag zu Paper I 8

1.2 Beitrag zu Paper II 8

2. Einleitung **9**

2.1. Demenzerkrankungen und FDG-PET 9

2.2 Frontotemporale Lobärdegeneration 9

2.3 Klinische/ neuropsychologische Diagnostik 13

2.4 Bildgebene Diagnostik 17

2.4.1 Magnetresonanztomographie 17

2.4.2. Nuklearmedizinische Verfahren 18

2.4.2.1 IZBM-SPECT 18

2.4.2.2 FDG-PET 19

2.4.2.3 Tau-PET 20

2.5 Zielsetzung 21

3. Inhalte der Promotionsarbeit **22**

3.1 FDG-PET als Gatekeeper für eine weitere Diagnostik mittels TAU-PET 22

3.2 Kognitive Reserve bei FTD 27

4. Zusammenfassung: **31**

5. Abstract (English): **32**

6. Paper I **34**

7. Paper II **44**

8. Literaturverzeichnis **52**

Danksagung **60**

Lebenslauf **61**

Abkürzungsverzeichnis

3R/4R	Isoform des Tau-Proteins (3-/4-Repeat)
AD	Alzheimer's disease (Alzheimer-Krankheit)
ASOs	Antisense-Oligonukleotide
Aβ	β-Amyloid-Protein
bvFTLD	Verhaltensvariante der frontotemporalen Demenz
CBD	Corticobasale Degeneration
CBS	Corticobasales Syndrom
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
EWS	Ewing-Sarkom-Protein
FDG	[^{18}F]-markierte Fluordesoxyglucose
FTD	Frontotemporale Demenz
FTLD	Frontotemporale Lobärdegeneration
FUS	Fused in sarcoma
GRN	Granulin
HC	Healthy controls
IQ	Intelligenzquotient
MAPT	Microtubule-associated protein tau
MMSE	Mini-Mental State Examination
mRNA	Mitochondriale Ribonukleinsäure
MRT	Magnetresonanztomographie
NINDS-SPSP	The National Institute of Neurological Disorders and Stroke-Society for Progressive Supranuclear Palsy
NPV	Negativer prädiktiver Wert
OGA	O-GlcNacase, O-verknüpftes N-Acetylglucosamin
PD	Parkinson's disease (Parkinson-Krankheit)
PET	Positronen-Emissions-Tomographie
PPA	Primär progressive Aphasie
lv	Logopenische Variante
nfv	Nicht flüssige Variante
sv	Semantische Variante
PPV	Positiver prädiktiver Wert

PSP	Progressive supranukleäre Blickparese
p-Tau	Phosphoryliertes Tau-Protein in der Liquorflüssigkeit
siRNA	Small interfering Ribonukleinsäure
SPECT	Einzelphotonen-Emissionscomputertomographie
SUVR	Standardized uptake value ratio
TAF15	TATA-binding protein-associated factor 15
T+ APS	Taupositives atypisches Parkinsonsyndrom
t-Tau	Gesamtlast des Tau-Proteins in der Liquorflüssigkeit (Total-Tau)

Publikationsliste

Clinical Routine FDG-PET Imaging of Suspected Progressive Supranuclear Palsy and Corticobasal Degeneration: A Gatekeeper for Subsequent Tau-PET Imaging?
Beyer, L.*; **Meyer-Wilmes, J.*;** Schoenecker, S.; Schnabel, J.; Brendel, E.; Prix, C.; Nübling, G.; Unterrainer, M.; Albert, N. L.; Pogarell, O.; Perneczky, R.; Catak, C.; Bürger, K.; Bartenstein, P.; Bötzel, K.; Levin, J.; Rominger, A.; Brendel, M. **Geteilte Erstautorenschaft*
Front Neurol. 2018 Jun 20;9:483. doi: 10.3389/fneur.2018.00483. eCollection 2018.
IF 2.635

Cognitive Reserve Hypothesis in Frontotemporal Dementia: A FDG-PET Study.
Beyer, L.; **Meyer-Wilmes, J.;** Schönecker, S.; Schnabel, J.; Sauerbeck, J.; Scheifele, M.; Prix, C.; Unterrainer, M.; Catak, C.; Pogarell, O.; Palleis, C.; Perneczky, R.; Danek, A.; Buerger, K.; Bartenstein, P.; Levin, J.; Rominger, A.; Ewers, M.; Brendel, M.
Neuroimage Clin. 2021;29:102535. doi: 10.1016/j.nicl.2020.102535. Epub 2020 Dec 16.
IF 4.881

Beitrag zu den Veröffentlichungen

1.1 Beitrag zu Paper I

Datenakquise, Klassifizierung der Patienten gemäß Diagnosekriterien (NINDS-SPSP-Kriterien (PSP) und den Diagnosekriterien von Armstrong et al. (CBD), Auswertung der Bilder, statistische Auswertung (Überprüfung der Normalverteilung durch Kolmogorov-Smirnov-Test, Verwendung des nichtparametrischen χ^2-Test zur signifikanten Differenzierung der Subgruppen, Berechnung von PPV, NPV, Sensitivität und Spezifität), Schreiben wesentlicher Inhalte, kritische Überarbeitung und Beitrag zur Finalisierung

1.2 Beitrag zu Paper II

Datenakquise, Klassifizierung der Patienten gemäß Diagnosekriterien, Normierung der Bilder auf ein hausinternes FDG-PET- Template, Skalierung der Bilder, statistische Auswertung (voxelbasierte Analyse mittels eines ungepaarten *t*-Tests, lineare Regressionsanalyse), kritische Überarbeitung und Beitrag zur Finalisierung

2 Einleitung

2.1 Demenzerkrankungen und FDG-Positronen-Emissions-Tomographie

Bedingt durch den demographischen Wandel steigt der Anteil älterer Menschen an der Weltbevölkerung. Dies ist verbunden mit einer zunehmenden Anzahl von Demenzerkrankungen auf geschätzt 115 Millionen bis zum Jahr 2050 (Tiwari, Atluri, Kaushik, Yndart, & Nair, 2019). Aus der stetig steigenden Inzidenz resultiert ein globales Problem für das Gesundheitssystem (Wimo, Jönsson, Bond, Prince, & Winblad, 2013).Trotz weitreichender Bemühungen ist bislang bei nahezu allen Demenzformen keine kausale Therapie bekannt. Bisher umfasst die pharmakologische Behandlung hauptsächlich Medikamente zur symptomatischen Behandlung. In Hinblick auf potenzielle Therapieoptionen ist es entscheidend, die Pathophysiologie neurogenerativer Erkrankungen besser zu verstehen und Biomarker zu entwickeln, die bereits vor dem Tod eine Diagnose der Erkrankung ermöglichen (Tsai & Boxer, 2016). Die Positronen-Emissions-Tomographie (PET) mit radioaktiv markierter Glukose ([^{18}F]Fluordesoxyglucose [FDG]) wird bereits klinisch zur diagnostischen Abklärung verschiedener Demenzerkrankungen eingesetzt. Insbesondere bei der Differentialdiagnostik zwischen klinisch ähnlichen Syndromen kann eine höhere diagnostische Sicherheit erreicht werden, um perspektivisch eine rechtzeitige Zuführung zu möglichen neuen Therapieformen zu erlangen (Nestor et al., 2018).

2.2 Frontotemporale Lobärdegeneration

Die frontotemporale Lobärdegeneration (FTLD) umfasst ein Spektrum von neurodegenerativen Erkrankungen mit unterschiedlichen klinischen Phänotypen, die alle mit einer Pathologie im Frontal- und Temporallappen des Gehirns einhergehen. Die

Ursache des neuronalen Zellverlusts kann auf verschiedene neuropathologische Befunde zurückgeführt werden (Woalder, 2017). Insgesamt zeigen sich klinisch überlappende Symptome, sodass die verschiedenen Erkrankungen teilweise auch als Subtypen einer Erkrankung diskutiert werden (Sha, Hou, Viskontas, & Miller, 2006). Zu den Erkrankungen des frontotemporalen Formenkreises zählen neben der frontotemporalen Demenz (FTD) als Verhaltensvariante (behavioral FTD [bvFTD]) verschiedene Subvarianten mit Einschränkung der Sprache oder des Sprachverständnisses (primär progressive Aphasie [PPA]), die amyotrophe Lateralsklerose mit FTD sowie als atypische Parkinsonsyndrome das corticobasale Syndrom (CBS) und die progressive supranukleäre Blickparese (PSP) (Woalder, 2017). Die Hauptentität des frontotemporalen Formenkreises ist die FTD, die mit einer Prävalenz von 1–22 pro 100 000 die dritthäufigste Form von Demenz hinter der Alzheimer-Krankheit (AD) und der Lewy-Körper-Demenz darstellt. Nach klinisch dominierender Symptomatik wird die FTD in zwei Hauptgruppen unterteilt, bestehend aus PPA und bvFTD (Neary et al., 1998). Erstere lässt sich nochmals in drei Unterformen unterteilen: die nicht flüssige Variante (nfvPPA), die semantische Variante (svPPA) sowie die logopenische Variante (lvPPA) (M. Gorno-Tempini, 2011). Die Verhaltensvariante zeichnet sich durch Veränderungen der Persönlichkeit, des Verhaltens und der Emotionen aus (Rascovsky et al., 2011). Diese Verhaltensstörungen sind beispielsweise Apathie, Enthemmung oder neu aufgetretene Zwänge. Die svPPA tritt mit überwiegend sprachbasierten Symptomen auf sowie einem langsamen Verlust des semantischen Wissens. Bei der nfvPPA stehen ebenfalls sprachliche Probleme im Vordergrund, die sich jedoch im Vergleich zur svPPA auf die Grammatik und Wortfindung beziehen. Patienten mit lvPPA haben vorranging Defizite bei Satzwiederholungen und leiden unter Wortfindungsstörungen. Im Verlauf der

Erkrankung entwickelt sich eine Beeinträchtigung des Satzverständnisses (M. Gorno-Tempini, 2011).

PSP tritt mit einer Prävalenz von 5–10 pro 100 000 und in einem Durchschnittsalter der Patienten von 65 Jahren auf; das Geschlechterverhältnis ist größtenteils ausgewogen (Stamelou et al., 2010). Die klinische Manifestation von PSP ist sehr vielfältig (Stamelou et al., 2010). Das Richardson-Syndrom ist die häufigste klinische Unterform (ca. 40 %) mit Levodopa-resistenten akinetisch-starren Symptomen, die die Axialmuskulatur betreffen, einer Tendenz zum Rückfall und einer vertikalen Blickparese (Stamelou et al., 2010). Ebenfalls typisch ist ein Frontallappensyndrom mit Apathie und beeinträchtigter Exekutivfunktion, welches klinisch schwierig von der bvFTD abzugrenzen ist. In etwa 20 % der Fälle weist die PSP beginnend einen Levodopa-ansprechenden Parkinsonismus auf, der bis zum Einsetzen der vertikalen Blickparese die Unterscheidung von der Parkinson-Krankheit (PD) erschwert. Zudem zeigt sich in 10 % der Fälle ein CBS, welches vorrangig bei Patienten mit corticobasaler Degeneration (CBD) klinisch dominiert (Respondek et al., 2014). Einschlüsse mit Tau-Proteinen sind bei PSP im Wesentlichen im Hirnstamm zu finden. Im Kortex sind sie vorrangig im primären motorischen Kortex und im Bereich der Augenfelder lokalisiert (Woalder, 2017). CBD zählt als atypisches Parkinsonsyndrom ebenso zu den Entitäten der FTLD. Die Tau-Ablagerungen befinden sich in hierbei in den distalen Fortsätzen der Astrozyten und im Gegensatz zur PSP ist die kortikale Beteiligung der Ablagerungen deutlich höher (Bürger, Arzberger, Stephan, Levin, & Edbauer, 2017). Die Prävalenz der Erkrankung liegt bei 1 pro 100 000 und sie tritt etwa zwischen dem 6. und 7. Lebensjahrzehnt auf (Wenning et al., 1998). Vorrangiges Symptom ist das CBS, welches eine Konstellation von Symptomen ist, die man auf die Schädigung der Basalganglien und der Großhirnrinde zurückführt und die asymmetrisch auftreten (Rebeiz, Kolodny, & Richardson, 1967). Neben dem CBS als klinische Diagnose sind

bei der neuropathologisch gesicherten CBD ebenfalls klinische Syndrome wie das Frontallappensyndrom und das Richardson-Syndrom zu verzeichnen (Levin, Kurz, Arzberger, Giese, & Höglinger, 2016). Gegenwärtig gibt es weder für die CBD noch für die PSP eine kausale Behandlung der Erkrankung. Symptomatische Behandlungen sind nur von begrenzter Wirksamkeit und von geringer Evidenz gestützt. Neuropathologisch können, bei deutlicher Überlappung der klinischen Symptomatik, vier zugrundeliegende Pathologien differenziert werden: FTLD-TAU, FTLD-TDP, FTLD-FET und FTLD-UPS (MacKenzie et al., 2010).

Die abnorme intrazelluläre Akkumulation von hyperphosphoryliertem Tau-Protein zählt insbesondere bei den atypischen Parkinsonsyndromen (PSP, CBS), aber auch bei einem signifikanten Anteil der übrigen Erkrankungen aus dem frontotemporalen Formenkreis, zu einer häufigen neuropathologischen Ursache (siehe Abbildung 1).

Darüber hinaus ist das Tau-Protein auch bei weiteren neurodegenerativen Erkrankungen, insbesondere der AD, nachweisbar. All diese Erkrankungen werden als Tauopathien zusammengefasst (Lee & Leugers, 2013). Durch entweder drei oder vier Wiederholungen der Mikrotubuli-Bindungsdomänen entstehen die Tau-Isoformen 4R-TAU und 3R-TAU sowie 3R/4R-TAU (Mandelkow & Mandelkow, 2012). Zu FTLD-TAU werden folgende neurodegenerative Erkrankungen gerechnet: Morbus Pick mit vorherrschender Ablagerung von 3R-TAU, sowie CBD, PSP, globale gliale Tauopathie und die Silberkornkrankheit mit vorherrschend 4R-TAU.

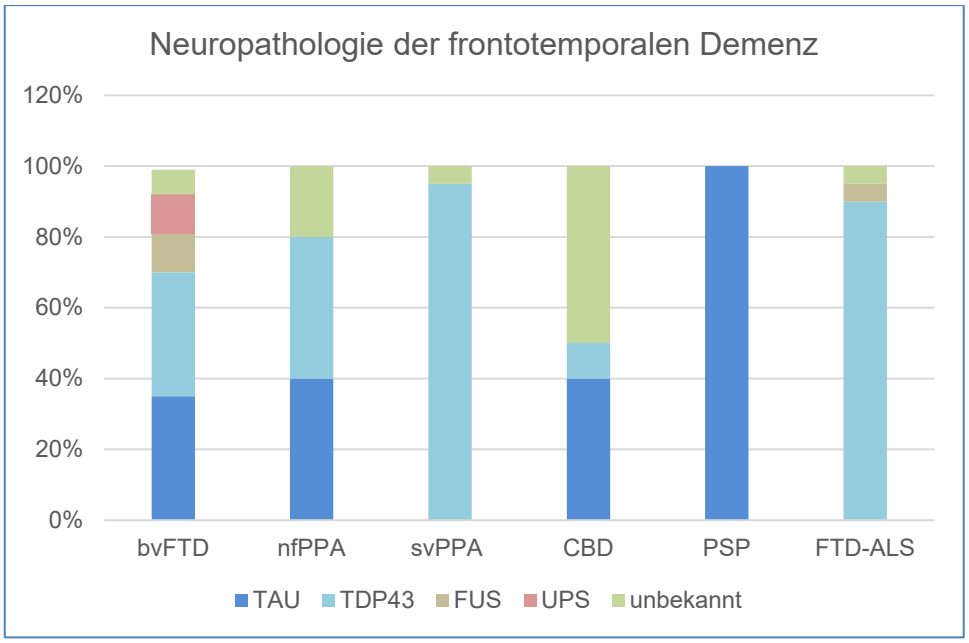


Abbildung 1: Die Häufigkeitsverteilung der aggregierenden Proteine in den klinischen Syndromen (modifiziert nach Bürger et al., 2017).

Die Diagnosestellung gestaltet sich schwierig, da Patienten mit einer Erkrankung aus dem frontotemporalen Formenkreis eine große Ähnlichkeit untereinander aufweisen, weshalb die endgültige Bestätigung der Diagnose derzeit nur mittels Autopsie erfolgen kann. Insbesondere in Hinblick auf künftig verfügbare Therapien ist eine Diagnosestellung vor dem Tod jedoch höchst relevant und eine zuverlässige klinische und bildmorphologische Diagnostik wird zunehmend wichtiger.

2.3 Klinische/neuropsychologische Diagnostik

Im Rahmen der diagnostischen Abklärung frontotemporaler Erkrankungen erfolgt eine ausführliche Eigen-, Fremd-, Medikamenten-, Familien- und Sozialanamnese, um die Hauptsymptome, den Schweregrad und den bisherigen Verlauf besser einschätzen zu können. Zur Quantifizierung und Schweregradeinteilung der kognitiven Defizite wird die Mini-Mental State Examination (MMSE) im Rahmen des Screenings auf kognitive Defizite angewendet. Außerdem erfolgt in der Regel eine detaillierte neuropsychologische Testung zur genaueren Differenzierung. Ein weiterer Bestandteil

der klinischen Routinediagnostik ist die Untersuchung des Blutes zum Ausschluss von Differentialdiagnosen wie beispielsweise Hypothyreoidismus oder Vitamin-B_{12}-Mangel, welche eine kognitive Störung hervorrufen können. Zudem wird die Untersuchung der Neurodegenerationsmarker Amyloid-β_{1-42} ($A\beta_{42}$), Gesamt-Tau (t-Tau) und phosphoryliertes Tau (p-Tau) im Liquor zur sensitiven Abgrenzung von AD empfohlen. Des Weiteren empfiehlt die aktuelle S3-Leitlinie „Demenzen“ eine konventionelle kraniale Computertomographie oder kraniale Magnetresonanztomographie zum Ausschluss möglicher vaskulärer Ursachen einer Demenz (Mathias & Burke, 2009) (Targosz-Gajniak, Siuda, Ochudło, & Opala, 2009).

Gemäß der S3-Leitlinie für Frontotemporale Demenz von Januar 2016 ergeben sich folgende Diagnosekriterien. Für die bvFTD muss eine fortschreitende Zunahme von Verhaltensdefiziten oder kognitiven Defiziten nachgewiesen werden. Um eine mögliche bvFTD zu diagnostizieren, müssen mindestens drei der folgenden Symptome zutreffen. Darunter fällt frühe Verhaltensenthemmung, frühe Apathie oder Passivität, früher Verlust von Sympathie oder Empathie, stereotypes oder zwanghaftes/ritualisiertes Verhalten, Hyperoralität oder Veränderung der Ernährungsgewohnheiten und schließlich ein neuropsychologisches Profil. Für die bvFTD gilt, dass die Kriterien für eine mögliche FTD erfüllt werden müssen. Außerdem muss ein signifikantes Fortschreiten funktioneller Defizite erkennbar sein und die Ergebnisse der Bildgebung müssen konsistent mit der Diagnose einer bvFTD sein.

Die allgemeinen Diagnosekriterien für das Vorliegen einer PPA schließen folgende drei Kriterien ein. Auftreten von Sprachschwierigkeiten sowie dadurch verursachte Einschränkung im alltäglichen Leben und als Drittes, dass die Aphasie bei Symptomerstmanifestation in der initialen Phase der Erkrankung das Hauptsymptom darstellen muss.

Für die klinische Diagnose der nfvPPA muss einer der folgenden Hauptkriterien vorliegen. Entweder Agrammatismus in der expressiven Sprache oder angestrengtes, stockendes Sprechen mit inkonsistenten Lautfehlern und Lautentstellungen (Sprechapraxie). Zudem müssen zwei von drei Nebenkriterien erfüllt werden. Diese umfassen beeinträchtigtes Verständnis von syntaktisch komplexen Sätzen, intaktes Einzelwortverständnis oder intaktes Objektwissen. Die Diagnose der svPPA ist dann erfüllt, wenn eine Beeinträchtigung des Einzelwortverständnisses und eine Beeinträchtigung beim Benennen von Wörtern vorliegt. Zusätzlich müssen weitere drei von vier Nebenkriterien zutreffen. Diese beinhalten beeinträchtigtes Objektwissen, intaktes Nachsprechen, intakte Sprachproduktion und Oberflächendyslexie/Dysgraphie (M. Gorno-Tempini, 2011). Folgende Hauptmerkmale müssen sich zur Diagnosestellung einer lvPPA bewahrheiten. Wortfindungsstörungen für Einzelworte in Spontansprache sowie ein beeinträchtigtes Nachsprechen auf Satz- und Phrasenebene. Außerdem müssen drei der folgenden Nebenkriterien erfüllt sein. Phonematische Paraphasie in Spontansprache und Benennen, intaktes Einzelwortverständnis und Objektwissen, intakte Sprechmotorik und kein offenkundiger Agrammatismus.
Zur Diagnostik der CBD, die in eine mögliche CBD und eine wahrscheinliche CBD eingeteilt wird, gelten folgende Kriterien: Die Erkrankung muss einen progredienten Verlauf nehmen und seit mindestens 1 Jahr bestehen. Zusätzlich muss mindestens ein Symptom des CBS, beziehungsweise zwei bei wahrscheinlicher CBD, vorliegen. Diese Symptome sind Rigor, Akinesie, Dystonie, Myoklonus, Extremitätenapraxie, kortikal-sensorische Ausfälle und das Alien-Limb-Phänomen (Shimohata, Aiba, & Nishizawa, 2015). Trotz zahlreicher Überarbeitungen der diagnostischen Kriterien der CBD erweist sich diese Krankheit für Ärzte als diagnostische Herausforderung, da die Vorhersage einer Neuropathologie nur in 56 % der Fälle mit der Autopsie übereinstimmt (Armstrong et al., 2013). In vielen klinischen Fällen gibt es eine signifikante

Überschneidung mit PSP. Über 50 % der Patienten, bei denen ein CBS diagnostiziert wurde, besaßen eine PSP-Pathologie (Woalder, 2017). Die vom National Institute of Neurological Disorders and Stroke-Society for PSP (NINDS-SPSP) vorgeschlagenen klinischen Kriterien sind diejenigen, die auch in unserer Studie als Diagnosekriterien für PSP genutzt wurden. Die Kriterien weisen eine sehr hohe Spezifität von etwa 95–100 % für wahrscheinliche PSP und 80–93 % für mögliche PSP auf (Litvan et al., 1996) ((Lopez et al., 1999) ((Osaki et al., 2004). Die Sensitivität ist jedoch begrenzt und liegt im Median nur bei 24 % (Lopez et al., 1999). In der Regel erfolgt die Diagnosestellung erst nach 3–4 Jahren, wenn die Kardinalsymptome wie Stürze und supranukleäre Blicklähmung schon eindeutig erkennbar sind (Respondek et al., 2013). PSP teilt man in vier diagnostische Stufen ein. Diese beinhalten definitive, wahrscheinliche, mögliche und suggestive PSP. Die definitive Stufe kann derzeit nur neuropathologisch sicher festgestellt werden. Wahrscheinliche PSP wird beim Vorhandensein hochspezifischer klinischer Kriterien diagnostiziert, mögliche PSP hingegen durch weniger spezifische, jedoch hochsensitive Kriterien. Suggestive PSP eignet sich zur Früherkennung von PSP-Patienten, deren Kriterien nicht ausreichen, um in die „wahrscheinliche“ oder „mögliche“ PSP-Untergruppe zu fallen (Josephs, Lang, & Mollenhauer, 2018). Das Kriterium mit der größten Relevanz aufgrund der hohen Spezifität und Sensitivität ist die vertikale supranukleäre Lähmung (Höglinger et al., 2017). Kriterien mit hoher Sensitivität aber reduzierter Spezifität sind Parkinsonismus, Tremor und/oder Asymmetrie und/oder Levodopa-Aufnahme. Eine sehr niedrige Sensitivität bei hoher Spezifität weisen Gangblockaden auf. Dieses Symptom hat somit einen hohen Vorhersagewert für die Erkrankung (Höglinger et al., 2017). Das CBS stellt ein Symptom mit niedriger Sensitivität und niedriger Spezifität dar, welchem mehrere Pathologien zugrunde liegen können (Höglinger et al., 2017). In frühen Stadien ist PSP schwierig zu diagnostizieren, da sie sich noch mit vielen anderen Syndromen

überschneidet (Woalder, 2017). Hingegen konnte bei der Abschlussuntersuchung eine 80-prozentige Überschneidung mit der Pathologie festgestellt werden.

2.4 Bildgebende Diagnostik

Mit der oben beschriebenen Routinediagnostik wird häufig eine Verdachtsdiagnose gestellt. Um die Demenzform jedoch genauer zu klassifizieren und somit von anderen Differentialdiagnosen abgrenzen zu können, ist häufig eine weiterführende Diagnostik notwendig.

2.4.1 Magnetresonanztomographie

Mittels Magnetresonanztomographie (MRT) zeichnet sich ein regionenspezifisches Neuropathologiemuster der jeweiligen Demenzform ab. Das in der MRT nachweisbare bvFTD-Atrophiemuster ist eine Kombination aus medial-frontaler, orbital-insularer und anterior-temporaler Atrophie. Der mediale Temporallappen ist anterior stärker betroffen. Die Hirnatrophie bei bvFTD umfasst in manchen Fällen auch subkortikale Strukturen wie das Striatum, den Thalamus und den Hypothalamus (Filippi et al., 2012). Außerdem zeigt sich im MRT eine Erweiterung des III. Seitenventrikels (Filippi et al., 2012). Bei der svPPA weist das MRT eine Atrophie des anterior-temporalen Lappens und anterioren Hippocampus auf. Die nfvPPA ist mit einem charakteristischen Muster der linken anterioren Peri-Sylvian-Atrophie assoziiert, an dem der untere, der operkuläre und der insuläre Teil des Frontallappens beteiligt sind. Motorische und prämotorische Regionen sowie das Broca-Areal sind ebenfalls betroffen. In der lvPPA beeinflusst das Atrophiemuster hauptsächlich den linken temporoparietalen Übergang, einschließlich der oberen und mittleren temporalen Gyri sowie der unteren parietalen Lappen (M. L. Gorno-Tempini et al., 2004). Das strukturelle MRT zeigt bei PSP

typischerweise eine Atrophie im Mittelhirn und den oberen Kleinhirnstielen. Bei T2-Hyperintensität und Atrophie des Tegmentums unter relativer Erhaltung des Mittelhirn-Tectums und der Hirnstiele zeigt sich das Mickey-Mouse-Zeichen. Zeigt sich eine alleinige Atrophie des Mittelhirn-Tegmentums, spricht man vom Morning-Glory-Zeichen. Bei CBD wird häufig eine asymmetrische kortikale Atrophie im Frontoparietallappen beobachtet, die kontralateral zur klinisch stärker betroffenen Körperseite verläuft. Im Vergleich zur PSP wurde bei der CBD eine stärkere Atrophie im dorsofrontalen und parietalen Kortex beobachtet (Saeed, Lang, & Masellis, 2020).

2.4.2 Nuklearmedizinische Verfahren

Neben der Basisdiagnostik via MRT ist häufig eine weiterführende Diagnostik notwendig. Nuklearmedizinische Verfahren, insbesondere die PET, bieten neben der Erfassung des topographischen Ausmaßes der Krankheit den Vorteil, Aussagen über die aktuelle Funktion der Hirnregion zu treffen.

2.4.2.1 IBZM-SPECT

Als weiterführendes diagnotisches Mittel ist die SPECT (Einzelphotonen-Emissionscomputertomographie bzw. single photon emission computed tomography) aufzuführen. PSP und CBD besitzen zahlreiche Neuronensysteme des zentralen Nervensystems, auch GABAerge Neuronen im Striatum, die postsynaptische Dopamin-D2-Rezeptoren tragen. IBZM (^{123}I-Iodobenzamid), ein Analogon der Benzamid-Neuroleptika Sulpirid und Tiaprid, bindet an D2-Rezeptoren und ermöglicht die Untersuchung des postsynaptischen dopaminergen Systems mittels SPECT (Brücke et al., 1991). Bei der CBD kommt es zu einer asymmetrischen Reduktion der striatalen Aktivität, kontralateral zu den bestehenden Symptomen, wohingegen die striatale

Aktivität bei der PSP symmetrisch vermindert ist (Lizarraga, Gorgulho, Chen, & Salles, 2016). Dagegen ergibt die IBZM-SPECT bei der PD typischerweise einen Normalbefund. PSP kann somit aufgrund der verminderten Aktivität bei der postsynaptischen D2-Rezeptor-Bildgebung von PD unterschieden werden (Broski et al., 2014). Bei der CBD kommt es im Gegensatz zur PSP seltener zum Verlust postsynaptischer Dopamin-D2-Rezeptoren, weshalb die Spezifität und die Sensitivität der Bildgebung deutlich verringert sind (Brücke et al., 1991).

2.4.2.2 FDG-PET

Mittels FDG-PET Untersuchung können Regionen mit verminderter Stoffwechselaktivität sichtbar gemacht werden. Der Glukosemetabolismus nimmt bei neuronaler Degeneration und synaptischer Dysfunktion ab. Bei der FTD manifestiert sich das typische Hypometabolismus-Muster im Frontallappen und anterioren Temporallappen (Ishii et al., 2020). Des Weiteren zeigen diese Patienten einen Hypometabolismus im Bereich der medialen Thalamusregion, der Gyri cinguli und der Insula sowie in den subkortikalen Bereichen einschließlich der Basalganglien (Kato, Inui, Nakamura, & Ito, 2016). In fortgeschrittenen Stadien breitet sich der Hypometabolismus zu den parietalen und temporalen Kortizes aus (Diehl-Schmid et al., 2007). Der lokale Hypometabolismus wird bei svPPA in der Temporalregion, bei bvFTLD in der Frontalregion und bei nfvPPA in der Peri-Sylvian-Region beobachtet (Che, Song, Gao, Ren, & Wang, 2018). Bei CBD findet sich in der stärker betroffenen Hemisphäre ein asymmetrischer Hypometabolismus im frontotemporalen Kortex, im frontoparietalen Kortex, im Nucleus caudatus und im Thalamus. In der weniger betroffenen Hemisphäre befindet er sich vorrangig im Nucleus caudatus und im motorischen Kortex (Pardini et al., 2019). Das Muster zeigt eine Übereinstimmung mit der pathologisch bestätigten Diagnose sowie mit den Befunden der Tau-PET (Josephs et

al., 2016) (Perani et al., 2016). Bei PSP zeigt sich der Hypometabolismus im medialen und dorsolateralen Frontallappen, im Nucleus caudatus, im Thalamus und im Mittelhirn (Meyer, Frings, Rücker, & Hellwig, 2017). Im Frontallappen ist der Hypometabolismus im Vergleich zur PD und Multisystematrophie stärker ausgeprägt (Tripathi et al., 2013). Mithilfe der FDG-PET ist es möglich, CBD und PSP mit einer Sensitivität und Spezifität von 91 % von der PD zu unterscheiden (Ling & Macerollo, 2018) (Vlaar, van Kroonenburgh, Kessels, & Weber, 2007) (Bohnen et al., 2011). Weniger erfolgreich dagegen zeigt sich die Differenzierung zwischen PSP und CBD. Häufig wird PSP fälschlicherweise als CBD diagnostiziert (Hellwig et al., 2012).

In allen aktuellen Leitlinien gibt es den allgemeinen Konsens, dass Patienten mit einem klinischen Demenzsyndrom mindestens einmal bei der Feststellung der Diagnose einer strukturellen Bildgebung unterzogen werden sollten (Sheikh-Bahaei, Sajjadi, & Pierce, 2017) (Soucy et al., 2013) (Filippi et al., 2012). FDG-PET gilt als ein etablierter Biomarker, um eine akkurate Diagnose zu stellen, und sie hilft bei der Differenzierung zwischen weiteren Diagnosen, insbesondere zwischen AD und FTD. Hierbei zeigte sich eine Sensitivtät von 73 % bei einer Spezifität von 98 % (Foster et al., 2007) (Diehl-Schmid et al., 2007) (Tosun et al., 2016).

2.4.2.3 Tau-PET

Neben der Abbildung der Stoffwechselaktivität können durch die Entwicklung spezifischer Radiotracer weitere molekulare Biomarker neurodegenerativer Erkrankungen mittels PET dargestellt werden. Hierzu zählen Tau-spezifische Radiotracer, die potenziell in der erweiterten Diagnostik der Tauopathien, zu denen auch die Erkrankungen des frontotemporalen Formenkreises teilweise zählen, eingesetzt werden. Die bisher entwickelte erste Generation der Radiotracer wie [^{11}C]PBB3,

[^{18}F]AV1451 und [^{18}F]THK5351 hat eine hohe spezfische Bindungsffinität bei Formen von AD, die eine 3R/4R-TAU-Isoform aufweisen (Beyer & Brendel, 2020). Aufgrund der geringfügigen Bindung dieser Radiotracer bei reinen 4R- oder 3R-Tauopathien kam es zu einer weiteren Entwicklung von Tracern, bei denen eine erhöhte Tracer-Spezifität erzielt werden sollte. Bei PSP-Patienten zeigte eine postmortale Autoradiographie eine Bindung des [^{18}F]flortaucipir -Tracers an Tau-Ablagerungen (Spinelli et al., 2017). Des Weiteren konnte in einer In-vitro-Analyse eine signifikante Tracer-Bindung in allen subkortikalen PSP-Zielregionen festgestellt werden, dies jedoch ohne eine signifikante Korrelation mit Alter, Schweregrad und Dauer der Erkrankung (Spinelli et al., 2017). Eine durchgeführte Studie mit dem [^{18}F]PM-PBB3-Tracer konnte in vitro eine Bindung an 4R-TAU demonstrieren, sowie eine In-vivo-Retention bei CBD-Patienten im motorischen Kortex (Tagai et al., 2020). Zusammenfassend lässt sich sagen, dass eine Tau-PET-Bildgebung von 4R-Tauopathien potentiell mit diesen neu entwickelten Tracern durchgeführt werden kann. Neben der Erstellung einer früheren und zuverlässigen Diagnose kann mittels Tau-PET außerdem die Wirksamkeit der Behandlung mit Tau-Targeting-Therapien in vivo überwacht werden, was einen weiteren vielversprechenden Bereich für die Verwendung dieser Liganden darstellt (Beyer & Brendel, 2020).

2.5 Zielsetzung

Durch Tau-PET können bestimmte Patientengruppen mit Tauopathien von der Feststellung einer frühzeitigen, akkuraten Diagnose profitieren. In der ersten Veröffentlichung nutzten wir die FDG-PET hierbei als Gatekeeper, um dieses Patientenkollektiv zu identifizieren.

In der zweiten Veröffentlichung wurde die kognitive Reserve als Paradigma bei FTD untersucht. Ziel war es festzustellen, ob Bildung bei Patienten mit FTD eine höhere Widerstandsfähigkeit gegen eine Funktionsbeeinträchtigung des Gehirns bietet.

3 Inhalte der Promotionsarbeit

3.1 FDG-PET als Gatekeeper für eine weitere Diagnostik mittels TAU-PET

Im Rahmen meiner Promotion wurde zunächst untersucht, ob die FDG-PET als möglicher Gatekeeper für eine Tau-PET-Untersuchung bei Patienten mit Verdacht auf PSP/CBD fungieren könnte. Hierzu wurde eine Patientensubgruppe identifiziert, die von einer zusätzlichen Tau-PET-Untersuchung in Hinblick auf die Diagnosesicherung profitieren würde. In die Studie wurden 117 Patienten mit suspekter CBD/PSP in einem Zeitraum von 2013–2018 an der Abteilung für Nuklearmedizin des LMU Klinikums München eingeschlossen. Anschließend wurden die Befunde der Patienten nach den NINDS-SPSP-Kriterien (PSP) bzw. gemäß den Diagnosekriterien von Armstrong et al. (CBD) als wahrscheinliche oder mögliche PSP/CBD klassifiziert (Alexander et al., 2014). Um metabolische Ursachen für ein dementielles Syndrom auszuschließen, wurde das Serum der Patienten laborchemisch auf Thiamin-Mangel, Vitamin-B_{12}-Mangel und Hypothyreoidismus untersucht. Die Kognition der Patienten wurde mittels MMSE getestet. Zur weiteren differentialdiagnostischen Abgrenzung standen die Liquorwerte von p-Tau, t-Tau und $A\beta_{42}$ sowie die MRT-Bilder der Patienten zur Verfügung. Die FDG-PET-Bilder der Patienten wurden durch hausinterne Nuklearmediziner befundet. Basierend auf dem anatomischen Muster des Hypometabolismus wurden die FDG-PET-Bilder zunächst auf die Wahrscheinlichkeit (hoch = A / mittel = B / niedrig = C) eines für PSP oder CBD typischen neurodegenerativen Metabolismus-Musters bewertet. Darauffolgend wurden die FDG-PET-Scans auf die Wahrscheinlichkeit

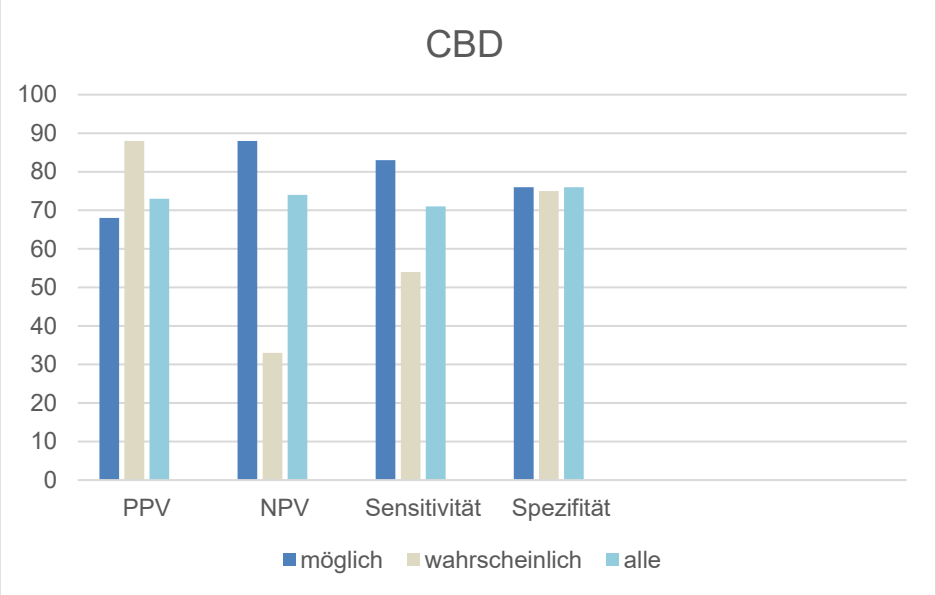
(hoch = A / mittel = B / niedrig = C) eines Metabolismus-Musters bewertet, das für eine andere neurodegenerative Erkrankung als PSP oder CBD typisch ist (insbesondere AD, PD, FTLD oder Multisystematrophie). Anhand der visuellen Auswertung wurden neun Untergruppen definiert (siehe Abbildung 2)(Beyer et al., 2018).

PSP/CBD	hoch	mittel	niedrig
Andere			
niedrig	A-0	B-0	C-0
mittel	A-1	B-1	C-1
hoch	A-2	B-2	C-2

Abbildung 2: Untergruppen bei FDG-PET-Befunden mit der Wahrscheinlichkeit für PSP/CBD (A–C) und andere neurodegenerative Erkrankungen (0–2) (modifiziert nach Beyer et al., 2018).

Im nächsten Schritt wurde die statistische Analyse durchgeführt. Die Normalverteilung der Daten wurde durch den Kolmogorov-Smirnov-Test geprüft. Anschließend wurde unter den Subgruppen der nichtparametrische χ^2-Test zur signifikanten Differenzierung zwischen der Wahrscheinlichkeit eines FTLD-spezifischen FDG-PET-Musters (hoch, mittel, niedrig) verwendet. In den Subgruppen wurde danach untersucht, inwiefern eine Wahrscheinlichkeit für ein FTLD-spezifisches FDG-PET-Muster vorlag. Die diagnostische Genauigkeit wurde mit der Sensitivität, der Spezifität sowie den positiven und negativen prädiktiven Werten (PPV/NPV) anhand des FDG-PET-Musters in Bezug auf die finale klinische Diagnose nach einem Jahr berechnet. Hierbei ergaben sich bei PSP 84 % für die Sensitivität und 91 % für die Spezifität sowie ein PPV von 93 % und ein NPV von 80 %. Bei CBD lag die Sensitivität bei 71 %, die Spezifität bei 76 %, der PPV bei 73 % und der NPV bei 74 % (Beyer et al., 2018). Die Wahrscheinlichkeit des Erfassens der korrekten Diagnose durch die Klinik im Vergleich zur Wahrscheinlichkeit des Erfassens der korrekten Diagnose durch die FDG-PET ergab diskrepante Ergebnisse. Diejenigen CBD-Patienten, die die Kriterien für eine wahrscheinliche CBD

erfüllten, wiesen im Vergleich zur gesamten Kohorte einen höheren PPV, aber einen geringeren NPV und eine geringere Sensitivität (bei gleicher Spezifität) auf. Schließlich zeigten die vermuteten CBD-Patienten mit nur möglichen oder unvollständigen Krankheitskriterien im Vergleich zur gesamten Kohorte eine höhere Sensitivität und einen höheren NPV. Diejenigen PSP-Patienten, die die Kriterien für eine wahrscheinliche Krankheit erfüllten, zeigten durchgehend höhere Werte für PPV, NPV, Sensitivität und Spezifität als die gesamte Kohorte, während diejenigen PSP-Patienten, die nur mögliche oder unvollständige Krankheitskriterien erfüllten, niedrigere Werte hatten (Abbildungen 3 und 4) (Beyer et al., 2018)



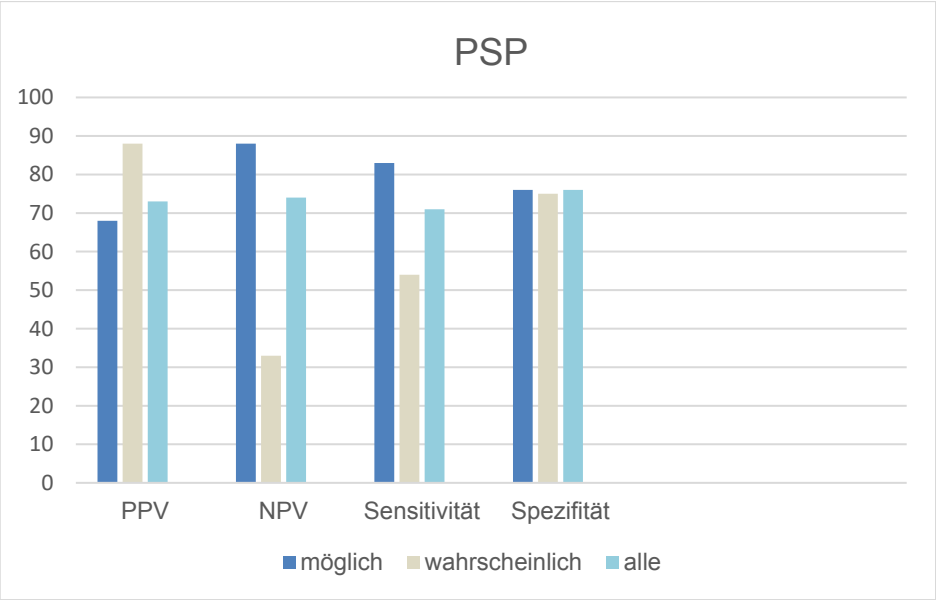
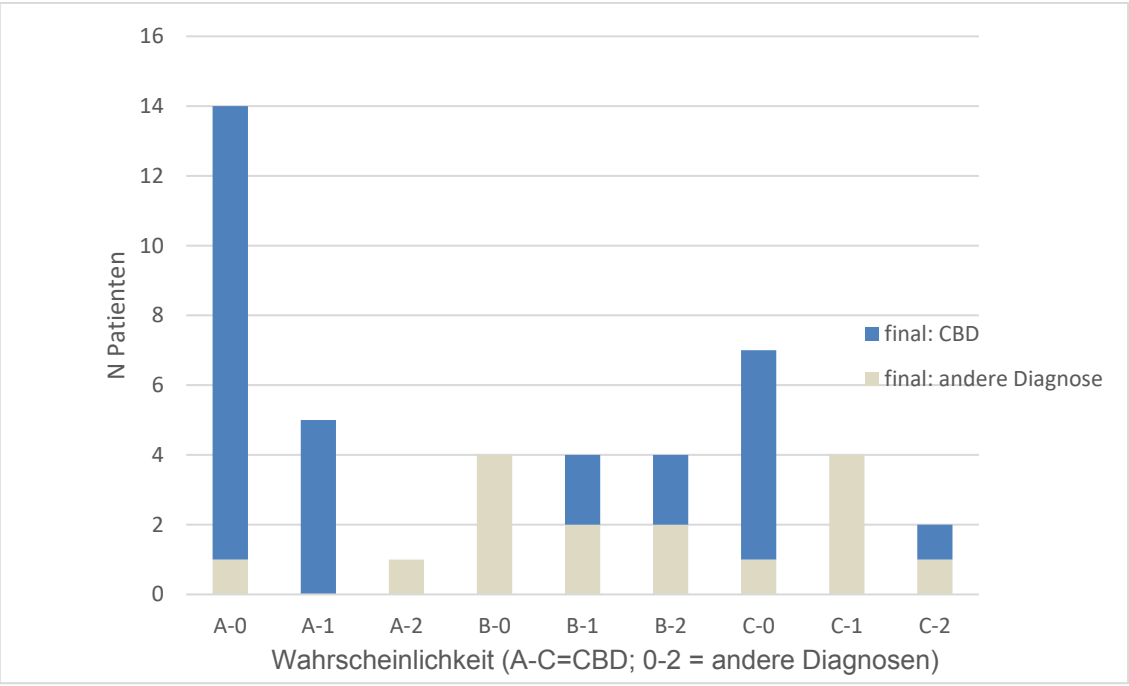


Abbildung 3: Ergebnisse der FDG-PET in den klinischen Untergruppen. PPV, NPV, Sensitivität und Spezifität werden für alle vermuteten PSP-Patienten und CBD-Patienten **d**argestellt und in eine Gruppe mit möglichen positiven diagnostischen Kriterien sowie in eine Gruppe mit wahrscheinlichen positiven klinischen Kriterien eingeteilt (modifiziert nach Beyer et al., 2018).



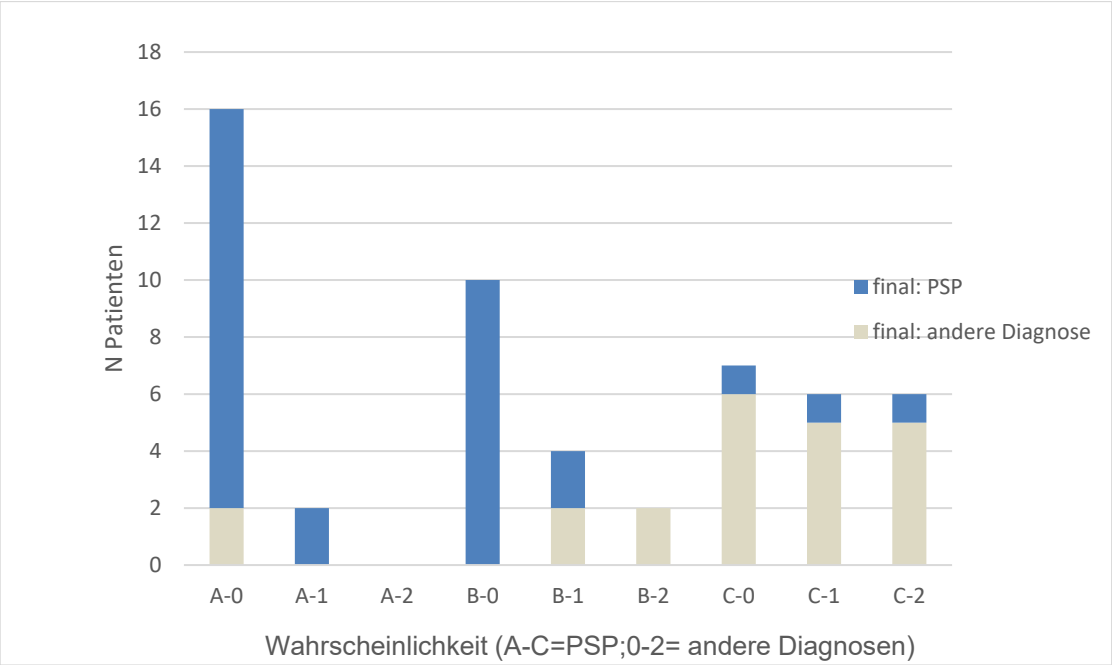


Abbildung 4: Erfolg der FDG-PET in den auf Bildgebung basierenden Wahrscheinlichkeiten der Untergruppen. Die finale Diagnose konnte häufig bestätigt werden, wenn die FDG-PET eine hohe Wahrscheinlichkeit für CBD/PSP und nur eine geringe bis mittlere Wahrscheinlichkeit für andere neurodegenerative Erkrankungen (Gruppen A-0 und A-1) aufwies. Die finale Diagnose CBD/PSP war selten, bei geringer Wahrscheinlichkeit in der FDG-PET für eine 4R-Tauopathie (Gruppen C-0, C-1, C-2) (modifiziert nach Beyer et al., 2018).

Insgesamt ergab sich ein hoher PPV, wenn die FDG-PET eine hohe Wahrscheinlichkeit für ein Tau-positives atypisches Parkinsonsyndrom (T+ APS) in Kombination mit einer geringen bis mäßigen Wahrscheinlichkeit einer anderen neurodegenerativen Erkrankung zeigte. Der PPV war deutlich niedriger, wenn die FDG-PET nur eine mäßige Wahrscheinlichkeit für ein T+ APS zeigte oder wenn andere neurodegenerative Störungen als gleich wahrscheinlich angesehen wurden. Der NPV bei einer geringen Wahrscheinlichkeit für T+ APS in der FDG-PET war hoch. Bei zwei Dritteln der Patienten waren die Ergebnisse der FDG-PET sehr eindeutig. Entweder zeigte sich ein klarer Hinweis auf CBD/PSP oder eine 4R-Tauopathie konnte ausgeschlossen werden. Bei einem Drittel zeigte sich kein eindeutiges Muster einer 4R-Tauopathie oder ein

gleichzeitig vorhandenes Muster typisch für eine andere neurodegenerative Erkrankung. Diese Gruppe könnte somit von einer weiteren Untersuchung mittels Tau-PET profitieren. Insbesondere die Untergruppe der PSP-Patienten mit möglichen diagnostischen Kriterien und einem niedrigen NPV bei einem negativen FDG-PET-Befund würde von einer Untersuchung mit einem spezifischen Radiotracer profitieren. Zudem würden auch die Untergruppe der CBD-Patienten, die eine hohe klinische Wahrscheinlichkeit, jedoch nur einen geringen NPV bei negativem PET-Befund aufweisen, sowie die Untergruppe der CBD-Patienten mit nur möglichen klinischen Kriterien und einem moderaten PPV bei positivem FDG-PET-Befund profitieren. Die Ergebnisse wurden im Rahmen meiner Arbeit in geteilter Erstautorenschaft „Clinical Routine FDG-PET Imaging of Suspected Progressive Supranuclear Palsy and Corticobasal Degeneration: A Gatekeeper for Subsequent Tau-PET Imaging?“ im Juni 2018 in der Zeitschrift *Frontiers in Neurology* veröffentlicht.

3.2 Kognitive Reserve bei FTD

Im Rahmen meiner Arbeit in Co-Autorschaft „Die Hypothese der kognitiven Reserve bei frontotemporaler Demenz: eine FDG-PET-Studie“ wurde sich mit der These beschäftigt, ob eine kognitive Reserve – welche die Fähigkeit beschreibt, kognitive Funktionen auf einem bestimmten pathologischen Niveau aufrechtzuerhalten – bei Patienten mit FTD vorhanden ist. Daher wurde untersucht, ob Bildung trotz des Vorhandenseins von Hypometabolismus bei FTLD zu einem geringeren Rückgang der kognitiven Leistung beiträgt. Die Auswertung umfasste 66 FTLD-Patienten (Alter 67 ± 8 Jahre) und 24 kognitiv gesunde Teilnehmer einer vorbestehenden Kontrollgruppe. Die Probanden erhielten eine klinische Demenzuntersuchung einschließlich detaillierter kognitiver Tests sowie eine klinisch indizierte FDG-PET-

Untersuchung. Alle FDG-PET-Daten wurden auf ein hausinternes FDG-PET-Template normiert. Als FDG-PET-Template diente eine interne Datenbank von 24 bezüglich Alter übereinstimmenden, kognitiv gesunden Patienten, die auch zum Vergleich der Gruppen herangezogen wurden. Zur Normalisierung wurden die Bilder durch eine Referenzregion aus Kleinhirn und Hirnstamm skaliert (standardized uptake value ratio [SUVR]). Zur klinischen Beurteilung und kognitiven Testung wurde als Paradigma für kognitive Beeinträchtigung die MMSE durchgeführt und zur Einteilung des Bildungsniveaus wurden die Bildungsjahre aufgezeichnet. Um den FDG-PET-Hypometabolismus bei FTLD zu analysieren, führten wir eine voxelbasierte Analyse mittels eines ungepaarten *t*-Tests zwischen den FTLD-Probanden und den gesunden Kontrollprobanden durch. Dies resultierte in einem bilateralen frontotemporalen Cluster (siehe Abbildung 5A). Um diejenigen Regionen zu identifizieren, bei denen FDG-PET-Veränderungen mit globaler Kognition korrelieren, wurde eine Regressionsanalyse zwischen MMSE und FDG-PET-SUVR durchgeführt. Hierbei zeigte sich im linken temporalen Kortex ein Cluster, in welchem der FDG-PET-Hypometabolismus mit der Kognition korrelierte (siehe Abbildung 5B).

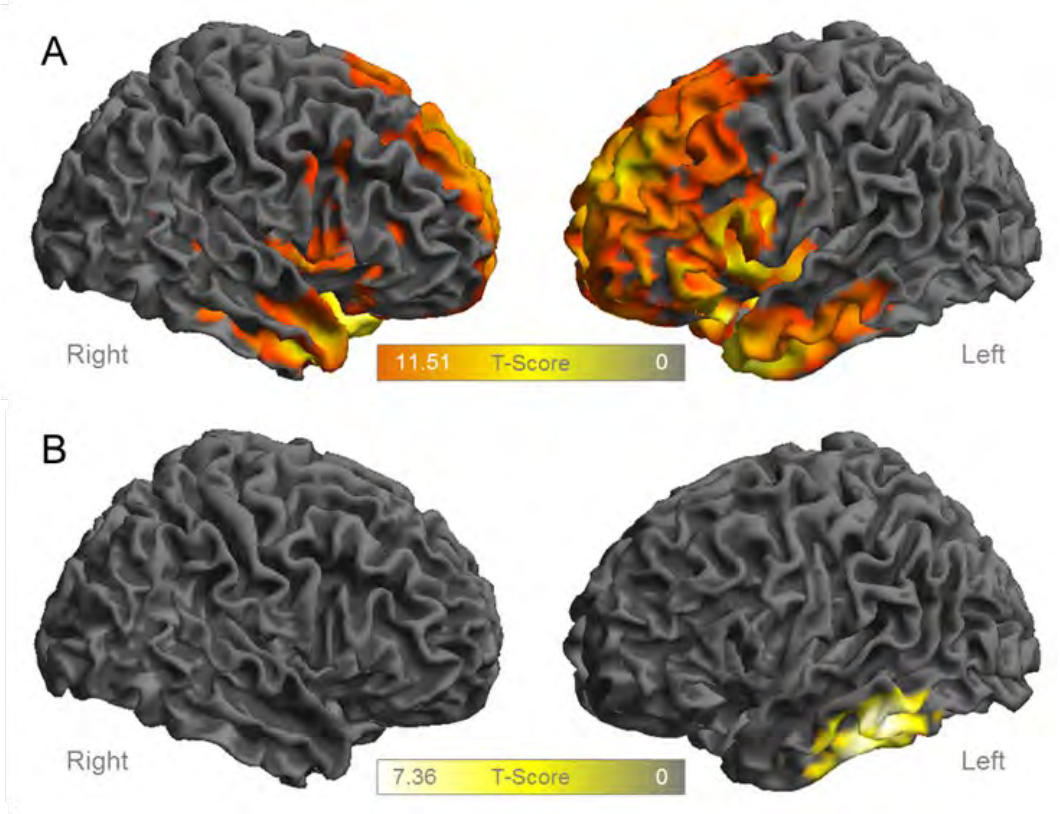


Abbildung 5: Oberflächenprojektion der rechten (auf der linken Seite) und der linken Hemisphäre (auf der rechten Seite) in der FTLD-Kohorte (n = 66) **A** Regionen mit signifikantem Hypometabolismus (p < 0,05, FWE-korrigiert, k >50 Voxel) in FDG-PET gegen gesunde Kontrollprobanden (n = 24). **B** Korrelationscluster von FDG-PET mit MMSE (p < 0,05, FWE-korrigiert, k >50 Voxel) (modifiziert nach (Beyer et al., 2021)).

Aus dem resultierenden Cluster wurden die FDG-PET-Werte extrahiert. In der darauffolgenden linearen Regressionsanalyse mit dem MMSE-Wert als abhängiger Variable und den FDG-PET-SUVR-Werten als Prädiktor (kontrolliert für Alter und Geschlecht) wurden die Residuen berechnet. Es wurden die Bildungsjahre direkt mit den FDG-PET-SUVR-Werten korreliert (korreliert für Alter und Geschlecht) und anschließend wurden die aus der linearen Regressionsanalyse hervorgehenden residualisierten MMSE-Werte mit den Bildungsjahren als Surrogat der kognitiven Reserve korreliert.

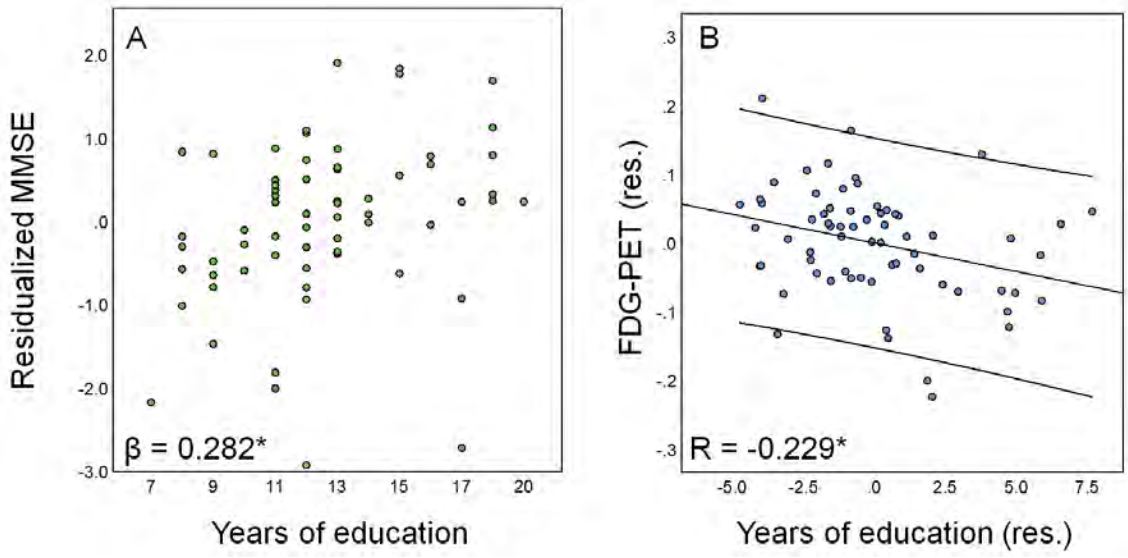


Abbildung 6: **A** Korrelationsdiagramm zwischen den Bildungsjahren und den residualisierten MMSE-Werten für die gesamte FTLD-Kohorte. **B** Regressionsdiagramm zwischen den FDG-PET-Werten aus dem linken temporalen Cluster und den Bildungsjahren, gemessen für Alter, Geschlecht und MMSE-Werte für die gesamte FTLD-Kohorte (modifiziert nach Beyer et al., 2021).

Die Ergebnisse der Regressionsanalyse zeigen, dass eine größere Anzahl an Bildungsjahren mit höheren residualisierten MMSE-Werten assoziiert ist. Dies suggeriert, dass sich basierend auf dem links-frontalen FDG-PET-Hypometabolismus bei FTLD-Patienten höhere MMSE-Werte als erwartet ergeben haben (R = 0,282, p = 0,022, siehe Abbildung 6A). Die zweite Analyse ergibt, dass ein höheres Bildungsniveau mit niedrigeren FDG-PET-SUVR-Werten korreliert (R = –0,229, p = 0,015, siehe Abbildung 6B). Demnach bedeutet dies, dass Patienten mit höherer Bildung mehr FDG-PET-Metabolismus tolerieren können. Somit geht eine höhere Anzahl Bildungsjahre mit einer größeren Widerstandsfähigkeit der kognitiven Leistung bei einem bestimmten Grad an pathologischer Gehirnschädigung einher. Das Bildungsniveau stellt dementsprechend ein Surrogat der kognitiven Leistung dar und

erklärt die Diskrepanz zwischen dem Hypometabolismus im linken temporalen Kortex und der globalen Kognition und unterstützt die These der kognitiven Reserve.

4 Zusammenfassung

FDG-PET als Maß für neuronale Schädigung wird bei verschiedenen neurodegenerativen Erkrankungen aus dem frontotemporalen Formenkreis diagnostisch eingesetzt. In der weiterführenden Diagnostik kommen darüber hinaus spezifische Radiotracer zum Einsatz. Hierbei befindet sich die Tau-PET aktuell in klinischer Erprobung.

In der dargestellten Arbeit konnte bei Patienten mit T+ APS bei zwei Dritteln der Patienten eine zufriedenstellende Diagnosesicherheit erzielt werden. Ein Drittel der Patienten würde demnach von einer weiteren Bewertung mit spezifischeren Radioliganden profitieren. Bei Patienten mit Verdacht auf PSP schnitt die FDG-PET besser ab als bei Patienten mit Verdacht auf CBD. Die verbesserte Diagnostik geht einher mit der Möglichkeit neuer spezifischer Therapieansätze, insbesondere was den Einschluss in prospektive Therapiestudien angeht.

In einer zweiten Arbeit wurde untersucht, ob Bildung bei Patienten mit FTD eine höhere Widerstandsfähigkeit bei einer Funktionsbeeinträchtigung des Gehirns bietet. Hierzu wurden 66 FTLD-Patienten (Alter 67 ± 8 Jahre) und 24 kognitiv gesunde Kontrollprobanden bewertet. Durch eine voxelbasierte Analyse konnten die FTLD-assoziierten Regionen mit Hypometabolismus in der FDG-PET im Vergleich zu gesunden Kontrollprobanden dargestellt werden und einzelne FDG-PET-Werte wurden aus signifikanten Hirnregionen extrahiert. Bei der Korrelation dieser Werte mit MMSE-Werten ergab sich ein Cluster im linken temporalen Kortex, der mit dem FDG-PET-

Hypometabolismus übereinstimmte. Die Werte dieses Clusters wurden für die Residualisierungsanalyse der kognitiven Leistung genutzt.

Residualisierte MMSE-Werte korrelieren mit einer höheren Anzahl an Bildungsjahren und gelten als ein Surrogat der kognitiven Reserve. Insgesamt sprechen die Ergebnisse somit für ein Vorliegen einer kognitiven Reserve auch bei Patienten mit FTD. Im klinischen Alltag müssen daher bei der Interpretation der FDG-PET-Befunde von FTLD-Patienten die Bildungsjahre mitberücksichtigt werden.

5 Abstract

FDG-PET as a measure of neuronal damage is used for various neurodegenerative diseases of the frontotemporal lobe. Specific radiotracers are used in further diagnostics; tau-PET, for instance, is currently investigated in clinical trials. In the present work, a satisfactory diagnostic result via FDG-PET was achieved in two-thirds of the patients with T+ APS. Therefore, one-third of the patients would benefit from further assessment using more specific radioligands.

In patients with suspected PSP, FDG-PET performed better than in patients with suspected CBD. The improved diagnostics may lead to the possibility of new specific therapeutic approaches, especially in regard to prospective therapy studies.

Furthermore, it was investigated whether education offered greater resistance to functional impairment of the brain in patients with FTD. Therefore, 66 FTLD patients (age 67 ± 8 years) and 24 cognitively healthy controls were evaluated. In a voxel-based analysis, the FTLD regions with hypometabolism on FDG-PET could be compared to the healthy controls, and individual FDG-PET values were extracted from significant brain

regions. The correlation of these values with MMSE scores resulted in a cluster in the left temporal cortex.

The values of this cluster were used for the residualization analysis of the cognitive performance. The residualized MMSE values correlated with a higher number of years of education as a surrogate for cognitive reserve. Overall, the results suggest that there is a cognitive reserve even in patients with FTD. Therefore, the years of education should be taken into account when interpreting the FDG-PET findings of FTLD patients.

6 Paper I

frontiers in Neurology

ORIGINAL RESEARCH
published: 20 June 2018
doi: 10.3389/fneur.2018.00483

Clinical Routine FDG-PET Imaging of Suspected Progressive Supranuclear Palsy and Corticobasal Degeneration: A Gatekeeper for Subsequent Tau-PET Imaging?

Leonie Beyer[1†], Johanna Meyer-Wilmes[1†], Sonja Schönecker[2], Jonas Schnabel[1], Eva Brendel[1], Catharina Prix[2], Georg Nübling[2], Marcus Unterrainer[1], Nathalie L. Albert[1], Oliver Pogarell[3], Robert Perneczky[3,4,5,6], Cihan Catak[7], Katharina Bürger[4,7], Peter Bartenstein[1,8], Kai Bötzel[2], Johannes Levin[2,4], Axel Rominger[1,8,9] and Matthias Brendel[1,8†]*

[1] Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany, [2] Department of Neurology, University Hospital, LMU Munich, Munich, Germany, [3] Department of Psychiatry, University of Munich, Munich, Germany, [4] German Center for Neurodegenerative Diseases (DZNE), Munich, Germany, [5] Neuroepidemiology and Ageing Research Unit, School of Public Health, Imperial College, London, United Kingdom, [6] West London Mental Health NHS Trust, London, United Kingdom, [7] Institute for Stroke and Dementia Research, University of Munich, Munich, Germany, [8] Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [9] Department of Nuclear Medicine, Inselspital, University Hospital Bern, Bern, Switzerland

OPEN ACCESS

Edited by:
Huifang Shang,
Sichuan University, China

Reviewed by:
Mário M. Rosa,
Universidade de Lisboa, Portugal
Gennaro Pagano,
King's College London, United Kingdom
Matteo Bologna,
Sapienza Università di Roma, Italy
Pratap Chand,
Saint Louis University, United States

***Correspondence:**
Matthias Brendel
matthias.brendel@med.uni-muenchen.de

[†]These authors have contributed equally to this work.

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *24 January 2018*
Accepted: *04 June 2018*
Published: *20 June 2018*

Citation:
Beyer L, Meyer-Wilmes J, Schönecker S, Schnabel J, Brendel E, Prix C, Nübling G, Unterrainer M, Albert NL, Pogarell O, Perneczky R, Catak C, Bürger K, Bartenstein P, Bötzel K, Levin J, Rominger A and Brendel M (2018) Clinical Routine FDG-PET Imaging of Suspected Progressive Supranuclear Palsy and Corticobasal Degeneration: A Gatekeeper for Subsequent Tau-PET Imaging? Front. Neurol. 9:483. doi: 10.3389/fneur.2018.00483

Background: F-18-fluordeoxyglucose positron emission tomography (FDG-PET) is widely used for discriminative diagnosis of tau-positive atypical parkinsonian syndromes (T+APS). This approach now stands to be augmented with more specific tau tracers. Therefore, we retrospectively analyzed a large clinical routine dataset of FDG-PET images for evaluation of the strengths and limitations of stand-alone FDG-PET.

Methods: A total of 117 patients (age 68.4 ± 11.1 y) underwent an FDG-PET exam. Patients were followed clinically for a minimum of one year and their final clinical diagnosis was recorded. FDG-PET was rated visually (positive/negative) and categorized as high, moderate or low likelihood of T+APS and other neurodegenerative disorders. We then calculated positive and negative predictive values (PPV/NPV) of FDG-PET readings for the different subgroups relative to their final clinical diagnosis.

Results: Suspected diagnoses were confirmed by clinical follow-up (≥1 y) for 62 out of 117 (53%) patients. PPV was excellent when FDG-PET indicated a high likelihood of T+APS in combination with low to moderate likelihood of another neurodegenerative disorder. PPV was distinctly lower when FDG-PET indicated only a moderate likelihood of T+APS or when there was deemed equal likelihood of other neurodegenerative disorder. NPV of FDG-PET with a low likelihood for T+APS was high.

Conclusions: FDG-PET has high value in clinical routine evaluation of suspected T+APS, gaining satisfactory differential diagnosis in two thirds of the patients. One third of patients would potentially profit from further evaluation by more specific radioligands, with FDG-PET serving gatekeeper function for the more expensive methods.

Keywords: atypical parkinsonian syndrome, progressive supranuclear palsy, corticobasal degeneration, F-18-FDG, PET, clinical routine

INTRODUCTION

Atypical parkinsonism refers to a group of neurodegenerative syndromes presenting symptoms resembling those of Parkinson's disease (PD), but generally with earlier onset, faster progression, and poor response to dopamine replacement treatments. Chief among the atypical parkinsonian syndromes are progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS), which both represent tauopathies. Whereas PSP predominantly presents with a predominantly supranuclear vertical gaze palsy and early postural instability with falls, CBS typically manifests as markedly asymmetrical parkinsonism in conjunction with apraxia or cortical sensory disturbance (1). The incidence of atypical parkinsonism syndromes is low relative to PD (2), but their more aggressive course calls for improved discriminative diagnosis methods and disease specific therapies, such as anti-tau regimens for PSP and CBS.

The past decade has seen extensive investigations of brain glucose metabolism by F-18-fluorodeoxyglucose positron-emission-tomography (FDG-PET) in PSP and CBS patients (3–8), aiming to detect disease-specific patterns of altered glucose consumption. Significant reductions of FDG uptake were observed in PSP subjects in the bilateral anterior cingulate gyrus and the midbrain (6). In CBS subjects, glucose hypometabolism was found in the central region, the frontal and parietal association areas, the putamen contralateral to the clinically affected side and the bilateral thalamus (7).

Until recently, molecular imaging of glucose metabolism was not considered by diagnostic (9, 10), even though FDG-PET is often requested to determine the presence of neurodegeneration in suspected PSP and corticobasal degeneration (CBD) as the major subgroup of CBS; however recently proposed diagnostic criteria now include imaging findings by FDG-PET for PSP (11). The importance of FDG-PET is underlined by the fact that the correlation between the clinical diagnostic criteria and a neuropathological confirmation is still insufficient in suspected PSP and CBD (12, 13).

Most of the mentioned molecular imaging studies were performed in academic settings with highly characterized patient populations to evaluate the FDG uptake patterns, sometimes with machine learning algorithms. Sensitivity, specificity, positive and negative predictive values for differential diagnosis of different parkinsonian syndromes were consistently > 80% in a recent test of an automated image-derived classification procedure (14). In clinical routine of a nuclear medicine department, the demands for differential diagnosis of suspected atypical parkinsonism by FDG-PET is often more complicated, and hindered by the less extensive clinical information, a broad spectrum of possible diagnoses, and missing follow-up data. Besides the high sensitivity for concomitant dementia in parkinsonian syndromes even in clinical routine, FDG-PET imparts inherently unspecific information about synaptic dysfunction, which is the common thread of all neurodegenerative disorders (15). More recent developments in molecular imaging for discriminative diagnosis of PD, atypical parkinsonism, and neurodegenerative diseases in general focus on disease-specific neuroreceptor changes (16) and neuropathological hallmarks (17, 18).

The advent of tau-PET imaging presents new prospects for identification of PSP and CBD with the pyridoindole F-18-AV1451 (19, 20) and arylquinoline F-18-THK5351 (21, 22) and their derivatives. In nuclear medicine clinical routine it would be critical to establish suitable diagnostic algorithms guiding the decision to augment an established and relatively inexpensive tracer (FDG) with a less conventional and more expensive tau-PET investigation; the higher cost must be justified by the additive diagnostic value. Therefore, we made a retrospective analysis of clinical routine FDG-PET data obtained during a 7-year period for complex cases referred to a tertiary center with suspected tau-positive atypical parkinsonism. Our objective was to determine if FDG-PET findings, in the light of follow-up to a definite diagnosis, can predict cases where additional tau-PET examination would potentially have resolved the initial diagnostic uncertainty. By making this identification of patient groups we aimed to create a basis for future prospective treatment trials.

MATERIALS AND METHODS

Study Design and Patient Enrollment

All participants were examined at the Departments of Neurology and Psychiatry, respectively, and Institute for Stroke and Dementia Research, and were scanned in a clinical routine setting at the Department of Nuclear Medicine between 2009 and 2015. After undergoing cognitive testing and partially assessments of nigrostriatal innervation by DaTSCAN-SPECT, structural MRI imaging and CSF sampling, patients with a differential diagnosis of suspected PSP/CBD were referred for FDG-PET examination. To avoid a selection bias, all patients with suspected PSP/CBD in the observation period were considered as a primary sample ($n = 151$). Inclusion criteria were defined by at least one year of clinical follow-up ($n = 122$) and successful FDG-PET imaging scan (i.e., no early termination by the patient or not correctable head motion). Exclusion criteria were earlier events of stroke ($n = 3$) or current severe affective disorders ($n = 2$), which might influence FDG-PET pattern or clinical features. A final clinical diagnosis was recorded at clinical follow-up, based on current diagnostic criteria of parkinsonian syndromes and other neurodegenerative disorders. One hundred and seventeen patients with suspected PSP/CBD were eligible for the final analysis.

Clinical Assessments, MRI and CSF

The majority of patients (61%; 71/117) received neuropsychological testing including cognitive evaluation at the time of the FDG-PET scan [Mini-Mental-State Examination (MMSE)]. Years of education were recorded and a neurological examination was performed. Symptom categories for clinical classification of PSP and CBS were assessed binarized (as Yes/No) at the time of the FDG-PET scan. Patients with suspected PSP were classified for probable or possible PSP according to NINDS-SPSP criteria (10), as the observation period of this retrospective analysis took place before publication of newest PSP criteria (11). Patients with suspected CBD were classified for probable or possible CBS according to criteria defined by Armstrong et al.

(9). The Supplementary Material gives an overview on symptom categories and their necessary composition for the establishment of a clinical diagnosis.

Structural MRI ($n = 96$) and CSF samples ($n = 97$) were available from >80% of the 117 patients, whereas DaTSCAN was performed in less than half of the patients ($n = 49$; 42%).

PET Imaging

FDG PET Acquisition

FDG-PET images were acquired on a GE Discovery 690 PET/CT scanner or a Siemens ECAT EXACT HR+ PET scanner. All patients had fasted for at least 6 h, and had a maximum plasma glucose level of 150 mg/dl at time of scanning. A single intravenous dose of 140 ± 7 MBq FDG was administered while the patients rested in a room with dimmed light and low noise level, where they remained undisturbed for 20 min. After positioning in the scanner, a series of three static emission frames of 5 min each was acquired from 30 to 45 min p.i. on the GE Discovery 690 PET/CT, or from 30 to 60 min p.i. on the Siemens ECAT EXACT HR+ tomograph. A low-dose CT scan or a transmission scan with external ^{68}Ge-source performed just prior to the static acquisition was used for attenuation correction. PET data were reconstructed iteratively (GE Discovery 690 PET/CT) or with filtered-back-projection (Siemens ECAT EXACT HR+ PET). After correction for movement between frames, the static scans were averaged.

Visual Analysis of FDG-PET

For visual image interpretation of FDG-PET images, three-dimensional stereotactic surface projections (3D-SSP) (23) were generated using the software Neurostat (Department of Radiology, University of Washington, Seattle, WA, U.S.A.). A senior expert in Nuclear Medicine visually assessed axial and sagittal slices and the 3D-SSP images depicted as normalized tracer uptake and Z-score maps against reference images from a group of age-matched healthy controls. The reader had access to clinical information (available in all cases) and, when available, DaTSCAN and/or structural MRI information. Based on the anatomic pattern of hypometabolism the FDG-PET images were first rated for likelihood (high = A/moderate = B/low = C likelihood) of a neurodegenerative metabolism pattern typical for PSP or CBD (24). Next, the FDG-PET scan was rated for likelihood (high = 2/moderate = 1/low = 0) of a metabolism pattern typical of a neurodegenerative condition other than PSP or CBD (mainly Alzheimer's disease, PD, frontotemporal lobar degeneration, multiple system atrophy). Based on permutations of the FDG-PET findings we defined nine possible subgroups (see **Table 1** and **Figure 1**).

Additionally the reader had to assert positivity or negativity for PSP/CBD as a binarized read-out. A likelihood for PSP/CBD exceeding the likelihood for other neurodegenerative diseases was defined as positive in this regard, whereas equal or lower likelihoods in the same comparison were defined as negative.

TABLE 1 | Subgroup definition by FDG-PET findings according to the likelihood for PSP/CBD (A-C) and other neurodegenerative diseases (0-2).

Other \ PSP/CBD	High	Moderate	Low
Low	A-0	B-0	C-0
Moderate	A-1	B-1	C-1
High	A-2	B-2	C-2

Statistical Analysis

Normality of data distribution was assessed by the Kolmogorov-Smirnov test. The nonparametric χ^2 test was used to test for significantly differing probability of trichotomous likelihood of disease-typical FDG-PET patterns (high, medium, low) among subgroups. The diagnostic accuracy was tested by calculating the sensitivity, specificity and positive/negative predictive value (PPV/NPV) using the final clinical diagnosis after ≥ 1 year of follow-up as the truth. We did not perform an a priori sample size calculation. A significance level of $p < 0.05$ for rejection of the null hypothesis was applied in all analyses. All statistical tests were performed using SPSS (version 23.0, IBM, Chicago, IL).

RESULTS

Demographics

A total of 117 subjects (51% male) were included in the study (**Table 2**). Fifty-three patients (34% male) had been referred with suspected PSP and 64 patients (52% male) with suspected CBD. 16 patients were referred with both possible differential diagnoses, and were assigned to one of the two aforementioned subgroups according to their more likely diagnosis. The mean age was 68.4 years (SD ± 11.1). The clinical diagnosis was confirmed by clinical follow-up ≥ 1 year in 31/53 (59%) patients with suspected PSP and in 31/64 (48%) patients with suspected CBD. Additional findings from neuropsychological testing and a summary of presence or absence of single symptom categories are provided in the Supplemental Results.

FDG-PET Findings

Proportions of Likelihood Subgroups

According to the matrix defined in section Visual Analysis of FDG-PET we found 32% of all patients fell in the subgroups of high likelihood for PSP/CBD in conjunction with low to moderate likelihood for another neurodegenerative disorder. A high likelihood for PSP/CBD was assigned when there was a pronounced FDG hypometabolism in regions characteristic for PSP (prefrontal cortices, anterior cingulate gyrus, midbrain)/CBD (central region, putamen, thalamus), as illustrated and described in **Figure 1**. Another 32% of the patients indicated a moderate likelihood for PSP/CBD or equal likelihood for other neurodegenerative disorders, meaning that the hypometabolism pattern was of only moderate severity in the characteristic regions. Thirty-six percent had a low likelihood for PSP/CBD (**Table 3**).

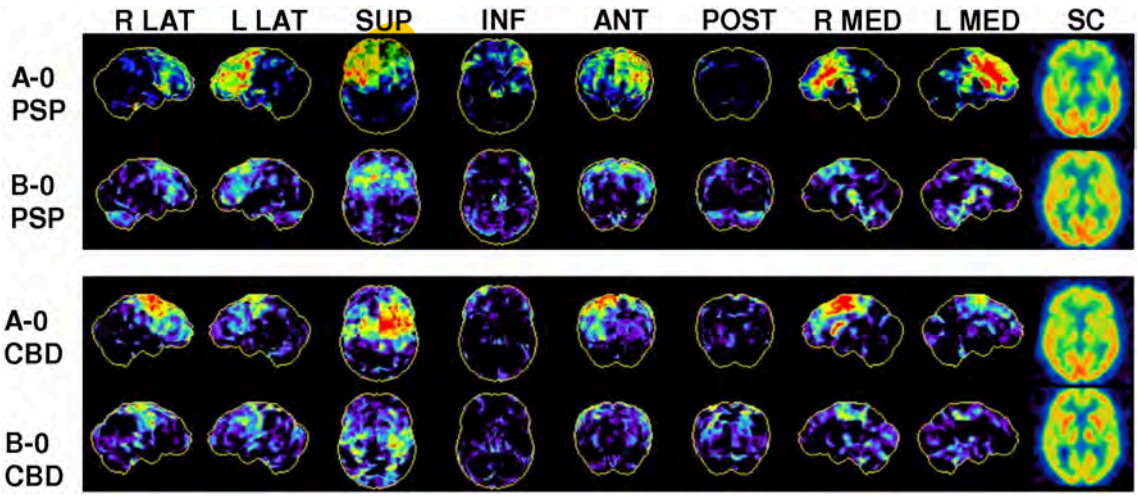


FIGURE 1 | Representative FDG-PET images of study subgrous: Three-dimensional stereotactic surface projections (3D-SSP) of normalized FDG uptake from right/left lateral (R LAT/L LAT), superior (SUP), inferior (INF), anterior (ANT), posterior (POST), right/left medial (R MED/L MED) views and a subcortical (SC) section image in the axial pain for four out of nine defined subgroups according to their likelihood for PSP/CBD. In PSP subjects, asymmetrical or bilateral hypometabolism was found predominantly in the prefrontal cortices, the anterior cingulate gyrus, and the midbrain. In CBS, asymmetrical hypometabolism was observed in the central region, the putamen and thalamus.

TABLE 2 | Demographics and composition of the study collective.

	N	Final diagnosis PSP/CBS	Age (y)	Gender (♂, male, ♀, female)	Education (y)	MMSE
All	117	62 (53%)	68.4 ± 11.1	51 ♂ 56 ♀	13.8 ± 3.6	25.5 ± 4.2
PSP	53	31 (59%)	72.3 ± 8.0	27 ♂ 26 ♀	14.2 ± 3.5	24.8 ± 4.3
Probable	22	15 (68%)	70.7 ± 7.7	11 ♂ 11 ♀	13.8 ± 2.5	25.1 ± 3.6
Possible	23	14 (61%)	71.9 ± 7.8	12 ♂ 11 ♀	14.3 ± 4.5	24.2 ± 4.9
Criteria not fulfilled	8	2 (25%)	77.9 ± 7.8	4 ♂ 4 ♀	15.0 ± 3.6	25.5 ± 5.8
CBS	64	31 (48%)	65.2 ± 12.3	33 ♂ 31 ♀	13.6 ± 3.7	26.0 ± 4.1
Probable	17	13 (77%)	70.8 ± 7.3	9 ♂ 8 ♀	13.6 ± 3.3	26.0 ± 5.7
Possible	21	9 (43%)	61.2 ± 14.0	9 ♂ 12 ♀	12.3 ± 2.2	25.6 ± 4.4
Criteria not fulfilled	26	9 (35%)	64.9 ± 12.5	15 ♂ 11 ♀	14.6 ± 4.8	26.2 ± 2.0

TABLE 3 | Proportions of subgroups ($n = 117$) defined by the likelihood for PSP/CBD and for other neurodegenerative disorders by visual analysis of FDG-PET.

PSP/CBD / Other	High (%)	Moderate (%)	Low (%)
Low (%)	26	18	18
Moderate (%)	6	7	11
High (%)	1	6	7

Overall Performance of FDG-PET

Overall performance of binarized FDG-PET (for likelihood PSP/CBD > other ND) for the prediction of a final clinical diagnosis of PSP gave 84% sensitivity, 91% specificity, PPV of 93%, and NPV of 80%. Overall performance of binarized FDG-PET for the prediction of a final clinical diagnosis of suspected CBD was slightly lower, at 71% sensitivity, 76% specificity, PPV of 73%, and NPV of 74%.

Influence of Clinical Probability on FDG-PET Findings

The higher clinical probability by diagnostic criteria indicated tendencies toward greater likelihood of PSP/CBD and lower likelihood of other neurodegenerative diseases in FDG-PET. However, statistical testing did not indicate a significance in these probabilities (PSP_{CLINIC} – PSP_{FDG}: $\chi^2 = 6.6$; $p = 0.16$/PSP_{CLINIC} – $otherND_{FDG}$: $\chi^2 = 0.7$; $p = 0.95$/CBS_{CLINIC} – CBD_{FDG}: $\chi^2 = 2.4$; $p = 0.66$/CBS_{CLINIC} – $otherND_{FDG}$: $\chi^2 = 6.4$; $p = 0.17$), and positive as well as negative PET scans were found in each clinical category (**Table 4**).

Overall Performance of FDG-PET in Combination With Clinical Parameter

The combined evaluation of clinical probability and binarized FDG-PET for the prediction of the clinical outcome gave

TABLE 4 | FDG-PET likelihoods for PSP/CBD and other ND for all subgroups.

	Subjects (n = 117)	FDG-PET likelihood PSP/CBD			FDG-PET likelihood other ND		
		Low	Moderate	High	Low	Moderate	High
Probable PSP	22	5	7	10	13	6	3
Possible PSP	23	9	6	8	15	4	4
PSP criteria not fulfilled	8	5	3	0	5	2	1
Probable CBS	17	4	7	6	9	4	4
Possible CBS	21	8	5	8	17	3	1
CBS criteria not fulfilled	26	11	8	7	13	9	4

discrepant results for suspected PSP and CBD patients. Thus, the suspected PSP patients meeting criteria for probable disease criteria had consistently higher values for PPV, NPV, sensitivity and specificity by FDG-PET when compared to the whole cohort, whereas the suspected PSP patients with only possible or incomplete disease criteria had lower values of these diagnostic accuracy parameters (**Figure 2A**). Suspected CBD patients meeting probable disease criteria for CBD had a higher PPV but lesser NPV and sensitivity (at equal specificity) by FDG-PET when compared to the whole cohort. Finally, the suspected CBD patients with only possible or incomplete disease criteria showed more sensitivity and higher NPV for FDG-PET when compared to the whole cohort (**Figure 2B**).

Performance of FDG-PET in Different Likelihood Subgroups

Proportions of patients with a final clinical diagnosis of PSP/CBD differed substantially between the subgroups as defined by FDG-PET (**Figure 3**). PPV was excellent when FDG-PET indicated a high likelihood for PSP/CBD in combination with low to moderate likelihood for another neurodegenerative disorder (PSP: 95%/CBD: 89%). PPV was distinctly lower when FDG-PET indicated only a moderate likelihood for PSP/CBD or when the likelihood for other neurodegenerative disorders was equal (PSP: 75%/CBD: 41%). FDG-PET had a high NPV for absence of PSP/CBD to clinical follow-up when the initial visual read indicated a low likelihood for PSP/CBD (PSP: 84%/CBD: 83%).

Notably, detection of a metabolism pattern indicative of moderate synaptic dysfunction in brain regions typical for PSP, but no suspicion of other neurodegenerative disorders had a far higher congruency with a positive final clinical diagnosis when compared to the same constellation in patients with suspected CBD (compare subgroups B-0 in **Figures 3A,B**).

Binarized analysis of FDG scans revealing a positive pattern for PSP indicated a distinctly higher PPV in the absence of any indication of likelihood for another neurodegenerative disease, when compared to cases with PSP-positive pattern in combination with coexisting likelihood for another neurodegenerative disease (92 vs. 50%). This distinction was less evident for CBD (68 vs. 63%; **Figure 4**).

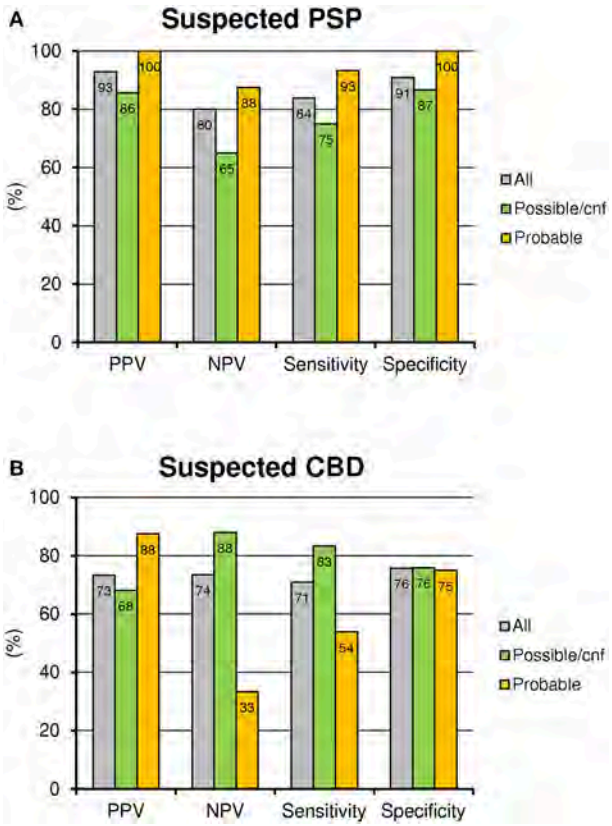


FIGURE 2 | Performance of FDG-PET in clinical subgroups: PPV, NPV, sensitivity and specificity are illustrated for all suspected PSP **(A)** and CBD **(B)** patients and subdivided into possible or incomplete diagnostic criteria (cnf) and probable clinical criteria.

Impact of DaTSCAN Results

DaTSCAN (n = 49) indicated a dopamine transporter deficit in 65%, a borderline result in 22% and a negative result in 12% of the examined cases. Sixty-six percent of those patients with a pathological DaTSCAN were ultimately diagnosed as PSP/CBS. Of all 28 patients with the final diagnosis PSP/CBS and an available DaTSCAN, 75% showed a pathological result, 21% a borderline result and 4% a negative result. When available, a pathological DaTSCAN together with a pathological FDG-PET (binarized) result for PSP/CBD (n = 21) gave a PPV of 76%. Only four patients had overall negative results to the two imaging modalities, which did not support a valid calculation of a NPV. PPV was higher and the NPV was

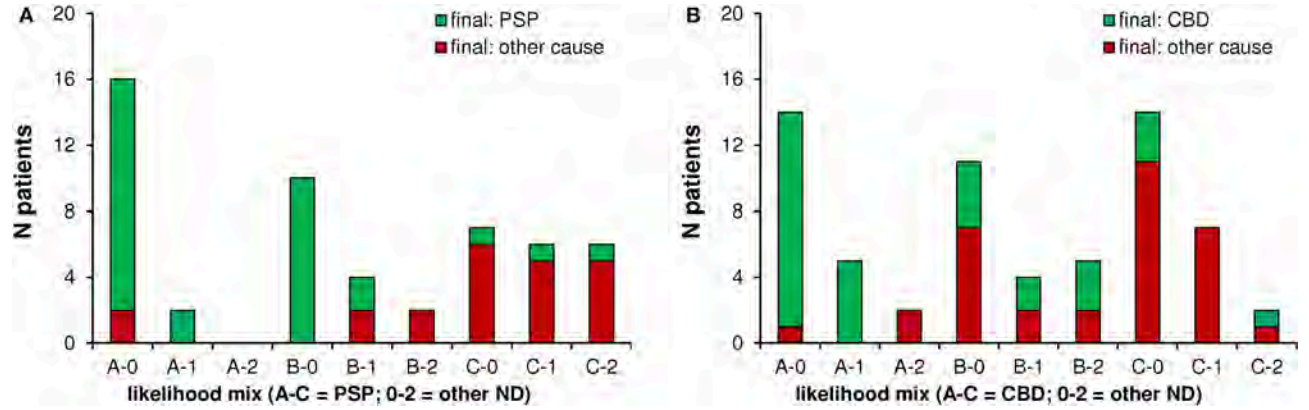


FIGURE 3 | Performance of FDG-PET in imaging based likelihood subgroups: A confirming final diagnosis was frequent when FDG-PET indicated a high likelihood for PSP **(A)**/CBS **(B)** and only a low to moderate likelihood for other neurodegenerative diseases (Groups A-0 and A-1). A final diagnosis of PSP **(A)**/CBS (**B**) was rare when FDG-PET indicated only a low likelihood for a 4R-tauopathy (groups C-0, C-1, and C-2). ND, neurodegenerative disease.

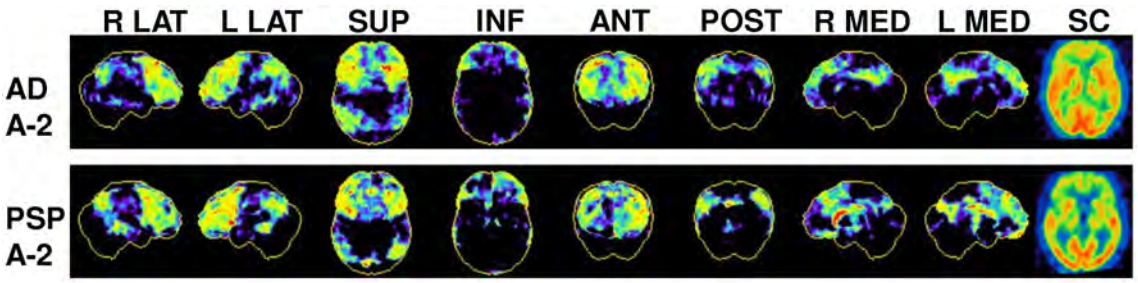


FIGURE 4 | Examples of conflicting FDG-PET findings in two patients with suspected PSP: Representative 3D-SSP for FDG-PET from right/left lateral (R LAT/L LAT), superior (SUP), inferior (INF), anterior (ANT), posterior (POST), right/left medial (R MED/L MED) and a subcortical (SC) horizontal plane image of SUV for comparison of typical AD and PSP metabolic patterns. Note that both patients showed a frontal pronounced hypometabolism but as well an AD-like hypometabolism in the posterior cingulate cortex and in parietal cortices. Clinical follow-up identified one patient as AD and one as PSP.

TABLE 5 | PPV/NPV values of FDG-PET for PSP and CBD for all subjects and divided whether a DaTSCAN was available.

FDG-PET	PPV (%)	NPV (%)
All subjects ($n = 117$)	83	76
DaTSCAN available ($n = 49$)	74	64
No DaTSCAN available ($n = 68$)	90	84

lower for FDG-PET of the ($n = 68$) subjects without an available DaTSCAN compared to all subjects and those with an available DaTSCAN (see **Table 5**) irrespective of the DaTSCAN result.

DISCUSSION

In this clinical study we evaluate FDG-PET in a large dataset of patients with suspicion of PSP or CBD. Previous studies have established the suitability of FDG-PET for the differential diagnosis of PSP and CBD (6, 25, 26). However, most of these investigations were performed in investigational academic settings with a previously selected patient cohort. Studies in nuclear medicine routine settings remain rare and challenging because of more patients with less specific clinical findings and multiple differential diagnoses in the early stage of disease. Therefore, we investigated all subjects referred for a FDG-PET with suspected tau-positive parkinsonism over a period of 7 years. For selected patient cohorts with PSP and/or CBD, the typical FDG-PET patterns have already been demonstrated in group-wise comparisons (5, 7). In clinical routine cases, the confirmation or exclusion of the suspected diagnosis is based on a single PET scan of an individual patient which highlights the importance of a high PPV and NPV for the chosen method.

Our FDG-PET-findings underline the complexity of the diagnostic proceeding for patients with clinically diagnosed parkinsonism with only one third of the patients presenting a high likelihood for PSP/CBD in the visual FDG-PET analysis. Nonetheless, performance of FDG-PET was excellent in those two thirds of the patients, who showed either no clear evidence of a 4R tauopathy pattern (high NPV) or a typical PSP/CBD

pattern without conflicting hypometabolism suggestive for other neurodegenerative disorders (high PPV).

However, one third of patients returned inconclusive scans, which gave only low likelihood for a 4R-tauopathy or coexistent hypometabolism patterns typical of other neurodegenerative diseases. Such patients likely benefit from an additional evaluation by more specific PET tracers. Recently developed tau ligands still have some issues that need to be solved, mainly consisting of off-target binding to MAO-B (27). Nonetheless, first human tau PET studies of PSP and CBD already indicated promising results by F-18-THK5351 (18) and F-18-AV1451 (T807) (19, 28, 29). Moreover, new generation tau tracers promise to support a differentiation between 3R and 4R tauopathies. Thus, it seems likely that future tau radioligands will even provide stronger molecular imaging derived differential diagnosis of 4R tauopathies. With regards to cost-effectiveness, the decision to apply such specific but expensive ligands will need to be weighed carefully. Results of the current study suggest that FDG-PET should be performed first in a potential diagnostic algorithm because most clinical suspected diagnosis can be well-supported by a specific FDG-PET pattern at high PPV and NPV. Although unspecific for different protein depositions, FDG-PET offers an advantage as primary molecular imaging method because of the potential detection of tau-negative neurodegenerative disorders through their distinct hypometabolism pattern. This is highly relevant in cohorts of suspected PSP and CBS patients, as tau-negative variants of fronto-temporal dementia and multiple system atrophy are potential differential diagnoses. Based on our current analysis, FDG-PET can also identify subjects who need further evaluation with additional molecular imaging such as tau-PET imaging. The current dataset creates the basis for future prospective trials evaluating diagnostic algorithms and the additive value of tau-PET in PSP and CBD.

FDG-PET performed better in patients with suspected PSP than for patients with suspected CBD probably due to a more difficult clinical diagnosis (30, 31) and a FDG-pattern less distinct from other neurodegenerative diseases (6). In conclusion, suspected CBD patients with conflicting clinical findings might even profit from an evaluation by a more specific biomarker such as tau radioligands prior to FDG-PET. However, since newest PSP criteria now consider non PSP-RS entities as well, the situation for PSP could as well get more complex, with an assumed benefit by imaging techniques (11). Dual PET tracer studies with randomized sequence will be needed to answer this question.

Our data indicate that clinical probability should be considered when interpreting a FDG-PET of PSP or CBD patients and when planning further evaluation. For PSP patients with a probable clinical likelihood, the higher overall performance of the method needs to be considered in comparison with patients that have only possible or absent diagnostic criteria. Especially the low NPV of a negative FDG-PET read out in the subcohort of suspected PSP patients with possible or absent diagnostic criteria has to be stressed. This subgroup should benefit from further evaluation, where tracers with higher sensitivity are demanded.

The situation in suspected CBD patients presented even more complex: First, CBD patients with a probable clinical likelihood had a very high PPV by a positive FDG-PET, which implies that positive scans of such patients lead to a very high diagnostic confidence. On the other hand, we observed only a very low NPV by a negative FDG-PET in this subcohort. Thus, negative FDG-PET results of CBD patients with high clinical likelihood have only a low meaningfulness and further evaluation by a more sensitive tracer will definitely improve the diagnostic accuracy in this subgroup. Furthermore the PPV of a positive FDG-PET in the subgroup of CBD patients with possible or absent diagnostic criteria was only moderate and indicated another potential target group for beneficial further evaluation.

For the detection of PSP, automatic analysis strategies such as machine learning algorithms revealed a slightly lower PPV (91 vs. 93%) but a noticeable higher NPV (92 vs. 80%) than we observed in our sample (14). This comparison should be interpreted with caution due to the differing population characteristics. Nevertheless, the majority of clinical nuclear medicine departments still use visual inspection of axial slices and surface projection Z-score maps for FDG-PET of patients vs. in house norm collectives. Although one third of patients did not show distinct visual FDG-PET patterns to confirm the diagnosis, the diagnostic modality helps the nuclear medicine clinician to decide upon a rational recommendation for further evaluation of the patient.

Dopamine transporter availability was only performed in less than half of the patients ($n = 49/117$). This was probably related to certainty of clinicians about the present parkinsonism in most of the analyzed patients. Interestingly, the PPV for combined pathological DaTSCAN and FDG-PET was lower than for patients with only a pathological FDG-PET. Moreover, patients without an available DaTSCAN showed a higher PPV for detecting PSP/CBD by FDG-PET compared to those with an available DaTSCAN. This indicates the unfavorable consequence when clinicians order an additional DaTSCAN if the clinical presentation is inconclusive, which results in a lower pretest probability, thus presenting a greater diagnostic challenge for FDG-PET. Due to the limited number of cases with an available DaTSCAN, we cannot test if dopamine transporter SPECT would have facilitated the establishment of a correct differential diagnosis in cases inconclusive to FDG-PET alone.

LIMITATIONS

The impact of MRI results on the diagnostic accuracy has not been investigated in this setting. In the present workup, patients with clear findings in MRI were normally not referred for molecular imaging by FDG-PET. Thus, we did not assume an increasing value of analyzing inhomogeneous MRI findings which do not reflect the patient cohort initially referred to MRI. It should be noted that this cohort of clinical routine imaging in nuclear medicine at a tertiary center definitely underwent preselection steps before going

to FDG-PET. Thus, the present investigation potentially presents more complex patients when compared to PSP or CBD patients referred to a primary care center. Final diagnoses were based on clinical follow-up $\geq$ 1 year without histopathological validation and thus no gold standard was available as "true" diagnosis. Furthermore, imaging findings of FDG-PET certainly contributed to the initial establishment of a clinical diagnosis, especially in cases that did not fulfill the diagnosis criteria completely. Therefore, some degree of circular interference cannot be completely ruled out in such a clinical dataset, but the verification of all single items within the retrospective survey strengthened the validity of clinical diagnoses.

CONCLUSIONS

We investigated clinical routine cases with the differential diagnosis of PSP/CBD referred for a FDG-PET to reveal the diagnostic value for the final diagnosis. FDG-PET showed a high PPV for subjects with a typical PSP/CBD pattern and a low likelihood for another ND as well as a high NPV for subjects without a typical PSP/CBD pattern. One third of patients (CBD > PSP) showed inconclusive scans and might profit from further evaluation with more specific radioligands (e.g., tau), where FDG-PET can act as a gatekeeper for such more expensive methods. This subgroup represents an ideal cohort for testing the additive value of tau radioligands in prospective trials for 4R tauopathies. Clinical probability by diagnostic criteria should be considered together with FDG-PET findings when evaluating the benefit of scanning with additional ligands.

ETHICS STATEMENT

Retrospective analysis of PET data was approved by the local ethics committee of the LMU Munich (399-09).

AUTHOR CONTRIBUTIONS

LB: conception and design, acquisition of data, analysis and interpretation of data, document writing and editing. JM-W: acquisition of data, analysis and interpretation of data, document writing. JS, EB, MU, NA, and PB: interpretation of molecular imaging data, acquisition of data, revising of the manuscript. SS, CP, GN, OP, RP, CC, KBu, and KBö: acquisition of patient data, drafting and revising of the manuscript. JL: acquisition of patient data, conception and intellectual input, drafting and revising of the manuscript. AR: interpretation of molecular imaging data, conception and intellectual input, drafting and revising of the manuscript. MB: conception and design, acquisition of data, document editing, final manuscript approval for submission and publication.

ACKNOWLEDGMENTS

Parts of this paper originated from the doctoral thesis of JM-W. We note editing of the manuscript by Inglewood Biomedical Editing.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00483/full#supplementary-material

REFERENCES

1. Levin J, Kurz A, Arzberger T, Giese A, Höglinger GU. The differential diagnosis and treatment of atypical parkinsonism. *Dtsch Arztebl Int.* (2016) 113:61–9. doi: 10.3238/arztebl.2016.0061
2. Winter Y, Bezdolnyy Y, Katunina E, Avakjan G, Reese JP, Klotsche J, et al. Incidence of Parkinson's disease and atypical parkinsonism: Russian population-based study. *Mov Disord.* (2010) 25:349–56. doi: 10.1002/mds.22966.
3. Amtage F, Maurer C, Hellwig S, Tüscher O, Kreft A, Weiller C, et al. Functional correlates of vertical gaze palsy and other ocular motor deficits in PSP: an FDG-PET study. *Parkinsonism Relat Disord.* (2014) 20:898–906. doi: 10.1016/j.parkreldis.2014.05.013
4. Hellwig S, Frings L, Amtage F, Buchert R, Spehl TS, Rijntjes M, et al. 18F-FDG PET Is an early predictor of overall survival in suspected atypical parkinsonism. *J Nucl Med.* (2015) 56:1541–6. doi: 10.2967/jnumed.115.159822
5. Niethammer M, Tang CC, Feigin A, Allen PJ, Heinen L, Hellwig S, et al. A disease-specific metabolic brain network associated with corticobasal degeneration. *Brain* (2014) 137(Pt 11):3036–46. doi: 10.1093/brain/awu256
6. Zhao P, Zhang B, Gao S. 18F-FDG PET study on the idiopathic Parkinson's disease from several parkinsonian-plus syndromes. *Parkinsonism Relat Disord.* (2012) 18(Suppl. 1):S60–2. doi: 10.1016/S1353-8020(11)70020-7
7. Mille E, Levin J, Brendel M, Zach C, Barthel H, Sabri O, et al. Cerebral glucose metabolism and dopaminergic function in patients with corticobasal syndrome. *J Neuroimaging* (2017) 27:255–61. doi: 10.1111/jon.12391
8. Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S et al. Abnormal metabolic networks in atypical parkinsonism. *Mov Disord.* (2008) 23:727–33. doi: 10.1002/mds.21933
9. Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology* (2013) 80:496–503. doi: 10.1212/WNL.0b013e31827f0fd1
10. Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology* (1996) 47:1–9.
11. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord.* (2017) 32:853–64. doi: 10.1002/mds.26987
12. Respondek G, Roeber S, Kretzschmar H, Troakes C, Al-Sarraj S, Gelpi E et al. Accuracy of the national institute for neurological disorders and stroke/society for progressive supranuclear palsy and neuroprotection and natural history in parkinson plus syndromes criteria for the diagnosis of progressive supranuclear palsy. *Mov Disord.* (2013) 28:504–9. doi: 10.1002/mds.25327
13. Alexander SK, Rittman T, Xuereb JH, Bak TH, Hodges JR, Rowe JB. Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. *J Neurol Neurosurg Psychiatry* (2014) 85:925–9. doi: 10.1136/jnnp-2013-307035
14. Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol.* (2010) 9:149–58. doi: 10.1016/S1474-4422(10)70002-8

15. Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: a review of the recent literature. *J Nucl Med*. (2012) 53:59–71. doi: 10.2967/jnumed.111.096578
16. la Fougère C, Pöpperl G, Levin J, Wängler B, Böning G, Uebleis C, et al. The value of the dopamine D2/3 receptor ligand 18F-desmethoxyfallypride for the differentiation of idiopathic and nonidiopathic parkinsonian syndromes. *J Nucl Med*. (2010) 51:581–7. doi: 10.2967/jnumed.109.071811
17. Boccardi M, Altomare D, Ferrari C, Festari C, Guerra UP, Paghera B, et al. Assessment of the incremental diagnostic value of florbetapir f 18 imaging in patients with cognitive impairment: the incremental diagnostic value of amyloid PET with [18F]-florbetapir (INDIA-FBP) study. *JAMA Neurol*. (2016) 73:1417–24. doi: 10.1001/jamaneurol.2016.3751
18. Harada R, Okamura N, Furumoto S, Tago T, Yanai K, Arai H, et al. Characteristics of Tau and its ligands in PET imaging. *Biomolecules* (2016) 6:7. doi: 10.3390/biom6010007
19. Whitwell JL, Lowe VJ, Tosakulwong N, Weigand SD, Senjem ML, Schwarz CG, et al. [18 F]AV-1451 tau positron emission tomography in progressive supranuclear palsy. *Mov Disord*. (2017). 32:124–33. doi: 10.1002/mds.26834
20. Josephs KA, Whitwell JL, Tacik P, Duffy JR, Senjem ML, Tosakulwong N, et al. [18F]AV-1451 tau-PET uptake does correlate with quantitatively measured 4R-tau burden in autopsy-confirmed corticobasal degeneration. *Acta Neuropathol*. (2016) 132:931–3. doi: 10.1007/s00401-016-1618-1
21. Ishiki A, Harada R, Okamura N, Tomita N, Rowe CC, Villemagne VL, et al. Tau imaging with [18 F]THK-5351 in progressive supranuclear palsy. *Eur J Neurol*. (2016) 24:130–6. doi: 10.1111/ene.13164
22. Kikuchi A, Okamura N, Hasegawa T, Harada R, Watanuki S, Funaki Y, et al. *In vivo* visualization of tau deposits in corticobasal syndrome by 18F-THK5351 PET. *Neurology* (2016) 87:2309–16. doi: 10.1212/WNL.0000000000003375
23. Minoshima S, Frey KA, Koeppe RA, Foster NL, Kuhl DE. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. *J Nucl Med*. (1995) 36:1238–48.
24. Meyer PT, Frings L, Rücker G, Hellwig S. 18F-FDG PET in Parkinsonism: differential diagnosis and cognitive impairment in Parkinson's disease. *J Nucl Med*. (2017) 58:1888–98. doi: 10.2967/jnumed.116.186403
25. Hellwig S, Amtage F, Kreft A, Buchert R, Winz OH, Vach W, et al. [F]FDG-PET is superior to [I]IBZM-SPECT for the differential diagnosis of parkinsonism. *Neurology* (2012) 79:1314–22. doi: 10.1212/WNL.0b013e31826c1b0a
26. Zalewski N, Botha H, Whitwell JL, Lowe V, Dickson DW, Josephs KA. FDG-PET in pathologically confirmed spontaneous 4R-tauopathy variants. *J Neurol*. (2014) 261:710–6. doi: 10.1007/s00415-014-7256-4
27. Ng KP, Pascoal TA, Mathotaarachchi S, Therriault J, Kang MS, Shin M et al. Monoamine oxidase B inhibitor, selegiline, reduces 18F-THK5351 uptake in the human brain. *Alzheimers Res Ther*. (2017) 9:25. doi: 10.1186/s13195-017-0253-y
28. Kantarci K, Lowe VJ, Boeve BF, Senjem ML, Tosakulwong N, Lesnick TG, et al. AV-1451 tau and beta-amyloid positron emission tomography imaging in dementia with Lewy bodies. *Ann Neurol*. (2017) 81:58–67. doi: 10.1002/ana.24825
29. Smith R, Schöll M, Widner H, van Westen D, Svenningsson P, Hägerström D, et al. *In vivo* retention of 18F-AV-1451 in corticobasal syndrome. *Neurology* (2017) 89:845–53. doi: 10.1212/WNL.0000000000004264
30. Wadia PM, Lang AE. The many faces of corticobasal degeneration. *Parkinsonism Relat Disord*. (2007) 13 (Suppl. 3):S336–40. doi: 10.1016/S1353-8020(08)70027-0
31. Ling H, O'Sullivan SS, Holton JL, Revesz T, Massey LA, Williams DR, et al. Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain* (2010) 133(Pt 7):2045–57. doi: 10.1093/brain/awq123

Conflict of Interest Statement: PB declares a research collaboration with GE. AR received speaker honoraria from Piramal Imaging and GE Healthcare.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Paper II

NeuroImage: Clinical 29 (2021) 102535

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cognitive reserve hypothesis in frontotemporal dementia: A FDG-PET study

Leonie Beyer [a], Johanna Meyer-Wilmes [a], Sonja Schönecker [b], Jonas Schnabel [a], Julia Sauerbeck [a], Maximilian Scheifele [a], Catharina Prix [b], Marcus Unterrainer [a,c], Cihan Catak [d], Oliver Pogarell [e], Carla Palleis [b,f], Robert Perneczky [e,f,g,i], Adrian Danek [b], Katharina Buerger [d,f], Peter Bartenstein [a,g], Johannes Levin [b,f], Axel Rominger [a,g,h], Michael Ewers [f], Matthias Brendel [a,g,*]

[a] Dept. of Nuclear Medicine, University Hospital, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 Munich, Germany
[b] Dept. of Neurology, University Hospital, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 Munich, Germany
[c] Department of Radiology, University Hospital, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 Munich, Germany
[d] Institute for Stroke and Dementia Research, University Hospital, Ludwig-Maximilians-Universität München, Feodor-Lynen-Str. 17, 81377 Munich, Germany
[e] Dept. of Psychiatry, University Hospital, Ludwig-Maximilians-Universität München, Nußbaumstr. 7, 80336 Munich, Germany
[f] DZNE – German Center for Neurodegenerative Diseases, Feodor-Lynen-Str. 17, 81377 Munich, Germany
[g] Munich Cluster for Systems Neurology (SyNergy), Feodor-Lynen-Str. 17, 81377 Munich, Germany
[h] Dept. of Nuclear Medicine, University of Bern, Inselspital, Freiburgstr. 18, 3010 Bern, Switzerland
[i] Ageing Epidemiology (AGE) Research Unit, School of Public Health, Imperial College, Level 2, Faculty Building, South Kensington Campus, London SW7 2AZ, United Kingdom

ARTICLE INFO

Keywords:
Cognitive reserve
Frontotemporal dementia
FDG-PET
Hypometabolism

ABSTRACT

Background and objective: Reserve is defined as the ability to maintain cognitive functions relatively well at a given level of pathology. Early life experiences such as education are associated with lower dementia risk in general. However, whether more years of education guards against the impact of brain alterations also in frontotemporal dementia (FTD) has not been shown in a large patient collective. Therefore, we assessed whether education is associated with relatively high cognitive performance despite the presence of [^{18}F]-fluorodeoxyglucose positron-emission-tomography (FDG-PET) hypometabolism in FTD.

Methods: Sixty-six FTD subjects (age 67 ± 8 years) and twenty-four cognitively healthy controls (HC) were evaluated. Brain regions with FTD-related glucose hypometabolism in the contrast against HC and brain regions that correlate with the cognitive function were defined by a voxel-based analysis and individual FDG-PET values were extracted from all frontotemporal brain areas. Linear regression analysis served to test if education is associated with residualized cognitive performance and regional FDG-PET hypometabolism after controlling for global cognition.

Results: Compared to healthy controls, patients with FTD showed glucose hypometabolism in bilateral frontal and temporal brain areas whereas cognition was only associated with deteriorated glucose metabolism in the left temporal lobe. The education level was significantly correlated with the residualized cognitive performance (residuals from regression analysis between hypometabolism and cognitive function as a quantitative index of reserve) and also negatively correlated with left temporal FDG-PET hypometabolism after controlling for cognition.

Conclusions: In patients with FTD, the education level predicts the existing left temporal FDG-PET hypometabolism at the same cognition level, supporting the cognitive reserve hypothesis in FTD.

1. Introduction

Among the spectrum of neurodegenerative diseases, frontotemporal dementia (FTD) is the second most common cause of presenile early onset dementia (Vieira et al., 2013). The prevalence of FTD ranges from 1 to 22 per 100 000 (Lambert et al., 2014; Knopman and Roberts, 2011).

* Corresponding author at: Department of Nuclear Medicine, University of Munich, Marchioninistr. 15, 81377 Munich, Germany.
E-mail address: matthias.brendel@med.uni-muenchen.de (M. Brendel).

https://doi.org/10.1016/j.nicl.2020.102535
Received 27 August 2020; Received in revised form 17 November 2020; Accepted 12 December 2020
Available online 16 December 2020

According to clinical criteria, the core forms of FTD include behavioural-variant FTD (bvFTD) (Rascovsky et al., 2011), non-fluent variant primary progressive aphasia (nfPPA) and semantic-variant PPA (svPPA) (Bang et al., 2015). In subjects with FTD, positron emission tomography (PET) with [^{18}F]-fluorodeoxyglucose (FDG) allows to detect a characteristic pattern of FDG-PET hypometabolism in frontal and temporal lobe regions (Ishii et al., 1998; Grimmer et al., 2004) which distinguishes FTD from other neurodegenerative diseases such as Alzheimer's disease (AD) (Foster et al., 2007). Although FDG-PET hypometabolism is predictive of lower cognitive performance in FTD (Nazem et al., 2018; Robb et al., 2017; Machulda et al., 2017), protective environmental factors such as education may modulate the association between pathological brain alterations and cognitive impairment. The theory of cognitive reserve postulates that life experiences that are cognitively stimulating, such as education, may enhance the capability to maintain cognitive performance relatively well in aging and disease (Stern et al., 1992; Stern, 2002). Support for the hypothesis of protective effects of education has been best established in AD so far (Stern, 2012). At preclinical, prodromal or dementia stages of AD, more years of education were associated with stronger FDG-PET hypometabolism when controlling for cognitive performance (Perneczky et al., 2006; Ewers et al., 2013), suggesting that patients with higher education can sustain similar levels of cognitive performance in the presence of more severe pathology. However, in FTD, only few studies have investigated the association of proxy measures of reserve and cognition. Higher education was negatively associated with FDG-PET and brain perfusion in the bilateral frontal cortex for FTD subjects when controlled for demographic variables and cognitive performance (Perneczky et al., 2007a; Borroni et al., 2009; Maiovis et al., 2018) whereas a similar association was observed in the left inferior temporal, parahippocampal, and supramarginal gyri in a small cohort of eleven subjects with nfPPA (Perneczky et al., 2007b). In summary, these studies provided indirect evidence that higher education allows to tolerate more pathology at a given level of cognition. However, they did not quantify reserve, i.e. the extent to which cognition was higher than expected based on a given level of pathology. Here we used the residualization approach to derive a quantitative index of reserve. In regression analytical analysis, the residual of cognitive performance after accounting for pathological brain alterations were derived, where higher positive residuals indicate higher cognitive performance than expected based on FTD brain pathology. As the pathological marker we used regional FDG-PET hypometabolism, which is predictive of global cognition. Our primary hypothesis was that more years of education is positively associated with cognitive residuals, i.e. indicating that higher education is associated with higher resilience of cognitive performance relative to a given level of FDG-PET hypometabolism in clinically confirmed FTD.

2. Material and methods

2.1. Study design and patient enrollment

The study entailed patients with a clinical diagnosed FTD at the time of PET imaging (Rascovsky et al., 2011; Gorno-Tempini et al., 2011). Suspected tau positive FTD cases presenting with progressive supranuclear palsy or corticobasal syndrome phenotype (Höglinger et al., 2017) were not included in the analysis. The clinical phenotype was nfPPA in eight cases, svPPA in 34 cases, and bvFTD in 24 cases. All subjects were recruited at the University Hospital of Munich, and were scanned in a clinical setting at the Department of Nuclear Medicine between 2010 and 2017. Patients were referred by the Departments of Neurology, Psychiatry and Institute for Stroke and Dementia Research. All subjects underwent clinical dementia workup including detailed cognitive testing and FDG-PET. Inclusion was performed for all levels of cognitive impairment as long as patients met criteria for FTD. All patients maintained a clinical diagnosis of FTD during a mean follow up of 21 months.

2.2. Clinical assessment and cognitive testing

A clinical neurological examination and neuropsychological testing including Mini-Mental-State Examination (MMSE) (Folstein et al., 1975) assessment was performed in all FTD patients. Years of education (YoE) were recorded, and laboratory parameters for metabolic causes of cognitive impairment (vitamin B_{12}, thiamine and folate levels, thyroid and liver function) were assessed.

2.3. FDG-PET acquisition and pre-processing

FDG was purchased commercially. FDG-PET images of both FTD patients and healthy controls were acquired using a 3-dimensional GE Discovery 690 PET/CT scanner or a Siemens ECAT EXACT HR + PET scanner. All patients fasted for at least six hours, and had a plasma glucose level <120 mg/dl (6.7 mM) at time of scanning. A dose of 142 ± 8 MBq FDG was injected as a slow intravenous bolus while the subject sat quietly in a room with dimmed light and low noise level. A static emission frame was acquired from 30 min to 50 min p.i. for the GE Discovery 690 PET/CT, or from 30 to 60 min p.i. for the Siemens ECAT EXACT HR + PET scanner. A low-dose CT scan (GE) or a transmission scan with external ^{68}Ge-sources (Siemens) was performed prior to the static acquisition for attenuation correction. PET data were reconstructed iteratively (GE) or with filtered back-projection (Siemens).

All individual FDG-PET image volumes were spatially normalized to an in-house FDG-PET template (voxel-size 2 × 2 × 2 mm) within the MNI space (Daerr et al., 2017) using PMOD software (version 3.5, PMOD Technologies Ltd., Zürich, Switzerland). Non-linear warping and transient input smoothing (8 × 8 × 8 mm) was used for the spatial normalization. An in house database of 24 age matched cognitively normal individuals served as FDG-PET template and was also used for group wise comparisons. Scaling by a reference region containing the whole cerebellum and the brainstem served for normalization to standardized-uptake-value-ratio (SUVr) images and regional values of predefined brain regions of the Hammer's atlas (Yakushev et al., 2008; Dukart et al., 2013; Hammers et al., 2003). A Gaussian filter of 8 mm was used prior to voxel-wise comparisons.

2.4. Statistical analysis

In order to identify regional FDG-PET hypometabolism in the FTD patients, we performed a voxel-wise comparison between FTD subjects and cognitively healthy controls using an unpaired *t*-test with family-wise error rate (FWE) correction for multiple comparisons ($p < 0.05$, FWE-corrected, $k > 50$ voxel) with age and sex as covariates. In sub-analyses, those voxel-wise comparisons were repeated for (i) the bvFTD/ PPA subgroup against HC and (ii) subjects with lower/ higher education levels (≤12 years/>12 years).

In order to identify which areas of FDG-PET alterations were associated with global cognition, i.e. were of relevance for differences in cognitive abilities, we tested in a separate voxel-wise regression analyses the association between MMSE and FDG-PET SUVr, controlling for age and sex ($p < 0.05$, FWE-corrected, $k > 50$ voxel). This latter analysis resulted in a single cluster, which overlapped with regions of FDG-PET hypometabolism (in the left temporal cortex). FDG-PET values were averaged across voxels within that cluster and were used for the subsequent residualization approach.

Voxel-based SUVr values from clusters of significant hypometabolism were extracted using PMOD (V3.5, PMOD technologies, Basel, Switzerland) and averaged across voxels within each cluster for further analysis. Quantitative FDG-PET SUVr were compared between phenotypes of FTD and HC, respectively, in the whole frontotemporal and the left temporal cluster using student's *t*-test.

In order to residualize global cognitive performance as a measure of reserve in the FTD patients, we employed in linear regression analysis MMSE as the dependent variable, and with FDG-PET SUVr cluster value

(identified in the previous analysis step, see above) as the main predictor, controlled for age and sex. This resulted in residualized MMSE values as our primary index of reserve. In a secondary analysis, we tested whether we can replicated previous results of a negative association between education and FDG-PET when controlling for global cognitive performance, i.e. we used linear regression analysis with FDG-PET SUVr cluster values as the dependent variable with the education level (YoE) as the predictor controlled for MMSE, age, sex. Regression analyses were performed separately for all single frontal and temporal regions and p-values were controlled for multiple testing with the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995).

SPSS (version 25, IBM, Chicago, IL) was used for all statistical and Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Cognitive Neurology) implemented in MATLAB (version 2016; MathWorks Inc.) for voxel-wise analyses. A significance level of $p < 0.05$ was applied in all analyses (with additional FWE correction for all SPM analyses).

3. Results

3.1. Demographics

The study population consisted of 66 individuals (50% male) with a clinical diagnosis of FTD (n = 24 bvFTD, n = 42 PPA). Mean MMSE was 24.0 (±5.5) at the time of clinical dementia work-up. For details of the study population see table 1.

3.2. Regional neuronal injury patterns and cognition

Compared to healthy controls, patients with FTD showed lower FDG-PET in frontal and temporal cortices in voxel-wise analysis (Fig. 1A), using p values of <0.05 controlled for multiple comparisons by FWE correction. The analysis revealed one large bilateral fronto-temporal cluster with a peak at −34/8/−26 mm (67878 voxels, T-Score 11.51) and two sub-peaks at 0/8/−18 mm (T-Score 10.75) and −26/4/−26 mm (T-Score 10.49). Compared to healthy controls, the majority of patients showed a significantly reduced glucose metabolism in the fronto-temporal cluster (SUVr < 2 standard deviations from the mean of HC) for both phenotypes (PPA: 27/42, bvFTD: 14/24). The hypometabolism in the frontotemporal cluster was not significantly different between PPA and bvFTD phenotypes (SUVr 0.757 vs 0.771, p = 0.208). The hypometabolism pattern of patients with bvFTD and PPA phenotype was similar to the whole FTD cohort, but the PPA subgroup indicated the expected emphasis in temporal cortices, whereas there was a stronger involvement of frontal cortices in bvFTD.

In order to test which FDG-PET alterations are associated with a decrease in cognitive performance, we computed voxel wise analysis with MMSE as the predictor, controlled for age and sex. Results showed that lower MMSE was associated with lower FDG-PET in a solitary cluster within the lateral left-temporal lobe (Fig. 1B) with a peak at −60/−22/−34 (1814 voxels, T-Score 7.36), which overlapped with the hypometabolic regions.

Comparing the FDG-PET values in this cluster between HC and FTD phenotypes, both PPA and bvFTD patients showed significantly reduced glucose metabolism (PPA: p < 0.001, bvFTD: p = 0.025).

We used the averaged FDG-PET uptake in this left temporal cluster for the subsequent analysis on reserve, i.e. global cognition that is higher than expected based on FDG-PET hypometabolism.

To validate the left temporal cluster extracted in the voxel-wise analysis, we performed atlas based regional correlations of all brain areas with a significant hypometabolism in FTD patients. Again, only FDG-PET SUVr in left temporal brain regions indicated a significant association with MMSE after controlling for age, sex and multiple comparisons (see Table 2).

3.3. Education as a predictor of residualized cognitive performance

We tested whether higher education is associated with higher cognitive residuals after accounting for the influence of FDG-PET hypometabolism present in the previously identified left temporal cluster. Results of the regression analysis showed that more years of education were associated with higher residualized MMSE, i.e. higher MMSE than expected based on the level of left-frontal FDG-PET hypometabolism in the FTD patients (R = 0.282, p = 0.022, see Fig. 2A). In the separate analysis of PPA and bvFTD phenotypes, the correlation was even higher for the isolated PPA cohort (R = 0.403, p = 0.008), but did not reach significance in bvFTD (R = 0.041, p = 0.850).

In a secondary analysis, we tested whether at a given level of cognitive performance, higher education is associated with differences in the FDG-PET metabolism in the inferior temporal lobe cluster. More years of education were associated with lower FDG-PET SUVr (β = −0.229, p = 0.015, see Fig. 2B) when controlling for MMSE, age, sex, suggesting that subjects with higher education can tolerate more FDG-PET hypometabolism. This significant association was reproduced in the PPA subgroup (β = -0.405, p = 0.008), but not in bvFTD (β = 0.029, p = 0.892).

To test if subjects with lower education still have a detectable frontotemporal hypometabolism when compared to HC, we divided the FTD cohort in two subgroups of lower/ higher education level (≤12 years/ >12 years). Although the hypometabolism was more pronounced in the subgroup with high education, the voxel-wise comparison still revealed significant clusters of hypometabolism in frontal and temporal cortices in the subgroup with low education (see Fig. 3). Thus, FDG-PET indicated high enough sensitivity for detection of glucose metabolism alterations in patients with FTD and low education.

Table 1
Demographics, covariates, education and cognitive testing results of the study population. FTD, frontotemporal dementia; PPA, primary progressive aphasia; bvFTD, behavioural-variant FTD; HC, healthy control; SD, standard deviation; MMSE, mini-mental-state examination; TMT, Trail Making Test.

	FTD	PPA	bvFTD	HC
Number of subjects	66	42	24	24
Age (y, mean ± SD)	66.9 ± 8.3	68.9 ± 7.6	63.4 ± 9.3	64.5 ± 7.3
Sex (♂ / ♀)	♂ 33 / ♀ 33	♂ 18 / ♀ 24	♂ 15 / ♀ 9	♂ 15 / ♀ 9
Education (y, mean ± SD)	12.5 ± 3.0	12.7 ± 3.1	12.1 ± 2.9	
Follow-up (m, mean ± SD)	20.9 ± 19.8	25.5 ± 22.5	14.7 ± 13.7	
Neuropsychological evaluation				
MMSE (mean ± SD)	24.0 ± 5.5	23.2 ± 6.2	25.5 ± 4.0	30 ± 0
TMT-A (mean ± SD)	24.7 ± 24.9	15.3 ± 16.3	34.1 ± 28.9	
TMT-B (mean ± SD)	106.4 ± 77.3	72.2 ± 27.4	137.8 ± 95.0	
Naming (mean ± SD)	8.1 ± 4.6	5.6 ± 3.6	10.8 ± 4.0	
Semantic verbal fluency (mean ± SD)	8.7 ± 4.4	6.6 ± 3.5	11.0 ± 4.3	
Phonetic verbal fluency (mean ± SD)	9.1 ± 4.7	8.2 ± 2.7	10.0 ± 6.0	

4. Discussion

In the present study, we found higher education to be associated with ameliorated cognitive decline in the presence of FDG-PET hypometabolism. The cognitive reserve hypothesis is based on the observation that the actual cognitive performance is often not concordant with the existing neuronal injury. A substantial number of subjects show relatively stable cognitive performance despite advanced pathological brain alterations (Stern, 2009; Landau et al., 2011; Soldan et al., 2017), indicating that subjects with higher education can have lower FDG-PET

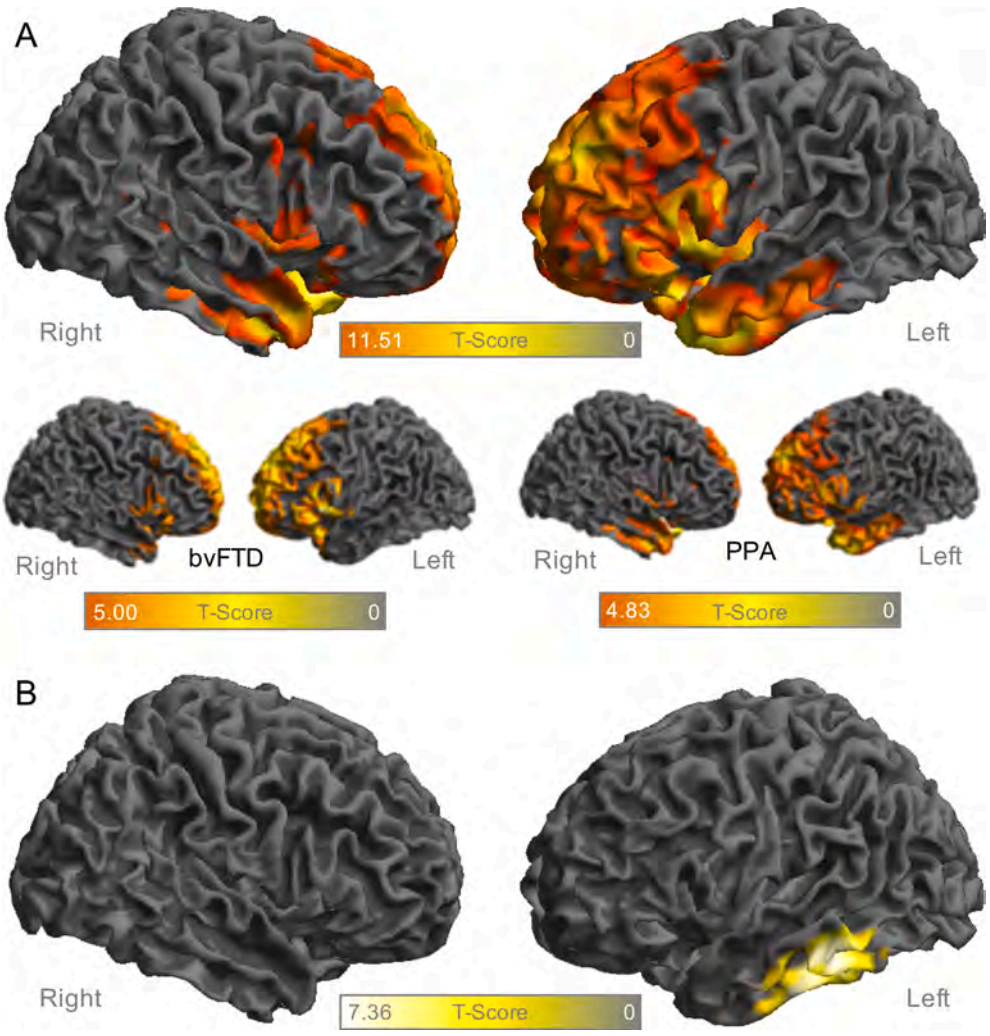


Fig. 1. Surface projections of the right (on the left) and left hemisphere (on the right) in the FTD cohort (n = 66) **A** Regions with significant hypometabolism ($p < 0.05$, FWE-corrected, $k > 50$ voxel) in FDG-PET against healthy controls (n = 24) for the whole cohort and separately for bvFTD and PPA **B** Correlation cluster of FDG-PET with MMSE ($p < 0.05$, FWE-corrected, $k > 50$ voxel) for the whole FTD cohort. FDG, fluordesoxyglucose; FTD, frontotemporal dementia; FWE, family-wise error rate; PPA, primary progressive aphasia; bvFTD, behavioural-variant FTD; MMSE, mini-mental-state-examination; PET, positron-emission-tomography.

metabolism to sustain their cognitive ability. In patients with FTD, few imaging studies showed a negative correlation of higher education with FDG-PET glucose metabolism, brain perfusion, or resting state fMRI assessed functional connectivity, controlling for cognitive performance (Perneczky et al., 2007a, 2007b; Borroni et al., 2009; Premi et al., 2013a). Additionally, at the behavioural level, higher education attenuated the effect of hypoperfusion on the disinhibited phenotype in the bvFTD phenotype (Premi et al., 2013b). However, there is a dearth of data in FTD on the question whether higher education is associated with higher cognitive performance than expected based on the level of brain alterations in FTD, i.e. the core concept of reserve.

In order to address this question, we first established in patients with FTD the spatial pattern of FDG-PET hypometabolism that is associated with changes in global cognition. Consistent with previous studies (Ishii et al., 1998; Grimmer et al., 2004), we found decreased FDG-PET metabolism in frontal and temporal regions compared to healthy controls for the whole FTD cohort. Divided by the clinical phenotypes of FTD, there was a significant hypometabolism for both PPA and bvFTD when compared to HC. This was also reflected at the single patient level, since the majority of patients from both phenotype groups indicated FDG-PET results ranging below two standard deviations from the mean of healthy controls. There was no significant difference of FDG-PET quantification between PPA and bvFTD, highlighting the overlap of FDG-PET hypometabolism patterns between clinical phenotypes.

Only a subset of frontotemporal regions in the left lateral temporal cortex was associated with MMSE. We chose that cluster rather than all regions of FDG-PET metabolism in order to enhance the sensitivity of our analysis of reserve, i.e. only those brain alterations that are linked to global cognitive performance for our residualization approach. Quantitative FDG-PET metabolism in the left temporal cluster was significantly lower in both studied phenotypes of FTD when compared to HC, which again emphasizes the metabolic overlap of PPA and bvFTD.

We found that higher education is associated with higher MMSE score than expected based on the level of left temporal FDG-PET hypometabolism, suggesting that education is associated with a systematic deviation of global cognition from the level of cognitive performance that would be expected based on the severity of metabolic alterations. In other words, higher education was associated with higher resilience against the impact of regional hypometabolism on global cognition. We adopted the residualization approach which was first proposed as a quantitative index in patients with Alzheimer's disease (Reed et al., 2010). This approach has been found to be useful as an index of reserve across several studies (Zahodne et al., 2013; Serra et al., 2017). One disadvantage of this approach is that the residual likely results from a mixture of random prediction error (e.g. due to measurement error) and a meaningful portion of variable that can be attributed to reserve. Despite this limitation, we found that education was associated with a positive deviation of MMSE residuals, supporting that protective factors may explain part of the portion of unexpectedly high cognitive performance despite manifest pathological brain alterations. Our findings are further supported by our auxiliary analyses, where education was associated with more severe FDG-PET metabolism when controlling for

Table 2
Regression coefficients of the correlation of glucose metabolism in FDG-PET and cognitive performance for all frontal and temporal cortical regions (covariate age and sex). β, regression coefficient; ***p-value < 0.001, **p value < 0.01, *p-value < 0.05. P-values are reported after false-discovery-rate correction for multiple comparisons. Age and sex served as covariates.

Cortical region	Left Hemisphere		Right Hemisphere	
	β	p-value	β	p-value
Frontal lobe - mid frontal gyrus	−0.045	0.831	−0.144	0.463
Frontal lobe - straight gyrus	0.309	0.072	0.202	0.320
Frontal lobe - orbitofrontal cortex - anterior orbital gyrus	0.157	0.498	0.015	0.947
Frontal lobe - inferior frontal Gyrus	0.061	0.769	−0.110	0.566
Frontal lobe - superior frontal Gyrus	−0.087	0.671	−0.134	0.472
Frontal lobe - orbitofrontal cortex -medial orbital gyrus	0.189	0.344	0.099	0.623
Frontal lobe - orbitofrontal cortex -lateral orbital gyrus	0.085	0.660	−0.032	0.880
Frontal lobe - orbitofrontal cortex -posterior orbital gyrus	0.218	0.278	0.007	0.977
Anterior cingulus - presubgenual cortex	0.333	0.051	0.149	0.482
Subcallosal area	0.240	0.233	0.163	0.472
Anterior cingulus - presubgenual cortex	0.214	0.280	0.111	0.551
Hippocampus	0.219	0.282	0.070	0.732
Amygdala	0.148	0.484	0.127	0.500
Anterior temporal lobe - medial	0.364	**0.018***	0.193	0.325
Anterior temporal lobe – inferior lateral	0.464	**0.001****	0.152	0.486
Parahippocampal gyrus	0.301	0.073	0.072	0.740
Posterior superior temporal gyrus	0.250	0.260	−0.143	0.486
Middle and inferior temporal gyrus	0.547	**<0.001*****	0.122	0.512
Fusiform gyrus	0.308	0.069	0.046	0.848
Posterior temporal lobe	0.501	**<0.001*****	0.005	0.966
Temporal anterior superior gyrus	0.454	**0.002****	0.145	0.447
Cingulate gyrus - anterior part	0.019	0.946	−0.038	0.859

cognitive performance, suggesting that patients with higher education can tolerate more FDG-PET hypometabolism before showing a similar level of cognitive impairment as those patients with lower levels of education (Stern et al., 1992; Stern, 2002). When analysing the clinical phenotypes bvFTD and PPA separately, we found that residualized memory function was significantly correlated with the education level in patients with PPA patients but not in patients with bvFTD. The even stronger results in the separate analysis of patients with PPA excluded that the main findings of our study were driven by the mixture of phenotypes. The phenotype differences could be related to the smaller sample size of the bvFTD or to differences of the phenotype itself. In this regard, an autopsy study in FTD reported an opposite positive correlation of cognitive reserve (expressed by the education level and the occupation index) with higher grey matter density in several frontal regions and no correlation of higher grey matter density in any brain region with lower cognitive reserve (Placek et al., 2016). The most relevant difference between both studies was the predominant bvFTD phenotype in the autopsy study in contrast to the predominant PPA phenotype in the present work. In our cohort, we only found significant correlations with temporal regions and neither positive nor negative correlations with frontal regions. Thus, in summary there could be a variable impact of reserve indices on neuropathology in different brain networks (i.e. temporal vs. frontal) underlying the different FTD phenotypes.

The understanding of the systematic deviation of cognitive abilities from what would be expected based on manifest FDG-PET hypometabolism has clinical implications: when FDG-PET is judged normal or abnormal in the workup of suspected FTD in patients, where seemingly subtle FDG-PET alterations can be accompanied by relatively strong cognitive impairment, i.e. when subjects show low education. Low to moderate reduced left temporal glucose metabolism combined with a low education results in a higher likelihood of FTD compared to a patient with a high education level and the same cognitive performance.

This is especially relevant since subjects with FTD often present with mild but not severe cognitive impairment (also reflected by a mean MMSE of 24.0 ± 5.5 in the current cohort). In our sub-analysis investigating patients with lower/ higher education levels separately, we found

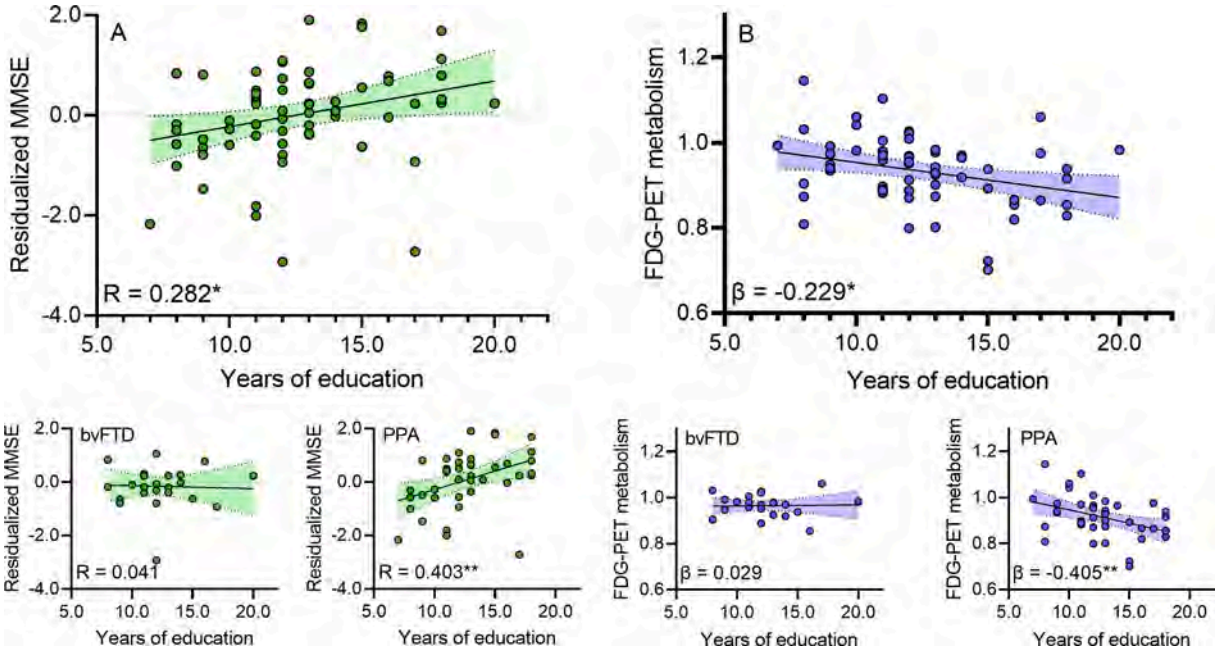


Fig. 2. **A** Correlation plots showing the residualized FDG-PET/ MMSE scores as a function of years of education for the whole FTD cohort and separately for the bvFTD and PPA subgroup. **B** Regression plots showing FDG-PET in the left temporal cluster as a function of years of education after control for age, sex and MMSE for the whole FTD cohort and separately for the bvFTD and PPA subgroup.. *p-value < 0.05. FDG, fluordesoxyglucose; MMSE, mini-mental-state-examination; PET, positron-emission-tomography; FTD, frontotemporal dementia; PPA, primary progressive aphasia; bvFTD, behavioural-variant FTD.

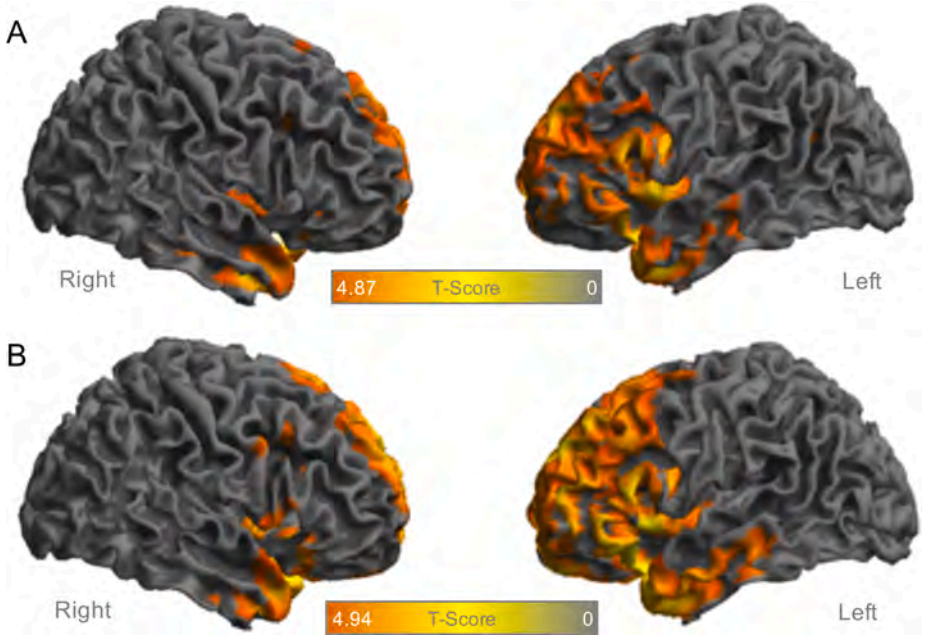


Fig. 3. Surface projections of the right (on the left) and left hemisphere (on the right) in the FTD cohort with significant hypometabolism ($p < 0.05$, FWE-corrected, $k > 50$ voxel) in FDG-PET against healthy controls ($n = 24$) separately for subjects with **A** lower education levels ($n = 37$) and **B** higher education levels ($n = 29$). FDG, fluordesoxyglucose; FTD, frontotemporal dementia; FWE, family-wise error rate; PET, positron-emission-tomography.

both groups to show significant hypometabolism in frontal and temporal cortices when compared to healthy controls. This is in line with a former study in AD patients that compared the diagnostic accuracy of FDG-PET between groups with higher and lower education levels and found education not to be a major confounder (Mainta et al., 2018). Therefore, different education levels need to be considered when interpreting FDG-PET images in FTD patients, but the sensitivity of the method should be high enough to detect subjects with low education levels.

The paradigm of cognitive reserve is also of interest in terms of further cognitive deterioration. It has been hypothesized that cognitive reserve helps to longer maintain cognitive functions, but with faster decline over time (Stern, 2009). This hypothesis was confirmed in patients with AD, where higher cognitive reserve expressed by the discrepancies between neuronal injury biomarkers and cognitive performance led to faster decline in clinical follow-up (Beyer et al., 2019). In a longitudinal evaluation of cognitive decline in bvFTD patients, higher lifetime cognitive experience demonstrated more rapid decline on measures of executive function (Massimo et al., 2019), but an overall longer survival (Massimo et al., 2015). Further longitudinal measurements of the relationship between cognitive reserve and levels of hypometabolism will be of great interest in the field of FTD.

5. Limitations

As limitations of this study, we note that the years of education is not the only proxy that has been shown to assess cognitive reserve. Other individual factors such as life activities and occupation levels have been shown to contribute to the cognitive reserve but those were not recorded due to the retrospective design of the study (Stern et al., 1992; Maiovis et al., 2018; Alexander et al., 1997). Furthermore, data about family history which could indicate a genetic background and precise recordings of the disease duration were not available.

Furthermore, MMSE as the commonly used instrument for measuring cognitive impairment cannot replace detailed neuropsychological testing and does not represent all aspects of cognitive decline. Especially frontal lobe functions are poorly represented by the MMSE score which may explain the missing voxel-wise associations between cognitive function (expressed by MMSE) and left temporal hypometabolism in the bvFTD subgroup. Nevertheless, both clinical phenotypes overlap and bvFTD patients also showed a significantly lower left-temporal metabolism compared to HC. Therefore, this temporal involvement can also occur in bvFTD and might be better represented by the MMSE score. More detailed cognitive testing would be favorable, however due to lacking standardization of cognitive testing in our cross-sectional FTD cohort, we focused on commonly used MMSE to gain results relevant for the majority of clinical institutions. We note that although we included patients at all levels of cognitive impairment there could be a selection bias since FTD patients with severe cognitive impairment likely had not undergone FDG-PET imaging at their clinical workup.

6. Conclusions

In the hitherto largest mixed collective of clinical assessed FTD patients, the education level as a surrogate of cognitive performance explains discrepancies between left temporal FDG-PET hypometabolism and global cognition supporting the concept of an existing cognitive reserve. As already proposed for other neurodegenerative diseases, higher education levels could potentially modify cognitive deterioration also in FTD.

CRediT authorship contribution statement

Leonie Beyer: Writing - original draft, Methodology, Formal analysis. **Johanna Meyer-Wilmes:** Methodology, Formal analysis. **Sonja Schönecker:** Validation. **Jonas Schnabel:** Validation. **Julia Sauerbeck:** Validation. **Maximilian Scheifele:** Validation. **Catharina Prix:** Validation. **Marcus Unterrainer:** Validation. **Cihan Catak:** Validation. **Oliver Pogarell:** Validation. **Carla Palleis:** Validation. **Robert Perneczky:** Validation. **Adrian Danek:** Validation. **Katharina Buerger:** Validation. **Peter Bartenstein:** . **Johannes Levin:** Validation. **Axel Rominger:** Validation. **Michael Ewers:** Conceptualization, Supervision. **Matthias Brendel:** Conceptualization, Writing - review & editing, Supervision, Methodology.

Acknowledgements

Competing interests M.B. received speaker honoraria from GE healthcare and LMI and is an advisor of LMI. R.P. is on the advisory board for Biogen, has consulted for Eli Lilly, is a grant recipient from Janssen Pharmaceutica and Boehringer Ingelheim, and has received speaker honoraria from Janssen-Cilag, Pfizer, and Biogen. All other authors do not declare competing interests.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent for publication Not required.

Ethics approval This retrospective study was approved by the local ethics committee in accordance with the declaration of Helsinki.

References

Vieira, R.T., Caixeta, L., Machado, S., et al., 2013. Epidemiology of early-onset dementia: a review of the literature. Clin. Pract. Epidemiol. Mental Health: CP & EMH 9, 88–95. https://doi.org/10.2174/1745017901309010088 [published Online First: 2013/07/24].

Lambert, M.A., Bickel, H., Prince, M., et al., 2014. Estimating the burden of early onset dementia; systematic review of disease prevalence. Eur. J. Neurol. 21(4), 563–569. doi: 10.1111/ene.12325 [published Online First: 2014/01/15].

Knopman, D.S., Roberts, R.O., 2011. Estimating the number of persons with frontotemporal lobar degeneration in the US population. J. Mol. Neurosci.:MN 45 (3), 330–335.

Rascovsky, K., Hodges, J.R., Knopman, D., et al., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain : J. Neurol.134(Pt 9), 2456–2477. doi: 10.1093/brain/awr179 [published Online First: 2011/08/04].

Bang, J., Spina, S., Miller, B.L., 2015. Frontotemporal dementia. The Lancet 386 (10004), 1672–1682.

Ishii, K., Sakamoto, S., Sasaki, M., et al., 1998. Cerebral glucose metabolism in patients with frontotemporal dementia. J. Nucl. Med.: Off. Publ. Soc. Nucl. Med. 39(11), 1875–1878. [published Online First: 1998/11/26].

Grimmer, T., Diehl, J., Drzezga, A., et al., 2004. Region-specific decline of cerebral glucose metabolism in patients with frontotemporal dementia: a prospective 18F-FDG-PET study. Dement. Geriatr. Cogn. Disord. 18 (1), 32–36. https://doi.org/10.1159/000077732 [published Online First: 2004/04/16].

Foster, N.L., Heidebrink, J.L., Clark, C.M., et al., 2007. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain :J. Neurol.130(Pt 10), 2616–2635. doi: 10.1093/brain/awm177 [published Online First: 2007/08/21].

Nazem, A., Tang, C.C., Spetsieris, P., et al., 2018. A multivariate metabolic imaging marker for behavioral variant frontotemporal dementia. Alzheimer's & dementia (Amsterdam, Netherlands) 10, 583–594. doi: 10.1016/j.dadm.2018.07.009 [published Online First: 2018/11/13].

Robb, C., Udeh-Momoh, C., Wagenpfeil, S., et al., 2017. Biomarkers and Functional Decline in Prodromal Alzheimer's Disease. J. Alzheimer's Disease: JAD 58 (1), 69–78. https://doi.org/10.3233/jad-161162 [published Online First: 2017/04/05].

Machulda, M.M., Hagen, C.E., Wiste, H.J., et al., 2017. Practice effects and longitudinal cognitive change in clinically normal older adults differ by Alzheimer imaging biomarker status. Clin. Neuropsychol. 31(1), 99-117. doi: 10.1080/13854046.2016.1241303 [published Online First: 2016/10/12].

Stern, Y., Alexander, G.E., Prohovnik, I., et al., 1992. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann. Neurol. 32(3), 371–375. doi: 10.1002/ana.410320311 [published Online First: 1992/09/01].

Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8 (3), 448–460 [published Online First: 2002/04/10].

Stern, Y., 2012. Cognitive reserve in ageing and Alzheimer's disease. The Lancet Neurology 11 (11), 1006–1012 [published Online First: 2012/10/20].

Perneczky, R., Drzezga, A., Diehl-Schmid, J., et al., 2006. Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. J. Neurol. Neurosurg. Psychiatry 77 (9), 1060–1063. https://doi.org/10.1136/jnnp.2006.094714 [published Online First: 2006/05/20].

Ewers, M., Insel, P.S., Stern, Y., et al., 2013. Cognitive reserve associated with FDG-PET in preclinical Alzheimer disease. Neurology 80 (13), 1194–1201, 10.1212/WNL.0b013e31828970c2 [published Online First: 2013/03/15].

Perneczky, R., Diehl-Schmid, J., Drzezga, A., 2007. Brain reserve capacity in frontotemporal dementia: a voxel-based 18F-FDG PET study. et al. Eur. J. Nucl. Med. Mol. Imaging 34 (7), 1082–1087, 10.1007/s00259-006-0323-z [published Online First: 2007/01/16].

Borroni, B., Premi, E., Agosti, C., et al., 2009. Revisiting brain reserve hypothesis in frontotemporal dementia: evidence from a brain perfusion study. Dement. Geriatr. Cogn. Disord. 28 (2), 130–135 doi: 10.1159/000235575 [published Online First: 2009/08/20].

Maiovis, P., Ioannidis, P., Gerasimou, G., et al., 2018. Cognitive Reserve Hypothesis in Frontotemporal Dementia: Evidence from a Brain SPECT Study in a Series of Greek Frontotemporal Dementia Patients. Neuro-degenerative Dis.18(2-3), 69–73. doi: 10.1159/000486621 [published Online First: 2018/03/08].

Perneczky, R., Diehl-Schmid, J., Pohl, C., Drzezga, A., Kurz, A., 2007. Non-fluent progressive aphasia: Cerebral metabolic patterns and brain reserve. Brain Res. 1133, 178–185 doi: 10.1016/j.brainres.2006.11.054 [published Online First: 2006/12/23].

Gorno-Tempini, M.L., Hillis, A.E., Weintraub, S., et al., 2011. Classification of primary progressive aphasia and its variants. Neurology 76 (11), 1006–1014 doi: 10.1212/WNL.0b013e31821103e6 [published Online First: 2011/02/18].

Höglinger, G.U., Respondek, G., Stamelou, M., et al., 2017. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Movement disorders 32 (6), 853–864 doi: 10.1002/mds.26987 [published Online First: 2017/05/04].

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatric Res. 12(3), 189–198. [published Online First: 1975/11/01].

Daerr, S., Brendel, M., Zach, C., et al., 2017. Evaluation of early-phase [18 F]-florbetaben PET acquisition in clinical routine cases. NeuroImage: Clin. 14, 77–86 doi: 10.1016/j.nicl.2016.10.005 [published Online First: 2017/02/01].

Yakushev, I., Landvogt, C., Buchholz, H.G., et al., 2008. Choice of reference area in studies of Alzheimer's disease using positron emission tomography with fluorodeoxyglucose-F18. Psychiatry Res. 164 (2), 143–153, 10.1016/j.pscychresns.2007.11.004 [published Online First: 2008/10/22].

Dukart, J., Perneczky, R., Forster, S., et al., 2013. Reference cluster normalization improves detection of frontotemporal lobar degeneration by means of FDG-PET. PloS one 8(2), e55415. doi: 10.1371/journal.pone.0055415 [published Online First: 2013/03/02].

Hammers, A., Allom, R., Koepp, M.J., et al., 2003. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Hum. Brain Mapp. 19 (4), 224–247 doi: 10.1002/hbm.10123 [published Online First: 2003/07/23].

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc.: Ser. B (Methodol.) 57 (1), 289–300.

Stern, Y., 2009. Cognitive reserve☆. Neuropsychologia 47 (10), 2015–2028 doi: 10.1016/j.neuropsychologia.2009.03.004 [published Online First: 2009/05/27].

Landau, S.M., Harvey, D., Madison, C.M., et al., 2011. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiol. Aging 32 (7), 1207–1218 doi: 10.1016/j.neurobiolaging.2009.07.002 [published Online First: 2009/08/08].

Soldan, A., Pettigrew, C., Cai, Q., Albert, et al., 2017. Cognitive reserve and long-term change in cognition in aging and preclinical Alzheimer's disease. Neurobiol. Aging 60, 164–172 doi: 10.1016/j.neurobiolaging.2017.09.002 [published Online First: 2017/10/03].

Premi, E., Gazzina, S., Bozzali, M., et al., 2013. Cognitive reserve in granulin-related frontotemporal dementia: from preclinical to clinical stages. PloS one 8(9), e74762. doi: 10.1371/journal.pone.0074762 [published Online First: 2013/09/17].

Premi, E., Garibotto, V., Gazzina, S., et al., 2013. Beyond cognitive reserve: Behavioural reserve hypothesis in Frontotemporal Dementia. Behav. Brain Res. 245, 58–62 doi: 10.1016/j.bbr.2013.01.030 [published Online First: 2013/02/06].

Reed, B.R., Mungas, D., Farias, S.T., et al., 2010. Measuring cognitive reserve based on the decomposition of episodic memory variance. Brain 133 (Pt 8), 2196–2209.

Zahodne, L.B., Manly, J.J., Brickman, A.M., et al., 2013. Quantifying cognitive reserve in older adults by decomposing episodic memory variance: replication and extension. J. Int. Neuropsychol. Soc. 19 (8), 854–862 doi: 10.1017/s1355617713000738 [published Online First: 2013/07/20].

Serra, L., Bruschini, M., Di Domenico, C., et al., 2017. Memory is not enough: the neurobiological substrates of dynamic cognitive reserve. J. Alzheimer's Dis.: JAD 58 (1), 171–184 doi: 10.3233/jad-170086 [published Online First: 2017/04/08].

Placek, K., Massimo, L., Olm, C., et al., 2016. Cognitive reserve in frontotemporal degeneration: Neuroanatomic and neuropsychological evidence. Neurology 87 (17), 1813–1819 doi: 10.1212/wnl.0000000000003250 [published Online First: 2016/10/26].

Mainta, I., Trombella, S., Morbelli, S., et al., 2018. Education-adjusted normality thresholds for FDG-PET in the diagnosis of Alzheimer disease. Neuro-degener. Dis 18 (2-3), 120–126 doi: 10.1159/000488915 [published Online First: 2018/06/06].

Beyer, L., Schnabel, J., Kazmierczak, P., et al., 2019. Neuronal injury biomarkers for assessment of the individual cognitive reserve in clinically suspected Alzheimer's disease. NeuroImage: Clin. 24, 101949. https://doi.org/10.1016/j.nicl.2019.101949 doi: 10.1016/j.nicl.2019.101949 [published Online First: 2019/08/10].

Massimo, L., Xie, S.X., Rennert, L., et al., 2019. Occupational attainment influences longitudinal decline in behavioral variant frontotemporal degeneration. Brain Imaging Behav. 13 (1), 293–301 doi: 10.1007/s11682-018-9852-x [published Online First: 2018/03/16].

Massimo, L., Zee, J., Xie, S.X., et al., 2015. Occupational attainment influences survival in autopsy-confirmed frontotemporal degeneration. Neurology 84 (20), 2070–2075 doi: 10.1212/wnl.0000000000001595 [published Online First: 2015/04/24].

Alexander, G.E., Furey, M.L., Grady, C.L., et al., 1997. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. Am. J. Psychiatry 154 (2), 165–172. https://doi.org/10.1176/ajp.154.2.165 [published Online First: 1997/02/01].

8 Literaturverzeichnis

Alexander, S. K., Rittman, T., Xuereb, J. H., Bak, T. H., Hodges, J. R., & Rowe, J. B. (2014). Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. *Journal of Neurology, Neurosurgery &Amp; Psychiatry*, *85*(8), 925 LP – 929. https://doi.org/10.1136/jnnp-2013-307035

Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., … Weiner, W. J. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology*, *80*(5), 496 LP – 503. https://doi.org/10.1212/WNL.0b013e31827f0fd1

Beyer, L., & Brendel, M. (2020). Imaging of Tau Pathology in Neurodegenerative Diseases: An Update. *Seminars in Nuclear Medicine*. https://doi.org/10.1053/j.semnuclmed.2020.12.004

Beyer, L., Meyer-Wilmes, J., Schönecker, S., Schnabel, J., Brendel, E., Prix, C., … Brendel, M. (2018). Clinical routine FDG-PET imaging of suspected progressive supranuclear palsy and corticobasal degeneration: A gatekeeper for subsequent tau-PET imaging? *Frontiers in Neurology*, *9*(JUN). https://doi.org/10.3389/fneur.2018.00483

Beyer, L., Meyer-Wilmes, J., Schönecker, S., Schnabel, J., Sauerbeck, J., Scheifele, M., … Brendel, M. (2021). Cognitive reserve hypothesis in frontotemporal dementia: A FDG-PET study. *NeuroImage: Clinical*, *29*. https://doi.org/10.1016/j.nicl.2020.102535

Bohnen, N. I., Koeppe, R. A., Minoshima, S., Giordani, B., Albin, R. L., Frey, K. A., & Kuhl, D. E. (2011). Cerebral glucose metabolic features of Parkinson disease and incident dementia: Longitudinal study. *Journal of Nuclear Medicine*, *52*(6), 848–855. https://doi.org/10.2967/jnumed.111.089946

Broski, S. M., Hunt, C. H., Johnson, G. B., Morreale, R. F., Lowe, V. J., & Peller, P. J. (2014). Structural and functional imaging in parkinsonian syndromes.

Radiographics : A Review Publication of the Radiological Society of North America, Inc, *34*(5), 1273–1292. https://doi.org/10.1148/rg.345140009

Brücke, T., Podreka, I., Angelberger, P., Wenger, S., Topitz, A., Küfferle, B., … Deecke, L. (1991). Dopamine D2 receptor imaging with SPECT: studies in different neuropsychiatric disorders. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *11*(2), 220–228. https://doi.org/10.1038/jcbfm.1991.53

Bürger, K., Arzberger, T., Stephan, J., Levin, J., & Edbauer, D. (2017). Pathomechanismen und klinische Aspekte der frontotemporalen Lobärdegeneration. *Der Nervenarzt*, *88*(2), 163–172. https://doi.org/10.1007/s00115-016-0259-x

Che, X. Q., Song, N., Gao, Y., Ren, R. jing, & Wang, G. (2018). Precision medicine of frontotemporal dementia: From genotype to phenotype. *Frontiers in Bioscience - Landmark*, *23*(6), 1144–1165. https://doi.org/10.2741/4637

Filippi, M., Agosta, F., Barkhof, F., Dubois, B., Fox, N. C., Frisoni, G. B., … Wahlund, L. O. (2012). EFNS task force: The use of neuroimaging in the diagnosis of dementia. *European Journal of Neurology*, *19*(12), 1487–1501. https://doi.org/10.1111/j.1468-1331.2012.03859.x

Foster, N. L., Heidebrink, J. L., Clark, C. M., Jagust, W. J., Arnold, S. E., Barbas, N. R., … Minoshima, S. (2007). FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain*, *130*(10), 2616–2635. https://doi.org/10.1093/brain/awm177

Gorno-Tempini, M. (2011). Classification_of_primary_progressive_aphasia_and_its_variants. *Neurology*, *76*(11), 1006–1014.

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L.,

Rosen, H. J., … Miller, B. L. (2004). Cognition and Amatomy in Three Variants of Primany Progressive Aphasia. *Annals of Neurology*, *55*(3), 335–346. https://doi.org/10.1002/ana.10825

Hellwig, S., Amtage, F., Kreft, A., Buchert, R., Winz, O. H., Vach, W., … Meyer, P. T. (2012). [¹⁸F]FDG-PET is superior to [¹²³I]IBZM-SPECT for the differential diagnosis of parkinsonism. *Neurology*, *79*(13), 1314 LP – 1322. https://doi.org/10.1212/WNL.0b013e31826c1b0a

Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E., … Bordelon, Y. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Movement Disorders*. https://doi.org/10.1002/mds.26987

Ishii, K., Sakamoto, S., Sasaki, M., Kitagaki, H., Yamaji, S., Hashimoto, M., & Imamura, T. (2020). *Cerebral Glucose Metabolism in Patients with Frontotemporal Dementia*.

Josephs, K. A., Lang, A. E., & Mollenhauer, B. (2018). Clinical Diagnosis of Progressive Supranuclear Palsy:The Movement Disorder Society Criteria. *2017*, *32*(6), 853–864. https://doi.org/10.1002/mds.26987

Josephs, K. A., Whitwell, J. L., Tacik, P., Duffy, J. R., Senjem, M. L., Tosakulwong, N., … Murray, M. E. (2016). [18F]AV-1451 tau-PET uptake does correlate with quantitatively measured 4R-tau burden in autopsy-confirmed corticobasal degeneration. *Acta Neuropathologica*, *132*(6), 931–933. https://doi.org/10.1007/s00401-016-1618-1

Lee, G., & Leugers, C. J. (2013). *NIH Public Access - Tau and Tauopathies*. 1–4. https://doi.org/10.1016/B978-0-12-385883-2.00004-7.Tau

Levin, J., Kurz, A., Arzberger, T., Giese, A., & Höglinger, G. U. (2016).

ÜBERSICHTSARBEIT: Differenzialdiagnose und Therapie der atypischen Parkinson-Syndrome. *Deutsches Arzteblatt International*, *113*(5), 61–69. https://doi.org/10.3238/arztebl.2016.0061

Ling, H., & Macerollo, A. (2018). Is it Useful to Classify PSP and CBD as Different Disorders? Yes. *Movement Disorders Clinical Practice*, *5*(2), 145–148. https://doi.org/10.1002/mdc3.12581

Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C., … Zee, D. S. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Neurology*, *47*(1), 1 LP – 9. https://doi.org/10.1212/WNL.47.1.1

Lizarraga, K. J., Gorgulho, A., Chen, W., & Salles, A. A. De. (2016). Molecular imaging of movement disorders. *World Journal of Radiology*, *8*(3), 226. https://doi.org/10.4329/wjr.v8.i3.226

Lopez, O. L., Litvan, I., Catt, K. E., Stowe, R., Klunk, W., Kaufer, D. I., … DeKosky, S. T. (1999). Accuracy of four clinical diagnostic criteria for the diagnosis of neurodegenerative dementias. *Neurology*, *53*(6), 1292 LP – 1292. https://doi.org/10.1212/WNL.53.6.1292

MacKenzie, I. R. A., Neumann, M., Bigio, E. H., Cairns, N. J., Alafuzoff, I., Kril, J., … Mann, D. M. A. (2010). Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: An update. *Acta Neuropathologica*, *119*(1), 1–4. https://doi.org/10.1007/s00401-009-0612-2

Mandelkow, E.-M., & Mandelkow, E. (2012). Biochemistry and {Cell} {Biology} of {Tau} {Protein} in {Neurofibrillary} {Degeneration}. *Cold Spring Harbor Perspectives in Medicine*, *2*(7), 1–25. https://doi.org/10.1101/cshperspect.a006247

Mathias, J. L., & Burke, J. (2009). Cognitive functioning in Alzheimer's and vascular dementia: a meta-analysis. *Neuropsychology*, *23*(4), 411–423.

https://doi.org/10.1037/a0015384

Meyer, P. T., Frings, L., Rücker, G., & Hellwig, S. (2017). 18F-FDG PET in Parkinsonism: Differential diagnosis and evaluation of cognitive impairment. *Journal of Nuclear Medicine*, *58*(12), 1888–1898. https://doi.org/10.2967/jnumed.116.186403

Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., … Benson, D. F. (1998). Frontotemporal lobar degeneration. *Neurology*, *51*(6), 1546 LP – 1554. https://doi.org/10.1212/WNL.51.6.1546

Nestor, P., Altomare, D., Festari, C., Drzezga, A., Rivolta, J., Walker, Z., … Frisoni, G. B. (2018). Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia. *Eur J Nucl Med Mol Imaging*, (in this issue). https://doi.org/10.1007/s00259-018-4035-y

Osaki, Y., Ben-Shlomo, Y., Lees, A. J., Daniel, S. E., Colosimo, C., Wenning, G. K., & Quinn, N. (2004). Accuracy of clinical diagnosis of progressive supranuclear palsy. *Movement Disorders*, *19*(2), 181–189. https://doi.org/10.1002/mds.10680

Pardini, M., Huey, E. D., Spina, S., Kreisl, W. C., Morbelli, S., Wassermann, E. M., … Grafman, J. (2019). FDG-PET patterns associated with underlying pathology in corticobasal syndrome. *Neurology*, *92*(10), e1121 LP-e1135. https://doi.org/10.1212/WNL.0000000000007038

Perani, D., Cerami, C., Caminiti, S. P., Santangelo, R., Coppi, E., Ferrari, L., … Magnani, G. (2016). Cross-validation of biomarkers for the early differential diagnosis and prognosis of dementia in a clinical setting. *European Journal of Nuclear Medicine and Molecular Imaging*, *43*(3), 499–508. https://doi.org/10.1007/s00259-015-3170-y

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the

behavioural variant of frontotemporal dementia. *Brain : A Journal of Neurology*, *134*(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179

Rebeiz, J. J., Kolodny, E. H., & Richardson, E. P. J. (1967). Corticodentatonigral degeneration with neuronal achromasia: a progressive disorder of late adult life. *Transactions of the American Neurological Association*, *92*, 23–26.

Respondek, G., Roeber, S., Kretzschmar, H., Troakes, C., Al-Sarraj, S., Gelpi, E., … Höglinger, G. U. (2013). Accuracy of the national institute for neurological disorders and stroke/society for progressive supranuclear palsy and neuroprotection and natural history in Parkinson plus syndromes criteria for the diagnosis of progressive supranuclear palsy. *Movement Disorders*, *28*(4), 504–509. https://doi.org/doi:10.1002/mds.25327

Respondek, G., Stamelou, M., Kurz, C., Ferguson, L. W., Rajput, A., Chiu, W. Z., … Höglinger, G. U. (2014). The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. *Movement Disorders : Official Journal of the Movement Disorder Society*, *29*(14), 1758–1766. https://doi.org/10.1002/mds.26054

Saeed, U., Lang, A. E., & Masellis, M. (2020). Neuroimaging Advances in Parkinson's Disease and Atypical Parkinsonian Syndromes. *Frontiers in Neurology*, *11*, 572976. https://doi.org/10.3389/fneur.2020.572976

Sha, S., Hou, C., Viskontas, I. V, & Miller, B. L. (2006). Are frontotemporal lobar degeneration, progressive supranuclear palsy and corticobasal degeneration distinct diseases? *Nature Clinical Practice. Neurology*, *2*(12), 658–665. https://doi.org/10.1038/ncpneuro0357

Sheikh-Bahaei, N., Sajjadi, S. A., & Pierce, A. L. (2017). Current Role for Biomarkers in Clinical Diagnosis of Alzheimer Disease and Frontotemporal Dementia. *Current Treatment Options in Neurology*, *19*(12). https://doi.org/10.1007/s11940-017-

0484-z

Shimohata, T., Aiba, I., & Nishizawa, M. (2015). [Criteria for the diagnosis of corticobasal degeneration]. *Brain and Nerve = Shinkei Kenkyu No Shinpo*, *67*(4), 513–523. https://doi.org/10.11477/mf.1416200168

Soucy, J., Bartha, R., Bocti, C., Borrie, M., Burhan, A. M., Jr, R. L., & Rosa-neto, P. (2013). *Clinical applications of neuroimaging in patients with Alzheimer ' s disease : a review from the Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012*. *5*(January 2012), 1–11.

Spinelli, E. G., Mandelli, M. L., Miller, Z. A., Santos-Santos, M. A., Wilson, S. M., Agosta, F., … Gorno-Tempini, M. L. (2017). Typical and atypical pathology in primary progressive aphasia variants. *Annals of Neurology*, *81*(3), 430–443. https://doi.org/10.1002/ana.24885

Stamelou, M., de Silva, R., Arias-Carrión, O., Boura, E., Höllerhage, M., Oertel, W. H., … Höglinger, G. U. (2010). Rational therapeutic approaches to progressive supranuclear palsy. *Brain : A Journal of Neurology*, *133*(Pt 6), 1578–1590. https://doi.org/10.1093/brain/awq115

Tagai, K., Ono, M., Kubota, M., Kitamura, S., Takahata, K., Seki, C., … Shimada, H. (2020). High-Contrast In Vivo Imaging of Tau Pathologies in Alzheimer's and Non-Alzheimer's Disease Tauopathies. *Neuron*. https://doi.org/10.1016/j.neuron.2020.09.042

Targosz-Gajniak, M., Siuda, J., Ochudło, S., & Opala, G. (2009). Cerebral white matter lesions in patients with dementia - from MCI to severe Alzheimer's disease. *Journal of the Neurological Sciences*, *283*(1–2), 79–82. https://doi.org/10.1016/j.jns.2009.02.314

Tiwari, S., Atluri, V., Kaushik, A., Yndart, A., & Nair, M. (2019). Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *International Journal of*

Nanomedicine, *14*, 5541–5554. https://doi.org/10.2147/IJN.S200490

Tosun, D., Schuff, N., Rabinovici, G. D., Ayakta, N., Miller, B. L., Jagust, W., … Rosen, H. J. (2016). Diagnostic utility of ASL-MRI and FDG-PET in the behavioral variant of FTD and AD. *Annals of Clinical and Translational Neurology*, *3*(10), 740–751. https://doi.org/10.1002/acn3.330

Tripathi, M., Dhawan, V., Peng, S., Kushwaha, S., Batla, A., Jaimini, A., … Mondal, A. (2013). Differential diagnosis of parkinsonian syndromes using F-18 fluorodeoxyglucose positron emission tomography. *Neuroradiology*, *55*(4), 483–492. https://doi.org/10.1007/s00234-012-1132-7

Tsai, R. M., & Boxer, A. L. (2016). Therapy and clinical trials in frontotemporal dementia: past, present, and future. *Journal of Neurochemistry*, *138*, 211–221. https://doi.org/10.1111/jnc.13640

Vlaar, A. M. M., van Kroonenburgh, M. J. P. G., Kessels, A. G. H., & Weber, W. E. J. (2007). Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes. *BMC Neurology*, *7*(1), 27. https://doi.org/10.1186/1471-2377-7-27

Wenning, G. K., Litvan, I., Jankovic, J., Granata, R., Mangone, C. A., McKee, A., … Pearce, R. K. (1998). Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. *Journal of Neurology, Neurosurgery, and Psychiatry*, *64*(2), 184–189. https://doi.org/10.1136/jnnp.64.2.184

Wimo, A., Jönsson, L., Bond, J., Prince, M., & Winblad, B. (2013). The worldwide economic impact of dementia 2010. *Alzheimer's and Dementia*, *9*(1), 1-11.e3. https://doi.org/10.1016/j.jalz.2012.11.006

Woalder. (2017). 乳鼠心肌提取 HHS Public Access. *Physiology & Behavior*, *176*(1), 139–148. https://doi.org/10.1016/j.physbeh.2017.03.040

Danksagung

Mein Dank gilt Herrn Prof. Dr. med. Axel Rominger von der Klinik und Poliklinik der Universität München für die Überlassung und Betreuung dieses interessanten und spannenden Projekts, die professionelle und gleichzeitig freundschaftliche Zusammenarbeit sowie das mir entgegengebrachte Vertrauen. Für die Initiierung danke ich Herrn Prof. Dr. med. Peter Bartenstein, Direktor der Klinik und Poliklinik für Nuklearmedizin der Universität München.

Meinem Betreuer, Herr PD. Dr. Matthias Brendel danke ich für seine zahlreichen Anregungen und seine hervorragende Unterstützung bei der Umsetzung einer kumulativen Dissertation. Die Intensität und Qualität der Betreuung war einmalig und seine fachliche Kompetenz hat ganz wesentlich zu dem Gelingen dieser Arbeit beigetragen. Zudem möchte ich den besonders freundlichen Umgang miteinander erwähnen.

Außerdem möchte ich mich bei Dr.med. Leonie Beyer bedanken, welche ebenfalls an meinem Projekt beteiligt war und mich sehr gut unterstützte.

Für das Ermöglichen des Studiums, und die herzliche Unterstützung gilt mein Dank meinen Eltern Karin Meyer-Wilmes und Dr. med. Thomas Meyer-Wilmes sowie meinen beiden Geschwistern Mareike Meyer-Wilmes und Dr. med. Philipp Meyer-Wilmes.

Lebenslauf

Persönliche Daten

Name:	Johanna Meyer-Wilmes
Anschrift:	Kaulbachstraße 35 80539 München
Geburtsdatum/ -ort:	24.03.1993 / Münster
Nationalität:	deutsch
Familienstand:	ledig
Mobil:	+49 16097898754
E-mail:	*Johanna.meyerwilmes@t-online.de*

Ausbildung und beruflicher Werdegang

02/2021	Assistenzärztin der Allgemein-, Viszeral- und Transplantationschirurgie der Universitätsklinik LMU München
04/2021-02/2021	Assistenzärztin der Urologie der Universitätsklinik TU München
12/2019	Drittes Staatsexamen/Approbation LMU München
11/2018 - 11/2019	Praktisches Jahr (München - Universitätsklinik TU, München - Klinikum Bogenhausen, Berlin - Charité)
10/2015 - 11/2019	Klinischer Abschnitt der Humanmedizin, Ludwig-Maximilians-Universität München
10/2013 - 08/2015	Vorklinischer Abschnitt der Humanmedizin, Ludwig-Maximilians-Universität München
09/2004 - 06/2012	Dietrich-Bonhoeffer-Gymnasium Wertheim