Investigation of the [18F]MK-6240 Tau-PET Tracer in Genetic Frontotemporal Dementia

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Abstract – English and French

Importance: Tau is one of several proteins which can cause frontotemporal dementia (FTD). While knowing which protein is causing a patient's disease is crucial, no biomarker currently exists for identifying the pathogenic protein in vivo.

Objective: To investigate the potential for the [18F]MK-6240 positron emission tomography (PET) tracer to bind to tau in vivo in genetic FTD

Methods: We enrolled subjects with genetic FTD, who constitute an ideal population for testing because their pathology is already known. Ten participants (three with symptomatic MAPT mutations expected to show tau binding, three with presymptomatic MAPT mutations, and four with non-tau mutations who act as controls) underwent tau-PET scanning with [18F]MK-6240, amyloid-PET imaging with [18F]NAV-4694 to rule out confounding Alzheimer's pathology, high-resolution structural magnetic resonance imaging (MRI), and neuropsychological testing.

Results: Tau-PET scans of all three symptomatic MAPT carriers demonstrated [18F]MK-6240 binding in expected regions. Two asymptomatic MAPT carriers estimated to be five years from disease onset both showed modest [18F]MK-6240 binding, while one approximately thirty years from disease onset did not reveal any binding. Additionally, four individuals with symptomatic FTD caused by a non-tau mutation were scanned (two C9orf72; one GRN; one VCP): their [18F]MK-6240 scans were all negative except for minimal non-specific binding in an advanced C9orf72 case. All ten amyloid-PET scans were negative.

Conclusions: Our findings of a variable degree of [18F]MK-6240 binding in three symptomatic MAPT patients and two asymptomatic MAPT carriers within five years of disease onset are

promising, particularly when combined with the lack of binding in participants with non-tau mutations. Although further studies will be necessary, our results support [18F]MK-6240 predominantly identifying tau neurofibrillary tangles based on the stronger binding observed in R406W vs. P301L MAPT, but also allude to potential binding to other tau conformations as well. Ultimately, this study highlights that a positive [18F]MK-6240 scan does not necessarily equate to Alzheimer's disease, and points towards a possible use for [18F]MK-6240 as a biomarker in non-Alzheimer's tauopathies such as FTD.

Importance: Le tau est l'une des nombreuses protéines qui peuvent causer la démence frontotemporale (DFT). Bien qu'il soit crucial de savoir quelle protéine est à l'origine de la maladie d'un patient, il n'existe actuellement aucun biomarqueur permettant d'identifier la protéine pathogène *in vivo*.

Objectif: Étudier la possibilité que le colorant [18F]MK-6240 pour la tomographie par émission de positrons (TEP) peut identifier le tau *in vivo* dans la DFT génétique.

Méthodes: Nous avons recruté des sujets atteints d'une DFT génétique, qui constituent une population idéale pour ce projet car leur pathologie est déjà connue. Dix participants (trois avec des mutations MAPT symptomatiques qui devraient avoir du tau, trois ayant des mutations MAPT présymptomatiques, et quatre ayant des mutations non-tau qui servent de contrôles) ont subi un scan tau-TEP avec [18F]MK-6240, une imagerie amyloïde-TEP avec [18F]NAV-4694 afin d'exclure la pathologie de la maladie d'Alzheimer, une imagerie par résonance magnétique (IRM) à haute résolution et des tests neuropsychologiques.

Résultats: Les scans tau-TEP des trois patients symptomatiques de MAPT ont montré une liaison [18F]MK-6240 dans les régions attendues. Deux porteurs de MAPT asymptomatiques, estimés à cinq ans de l'apparition de la maladie, ont montré une liaison modeste au [18F]MK-6240, tandis que un porteur, à environ trente ans de l'apparition de la maladie, n'a révélé aucune liaison. En outre, quatre personnes atteintes d'une DFT symptomatique causée par une mutation non-tau ont été examinées (deux C9orf72, un GRN et un VCP): leurs scans [18F]MK-6240 étaient tous négatifs, à l'exception d'une liaison minimale non-spécifique dans un cas avancé de C9orf72. Les dix scans TEP pour l'amyloïde étaient tous négatifs.

Conclusions: Nos résultats démontrant un degré variable de liaison de [18F]MK-6240 chez trois patients atteints de MAPT symptomatique et deux porteurs de MAPT asymptomatique dans les cinq ans précédant le début de la maladie sont prometteurs, en particulier parce qu'ils sont associés à l'absence de liaison chez les participants présentant des mutations non-tau. Bien que d'autres études soient nécessaires, nos résultats confirment que le [18F]MK-6240 identifie principalement les enchevêtrements neurofibrillaires tau en se basant sur la liaison plus forte observée dans le MAPT R406W par rapport au MAPT P301L, mais ils font également allusion à une liaison potentielle à d'autres conformations tau. En fin de compte, cette étude souligne qu'une analyse positive du [18F]MK-6240 n'équivaut pas nécessairement à la maladie d'Alzheimer, et indique une utilisation possible du [18F]MK-6240 comme biomarqueur dans les tauopathies non liées à la maladie d'Alzheimer telles que la DFT.

Acknowledgements

My involvement extended to every aspect of this study: I participated in study design, patient recruitment, and arranging the logistics of patient visits to Montreal (scheduling, transport, accommodation, financial reimbursements, etc.). I also administered the cognitive testing, was present for all the scans, and subsequently performed the analysis, interpreted the results, and wrote the manuscript.

However, I am extremely grateful to multiple people for their assistance in this endeavour:

- Dr. Simon Ducharme, my Supervisor, for his assistance and guidance with every aspect of this project, as well as his support and invaluable feedback.
- My committee members, Dr. Jean-Paul Soucy and Dr. Mallar Chakravarty, for their feedback on my thesis proposal.
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- The members of the Translational Neuroimaging Laboratory, especially Dr. Pedro Rosa Neto, Dr. Tharick Pascoal, Dr. Gleb Bezgin, and Mélissa Savard, for enabling the imaging analysis: teaching me about the methods for imaging analysis, aiding me with the processing, and allowing me to make use of their facilities for this purpose.

Contribution to Original Knowledge

I expect this project to contribute three main points of original knowledge.

Firstly, to the best of my knowledge, the approach of specifically recruiting patients with genetic FTD in order to be able to definitively know *in vivo* which pathology to expect is novel. This idea circumvents the inconvenient fact that at present autopsy is the only method of knowing for certain which pathology is causing a given case of sporadic FTD, and therefore could potentially influence future studies seeking to investigate potential biomarkers in the FTD spectrum.

In addition, the results presented in this thesis highlight that a positive MK-6240 tau-PET scan does not necessarily equate to a diagnosis of AD – an extremely important piece of information for clinicians who may one day come to regularly use tau-PET to diagnose dementia.

Lastly, and most importantly, this study points towards a potential use for [18F]MK-6240 as a biomarker in tauopathies other than AD. In particular, the clear binding detected in patients with *P301L MAPT* mutations represents the first evidence of this tracer binding *in vivo* to tau conformations other than NFTs – an exciting finding which certainly warrants further investigation. Additional patient recruitment as well as autopsy studies will be necessary to elaborate on these exciting results and to determine potential clinical applicability.

Contribution of Authors

I am the sole author of this thesis.

Introduction and Statement of Problem

Frontotemporal dementia (FTD) is an umbrella term for a group of devastating neurodegenerative disorders for which there are currently no therapeutic options. Moreover, at this time it is impossible to identify which of the several possible underlying pathological abnormalities is responsible for a particular patient's disease *in vivo*. Given that any future-disease modifying treatments will likely directly target the pathogenic proteins, there is a dire need at present to develop a reliable specific molecular diagnostic marker for FTD. This project attempts to address this significant problem by assessing the potential for the novel [18F]MK-6240 Positron Emission Tomography (PET) tracer to successfully bind to tau in live patients with genetic FTD.

Background Information

Frontotemporal dementia (FTD) is a term which refers to an impressively complex family of clinical entities. FTD encompasses several distinct symptom profiles, various pathologies, and an unusually significant proportion of cases directly caused by genetic mutations. This remarkable heterogeneity in three dimensions positions FTD as unique within the spectrum of neurological disorders, and renders it a particularly fascinating subject to study.

FTD is considered to be the second most common early-onset neurocognitive disorder after Alzheimer's disease (AD), with a prevalence between ages 65 and 69 estimated as high as 42.6/100,000 and a lifetime risk of 1/742[1]. The various disorders under the FTD umbrella all

classically engender progressive neurodegeneration of the frontal and temporal lobes of the brain; however, they feature divergent clinical presentations[1].

The most stereotypical form of FTD, and by far the most common clinical subtype[2], is the behavioural variant (bvFTD). A diagnosis of "possible" bvFTD necessitates three of the following persistent symptoms: early behavioural disinhibition, apathy or inertia, loss of sympathy or empathy, perseverative/stereotyped or compulsive/ritualistic behaviour, hyper-orality/dietary changes, and deficits in executive function with relative sparing of memory and visuospatial skills[3]. The diagnostic certainty is increased to "probable" with the addition of characteristic findings on imaging: either computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or single-photon emission computed tomography (SPECT). In order to be considered "definite" bvFTD diagnosis requires confirmation by histopathology (which in practice is almost never possible as it would require a brain biopsy), or the detection of a pathogenic mutation[3].

The two other important clinical entities which fall under the umbrella of FTD are the semantic and nonfluent/agrammatic variants of primary progressive aphasia (PPA), which are diagnosed based on the criteria described in 2011 by Gorno-Tempini et al[4]. Patients are first identified as suffering from PPA, a progressive disorder of language, and are subsequently classified into a subtype of PPA depending on the specific language difficulties they manifest. In semantic PPA (sPPA) confrontation naming and single-word comprehension are impaired, whereas nonfluent/agrammatic (nfPPA) is chiefly characterized by agrammatism and apraxia of speech. Diagnosis is subsequently divided into "possible", "probable", and "definite" according to the same principles as in bvFTD. In addition, a third variant of PPA exists ("logopenic PPA") but is

more frequently considered to be a form of AD rather than FTD, although some cases can be attributed to frontotemporal lobar degeneration pathology (FTLD; the neuropathological entity corresponding to clinical FTD, which will be discussed in more detail later)[4].

Of note, other clinical variants of FTD have been described beyond bvFTD, sPPA, and nfPPA, These less common diagnoses include the right temporal variant of FTD, which presents with mostly behavioral symptoms, often with prominent compulsions,[5] as well as FTD-ALS: a syndrome featuring both FTD and amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative disease causing progressive degeneration of both upper and lower motor neurons[6]. Furthermore, patients can also be characterized as combining multiple subtypes: for example, simultaneously demonstrating symptoms of both bvFTD and nfPPA.

FTD can additionally be divided into two categories based on the presence or absence of a causative genetic mutation. While the majority of FTD cases are considered to be sporadic, which is to say they're diagnosed in the absence of an identifiable underlying genetic etiology, up to 30% of patients have an autosomal dominant genetic mutation which is directly responsible for their disease[7]. Furthermore, these mutations are "full penetrance": all carriers are guaranteed to develop the disease eventually. By far the three most common mutations in FTD are *microtubule-associated protein tau* (*MAPT*), *chromosome 9 open reading frame 72* (*C9orf72*) *expansion*, and *progranulin* (*GRN*)[7]. However, other rarer mutations have also been identified, such as *valosin-containing protein* (*VCP*)[8]. Importantly, these mutations all manifest distinct phenotypes of FTD. They have been heavily studied since their discovery, as they provide important windows into the pathogenesis of neurodegenerative disease.

Finally, FTD is heterogeneous in terms of the underlying pathology that contributes to the disease. In fact, several different proteins are known to pathologically aggregate and cause FTLD, most notably TAR DNA-binding protein 43 (TDP-43) and tau[9], although other pathologies such as the rare FTLD-FUS (fused in sarcoma) have been described as well[10].

Importantly, which pathology occurs in FTD secondary to a genetic mutation has already been established. The *MAPT* mutation is the only one known to cause FTD due to a pathological aggregation of tau, whereas *C9orf72*, *GRN*, and *VCP* all lead to FTD secondary to TDP-43[7]. However, at present it is impossible to identify *in vivo* which protein is causing a given case of sporadic FTD; this is problematic as these represent the majority of cases and any future disease-modifying treatments will likely come from specifically targeting the underlying pathology[11]. The only way to definitively determine the pathology in FTD currently is by autopsy, unless the patient has a genetic form of the disease[12].

In Vivo Biomarkers of FTLD

A molecular diagnostic marker capable of reliably detecting the pathology in FTD *in vivo* could advance understanding of the distribution and progression of tau pathology in the disease, enable earlier and more accurate diagnosis and prognostication of FTD, and enhance clinical trials of specific disease-modifying drugs by enabling selection of patients by pathology[11,13].

In recent years, important advances have been made with respect to non-specific biomarkers for the many forms of FTD. One such diagnostic test which has been in the spotlight lately is neurofilament light chain (NfL), which can be measured in both serum and cerebrospinal fluid

(CSF) and has been shown to relate to the progression of neurodegenerative disorders. A landmark study published in December 2019 by the Genetic Frontotemporal Dementia Initiative (GENFI) consortium demonstrated the potential for NfL to function as a tool for identifying both symptom onset and disease progression in genetic FTD[14].

Several ground-breaking CSF biomarkers have also already shown promising results in FTD, including neuronal pentraxin 2 (which accumulates with synaptic dysfunction)[15], as well as YKL-40 and chitotriosidase (proteins derived from glia which may represent the pathological immune response in FTD)[16]. Neuroinflammation itself is another non-specific process which has yielded positive results in terms of an ability to diagnose and characterize FTD. For example, Bevan-Jones et al used the [11C]PK-11195 PET tracer, which binds to activated microglia, as an *in vivo* measure of neuroinflammation in 31 patients spanning the spectrum of FTD. They found that neuroinflammation was closely associated with protein aggregation, and was able to classify participants by clinical profile with impressive precision[17]. In addition, a huge quantity and variety of novel neuroimaging modalities that could yield valuable predictive information in FTD are also being proposed, from atrophy in specific brain regions to measures of cortical thickness in every form of FTD using MRI and PET and other modalities. For example, a recent paper from our laboratory suggested that cortical thinning and surface area loss could be an early predictor of FTD secondary to a *C9orf72* expansion[18].

Many studies of purported diagnostic markers have focused on genetic FTD, in part due to the pre-existing infrastructure provided by the GENFI consortium, but also because these full penetrance mutations provide a unique opportunity to study disease onset and evolution. For example, one key insight from studies of presymptomatic carriers – people in whom the presence

of an FTD mutation has been detected and who are therefore guaranteed to manifest the disease eventually – is that they display distinct patterns of brain atrophy several years prior to symptom onset[19]. Further large-scale neuroimaging studies on these individuals will no doubt lead to a deeper understanding of the evolution of FTD. In addition, biomarkers specific to particular mutations are already being developed, e.g. plasma glial fibrillary acidic protein in the *GRN* mutation[20], and dipeptide repeat proteins in the *C9orf72* repeat expansion[21] – however, importantly, these track disease progression rather than giving insight into pathology.

Overall, while progress is being made with non-specific biomarkers in dementia, the need for a reliable biomarker specific for the underlying pathology in the FTD spectrum persists. Although attempts are being made to use atrophy patterns on MRI as a proxy indicator for TDP-43 pathology[22], there are currently no specific biomarkers whatsoever for the TDP-43 protein, and specific biomarkers for tau in FTD are similarly lacking.

Tau Biomarkers in FTLD

In the context of this crucial need for a specific biomarker in FTD, tau-PET tracers are currently being explored as a promising method of identifying the tau protein *in vivo*[23]. PET broadly is a valuable and versatile functional imaging technique well-suited to investigating physiology (as opposed to MRI or CT which primarily provide structural imaging). It entails the use of radioactive ligands which are injected into the subject, diffuse into the target of interest, and emit positrons. These subsequently form gamma rays which can be reconstituted to visualize the ligand's distribution and concentration. The prototypical PET tracer is [18F]FDG, which was developed in

the 1970s and is widely used throughout clinical medicine and research studies for the purpose of identifying glucose metabolism as a proxy measure of tissue activity[24]. Since then, many PET radioligands have been created for a multitude of different targets, including well-validated markers for identifying neuropathologies such as the amyloid protein[25] and neuroinflammation[26].

However, developing a reliable tracer for the tau protein is proving to be challenging – in part due to the inherent heterogeneity of tau. In fact, there are six different isoforms of the tau protein, and these adopt different conformations in the various tauopathies[27]. The characteristic tau pathology found throughout Alzheimer's disease (AD) consists of neurofibrillary tangles (NFTs) comprised of all six tau isoforms. By contrast, the classic inclusions in Pick's Disease (a specific pathological subtype of bvFTD) are Pick bodies composed mainly of 3R tau, whereas the brains of patients affected by progressive supranuclear palsy and corticobasal syndrome chiefly contain 4R tau[27]. In genetic FTD secondary to a *MAPT* mutation, tau pathology is also heterogeneous: patients typically have predominantly 4R pathology, but may also form NFTs like in AD depending on the location of the mutation[28].

The most well-studied tau-PET tracers have thus far demonstrated limited utility for detecting tau outside of AD. For example: [18F]AV-1451 was found to have limited sensitivity and specificity for tau in FTD in a recent study[29], [18F]THK-5351 binding was shown to be significantly modulated by MAO-B[30], and [11C]PBB3, another first generation tracer, has limited value due to several technical issues, including a short half-life and a sensitivity to light which make it challenging to manufacture[31,32].

The [18F]MK-6240 tau-PET tracer, a pyridine isoquinolone amine derivative recently developed by Merck[33] has shown promising results not only *in vitro* and in animals[34,35], but also in human studies featuring healthy controls as well as subjects with mild cognitive impairment and AD[36,37]. In addition, computational modelling has determine that MK-6240 binds specifically to site 1 of tau's 4 high-affinity binding sites[38]. Furthermore, MK-6240 has exhibited strong specificity and sensitivity for tau without the influence of monoamine oxidase (MAO)[39]. While off-target binding to melanin and meninges is notable, and mild off-target binding to hemorrhage is observed as well, there is no off-target binding to key brain regions such as the basal ganglia as exhibited by certain other tracers[39].

Overall, these results highlight that MK-6240 is not only safe but also possesses favourable kinetics and encouraging binding properties *in vivo* in humans. Of note however, the aforementioned studies (including the work by Aguero et al[39] which represents the only autoradiography validation of MK-6240 conducted thus far) have only ever confirmed MK-6240 binding to tau in NFT conformation. Perforce, the effectiveness of MK-6240 in non-AD tauopathies featuring different forms of tau remains to be determined.

Rationale for the Study, Hypothesis, and Specific Aims

As discussed in more detail above, the advent of a reliable specific biomarker in the FTD spectrum would revolutionize our approach to FTD from both a research and a clinical perspective. The status quo is that it is impossible to identify the underlying pathology *in vivo* in a given case of sporadic FTD, which represents a fundamental barrier to one day developing a therapy for this

terrible disease. As such, the rationale for this study follows logically from this important gap in the current approach to FTD: to investigate the potential for the [18F]MK-6240 tau-PET tracer to function as a tau biomarker in FTD, in the context of its encouraging results in previous trials, as well as our site's relative expertise with manufacturing this sophisticated radioligand.

Given the previous findings suggesting the MK-6240 tracer's favourable properties for binding to tau, despite the paucity of evidence in non-AD tauopathies, our initial hypothesis when developing this project was that the tracer would show promise in FTD. However, the publication in March 2019 of a study by Aguero et al.[39] forced us to temper our expectations. This paper, which will be revisited later in this thesis, concluded "that MK-6240 strongly binds to neurofibrillary tangles in Alzheimer disease but does not seem to bind to a significant extent to tau aggregates in non-Alzheimer tauopathies". Of note, this paper used gold-standard autoradiography techniques to confirm binding, and featured two cases of Pick's disease and one P301L MAPT subject. These important results led us to revise our hypothesis to instead suggest that our study in genetic FTD would demonstrate that MK-6240 scans were unlikely to be useful in the FTD spectrum.

This project was designed around three key specific aims: 1) characterize binding in patients with a *MAPT* mutation, 2) verify the presence or absence of off-target binding in disease controls with symptomatic FTD cause by TDP-43 mutations, and 3) determine whether there is any confounding effect of amyloid.

Importantly, in order to accomplish this we sought to recruit patients with genetic FTD. We specifically recruited a small cohort of this extremely rare patient population who constitute an

ideal group for this project because, as mentioned previously, their pathology can be definitively known in advance: individuals with a *MAPT* mutation are known to have FTD caused by tau accumulation and thus should be expected to show MK-6240 binding; conversely, participants with mutations such as *C9orf72*, *GRN*, and *VCP* which cause FTD due to accumulation of TDP-43 act as tau-free disease controls who should not be expected to show MK-6240 binding[7].

Ultimately, the quintessential objective of this project is to scan these genetic FTD patients with MK-6240 in order to characterize this tracer and assess its potential utility as an *in vivo* tau biomarker in FTD.

Methods

In order to recruit a sufficient quantity of patients with genetic FTD (either symptomatic definite FTD confirmed by genetic testing, or presymptomatic carriers of the MAPT mutation), we collaborated with other researchers at McGill, as well as a network of sites in Quebec and Ontario, over an extended period of time (between December 2018 and February 2020). One challenge was that out of the research establishments participating in the project, only the Montreal Neurological Institute (MNI) had the capacity to produce the MK-6240 tau-PET tracer. As such, we arranged for all patients to be transported to Montreal and to stay overnight for their participation in the study. Our initial recruitment target was 12-16 subjects total, but we had to prematurely interrupt data acquisition in February 2020 due to the COVID-19 pandemic. As an aside, the study was funded by a grant from the Weston Brain Institute – in part in order to aid with this costly patient recruitment.

With respect to adequately characterizing the study participants, once at the MNI each subject underwent a battery of neuropsychological testing, MRI both as a measure of brain structure and also for later use in the analysis, tau-PET imaging with [18F]MK-6240, and an amyloid-PET scan with [18F]NAV-4694 (also known as AZD-4694) which was performed with the intention of ruling out confounding AD pathology.

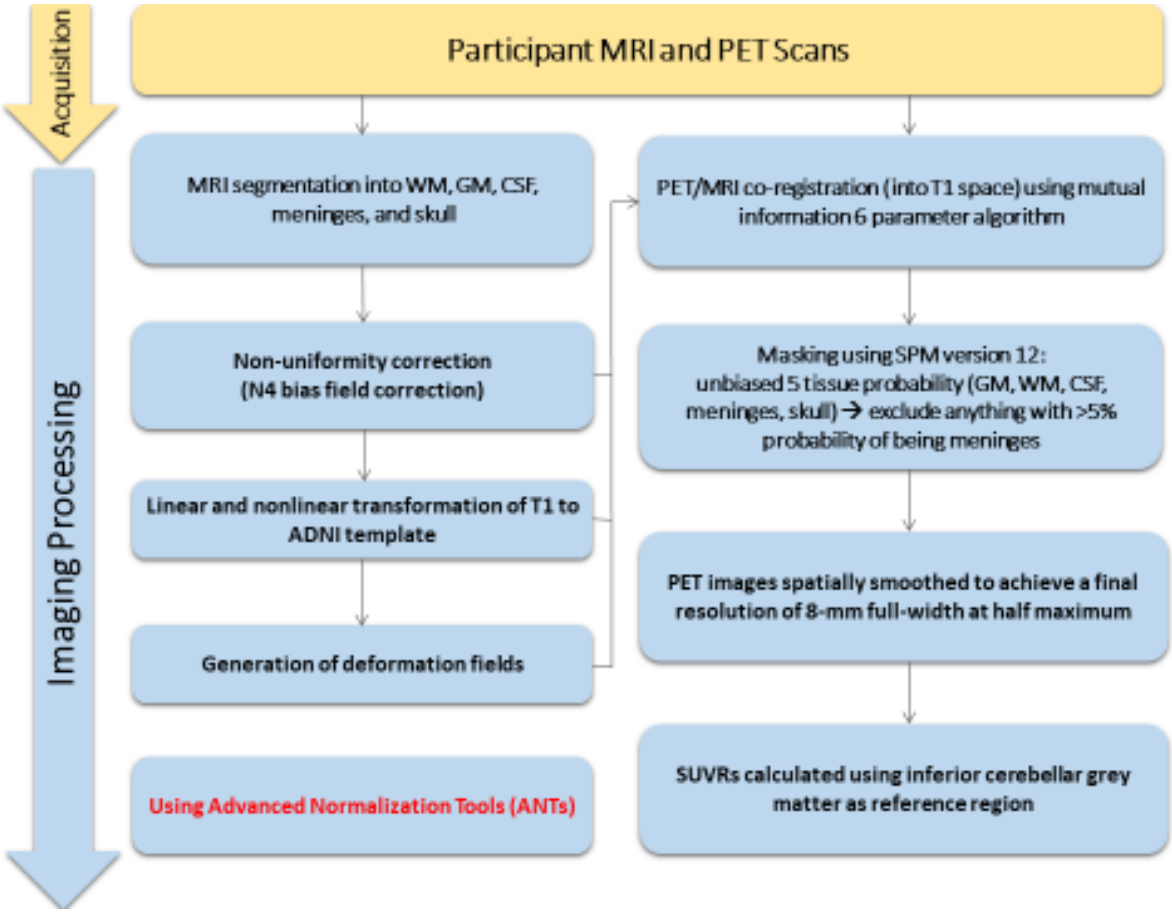
Cognitive testing featured a wide battery of assessments selected to efficiently evaluate multiple different aspects of higher brain function including attention, short-term memory, executive function, and various components of language such as naming, fluency, and vocabulary. Specific tests administered were the Mini-Mental State Examination (MMSE), digit span, Boston naming, D-KEFS fluency, D-KEFS colour-word interference, Rey Auditory Verbal Learning Test (RAVLT), WAIS-III vocabulary, and the WAIS-III digit symbol test. Furthermore, the CDR-FTLD was completed in order to assess the participant's degree of functionality in different spheres, as well as their overall severity status which was compiled from the average of the CDR-FTLD sum of boxes score[40].

Next, all participants were submitted to high-resolution 3D T1-weighted MRI with 1mm isometric slice thickness on a 3T Siemens scanner. PET scans were acquired on a high-resolution research tomograph (HRRT) Siemens scanner. [18F]MK-6240 images were obtained 90-110 minutes following administration of the tracer, and were reconstructed using an ordered-subsets expectation maximization (OSEM) algorithm on a 4D volume with 4 frames (4 x 300s)[41]. [18F]NAV-4694 scans were performed 40-70 minutes after intravenous injection of the tracer, and were reconstructed using the same OSEM algorithm on a 4D volume with 3 frames (3 x 600s)[25]. A 6-minute transmission scan for attenuation correction was completed with a rotating

Cesium-137 point source after each PET scan, and images were subsequently corrected for dead time, decay, and random and scattered coincidences[42]. Tracer radio-synthesis was performed on site at the MNI.

Images were subsequently analyzed in order to identify and quantify PET tracer binding by extracting standardized uptake value ratios (SUVRs). The processing methods use an in-house pipeline based around Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs/). Briefly: the MRI is first segmented into white matter, grey matter, cerebrospinal fluid, meninges, and skull[43] and non-uniformity corrected using the N4ITK tool to mitigate the bias field[44]. Following this, the T1-weighted image is non-linearly registered to the ADNI template space[42,45]. A rigid body transformation subsequently brings the native PET image into the native T1 space. Next, the scans are masked in order to minimize off-target binding to meninges. This is done using an unbiased tissue mask generated with version 12 of SPM[46]. The images are then spatially smoothed to yield a resolution of 8mm full-width at half maximum. Finally, SUVRs are calculated by dividing the intensity at each voxel by the average binding in a reference region, which in this case is the inferior cerebellar grey matter, in accordance with previously-established methods for analyzing these tracers[36,41]. Figure 1 outlines this image processing pipeline.

Figure 1



Results

Participants

Ten individuals are included in these results: three with symptomatic *MAPT* mutations, three asymptomatic *MAPT* carriers, and four with symptomatic TDP-43 mutations. Table 1 provides details about patient demographics, mutations, and disease characteristics.

These subjects will be presented as a case series: each scan will be discussed individually to describe the presence and distribution of any binding. This format was selected given the rarity of the study population which did not allow for recruitment of a sufficient quantity of patients to perform meaningful statistical comparisons, but also because the goal of the project is to

determine the utility of the tracer at the individual patient level as opposed to detecting small differences between groups.

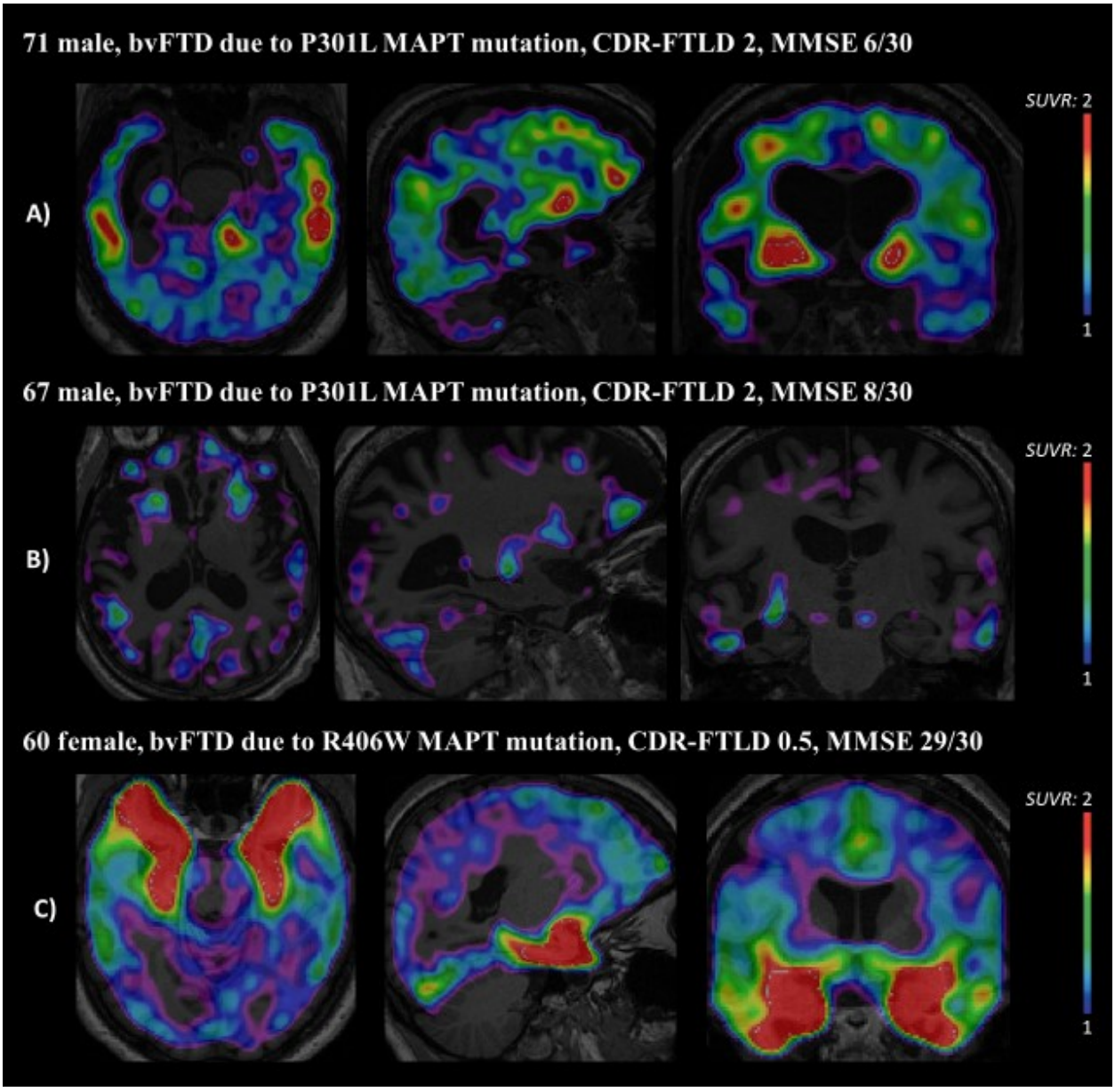
	Age	Gender	Mutation	Clinical Diagnosis	CDR-FTLD Global	MMSE
1	71	M	P301L MAPT	bvFTD	2	6
2	67	M	P301L MAPT	bvFTD	2	8
3	60	F	R406W MAPT	bvFTD	0.5	29
4	30	F	P301L MAPT	Asymptomatic (EYO = 30)	0	29
5	57	F	P301L MAPT	Asymptomatic (EYO = 1)	0	28
6	52	M	P301L MAPT	Asymptomatic (EYO = 5)	0	28
7	51	M	VCP	Mixed bvFTD/svPPA	0.5	23/25
8	41	M	C9orf72	bvFTD	0.5	27
9	44	M	C9orf72	bvFTD	2	12
10	61	M	GRN	bvFTD	1	19

Table 1: Patient Demographics
M = male; F = female
EYO = expected years to symptom onset
CDR-FTLD = Clinical Dementia Rating – Frontotemporal Lobar Degeneration; global scores obtained from averaging the sum of boxes
MMSE = Mini-Mental State Examination; out of 30 except where otherwise specified

Symptomatic MAPT carriers

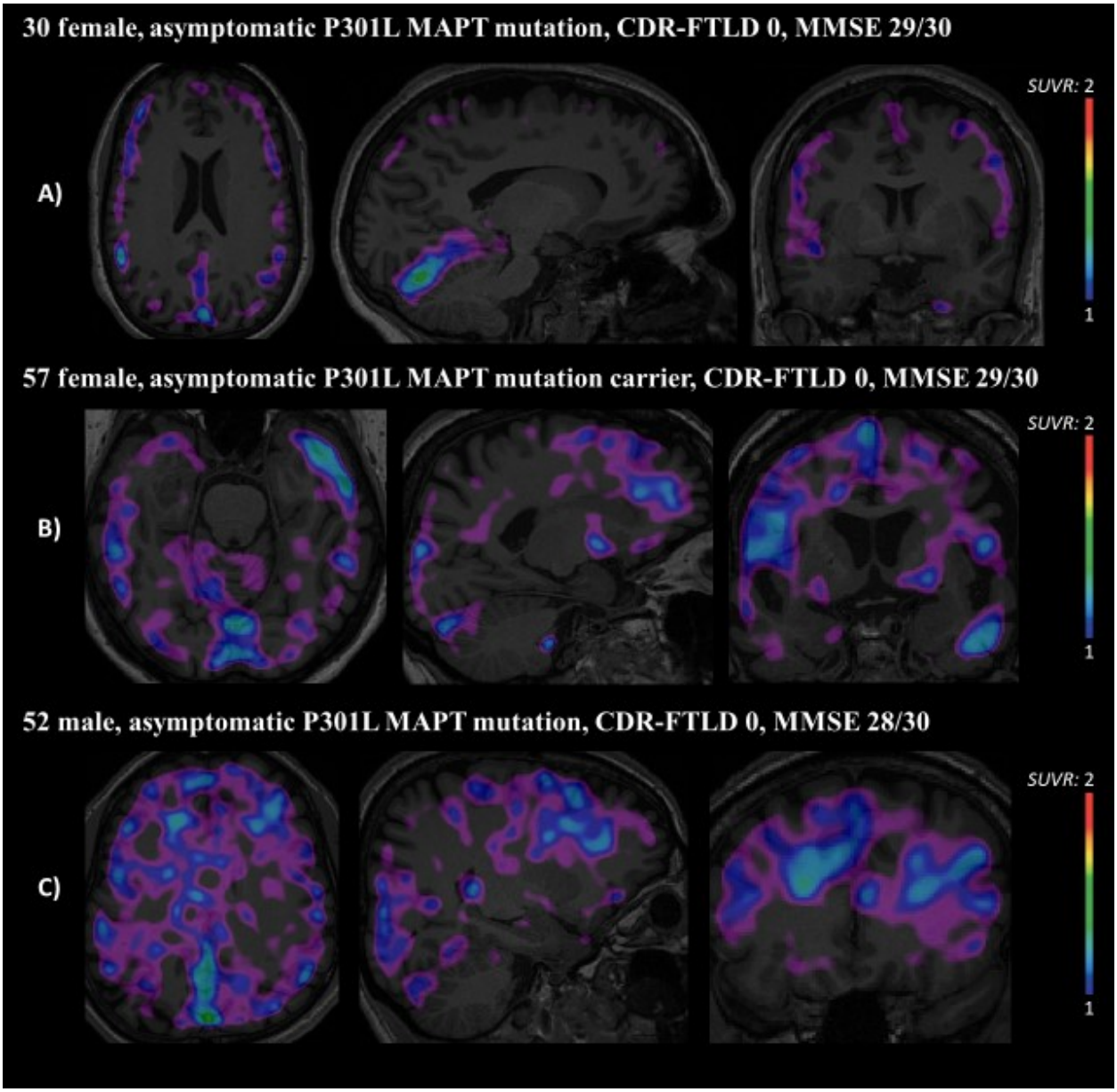
All three patients with a symptomatic *MAPT* mutation showed some degree of MK-6240 binding, as depicted in Figure 2. Figure 2a is a 71 year old man with clinically advanced behavioral variant FTD (CDR-FTLD = 2) due to a *P301L MAPT* mutation; the MK-6240 scan demonstrates binding of the tracer with SUVRs above 2 in regions classically associated with tau pathology in the disease: frontal lobes, temporal lobes, and basal ganglia bilaterally, as well as in the parietal lobes. Figure 2b is a 67 year old man with behavioral variant FTD (CDR-FTLD = 2) also due to a *P301L MAPT* mutation; the MK-6240 scan reveals binding of the tracer in similar regions as in patient 1, albeit with lower SUVRs in the 1.6 range – in the context of relatively more atrophy. Figure 2c is a 60

year old woman with clinically mild behavioral variant FTD (CDR-FTLD = 0.5) due to a *R406W MAPT* mutation; marked binding of the MK-6240 tracer with SUVRs above 4 is observed in the anteromedial temporal lobe bilaterally.



Asymptomatic MAPT Carriers

Figure 3 features the MK-6240 scans from three asymptomatic *P301L MAPT* mutation carriers. Figure 3a is a 30 year old woman approximately three decades before expected disease onset; the MK-6240 scan reveals no binding in the brain, although some off-target binding to meninges is observed. In Figure 3b, an asymptomatic 57 year old woman who tested positive for the *P301L MAPT* mutation and is one year from expected onset of symptoms demonstrates mild binding of MK-6240 with SUVRs around 1.4, particularly in the frontal and temporal lobes as well as the basal ganglia. Figure 3c is a 52 year old male carrier 5 years from expected symptom onset; scattered foci of MK-6240 binding with SUVRs up to 1.4 are observed throughout the cortex.

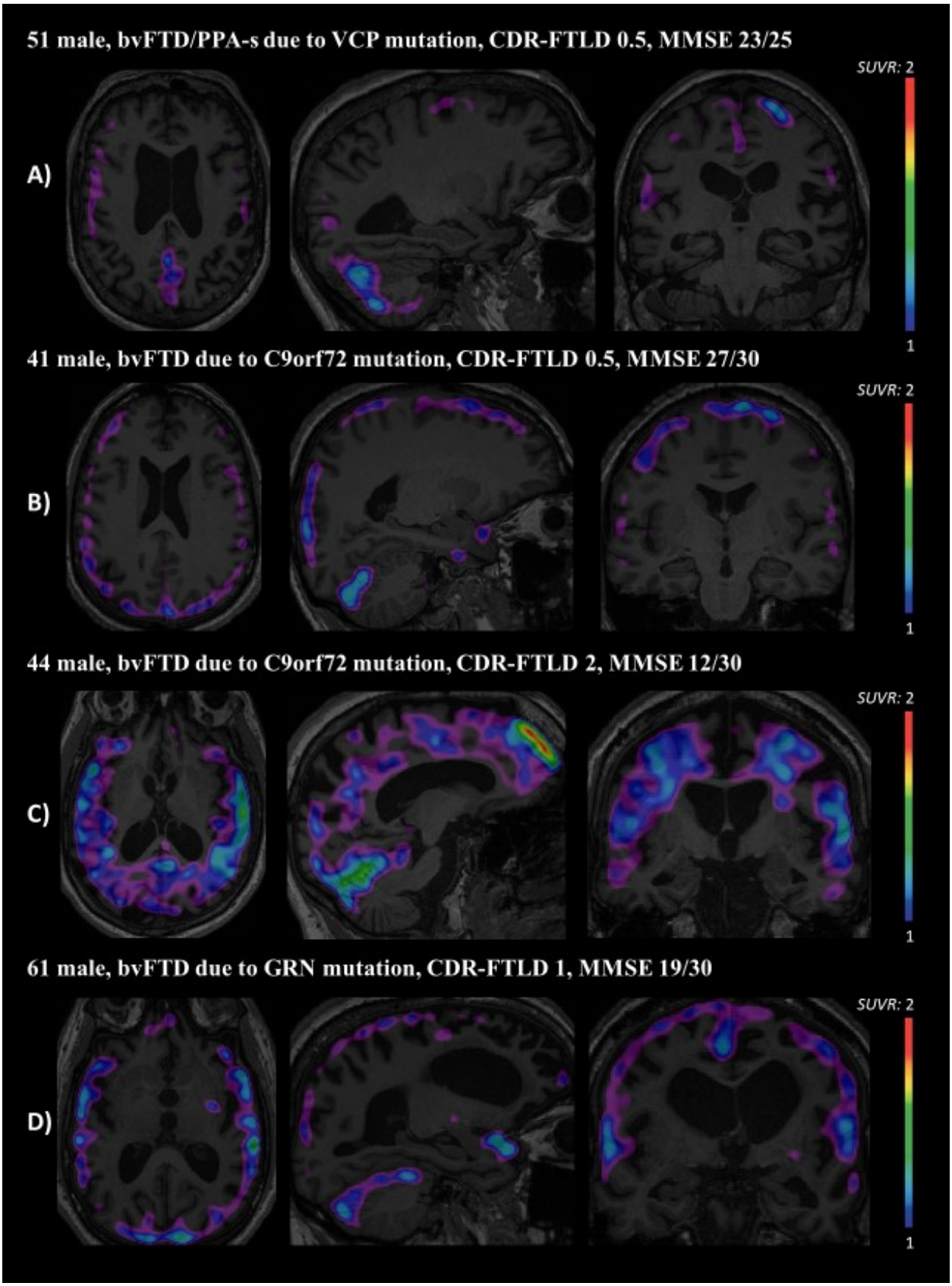


Other Genetic Mutations

Figure 4 includes the negative MK-6240 scans obtained from four patients with a symptomatic non-Tau mutation. Figure 4a is a 51 year old man with a mildly symptomatic mixed behavioral variant FTD and semantic primary progressive aphasia secondary to a *VCP* mutation (CDR-FTLD =

0.5). Figure 4b shows a 41 year old man with early behavioral variant FTD due to a *C9orf72* mutation (CDR-FTLD = 0.5). Figure 4c is a 44 year old man with moderately advanced behavioral variant FTD in the context of a *C9orf72* mutation (CDR-FTLD = 2). Figure 4d is a 61 year old man with behavioral variant FTD due to a *GRN* mutation (CDR-FTLD = 1). All four of these patients' MK-6240 scans did not show any significant tracer binding in the brain, with the exception of Figure 4c which demonstrates some off-target binding to meninges over the frontal lobe and cerebellum, as well as scattered mild binding which is difficult to interpret without autopsy confirmation in a clinically advanced case of *C9orf72*, which is known to accumulate tau pathology in some patients[47].

All ten subjects had negative amyloid-PET scans with NAV-4694, thereby ruling out the possibility of any AD pathology driving tau positivity.


51 male, bvFTD/PPA-s due to VCP mutation, CDR-FTLD 0.5, MMSE 23/25
SUVR: 2
A)
1
41 male, bvFTD due to C9orf72 mutation, CDR-FTLD 0.5, MMSE 27/30
SUVR: 2
B)
1
44 male, bvFTD due to C9orf72 mutation, CDR-FTLD 2, MMSE 12/30
SUVR: 2
C)
1
61 male, bvFTD due to GRN mutation, CDR-FTLD 1, MMSE 19/30
SUVR: 2
D)
1

Discussion

This study describes [18F]MK-6240 tau-PET scans in a cohort of ten subjects with genetic FTD, including five distinct mutations. These results represent the first MK-6240 scans *in vivo* in a non-AD tauopathy, as well as one of the largest groups of genetic FTD patients ever assembled in a PET study. We found MK-6240 binding in symptomatic *MAPT* patients in brain regions known to manifest pathology in FTD[19] and not associated with any significant off-target MK-6240 binding (as confirmed in an autoradiography study)[39]. Binding was unexpectedly present in the parietal lobes of the two symptomatic *P301L MAPT* cases (Figure 2a-b); however, although the parietal lobes are not classically implicated in the *MAPT* mutation, both of these patients were clinically advanced, and pathology is known to extend throughout the brain particularly later in the disease course[19]. In addition, notably higher SUVR values were obtained in the participant with an *R406W MAPT* mutation compared to milder binding in subjects with a *P301L MAPT* mutation. Furthermore, we detected subtle binding of unclear significance in presymptomatic *P301L MAPT* carriers within five years of expected disease onset. No notable MK-6240 binding was observed in symptomatic patients with non-tau mutations (*C9orf72*, *GRN*, and *VCP*), except for minimal scattered non-specific uptake in an advanced case of *C9orf72* mutation.

A multitude of preexisting evidence, including the tracer's previous success in AD[36,37], confirms MK-6240 binding to tau specifically in the NFT conformation. In fact, the only autoradiography study conducted thus far with MK-6240 on human postmortem brain tissue concluded by proposing "that MK-6240 strongly binds to neurofibrillary tangles in Alzheimer disease but does

not seem to bind to a significant extent to tau aggregates in non-Alzheimer tauopathies"[39]. The tracer preferentially binding to NFTs in particular could explain our finding of considerably stronger binding in a participant with a mildly symptomatic *R406W MAPT* mutation (Figure 2c), as *R406W* is one of the rare mutations in exon 13 of the *MAPT* gene that engenders AD-like NFT pathology[48]. However, our findings in subjects with a *P301L MAPT* mutation (Figure 2a-b, Figure 3b-c) are more difficult to explain. *P301L* is a mutation in exon 10 of the *MAPT* gene which causes accumulation of 4R tau, though 3R tau as well as wildtype tau are also present[28]; *P301L* neuropathological case series have mainly described mini-Pick bodies, twisted tau filaments, and pretangles[49,50]. As such, whether MK-6240 was binding to sparse NFTs in these patients, to pretangles, or to something else entirely remains ambiguous. Further patient recruitment for *in vivo* scanning, and especially additional autopsy studies of *MAPT* patients, will be essential for clarification.

Of note, the aforementioned MK-6240 autoradiography study by Aguero et al. featured one subject with a *P301L MAPT* mutation, in whom no MK-6240 binding was detected[39]. The apparent discrepancy between this finding and our results may be explained by the fact that only a single *P301L MAPT* patient was autopsied, and *P301L MAPT* can be a heterogeneous disease[50]. This further illustrates the necessity for larger autopsy studies of this population.

While the ability of MK-6240 to bind to conformations of tau other than NFTs requires further investigation, the negative scans obtained in control subjects with symptomatic TDP-43 mutations in our study imply a promising degree of specificity (Figure 4; with the caveat of the aforementioned questionable binding in Figure 4c). These results contrast with the well-studied tau-PET tracer flortaucipir ([18F]AV-1451), which also binds well to NFTs *in vivo*, but with

problematic off-target binding and therefore limited specificity – to the extent that flortaucipir has recently been used as "a proxy index of aggregated non-amyloid-β pathological proteins across the FTD spectrum" instead of as a marker for just tau[17].

On a related note, it is worthwhile to highlight the fact that flortaucipir remains one of the most widely used tau-PET tracers *in vivo*, despite its well-established lack of specificity[29]. Our results therefore make an important point: MK-6240 may be superior to AV-1451 as a tau-PET tracer; researchers should be aware of this and should likely strongly consider using MK-6240 instead of flortaucipir for tau-PET scans, subject to tracer availability of course.

In addition, our results draw attention to the general lack of reliable tau-PET tracers outside of AD at present, and reinforce the dire need for developing better specific diagnostic tests for FTD. While efforts are currently being made to assess multiple novel tau-PET tracers, results thus far have not been overly encouraging. For example, a recent study conducted in Sweden by Leuzy et al[51] investigated the [18F]RO948 tau-PET tracer in a large population of 613 participants, including 102 with non-AD neurodegenerative disorders, and even a few cases of FTD secondary to a *MAPT* mutation. Ultimately, they asserted that RO948 was very effective in NFT tau, but concluded that the tracer was unlikely to be clinically relevant in diseases manifesting conformations of tau other than NFTs[51].

Another finding from our study which prompts cautious excitement is the mild MK-6240 binding observed in presymptomatic *P301L MAPT* carriers in brain regions known to accumulate tau pathology in FTD (e.g. basal ganglia[28], frontal and temporal lobes[19]), as seen in Figure 3. The utility of tau-PET in presymptomatic patients has previously been questioned, as tau accumulation is

considered to be temporally related to symptom burden[13]. However, a study published earlier this year by Betthauser et al. proposed that MK-6240 may be an effective biomarker in preclinical AD[52], and our findings extend this to suggest that the tracer may also be useful in *MAPT* mutation carriers. Indeed, our results imply MK-6240 may be sensitive enough to pick up on small amounts of tau early in disease course. This may be due to the favorable binding properties of MK-6240 compared with other previously studied tau-PET tracers (for instance, MK-6240 has the lowest Kd value of the most common tau tracers)[23]. The ability of the MK-6240 tracer to bind to tau even in subjects without symptoms suggests a potential for this technique to enable earlier diagnosis of FTD secondary to tau.

Overall, our results align with MK-6240 binding to tau NFTs as previously established, and further support the tracer's ability to potentially act as an effective *in vivo* diagnostic marker in forms of FTD secondary to a *MAPT* mutation with NFT pathology. Importantly, this highlights to clinicians that a positive MK-6240 scan should not be automatically equated to a diagnosis of AD. This is a key result of this study, as tau-PET markers are increasingly approaching being integrated into clinical practice. Furthermore, while the sensitivity of MK-6240 as a molecular diagnostic marker remains to be further characterized, this study points towards it binding to tau with more specificity than previously-studied tau-PET tracers like flortaucipir. Finally, our findings in *P301L* mutation carriers suggest that the potential of MK-6240 to act as a biomarker may even extend beyond the tauopathies which purely engender NFT pathology – although this requires further investigation.

An effective tau-PET tracer would likely contribute towards a better understanding of tau spreading *in vivo* while simultaneously transforming the current clinical approach to FTD. A

reliable molecular diagnostic marker would constitute a crucial step towards eventually developing a treatment – in particular, by permitting selection of patients for trials of anti-tau therapies based on pathology, and by improving the ability to monitor treatment response and disease progression[11]. These exciting opportunities are indeed on the horizon – for example, the pharmaceutical company Ionis has already begun trials of a tau treatment, which the MNI is currently involved in testing (https://www.ionispharma.com/medicines/ionis-mapt/).

Strengths and Limitations

The main strength of this study is the recruitment of subjects with genetic FTD to be able to know *in vivo* which patients have tau pathology and which have TDP-43, thereby enabling us to confidently predict what results to expect from the MK-6240 scans. Furthermore, the size of the cohort (given the rarity of the disease) featuring diverse mutations is another asset. The major limitation is the lack of autopsy data to confirm results thus far. Even though the known mutations indicate the underlying pathology, the ambiguous nature of tau pathology renders it difficult to draw conclusions regarding whether the tracer is binding to anything other than NFTs – particularly in subjects with a *P301L MAPT* mutation.

Conclusion

In conclusion, this project showcases the [18F]MK-6240 tau-PET tracer binding *in vivo* in subjects with symptomatic FTD secondary to a *MAPT* mutation, as well as mild binding in two presymptomatic *MAPT* carriers within five years of disease onset. Binding occurred specifically in

regions associated with tau pathology in FTD, and was negligible in controls with symptomatic TDP-43 mutations.

Ultimately, multiple tau-PET tracers may be required given the heterogeneity of tau pathology. However, in an area that sorely lacks in specific diagnostic tests at present, the promising results presented in this paper suggest MK-6240 could eventually be one of these biomarkers.

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