

**BIOGRAPHICAL SKETCH**

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NAME: Floeter, Mary Kay

POSITION TITLE: Senior Clinician, CNP, DIR, NINDS, NIH

**EDUCATION/TRAINING**

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Illinois, Champaign IL	B.S.	6/1979	Psychology
Washington University, St. Louis MO	M.D.	6/1985	Medicine
Washington University, St. Louis MO	Ph.D.	6/1985	Neural Sciences
Jewish Hospital, St. Louis MO	Intern	6/1986	Internal Medicine
University of California San Francisco CA	Resident	6/1989	Neurology
University of California San Francisco CA	Post-doc	6/1990	Physiology
Lab Neural Control, NINDS, NIH Bethesda	Post-doc	7/1993	Physiology
EMG section, NINDS, NIH Bethesda MD	Clinical Fellow	8/1996	Clin Neurophysiol/ EMG/Neuromuscular

**A. Personal Statement**

The Motor Neuron Disease Unit's research program focuses on finding neuroimaging and physiology markers of disease progression in two rare motor neuron disorders. My clinical training as a neurologist and the experience gained over the last 25 years in physiology, imaging, and human subjects research provide me with the appropriate expertise and knowledge to lead this program. I am the principal investigator of a long-running natural history study of primary lateral sclerosis (PLS), a disorder of unknown cause that results in degeneration of motor cortex neurons. My group has experience in carrying out standardized clinical, physiological and cognitive assessments of disease progression longitudinally. We use neuroimaging as a window into pathological changes in the brain occurring during a patient's lifetime. Since 2006, we have been using quantitative MRI methods to study structural changes in the brain in motor neuron disorders. In some cases, we have been able to combine postmortem imaging with histology. I am also the principal investigator of a prospective longitudinal study of symptomatic and asymptomatic carriers of an expansion mutation in the gene *C9orf72* that began in 2013. This mutation can cause amyotrophic lateral sclerosis, frontotemporal dementia, or a mixture of motor and cognitive symptoms. The goal of the imaging and biofluid studies is to find biomarkers for use in future clinical trials. In addition to my experience as a principal investigator, I have considerable administrative experience managing projects and knowledge regarding human subjects research at NIH that facilitates my ability to implement clinical protocols. I served for a year in the NINDS Extramural Office of Clinical Research, which oversees clinical trials funded by NINDS grants. Within the NIH intramural program, I have served on committees in the Office of Human Subjects Research, developing standards, SOPs, and educational material for multidisciplinary clinical research teams.

**B. Positions and Honors**

1996 – 2014 Chief, EMG section, NINDS, NIH  
 2006 – 2011 Deputy Clinical Director, NINDS, NIH  
 2007 – 2011 Acting Clinical Director, NINDS, NIH  
 2012 – 2013 Program Director, Office of Clinical Research, DER, NINDS, NIH (50% detail)  
 1998 – present Adj. Assoc. Prof. of Neurology, School of Medicine, Uniformed Services University  
 1996 – present Chief, Motor Neuron Disorders Unit, DIR, NINDS, NIH (*formerly Spinal Physiology Unit*)

**C. Contributions to Science****I. Characterization of the natural history of primary lateral sclerosis.**

Our longitudinal prospective study of the progression of clinical symptoms in a large cohort of clinically defined PLS patients stands out as a particularly strong contribution to the field. Since 2000, we have evaluated approximately 140 patients with a referral diagnosis of PLS patients, with slightly more than half meeting criteria for clinical PLS. This represents the largest clinically characterized collection of PLS patients reported. Our data suggest that PLS is heterogeneous, and is best conceived as a syndrome that may have multiple causes (1). Although PLS patients have a median survival of more than a decade after symptom onset, the rate of progression is most rapid in the first years after symptoms begin, often reaching a plateau after seven to eight years (2). This clinical course suggests that there may be a limited time window during which corticospinal neurons degenerate, and when potential interventions should be targeted. Because the level of disability at the plateau varies among patients, individual susceptibility or resilience factors may contribute to each patient's final level of disability. We participated in a collaborative study that carried out exome sequencing in a cohort of PLS patients which found sequence variants in different genes known to cause neurological disease in many individual patients (3). That study was unable to assess whether variants were pathogenic. To follow-up on that study, we collected DNA from PLS trios (patients and both parents) to look for *de novo* mutations, and from a larger cohort of PLS individuals to look for variants in common. The 50 genomes have been sequenced, and are in the pipeline to be analyzed by a collaborator. The goal of this work in progress is to identify candidate genes that cause or predispose to PLS.

1. Zhai P, Pagan F, Statland J, Butman JA, **Floeter MK** (2003) Primary lateral sclerosis: a heterogeneous disorder composed of different subtypes? *Neurology* 60 (8):1258-1265.
2. **Floeter MK** and Mills R (2009) Progression in primary lateral sclerosis: a prospective study. *Amyotrophic Lateral Sclerosis* 10:339-346 [NIHMSID 403717]
3. Mitsumoto H, Nagy PL, Gennings C, Murphy J, Andrews H, Goetz R, **Floeter MK**, Hupf J, Singleton J, Barohn RJ, Nations S, Shoesmith C, Kasarskis E, Factor-Litvak P. Phenotypic and molecular analyses of primary lateral sclerosis. *Neurology Genetics*. 2015; 1(1):e3. PMID: 27066542, PMCID: PMC4821084
4. Statland JM, Barohn RJ, Dimachkie MM, **Floeter MK**, Mitsumoto H. Primary Lateral Sclerosis. *Neurologic clinics*. 2015; 33(4):749-60. PMID: 26515619, PMCID: PMC4628724

## II. Imaging and physiological studies of Primary Lateral Sclerosis

Neuroimaging has been important for providing clues to the anatomical changes in the brain underlying PLS. PLS was originally described as a clinico-pathological entity with sclerosis of the dorsolateral columns of the spinal cord. Although reports from the 1990's noted that atrophy of the motor cortex may be present, quantitative MRI studies of PLS patient groups were first published in the 2000's. We are among a handful of investigators who have made cross-section comparisons of neuroimaging between cohorts of patients with PLS and other motor neuron disorders. Our longitudinal imaging studies with a 2-year follow-up are a particular contribution (6). We showed that cortical thinning in PLS is very focal, confined to cortical motor regions, and that a slow rate of thinning continues even after 10 years of symptoms. We hypothesize that this progressive thinning is produced by glial scarring following neuronal loss and clearance of necrotic debris. Diffusion tensor imaging (DTI) showed loss of white matter integrity in the corticospinal tract – others had noted this – and we highlighted diffusion changes in the “motor” segment of the corpus callosum (5), which had received little attention at that point. Tractography of the white matter tracts, using a method in which diffusion measures were averaged for the whole tract that we found had good longitudinal reliability in healthy subjects (7), did not change over follow-up. This suggested that white matter changes likely preceded cortical thinning and volume loss. Understanding the sequence of imaging changes and determining whether imaging findings can be detected in the first years of symptoms is the focus of our current imaging studies which include structural and functional MRI. We expect functional imaging and physiology changes to occur early. In our initial PLS characterization in 2003, we reported that, with moderate loss of dexterity (finger tapping < 4/s), the cortex was generally inexcitable by transcranial magnetic stimulation. This finding has held true for most of the PLS patients we have seen subsequently. We also showed that functional changes occur outside primary motor cortex, with loss of the BP1, a movement related cortical potential component arising from premotor areas (8), and greater cerebro-cerebellar connectivity in resting state functional MRI in patients with long-standing PLS (9).

5. Iwata NK, Kwan JY, Danielian LE, Butman JA, Tovar-Moll F, Bayat E, **Floeter MK**. White matter alterations differ in primary lateral sclerosis and amyotrophic lateral sclerosis. *Brain*. 2011 Sep;134(Pt 9):2642-55. PubMed PMID: 21798965; PMCID: PMC3170531.
6. Kwan JY, Meoded A, Danielian LE, Wu T, **Floeter MK**. Structural imaging differences and longitudinal changes in primary lateral sclerosis and amyotrophic lateral sclerosis. *Neuroimage Clin*. 2012 Dec 24;2:151-60. PMID: 24179768; PMCID: PMC3778247.
7. Danielian LE, Iwata NK, Thomasson DM, **Floeter MK**. Reliability of fiber tracking measurements in diffusion tensor imaging for longitudinal study. *Neuroimage*. 2010 Jan 15;49(2):1572-80. PMID: 19744567; PMCID: PMC2789889.
8. Bai O, Vorbach S, Hallett M, **Floeter MK**. Movement-related cortical potentials in primary lateral sclerosis. *Ann Neurol*. 2006 Apr;59(4):682-90. PMID:16566016.
- 9: Meoded A, Morrisette AE, Katipally R, Schanz O, Gotts SJ, **Floeter MK**. Cerebro-cerebellar connectivity is increased in primary lateral sclerosis. *Neuroimage Clin*. 2014 Dec 9;7:288-96. PMID: 25610792; PMCID: PMC4300015.

### III. Longitudinal evaluations with biospecimen collection in *C9orf72* mutation carriers

In 2011 a hexanucleotide repeat expansion in a non-coding region of the *C9orf72* gene was found to account for a large proportion of familial ALS and familial FTD and 5-8% of cases classified as sporadic. Because patients had been identified retrospectively through ALS clinics or through dementia clinics, relatively little was known about the natural history in carriers of the *C9orf72* mutation: whether weakness and cognitive dysfunction occur independently and whether subtle abnormalities are detectable in carriers prior to the onset of symptoms. To address this need, I set up a “C9” clinic, i.e. a research protocol to carry out prospective longitudinal assessments and collection of biospecimens from symptomatic and asymptomatic carriers of *C9orf72* mutations. The protocol consists of clinical, neuropsychological, imaging and physiology testing, spinal taps, phlebotomy, and skin biopsy, with up to 4 3-day visits over 3 years and interim phone assessments. The clinic was designed as a collaborative effort with a neurogenetics colleague in intramural NIA; consent for data and specimen sharing with extramural researchers and commercial entities was built into the protocol. The depth and breadth of phenotyping and the specimen sharing make this effort an extremely valuable contribution to ALS research.

We found that short scales for 3 clinical domains – motor, executive function, and behavior – were able to distinguish among carriers who met clinical criteria for ALS, FTD, or both, and declined over 18 months of follow-up (10). We are using these brief scales as measures of clinical progression to correlate with our imaging and physiology biomarker studies. We have found that compared to sporadic ALS patients and healthy controls, symptomatic C9 carriers have diffuse brain atrophy that progresses over 6 months (11). Atrophy was greatest in C9-FTD patients. The motor score was associated with diffusion tensor imaging changes in the corticospinal tract, whereas cognitive and behavioral scores correlate with diffuse frontal affected white matter (Floeter 2018). The pattern of imaging changes reflects individual participant’s clinical impairment. Additionally, alterations in white matter diffusion measures spread from anterior regions of the hemisphere to posterior regions, and from deep to superficial subcortical white matter over a 6-month interval. These data indicate that volumetric and diffusion imaging measures could potentially be incorporated into a biomarker index of disease progression that shows change over the 6-12 month time-frame commonly used in ALS clinical trials. Neither measure was sufficiently sensitive in isolation. Physiology studies found cortical hyperexcitability in C9-ALS patients, as has been described in previous studies of sporadic ALS, but did not see definite changes over 6 months. To date we have not detected imaging or physiological changes in asymptomatic carriers, who are mostly younger than their affected relatives.

10. **Floeter MK**, Traynor BJ, Farren J, Braun LE, Tierney M, Wiggs EA, Wu T. Disease progression in *C9orf72* mutation carriers. *Neurology*. 2017 89:234-241. PMID: 28615433
11. **Floeter MK**, Bageac D, Danielian LE, Braun LE, Traynor BJ, Kwan JY. Longitudinal imaging in *C9orf72* mutation carriers: Relationship to phenotype. *NeuroImage. Clinical*. 2016; 12:1035-1043. PubMed [journal] PMID: 27995069, PMCID: PMC5153604
12. **Floeter MK**, Danielian LE, Braun LE, Wu T. Longitudinal diffusion imaging across

- the *C9orf72* clinical spectrum. *J Neurol Neurosurg Psychiatry*. 2018 89(1):53-60.
13. Schanz O, Bageac D, Braun L, Traynor BJ, Lehky TJ, **Floeter MK**. Cortical hyperexcitability in patients with C9ORF72 mutations: Relationship to phenotype. *Muscle & Nerve*. 2016 54(2):264-9. NIHMSID: NIHMS753632 PMID: 26799151, PMCID: PMC4940214

Our collection of longitudinal CSF samples from symptomatic and asymptomatic *C9orf72* mutation carriers has been a particularly valuable contribution to translational researchers in the field. There are currently 8 material transfer agreements with different academic and pharmaceutical entities to share specimens and limited clinical data. Of particular note is the work by two groups developing biomarkers to incorporate into clinical trials using antisense oligonucleotide treatment (Biogen and Mayo Jacksonville). We have shared longitudinal CSF samples and interacted extensively with clinicians to harmonize clinical data between sites, particularly cognitive data. This has led to my inclusion as a co-author on two papers, one showing that repeat-associated dipeptides in the CSF may be a useful marker of ASO target engagement (13) and another showing that the level of CSF neurofilament protein predicts survival (14).

14. Gendron TF ... **Floeter MK**, Rothstein JD, Boylan KB, Petrucelli L. Poly(GP) proteins are a useful pharmacodynamic marker for *C9orf72*-associated amyotrophic lateral sclerosis. *Sci Transl Med* Mar 29;9(383). pii: eaai7866 doi: 10.1126/scitranslmed.aai7866.
15. Gendron TF, Daugherty LM, Heckman MG, Diehl NN, Wu J, Miller TM, Pastor P, Trojanowski JQ, Grossman M, Berry JD, Hu WT, Ratti A, Benatar M, Silani V, Glass JD, **Floeter MK** Jeromin A, Boylan KB, Petrucelli L. Phosphorylated neurofilament heavy chain: A biomarker of survival for C9ORF72-associated amyotrophic lateral sclerosis. *Annals of neurology*. 2017; doi:10.1002/ana.24980. [Epub ahead of print] PMID: 28628244

#### IV. Histological correlates of MRI signal changes in ALS

A variety of signal changes are seen in MRIs of patients with ALS and PLS. Assumptions about the tissue changes that produce these MRI signals are largely based on animal studies with experimental manipulations such as cuprizone treatment or vascular occlusion. Tissue changes caused by degeneration may be quite different. To better understand the basis of MRI signal changes seen in ALS patients, we have carried out two studies correlating postmortem imaging and histology of the region containing the signal change in patients with ALS. Both studies implicate microglia as a contributor to the signal change. The hypointense T2/FLAIR "stripe" in the motor cortex of ALS patients was shown to be caused by ferritin-containing microglia (15), rather than by intracortical myelinated axons as reported for healthy brains. More recently, we showed that loss of fractional anisotropy in affected regions of the corpus callosum in ALS patients was associated with microglial invasion, in addition to axonal loss and astrogliosis (16). Microglial invasion was greater in two patients with *C9orf72* mutations than sporadic ALS. For this study, we used a specialized MRI sequence (DW-SSFP) which allows high b-values with short echo times. This sequence was developed by collaborators for carrying out diffusion weighted imaging in fixed postmortem brains, which was needed because diffusion is highly attenuated in fixed tissue.

15. Kwan JY, Jeong SY, Van Gelderen P, Deng HX, Quezado MM, Danielian LE, Butman JA, Chen L, Bayat E, Russell J, Siddique T, Duyn JH, Rouault TA, **Floeter MK**. Iron accumulation in deep cortical layers accounts for MRI signal abnormalities in ALS: correlating 7 tesla MRI and pathology *PLoS one*. 2012; 7(4):e35241. PMID: 22529995, PMCID: PMC3328441
16. Cardenas AM, Sarlls JE, Kwan JY, Bageac D, Gala ZS, Danielian LE, Ray-Chaudhury A, Wang HW, Miller KL, Foxley S, Jbabdi S, Welsh RC, **Floeter MK**. Pathology of callosal damage in ALS: An *ex vivo*, 7 T diffusion tensor MRI study. *NeuroImage. Clinical*. 2017; 15:200-208. PMID: 28529876, PMCID: PMC5429246

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