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**CREATION OF CLINICAL BIOMARKERS OF NEUROLOGICAL DISEASE: INTEGRATION OF MULTI-MODAL NEUROIMAGING DATA**

**CLINICAL BIOMARKER DEVELOPMENT**

Both the NIH and FDA have highlighted the critical need for qualified biomarkers to speed drug development, to aid diagnosis and staging of disease and as indicators of disease progression and treatment outcomes.

**WHAT IS A BIOMARKER?**

**Biological Marker (Biomarker)** – A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.

**Clinical Endpoint** – A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

**Surrogate endpoint** – A biomarker intended to substitute for a clinical endpoint. A clinical endpoint is an outcome that is typically measured by the patient, or by his or her health professional, and is designed to indicate the presence or absence of treatment success or failure. The investigator uses epidemiological, therapeutic, or other scientific evidence to determine that a biomarker is a substitute for a clinical endpoint. A clinical endpoint is a measure of an outcome that is typically measured by the patient, or by his or her health professional, and is designed to indicate the presence or absence of treatment success or failure.

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**DISTURBANCES OF SLEEP AND NEUROLOGICAL DISORDERS**

**Neurological Disorder**

- Multiple Sclerosis
- Parkinson’s Disease
- Supranuclear Palsy
- Alzheimer’s Disease
- Depression
- Bipolar Disorder
- Schizophrenia
- ADHD

**Related Sleep Disorders**

- Insomnia, SDB, RBD, narcolepsy, RLS/PLMS
- RBD, SDB, insomnia, RLS/PLMS
- RBD/REM without atonia, RLS/PLMS
- Insomnia, RBD, circadian rhythm disorder
- Insomnia, hypersomnia
- Insomnia, hypersomnia
- Insomnia, SDB
- RLS/PLMS, SDB, parasomnias

Sleep disruption is a core symptom of many psychiatric disorders, including major depression, bipolar disorder, PTSD and generalized anxiety disorder and a comorbidity in most neurodegenerative disorders.

**REM SLEEP BEHAVIOR DISORDER**

REM Sleep Behavior Disorder (RBD)

- REM Sleep Behavior Disorder is a parasomnia characterized by the loss of normal inhibitory control over REM sleep in which dream content is often acted on.

**Potential imaging biomarkers include functional connectivity, DTI/DTT, and PET. Several laboratories are working on the development of an α-synuclein ligand for investigation of such synucleinopathies as Parkinson’s.**

**MAJOR DEPRESSIVE DISORDER (MDD)**

Resting state functional connectivity studies suggest that alterations in default mode connectivity may be altered in MDD. In a pilot study looking at rTMS as a therapeutic intervention in non-responsive MDD patients, we see that it is possible to obtain resting state network connectivity in single subjects, a critical component of a clinically useful imaging biomarker. Pre-treatment subjects do show disrupted functional connectivity in the default mode network that extends to the loss of anti-correlated connections to attention-related networks (Larson-Prior, Garcia, Pierce, Nolan and Matthews).

**NEURODYNAMICS ACROSS SCALE**

Averaged responses across trials improves signal-to-noise.