PET/MRI imaging: novel metrics for early disease detection and effect of therapy assessment.

Highlights:

- In general, PET and MRI derived measured are highly complementary.
- Current knowledge of brain function supports evidence of interactions between neurochemical aspects and structural and functional networks. Disease is deemed to alter both in an interconnected fashion.
- Simultaneous PET and MRI data acquisition allows to accurately explore such interactions, leading to better disease identification, and is being instrumental in elucidating relationships between metabolic (PET) and hemodynamic and structural networks (MRI), as well as coupling between neurotransmitter activity (PET) and blood flow/functional MRI connectivity patterns.
- As treatment affects both neurochemistry and connectivity, combination of the two imaging techniques will provide a more sensitive tool to guide patient specific treatment
- Multi-modal imaging is this expected to significantly contribute to personalized disease management in neurodegeneration.

Recent understanding of brain function stresses the importance of the interaction between brain connectivity and underlying neurochemistry and metabolism, both in terms of energy cost of brain function as well as in terms of understanding of pathogenic processes. Indeed, the network degeneration hypothesis states that initiation and progression of disease-specific pathological changes occur within specific brain structural and functional networks (best investigated with MRI) and are mediated by abnormal protein aggregation, inflammation and impaired cellular energetics coupled to abnormal neurotransmission (best investigated with PET). The hybrid PET/MRI is thus ideally suited to study neurodegeneration in the context of this most recent understanding of brain function.

While multimodality imaging coupled with advanced image analysis methods, such as support vector machine or elastic net logistic regression, has been proven superior in identifying disease subtypes in dementia studies and predicting conversion between MCI and AD, perhaps the most exciting applications of the hybrid imaging capabilities of the PET/MR reside in the measurements that require input from both modalities. This includes investigation of the coupling between blood flow or oxygen utilization and glucose metabolism, and relationships between stimulus or pharmacological intervention induced neurotransmitter activity and brain connectivity, often denoted as neurovascular coupling. These processes are fundamental for proper brain function and deemed altered by many diseases. Examples include assessment of the energetic cost of brain functional connectivity, where regions of the brain that are most efficient at utilizing glucose are identified; identification of correlations between glucose metabolism and metrics describing resting state brain activity; and assessment of effective connectivity (EC), which, combining ^{18}F-FDG PET (glucose metabolism) with resting fMRI provides some information on the directionality of brain signalling (11).

Studies coupling PET-derived measures of pharmacologically induced dopamine receptor occupancy with estimated effects on blood flow are unravelling the effects of different interventions on neurovascular coupling. Such studies, which can be extended to

other neurotransmitter systems, will not only provide new information on brain function, but will also contribute to elucidating both PET- and MRI- derived signal changes. As many of these processes are also affected by treatment, information derived from PET/MRI is expected to guide treatment strategies on an individual subject level.