Session Title: Imaging Pharmacologic Modulation of Neural Activity in Diffuse Brain Injury: BOLD and Perfusion MRI, ERP, MEG
Facilitators: Francois Chollet and John Whyte
Summarizer: Anthony Chen

Proposed Discussion Questions:

- ❑ What are the pros and cons of these methods in distinguishing between cognitive/motor effects of drugs vs. direct vasoactive effects?
- ❑ How do drug-induced changes in activation relate to drug-induced performance changes?
- ❑ Can baseline imaging results serve as predictors of drug response?
- ❑ Can imaging markers of drug response serve as surrogate outcomes in screening for clinically useful drugs?

Summary of the discussion

Overall question raised by this symposium: What are some of the issues that need to be considered when designing studies that examine pharmacologic modulation of neural activity?

Introduction of general issues by Dr. John Whyte: Studies that strive to examine pharmacologic effects with imaging face a range of challenges that differ from strictly task-based functional imaging studies. Some of the questions to consider include:

- Repeatability of measurements over time.
- Distinguishing the primary effects of drug on vasculature from neural effects. The pharmacologic systems of greatest interest for rehabilitation studies are those that are involved in regulating vasculature—acetylcholine, dopamine and norepinephrine are among these.
- What is the study question? Two important general objectives are to better understand mechanisms of treatment and to predict the effects of drug on performance and/or recovery.

What are the appropriate study designs for pharmacologic imaging studies?
- The nature of the scientific question to be pursued needs to be defined, leading to different study designs. Some studies may have the objective of using imaging data to predict recovery or the likelihood of long-term benefits of a drug, while other studies may have the objective of understanding the mechanisms by which a drug acts to alter rehabilitation-relevant neural processes.
- The distinction between clinical trial design and designs appropriate for mechanistic studies should be considered. At the current time, imaging methods may be considered most appropriate for providing data for mechanistic questions, and are not necessarily appropriate for addressing clinical trial-type questions. Standard clinical trial designs may not be the most appropriate starting point for most imaging studies.
- As one important goal of pharmacotherapy in rehabilitation is to augment the effects of other interventions, study designs should reflect this. Bruce Dobkin discussed this as an 'enrichment' strategy. An important scientific question is how a drug changes rehabilitation-induced learning processes. In these scenarios, it may be important to design studies that examine neural changes during the course of therapy, as just measuring the baseline compared to post-treatment outcome may provide information on the consequences of treatment, but not necessarily the effects of treatment.
- Dr. Chollet) presented data from a series of studies that utilized double-blind placebo-controlled designs, with fMRI and TMS measurements. Significant questions were raised by this discussion, regarding the best study designs, optimal dosing, and appropriate outcome measures.

What are some dosage considerations when designing pharmacologic imaging studies?
- Basic studies utilizing a range of doses in order to determine dose response effects may be needed.
- In mechanistic studies, an important objective is to determine neural changes that correspond to successful treatments (that is, treatments that alter clinical variables). The dose at which this occurs is likely to be different for different individuals; therefore, it would be logical to include individualized dosing as part of the study design.
- Dr. Chollet presented a series of studies highlighting the following key points of general interest:
    - All significant clinical trials have until now been negative, including those of amphetamine compounds.
    - The published series have shown that drug-induced performance increases can be correlated with changes in the activity of specific cerebral networks. This is now demonstrated with both fMRI (BOLD changes) and evoked potential technique (TMS) and it suggests that neuroimaging tools might be used

as surrogate markers associated with clinical endpoints in clinical trials including a limited number of patients.
- The effects of chronic drug administration may be very different from those of acute single doses. We need to develop trials with chronic doses.
- Clinical trials associating drug-induced clinical performance and fMRI and/or TMS changes in recovering patients to date have tested acute performance but never learning or re-learning.

What are appropriate (neurophysiologic) measurements for pharmacologic imaging studies?
- Imaging methodology is a particularly important consideration for drug studies. Significant discussion of perfusion methods in preference to BOLD MRI were raised by John Detre as well as John Whyte, since the availability of a scalar measure of blood flow allows repeated testing in different drug conditions, and allows one to distinguish between primary vasoactive effects (by measuring baseline flow) and cognitively induced changes in flow.
- The issue of variability—is it possible that an effect of a drug is to alter variability (in physiology or neural responses) itself?
- Should anatomical outcome variables be considered, given the inherent variability in neurophysiologic variables?
- What are the most appropriate behavioral endpoints for a particular study? The dynamic range, repeatability and appropriateness of the endpoints for the hypothesized mechanisms of action should be considered. Furthermore, more fundamental studies that examine these endpoints may need to be done before embarking on a pharmacology imaging study.
- Dr. Junghoon Kim presented data from a study using CASL perfusion imaging to evaluate effects of methylphenidate. Key points of general interest included: determination of drug effects on a 'baseline' or 'resting' state in order to better interpret changes on task-related activity; the use of quantitative perfusion imaging to improve reliability of serial measurements, as above.

Can baseline imaging results serve as predictors of drug response?
- Dr. Steve Cramer presented data addressing the question of whether baseline measurements may predict the effects of intervention at a later time point, highlighting the following key points of general interest: the amount of improvement in brain function is generally likely to be related to baseline functioning, for example, lower motor cortex signal may suggest a higher capacity for improvement.

How do drug-induced changes in activation relate to drug-induced performance changes?
- It was generally agreed that examining the relationship between drug-induced neural changes and behavioral changes is particularly important in interpreting the significance of the measured neural changes. However, it was also argued that neural changes that occur in the absence of behavioral changes may also be particularly revealing regarding mechanisms of drug effects, since they lack the "performance confound" (the fact that distinctly different qualities and strategies of performance are always presumed to be associated with distinct patterns of neural activity) that plagues functional imaging research. For example, if changes in baseline regional CBF with drug predict improvements in active performance, the imaging changes cannot be confounded with that performance.

Can imaging be used for surrogate markers in drug studies?
- This was discussed only briefly, and no data were specifically presented or discussed that support this potential use of imaging as surrogate markers for clinical outcomes in drug studies. Indeed, extensive studies with this particular issue in mind would need to be done in order to establish specific imaging markers as surrogate markers. Furthermore, many of the participants would likely agree that the most important outcomes are clinical/behavioral outcomes. As repeated in a number of discussions, imaging may be most valuable for determining mechanisms of treatment effects, and potentially providing markers that may be predictive of treatment effects.

Synthesis/recommendations
Although specific consensus was not reached, the following were significant questions or themes that arose from the discussion:

- Study designs for pharmacologic imaging studies may require tailoring in order to best address the primary questions, which includes questions of mechanism or prediction, but rarely proof of efficacy. Thus, double-blind randomized placebo controlled designs utilizing a uniform standard dosing, although the 'gold standard' for clinical trials, may not be the best design depending on the study objectives.
- Qualities of the measurement methods need to be considered carefully, including inherent variability in the measurements for serial study designs and sensitivity of the measurements for processes most likely to be modulated by the chosen drugs.

References

1-A single dose of the serotonin neurotransmission agonist paroxetine enhances motor output: double-blind, placebo-controlled, fMRI study in healthy subjects. Loubinoux I, Pariente J, Boulanouar K, Carel C, Manelfe C, Rascol O, Celsis P, Chollet F. NeuroImage, 2002, 15, 26-36.

2- Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Pariente J, Loubinoux I, Carel C, Albucher JF, Leger A, Manelfe C, Rascol O, Chollet F. Ann.Neurol 2001, 50, 718-729.