Non-Invasive Fully Quantitative Positron Emission Tomography Imaging

Francesca Zanderigo, PhD

PROJECT ABSTRACT

Positron emission tomography (PET), a nuclear imaging technology for *in vivo* quantification of blood flow, metabolism, and protein distribution, is an invaluable tool for developing novel personalized therapies for high morbidity and mortality brain disorders (Benton *et al.*, 2007; Depression Guideline Panel, 1999; Michalak *et al.*, 2008; Trivedi, 2003; Vogt *et al.*, 1994).

PET gold-standard full quantification involves determining the plasmatic concentration of the injected radioligand, corrected for the fraction that is metabolized in the body (metabolite-corrected input function, cIF), a step essential for all the radioligands used in neuroreceptors studies other than [^{18}F]FDG. This invasive and costly procedure, that requires arterial catheter insertion and analysis of several blood samples, is difficult to apply in clinical practice, but it represents the only way to obtain *in vivo* the closest quantification to *in vitro* receptor density, the binding potential (BP_F) (Innis *et al.*, 2007).

Reference region approaches (RRA) (Cunningham *et al.*, 1991; Ichise *et al.*, 2003; Lammertsma *et al.*, 1996; Logan *et al.*, 1996) avoid arterial sampling by "considering as input" the radioligand activity in a reference region (RR) devoid of the receptors of interest. More precisely, they form an inferred relationship between regions based on the fact that such regions share the cIF, and the assumption that the non-displaceable volume of distribution (V_{ND}) of the radioligand, ideally the volume of distribution in a RR devoid of specific binding, is constant throughout the brain. However, RRA

(i) require the identification of a reliable RR (Oquendo *et al.*, 2007; Parsey *et al.*, 2005; Parsey *et al.*, 2010); and

(ii) only estimate the non-displaceable binding potential BP_{ND} (Innis *et al.*, 2007; Slifstein *et al.*, 2001), an outcome much less informative than BP_F.

Thus, measuring cIF is key for many radioligands for which RR is not available (Ginovart *et al.*, 2006; Henriksen *et al.*, 2008), and for correctly interpreting PET binding (Parsey *et al.*, 2006; Parsey *et al.*, 2010).

Tremendous progress has been achieved (Zanotti-Fregonara *et al.*, 2011a) in the effort to reduce or eliminate the amount of arterial blood required, while maintaining quantification accuracy relative to the cIF analysis, including image-derived input function approaches (IDIF) (Zanotti-Fregonara *et al.*, 2011a; Zanotti-Fregonara *et al.*, 2011b). However, none of these so-called non-invasive methods has so far shown the potential to be introduced in the future into clinical practice due to three major limitations (Zanotti-Fregonara *et al.*, 2011a; Zanotti-Fregonara *et al.*, 2011b).

(a) None works effectively for more than one radioligand.

(b) None per se accounts for metabolite correction.

(c) They still require multiple arterial samples for correction/scaling purpose.

Simultaneous estimation (SIME) (Wong *et al*., 2002) of cIF and tissue kinetic constants has the potential to achieve a truly non-invasive cIF estimation (Zanotti-Fregonara *et al.*, 2011a), given that it (a) is promising for multiple radioligands (Ogden *et al*., 2010; Zanotti-Fregonara *et al.*, 2011a), and (b) accounts for metabolite correction. Still, the need for one blood sample for scaling the cIF is a major barrier for its use in clinical practice.

We hypothesize that we can predict in each subject the scaling needed for SIME solely on the basis of non-invasive biometric measurements (e.g. net injected dose and mass, body mass index, age), thus solving one of the biggest challenges that hamper the routine use of PET in brain studies, the need for arterial blood. This will be tested on an already acquired rich PET archive, which includes arterial sampling and correlated biometric measurements for several radioligands and subjects.

REFERENCES

- Benton T, Staab J, Evans DL (2007) Medical Co-Morbidity in Depressive Disorders. Annals of Clinical Psychiatry, 19(4): 289–303.

- Cunningham VJ, Hume SP, Price GR, AHier RG, Cremer JE, Jones AK, (1991) Compartmental analysis of diprenorphine binding to opiate receptors in the rat in vivo and its comparison with equilibrium data in vitro. J Cereb Blood Flow Metab 11: 1-9.

- Depression Guideline Panel (1999). Depression in primary care, vol. 2: Treatment of major depression. clinical practice guideline, number 5. AHCPR Publication 93-0551, US Department of Health and Human Services.

- Ginovart N, Meyer JH, Boovariwala A, Hussey D, Rabiner EA, Houle S, Wilson AA (2006) Positron emission tomography quantification of [11C]-harmine binding to monoamine oxidase-A in the human brain. J Cereb Blood Flow Metab. 26(3): 330-44.

- Henriksen G, Willoch F (2008) Imaging of opioid receptors in the central nervous system. Brain; 131(Pt 5): 1171-96. Review.

- Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE (2003) Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab. 23(9): 1096-112.

- Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands.. J Cereb Blood Flow Metab. 27(9): 1533-9.

- Lammertsma AA, Hume SP (1996) Simplified Reference Tissue Model for PET Receptor Studies. Neuroimage 4: 153–8.

- Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996). Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab. 16(5): 834-40.

- Michalak EE, Murray G,Young AH, Lam RW (2008) Burden of Bipolar Depression. Impact of Disorder and Medications on Quality of Life. CNS Drugs 22(5): 389-406.

- Ogden RT, Zanderigo F, Choy S, Mann JJ, Parsey RV (2010) Simultaneous estimation of input functions: an empirical study. J Cereb Blood Flow Metab 30(4): 816-26.

- Oquendo MA, Hastings RS, Huang YY, Simpson N, Ogden RT, Hu XZ, et al. (2007) Brain serotonin transporter binding in depressed patients with bipolar disorder using positron emission tomography. Arch Gen Psychiatry 64(2): 201–8.

- Parsey RV, Arango V, Olvet DM, Oquendo MA, Van Heertum RL, Mann JJ (2005) Regional heterogeneity of 5-HT1A receptors in human cerebellum as assessed by positron emission tomography. J Cereb Blood Flow Metab 25(7): 785–93.

- Parsey RV, Oquendo M, Ogden RT, et al. (2006) Altered Serotonin 1A Binding in Major Depression: A [carbonyl-C-11]WAY100635 Positron Emission Tomography Study. Biol Psychiatry. 59: 106-113.

- Parsey RV, Ogden RT, Miller JM, Tin A, Hesselgrave N, Goldstein E, Mikhno A, Milak M, Zanderigo F, Sullivan GM, Oquendo MA, Mann JJ (2010) Higher Serotonin 1A Binding in a Second Major Depression Cohort: Modeling and Reference Region Considerations. Biological Psychiatry Vol. 68(2): 170-8.

- Slifstein M, Laruelle M. (2001) Models and methods for derivation of in vivo neuroreceptor parameters with PET and SPECT reversible radiotracers. Nucl Med Biol.28(5): 595-608.

- Trivedi MH (2003) Using treatment algorithms to bring patients to remission. Journal of Clinical Psychiatry 64: 8–13.

- Vogt T, Pope C, Mullooly J, Hollis J (1994) Mental Health Status as a Predictor of Morbidity and Mortality: A 15-Year Follow-Up of Members of a Health Maintenance Organization. American Journal of Public Health 84(2): 227-31.

- Wong KP, Meikle SR, Dagan F, Fulham MJ (2002) Estimation of input function and kinetic parameters using simulated annealing: application in a flow model. IEEE Trans Nucl Sci 49: 707–13.

- Zanotti-Fregonara P, Chen K, Liow JS, Fujita M, Innis RB (2011a) Image-derived input function for brain PET studies: many challenges and few opportunities. J Cereb Blood Flow Metab. 31(10): 1986-98. Review.

• Zanotti-Fregonara P, Liow JS, Fujita M, Dusch E, Zoghbi SS, Luong E, Boellaard R, Pike VW, Comtat C, Innis RB (2011b) Image-derived input function for human brain using high resolution PET imaging with [C](R)-rolipram and [C]PBR28. PLoS One 6(2).