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# Combined analysis of multimodal brain imaging data for the study and prevention of major depressive disorders in high-risk offspring

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## PROJECT ABSTRACT

The serotonin (5-HT) neurotransmitter system has been implicated in the pathogenesis of major depression (Blier *et al.*, 1990; Czesak *et al.*, 2006; Lemonde *et al.*, 2003; Stockmeier *et al.*, 1998). This system can be investigated *in vivo* via Positron Emission Tomography (PET), a nuclear imaging technology that uses radioactively labeled molecules (i.e. radioligands) to quantify and visualize biological processes, such as blood flow, brain metabolism, and distribution of proteins throughout the body. In investigations related to depression specifically, PET is used for measuring *in vivo* the closest quantification to *in vitro* concentration of available receptors of the serotonin system (i.e. the binding potential, $BP_F$) (Innis *et al.*, 2007).

By using PET, investigators found higher serotonin 1A ($5\text{-}HT_{1A}$) binding potential in subjects affected by major depressive disorder (MDD) (Parsey *et al.*, 2006; Parsey *et al.*, 2010), suggesting that this is a biologic trait of MDD. Preliminary data also suggest the same abnormality (i.e. higher $5\text{-}HT_{1A}$ binding) in healthy (i.e. not affected by mood disorder) offspring of MDD subjects, indicating familial transmission. It has been observed that MDD aggregates in families and the risk to develop MDD for relatives of depressive subjects (11%-18%) is significantly greater than the risk for relatives of healthy controls (HC) (0.7%-7%) (http://www.nimh.nih.gov/research/genetics.htm). The ability to identify the population at highest risk for developing MDD could help target potential preventive interventions and would further our understanding of the pathogenesis of depression, especially in adolescents and young adults.

Unfortunately, mental health professionals currently do not have objective tools to classify people at risk of developing MDD, identify genetic and environmental factors that lead from risk/vulnerability to illness, or select a treatment plan, which can be preventive or after manifestation of the illness, based on each individual's likelihood of remission. If such tools were developed, they could significantly reduce the morbidity and mortality resulting from ineffective treatment trials (Leuchter *et al.*, 2010; Taylor *et al.*, 2005).

Consequently, there is a critical need to both identify biologic traits (i.e. biomarkers) that objectively characterize a specific population with respect to HC (e.g. MDD, MDD offspring), and develop automatic algorithms that, working on the information provided by these biomarkers, help clinicians identify subjects at highest risk of MDD and consequently provide the optimal therapy on the basis of the prediction of each individual's response to treatment.

*In vivo* brain imaging techniques such as PET, structural Magnetic Resonance Imaging (MRI), functional MRI, Diffusion Tensor Imaging (i.e. a MRI technique that measures the restricted diffusion of water in tissue to produce neural tract images),

Arterial Spin Labeling (i.e. a MRI technique that measures cerebral perfusion), and Electroencephalography can each assess, in a non-invasive way, different brain structures and functions, and have already provided some neural predictors of response to treatment for MDD patients (Bruder *et al*., 2008; Chen *et al.*, 2007; Gong *et al.*, 2011; Konarski *et al.*, 2009; Milak *et al.*, 2009; Siegle *et al.*, 2006).

Furthermore, so far none has performed a multi-modalities investigation in the specific case of MDD offspring. The extent to which outcome measures derived via brain imaging, as biomarkers of MDD, can classify young subjects at risk of developing depression by virtue of being offspring of MDD probands has yet to be examined.

Therefore, on the basis of preliminary results, we aim to:

• determine whether the abnormality of higher serotonin 5-$HT_{1A}$ binding, which can only be assessed *in vivo* via PET, together with other structural biomarkers derived via MRI (e.g. cortical thickness, fractional anisotropy), can be used to automatically classify young subjects at higher risk for developing MDD by virtue of having parent(s) affected with recurrent MDD;

• investigate the genetic and environmental factors that lead from risk/vulnerability to illness, and predict each individual's likelihood of remission to specific treatments on the basis of PET, MRI, and potentially biomarkers derived from other brain imaging modalities, in order to select the optimal treatment.

As depression is a heterogeneous and complex disorder, whose occurrence and differential treatment prediction likely require information derived from a combination of imaging modalities, we propose the development of a technique that jointly analyzes data from multiple imaging modalities in order to identify biomarkers predictive of high risk for MDD for early preventive intervention. To achieve this, we will consider the use of advanced machine learning and data mining techniques, which have the potentiality of enhancing image-derived measures and elucidating function-structure networks (Sui *et al.*, 2011).

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