White Matter and Emotional and Cognitive Control in Late-Onset Depression

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Analyses for Primary Hypotheses:
Hypothesis 1. *Microstructural WM abnormalities in the emotional control system will distinguish LOD subjects from normal elders, especially in the presence of increased activation in emotional control structures (rostral ACC, amygdala) in response to an emotional control challenge*. Logistic regression analyses will test main effects and the interaction of FA and activation of emotional control structures. **Depression status (depressed, controls) will be the outcome variable.**

Hypothesis 2. *Microstructural WM abnormalities in the cognitive control system will distinguish LOD subjects from normal elders, especially in the presence of hypoactivation in cognitive control structures (dorsal ACC, DLPFC).* Similar to H1, logistic regression analyses will examine main effects and the interaction of FA and activation of the cognitive control structures with depression status as the outcome.

For **H1** and **H2** a significant main effect or interaction would provide empirical support for our hypothesis. A Likelihood ratio (LR) test comparing nested models with and without this interaction will examine the incremental contribution of the interaction term.

Analyses for Secondary Hypotheses: ***SH1.*** *In LOD subjects, microstructural WM abnormalities in the control system will be associated with slower decline of depressive symptoms (MADRS) during escitalopram treatment (target dose: 20 mg for 12 weeks), especially in the presence of hyperactivation in emotional control structures (rostral ACC, amydgala) in response to a control challenge.*
These analyses will include the depressed subjects. A mixed-effects linear regression model will include up to 7 repeated MADRS assessments over the open-label trial (baseline and weeks 2, 4, 6, 8, 10, 12) as the dependent variable. The model will include a random subject-specific intercept, a random slope, and fixed effects for baseline activation of emotional control structures and FA.

An LR test will examine the incremental contribution of 2 interactions using nested regression models: activation by time and FA by time. Analyses will be based on the principle of intention to treat - that is, all individuals with baseline visit data will be included.

SH2. *In LOD subjects, microstructural WM abnormalities in the cognitive control system will be associated with slower decline of depressive symptoms (MADRS) during escitalopram treatment especially in the presence of hypoactivation in control structures* SH2 and SH3 will be tested with mixed-effects linear model as described in SH1.

The sample size was determined based on statistical power analyses for the primary hypotheses H1 and H2. Our preliminary study demonstrated the feasibility of the proposed design. However, the pilot data sample size renders estimates too imprecise for power analyses Thus, a simulation study (with 1000 data sets per specification) examined statistical power of analyses proposed for H1 and H2 using SAS PROC LOGISTIC. Odds ratios for the interaction term varied (1.4, 1.5); the correlation between independent variables ranged (-0.2 to 0.2). Simulation results (Table 1), indicate that the proposed N (70 depressed vs. 70 controls) provides sufficient power (>80%) to detect meaningful relationships among white matter integrity, activation, and diagnostic group.

Table 1. Power for H1and H2 for N=140

Odds Ratio	Correlation between predictors	Power (Interaction)
1.4	-0.2	0.87
	-0.1	0.84
	0	0.81
	0.1	0.84
	0.2	0.87
1.5	-0.2	0.91
	-0.1	0.87
	0	0.84
	0.1	0.87
	0.2	0.90

C2.16. Attrition: H1 and H2 use cross-sectional data and thus attrition should not pose a problem. In contrast, SH1 and SH2 involve longitudinal data. Several steps have been taken to minimize the impact of attrition. First, in the spirit of ITT, every effort will be made to continue assessments for the entire course of treatment, even among those who

discontinue escitalopram. Second, mixed-effects models yield valid inferences assuming ignorable attrition.