Late Life Depression (LLD): Older adults are one of the fastest growing demographics in the US, with 10% of people aged 65 and over suffering from major depression. LLD results in increased risk of death, disability, suicide, hospitalization and nursing home placement, and subsequently considerable health care costs. Both anti-depressant medications and psychotherapy have been found to be successful treatments for older adults, but effectiveness trials of LLD indicate that treatment outcomes are not nearly as robust in the general public as they are in controlled clinical trials.

An integrated biological-psychosocial theory of treatment response in LLD: Experts in LLD agree that this illness is a function of age and disease related compromise of frontostriatal pathways and exposure to age-related psychosocial adversity. Older adults who exhibit executive dysfunction are at particular risk for LLD, and show a poor and unstable response to antidepressant treatments. Patients with executive dysfunction exhibit difficulty attending to important information needed for successful problem resolution, have trouble deciding among different solutions to overcome the problem, and subsequently have difficulty initiating a successful plan of action. Within the broader domain of executive dysfunction, poor response to antidepressant medication has been linked to performance on measures involving cognitive conflict. The cognitive conflict network (CCN) is responsible for filtering out irrelevant information while one is engaged in goal directed behavior. Evidence from biological studies of treatment response in LLD finds that older patients who demonstrate a poor performance in the Stroop task (a test of cognitive conflict) are less likely to respond to SSRI treatment, but respond well to PST. Additionally, structural and functional deficits in regions that comprise the CCN (dACC, DLPFC) are also associated with poor response to antidepressants. Behavioral theories of depression and treatment response, also point to the importance of filtering irrelevant, negative information in the effectiveness of psychotherapy. When we combine data from biological and psychosocial theories of depression treatment response in late life, we come to this conclusion: older adults with compromised cognitive conflict systems are at greatest risk for LLD and for poor response to treatment; unless that system is specifically addressed, patients may not respond well to depression treatments.

Targeting treatment of LLD and cognitive conflict: The theory above provides avenues for personalizing treatments for a group of people known to have a poor response to antidepressant treatment. One avenue is to select or develop interventions that compensate for deficits in cognitive conflict processes. These treatments are often referred to as strategic interventions. We have demonstrated that PST, a treatment that teaches patients a set of executive skills, is an effective intervention for older adults with LLD and executive dysfunction. Based on these findings PST may be a strategic intervention, one that compensates for deficits in cognitive conflict, but does not fix the deficit specifically. A different view is that through repeated practice of PST skills over a 6-12 week period, this intervention resembles a plasticity intervention, in that it improves network activation in the dACC, DLPFC and associated parietal regions. We wish to explore whether PST’s success is a function of better activation of the cognitive conflict system, or if it is simply a strategic intervention. Plasticity interventions aimed at increasing appropriate brain activation (also referred to as cognitive retraining models) could play a role in the treatment of LLD. We were previously able to demonstrate that patients with mild memory impairments exposed to a memory plasticity intervention and PST demonstrated significant early response to treatment. We suspect that LLD patients treated with either PST or Evolution (a plasticity intervention targeting cognitive conflict) will result in reduced depression and improved functional outcomes.
Plasticity interventions have the potential to address access barriers that interfere with the uptake of traditional therapies. Many of the programs are computerized, and as a result could be easily disseminated via the internet, smart phone/tablet applications, game consoles/systems or mobile health platforms. We will explore whether Evolution in combination with clinical management will have similar effects on mood as traditional PST.

**Inclusion/exclusion criteria (list):**

**INCLUSION:**
1) Aged 60 years or older
2) Diagnosis of major depressive disorder as defined by the SCID-R
3) HDRS (Hamilton Depression Rating Scale) of 20 or greater
4) MMSE of 24 or greater
5) English speaking
6) Able to physically participate in a research protocol
7) Able to provide written informed consent

**EXCLUSION:**
1) History of psychosis, mania, or currently using or abusing illicit drugs or alcohol
2) Diagnosis of dementia
3) Taking cognitive enhancers
4) Change in or newly began taking psychotropic medication within the last 6 months
5) Color blind
6) Movement disorder that prevents participation (unable to hold/use iPad)

**Method of contact/recruitment (be specific):**
These recruitment procedures have been approved by CHR. Upon DGIM approval we will obtain patient names and addresses for patients seen in UCSF's DGIM who are 60 years or older and have an ICD-9 code of 296.2 (single episode major depressive disorder or 2.96.3 (recurrent major depressive disorder) or who are currently prescribed antidepressant medication. This information will be queried from APEX. We will send the patient's physician a letter describing the study and related procedures and will ask the physician to indicate if their patient may or may not be appropriate for contact. If the physician indicates that their patient may not be eligible, we will not contact his/her patient. If the physician indicates that his/her patient may be eligible, we will contact the patient first by mail with an introductory letter and an "opt-out/opt-in" postcard to see if they are interested in hearing more about our study. To protect the confidentiality of potential participants, they will be assigned a unique 4-digit number which will be written on the postcard. If we do not receive the postcard within 2 weeks notifying us of a potential participant's disinterest in the study, we will contact them by phone to provide more information. Two phone call attempts will be made. If we do not receive a response from the physician after 2 weeks, we will resend the letter/email a second time. If we still do not receive a response from the physician, we will not contact their patient. In addition, we would like to request flyers to be made available in patient waiting area(s).

**Benefits/burden for participants (clearly identify potential for harm):**
Participants may experience an improvement in their depressive symptoms. Participants may experience emotional discomfort as a result of the questions from the assessment interviews. Participants may experience fatigue during or following an assessment interview, treatment session, or fMRI. Participants may experience some discomfort during the fMRI, e.g. hearing loud "clanging" noises or feeling "closed-in". Participants will be given opportunities to take breaks during the interview assessments; in addition, they may refuse to answer any question they do not wish to answer or stop the interview at any time. During the fMRI procedure, participants will be given ear plugs and will also be provided with a button to press if at any point they want to be removed from the scanner. The participant may discontinue any procedure in the study at any time.

**Any benefits or burden to DGIM practitioners?** No direct benefit; limited burden of patient referral.

**Timeline for recruitment (projected start and stop dates):** Upon DGIM approval thru December 31, 2015

**Funding source:** National Institute for Mental Health

**Potential for DGIM collaborators?** Yes

**Do you agree to notify us when recruitment is completed?** Yes

**Date form completed:** 4/10/14