

# R61/33 MH129380 (MPI: Charles, Schneier) 12/2023 – 11/2027

NIMH

Targeting Dopamine-Mediated Social Reward Sensitivity to Remediate Social Disconnection

Total Award Amount: \$7,911,288

Collaboration with USSD

**Abstract:** Social relationships contribute enormously to our health and well-being. Social disconnection is a common and disabling feature of anxiety and depressive disorders that does not respond sufficiently to our best available treatments. These outcomes suggest first-line treatments do not adequately engage the mechanisms that support positive connections with others. Animal and human research suggests the dopamine system plays an important role in responding to social reward cues and opportunities that drive our motivation and behavior toward connecting with others. Diminished social reward anticipation is observed across anxiety and depressive disorders – pointing to a trans-diagnostic mechanism that may underpin social disconnection. Directly modulating dopaminergic functioning in a dose-dependent manner would provide a strong causal test of social reward-mediated disconnection pathways. This is important because first-line pharmacotherapies for anxiety and depression do not directly target this system, which may explain in part why social disconnection persists for many patients following treatment. The proposed two-phase, milestone-driven project will address this gap by testing the hypothesis that modulating the dopamine system pharmacologically will enhance social reward anticipation (the treatment target) and therefore improve social connectedness (primary outcome) in individuals with clinical levels of anxiety or depression. We will selectively engage this system using pramipexole – a D2/D3 dopamine receptor agonist shown to enhance dopamine signaling in the striatum – thereby providing a strong proof of mechanism test. The R61 project will evaluate dose-dependent effects of pramipexole on striatal activation during social reward anticipation (primary outcome) and opportunities to disclose to others. Secondary outcomes will be measured during dyadic affiliation and shared experiences tasks. Aim 1 will test the hypothesis that pramipexole increases social reward anticipation compared to placebo following 6 weeks of treatment. Aim 2 will determine which dose of pramipexole produces a greater effect on social reward anticipation. Pramipexole blood concentrations will be used to confirm dose-dependent target engagement. If pramipexole is superior to placebo in increasing striatal activation to social reward anticipation, the R33 project will attempt to replicate the R61 findings (Aim 1) and examine whether increases in social reward anticipation are associated with improvements in social connectedness (Aim 2) following a 6-week double-blind, randomized, placebo-controlled trial (dose informed by the R61). Secondary outcomes will be change in positive and negative valence symptoms (e.g., social anhedonia, anxiety, depression). An exploratory aim will examine treatment effects on negative valence processes (e.g., threat sensitivity). Positive findings would validate a new CNS target for remediating social disconnection that could be studied in larger confirmatory efficacy trials. Regardless of study outcomes, important new information will be gained about the role of dopamine-mediated processes that are believed to govern whether and how we connect with others.

Role: Co-Investigator

Collaboration with UNIVERSITY OF CALIFORNIA, SAN DIEGO

Dr. Charles Taylor's

lab: <https://psychiatry.ucsd.edu/research/programs-centers/pearl/people/index.html>