2. SPECIFIC AIMS

Major depressive disorder (MD) is a serious public health problem, and adolescence is an "age of risk" for 1st onset of MD. Depression (Dep) is associated with a reduced sensitivity to rewards and low reward-related brain function in cortico-striatal circuitry. However, research has not yet tested whether *chronically* low reward responsivity (RR) or attenuated RR development during adolescence predicts 1st onset of MD. A separate literature documents elevated peripheral inflammation in Dep. Yet, research has not yet examined whether chronically elevated inflammation or increases in inflammation during adolescence predicts 1st onset of MD. Further, research on inflammation and RR mostly has proceeded in parallel. Recently, however, we and others have proposed neuroimmune network models of Dep. These models draw on research indicating that peripheral inflammatory mediators (e.g., cytokines) access the brain, where they lower RR. This is highly adaptive when regulated. It coordinates sickness behaviors (e.g., inactivity) that facilitate pathogen removal and wound healing by diverting resources to the immune system. When dysregulated, however, inflammation can lead to chronic reductions in RR, reflected in dysphoria and anhedonia. This low RR then is proposed to initiate unhealthy, self-medicating behaviors (substance use, poor diet) to manage the dysphoria, as well as sleep disruption and stress generation, which further heighten inflammation. Over time, dysregulation in RR and immune signaling may synergize to form a positive feedback loop, whereby dysregulation in each system exacerbates dysregulation in the other. We propose that reward-immune dysregulation is a two-hit vulnerability for the 1st onset of MD and increases in Dep symptoms (Sxs) in adolescence. Moreover, adversity and recent stressors influence both RR and inflammation, and may set the foundation for reward-immune dysregulation. This proposal is the first systematic test of these hypotheses. We use **a biobehavioral high-risk approach involving immune and RR measures at multiple units of analysis in a prospective longitudinal design to examine: 1) concurrent and longitudinal bidirectional associations between inflammation and RR; 2) mediators and moderators of their associations, and 3) inflammation and RR as separate and joint predictors of risk for 1st onset of MD and increases in Dep Sxs during adolescence.** We predict that chronically low RR and attenuated development of RR will be associated with elevated inflammation. We further predict that chronically high inflammation and increases in inflammation will combine with *chronically* low RR and attenuated development of RR to predict 1st onset of MD and Dep Sxs, *particularly anhedonia*. *Adversity in childhood and adolescence* will moderate and behaviors that increase inflammation (substance use, poor diet, sleep disturbance, stress-generation) will mediate RR-inflammation associations.

Three hundred 14-15 year old high school freshmen will complete a prospective, 3-year longitudinal study. Participants (Ps) with no prior history of MD will be selected along the entire dimension of self-reported RR, with oversampling at the low tail of the dimension to increase the likelihood of MD onsets. At Time 1 (T1), T3, and T5, each a year apart, Ps will complete blood draws to quantify inflammation, self-report and behavioral measures of RR, and fMRI scans of reward neural activity and functional connectivity during monetary and social reward tasks. At T1-T5 (with T2 and T4 6 mo. between the yearly sessions), Ps also will complete diagnostic interviews, and measures of Dep Sxs, recent life events coded for reward-relevance and stress generation, and behaviors that increase inflammation. Adversity history *from birth to T1* will be assessed at T1. *Unless otherwise specified in the aims below, we make comparable predictions for monetary and social RR.*

Aim 1: Reward responsivity (RR) and inflammation associations

Aim 1.1. We will examine concurrent associations between RR measured with multiple units of analysis (self-report, behavioral, neural) *and in two domains (monetary, social)* and peripheral inflammation at T1, T3, and T5. We predict that lower RR levels will be associated with higher peripheral inflammation at each time.

Aim 1.2. We will examine bidirectional, longitudinal associations of trajectories of each system with the other over time. Multiple RR units of analysis (i.e., "indices") and changes in these RR indices from T1 to T3 to T5 will predict changes in inflammation from T1 to T3 to T5 and vice versa, such that attenuated development of RR will be associated with increases in inflammation and vice versa.

Aim 2: Moderators and mediators of reward responsivity (RR) and inflammation associations

Aim 2.1. Childhood *and adolescent* adversity will be associated with chronically low RR and attenuated development of RR indices, chronically high inflammation and increases in inflammation over time, and stronger concurrent and longitudinal associations between RR and inflammation.

Aim 2.2. Inflammation-enhancing behaviors (substance use, high-fat/high-sugar diet, sleep disturbance, self-generated reward-deactivation events involving the failure to attain reward or loss of reward) from T1 to T5 will partially mediate RR predictors of change in inflammation from T1 to T5 and vice versa. *Self-generated reward deactivation events are predicted to be particularly relevant for the effects of social RR on inflammation.*

Aim 3: RR and inflammation as predictors of prospective 1st onset of MD and Dep Symptoms

Chronically low and attenuated trajectories of RR indices over time (T1 to T5) and chronically elevated and increasing trajectories of inflammation over time (T1 to T5) will be separate and joint predictors of 1st onset of MD and increases in Dep Sxs, *particularly anhedonia,* between T1 to T5. Reward-deactivation events (whether self-generated or not) and childhood *and adolescent* adversity each will moderate RR indices' prediction of 1st onset of MD and Dep Sxs and inflammation's prediction of 1st onset of MD and Dep Sxs over follow-up.