SPECIFIC AIMS

Recent epidemiologic reports indicated high levels of **chronic pain** experienced by sickle cell disease (SCD) patients [1-4]. Limited data suggests that central nervous system abnormalities may underpin chronic SCD pain [4-13]. Emerging neuroscience and psychological evidence suggests that social factors may increase vulnerability to chronic pain via both focal exposure (e.g., trauma) to major life stressors and chronic exposure to socially painful situation (e.g., stigma) resulting in **"social pain"** experienced through similar neural pathways as physical pain [14-20]. Additionally, a substantial body of evidence suggests that socio-environmentally shaped patients' cognitive, emotional, and behavioral coping responses to chronic pain play a significant role in determining their long-term health [21-26]. These emergent insights on pain etiology could be fruitfully utilized to characterize physical and social pain across racial and ethnic groups with high prevalence of SCD. Over 100,000 individuals largely of African, Caribbean and Hispanic origins have SCD in the United States [27, 28]. The incidence of annual SCD births globally ranged from 2000 babies in the United States to over 200,000 babies in sub-Saharan African (SSA) nations [29]. In the United States, there are documented reports of exposure to stigma, social injustice and healthcare disparity among SCD patients [30-32]. In SSA nations, lack of structured preventive care infrastructures may contribute to high SCD pain burden [33-36]. Also, lack of public knowledge of SCD causation perpetuates social stigma directed at SCD patients [37].

The study described in this proposal is integral to an ongoing longitudinal SCD Natural History Study Project in the SSA nation of Sierra Leone based on collaboration between the University of Cincinnati, Jericho Road Community Health Center, Sickle Cell Carers Awareness Network (public university, US–based nongovernmental agency, and a local advocacy group respectively). Undergirding this collaboration are World Health Organization and the Sickle Pan African Network pronouncements for research on large cohorts of comprehensively and consistently phenotyped patients to develop effective therapies for SCD patients [38-41].

Our study **main objective** is to robustly phenotype aspects (physiological and phenomenological) of the physically and socially painful experience of two racially matched (Black), ethically (African and African American) and geographically different (Sierra Leone and United States) SCD patient cohorts by investigating the neurologic and psychologic overlap between physical and social factors underlying pain experiences. The NIH Health Symptom Science Model will inform our study conceptual framework [42, 43]. Methodologically, we will use established quantitative sensory testing (QST) methods to determine ethnic differences in experimental pain sensitivity [11, 12, 44-46]. We will use validated pain questionnaire to measure physical pain longitudinally to determine pain frequency and intensity and correlate temporal pain with QST baseline measurements. Two analytic constructs, psychological distress and emotional intelligence, referenced from the social model of disability, transactional stress and coping framework will be used to characterize "social pain" and to appraise adaptation to chronic pain respectively [47,48]. Specifically, we will use a battery of validated questionnaires to measure pain history, psychological distress, emotional intelligence, resilience, stressful life events, social support, perceived ethnic discrimination, stigma, depressive symptoms, and quality of life. Our central hypothesis is that significant ethnic differences exist between SCD patients' clinical and experimental pain patterns and levels of psychosocial distress. We will test our central hypothesis with these aims:

Aim 1: Characterize experimental pain sensitivity, clinical pain intensity, frequency, chronicity and temporality in African and African American SCD patient cohorts.

Aim 2: Investigate ethnic (African, African American), biological (SCD), psychological (emotional intelligence, psychological distress, resilience) and social factors (discrimination, stigma, social support) interactions with multiple pain features to determine their relative and combined associations with pain in SCD patient cohorts.

If our main hypothesis is supported, our study will robustly expand current biopsychosocial understanding of chronic pain across ethnically distinct SCD patients. Our **short-term goal** is to identify pain outcomes that may be modifiable by combined medical and psychosocial interventions. Our **long-term goal** is to use data from our studies to configure SCD patient-specific treatment plans with varying emphasis on narcotic, non-narcotic based treatments and behavioral therapies for patients across the lifespan. Our **expected outcomes** are consistent with the National Institute for Nursing Research mission to support research which quantify and measure subjective disease symptoms and their biologic, psychologic, and genomic architectures to derive behavioral and clinical data to inform clinical application and precision medicine for symptom management and prevention [42, 49]. Our proposed study also aligns with several NIH research initiatives for Africa [50-56].

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