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CROSS-SPECIES VALIDATION OF INSOMNIA-ASSOCIATED LOCI IDENTIFIED THROUGH VARIANT-TO-GENE MAPPING IMPLICATES *PIGQ* AS A CONSERVED REGULATOR OF SLEEP DURATION

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Insomnia is a complex and prevalent sleep disorder with reports of high heritability. More than 200 genome-wide significant loci have been documented for insomnia, yet the underlying mechanism remains elusive. Many of the genome-wide association study (GWAS)- implicated single nucleotide polymorphisms (SNPs) fall within inter- or intragenic regions and are subsequently mapped to the nearest coding gene. This approach often mischaracterizes the true effector gene that may reside several thousands of nucleotides away. To tackle this complexity, our group has developed a variant-to-gene mapping approach that reveals effector genes linked to relevant GWAS signals. Using ATAC-seq and promoter-focused capture C methods in human induced pluripotent stem cell-derived neural progenitor cells, we identified a subset of candidate insomnia target coding genes with accessible promoter regions that were contacted by insomnia-associated SNPs residing in open chromatin. Target genes with known human orthologs and available *Drosophila* RNAi lines were then subjected to deep phenotyping of sleep traits. This pipeline revealed five genes producing robust sleep phenotypes, two of which increased sleep by more than 30 percent and three which decreased sleep more than 20 percent. To further characterize the contribution of these genes to sleep behavior in a vertebrate system, we used zebrafish since they have a developed nervous system and exhibit diurnal sleep characteristics similar to humans. We employed CRISPR/Cas9 mutagenesis in F0 zebrafish at the single cell stage to produce high-efficiency biallelic knockouts of the target genes. Interestingly, we found that loss of *pigq* significantly increased sleep duration in both *Drosophila*, and zebrafish, revealing a conserved, yet novel regulator of sleep duration. *Pigq* encodes phosphatidylinositol N-acetylglucosaminyl transferase subunit Q, which catalyzes the first step in glycosylphosphatidylinositol anchor biosynthesis. This gene has not been implicated in sleep previously, but it is involved in early infantile epileptic encephalopathy potentially underlying an important link between sleep and epilepsy. Our ongoing studies aim to characterize the contribution of other members of the glycosylphosphatidylinositol anchor biosynthesis pathway to sleep phenotypes both in *Drosophila* and zebrafish and to understand possible combinatorial effects due to disruption of this pathway.

DIGITAL COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA PROMOTES RESILIENCE DURING THE CORONAVIRUS DISEASE 19 (COVID-19) PANDEMIC

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Introduction: Stressful life events contribute to insomnia, psychosocial functioning, and illness. Though individuals with a history of insomnia may be especially vulnerable during stressful life events, risk may be mitigated by prior intervention. This study evaluated the effect of prior digital cognitive-behavioral therapy for insomnia (dCBT-I) versus sleep education on resilience during the COVID-19 pandemic.
Materials and Methods: COVID impact, insomnia, general- and COVID-related stress, depression, and global health were assessed in April 2020 in adults with a history of insomnia who completed a randomized controlled trial of dCBT-I ($n = 102$) versus sleep education control ($n = 106$) in 2016-2017. Regression analyses were used to evaluate the effect of intervention conditions on subsequent stress and health during the pandemic.
Results: Insomnia symptoms were significantly associated with COVID-19 related disruptions, and those previously received dCBT-I reported less insomnia symptoms, less general stress and COVID-related cognitive intrusions, less depression, and better global health than those who received sleep education. Moreover, the odds for resurgent insomnia was 51% lower in the dCBT-I versus control condition. Similarly, odds of moderate to severe depression during COVID-19 was 57% lower in the dCBT-I condition.
Conclusions: Those who received dCBT-I had increased resilience during the COVID-19 pandemic in adults with a history of insomnia and ongoing mild to moderate mental health symptoms. These data provide evidence that dCBT-I is a powerful tool to promote mental and physical health during stressors, including the COVID-19 pandemic.
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DIGITAL COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA (DCBT-I) AND EMOTION REGULATION AS EARLY INTERVENTION FOR EMPLOYEES IN THE WORKPLACE

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Insomnia is a serious public health concern and has been linked to impaired work productivity. Studies show a link between poor sleep and aspects of occupational functioning such as absenteeism, reduced productivity and low work satisfaction. One in every three workers in the UK are affected by sleep problems costing the economy around £36 billion/year due to loss of productivity in the workplace. This results in around 200,000 working days lost every year, and it is estimated that the cost to industry will rise steadily to £44 billion by 2030 if nothing is done about it. Few studies have evaluated the effectiveness of CBT-I in workplaces, and have found improvements in severity of insomnia and quality of sleep, and slight improvements in productivity and presenteeism, but not in absenteeism. While most interventions for insomnia are focused on the treatment of those above clinical thresholds, there is crucial need for early intervention/prevention of insomnia. This has been further exacerbated during the Covid-19 pandemic due to isolation, financial insecurities, loss of loved ones and fear of infection, causing extensive sleep problems as well as stress, anxiety and depressive symptoms. This study will examine the efficacy of a new hybrid dCBT-I for mild to severe insomnia and symptoms of depression and anxiety delivered to employees in the workplace.

This trial tests the efficacy of implementing a hybrid dCBT-I + emotion regulation (ER) in the workplace in a mixed methods evaluation with a two-arm randomised waitlist control (WLC) design. The dCBT-I+ER intervention is 8-weeks long and delivered via self-guided online platform and four videoconferencing therapy sessions. Primary outcomes are the Insomnia Severity Index, the Patient Health Questionnaire and the Generalised Anxiety Disorder. Secondary outcomes are job productivity, job satisfaction, well-being, quality of life, self-reported (sleep diary data) and objective (actigraphy) sleep parameters.

We recruited 163 workers with sleep and emotion regulation problems ranging from subclinical to clinical levels not engaged in treatment at the time of the trial. Due to the study design, analyses for the primary hypotheses will be done when the last enrolled participant provides post-intervention follow-up (1-month) outcome measures. We hypothesise that participants randomly allocated to dCBT-I+ER will demonstrate significantly greater improvements on the primary outcomes compared to WLCs post-intervention. They will also demonstrate significantly greater improvements on objective (actigraphy) and self-reported (sleep diary) sleep parameters. Exploratory analyses will also indicate the impact of the dCBT-I+ER on work productivity, job satisfaction, wellbeing, and quality of life.

Evaluation of an early intervention for workers with mild to severe symptoms of insomnia and emotion regulation difficulties will contribute to the understanding of benefits of early interventions in the workplace, and its impact on mental health and productivity. The mixed methods