**Scientific Final Report Bial Project 284/20**

"The whole is more than the sum of its parts: Elucidating the link between sleep quality and well-being by integrating cross-modal networks"

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## Aims

The project aims to elucidate the link between sleep and mood: Why do we feel better when we sleep better? Psychophysiology and brain imaging show a wealth of correlations between indicators of sleep quality and well-being but fail to provide an integrative account. We aim to take the next step in this integrative understanding by integrating key factors within and across modalities. To do so, the project aims to (i) extent novel network analyses techniques to take the dependencies among key factors into account and (ii) apply the extended model to distinguish direct from indirect effects as to identify the unique associations across this system, linking biology and cognition to emotion and behavior. Understanding these pathways through the complex system of sleep quality and mood will accelerate our mechanistic understanding of the link between sleep quality and mood.

## Methods

To accomplish the aim of creating an integrative account of the link between well-being and sleep through estimating cross-modal network models the project has two 'research lines' in parallel. First, the *overall research* line of identifying methodological needs (integration) and methodological innovation (development). Second, the application of network methodologies empirically (estimation and application), see **figure 1**.

The methodologies of the first two aims (integration and development) cannot be easily reported on in an ordinary scientific fashion because the 'integration' contained a review, and the 'development' is still in progress. Still, since identifying needs for integration and developing state-of-the-art methodologies that allow to start integrating different data sources in cross-modal network models are an integral and crucial part of the overall aim, I will incorporate them into the methods section. The estimation and application studies conducted within the current project will be reported on in ordinary fashion.

**Figure 1**. Schematic overview of the three main components of the current project: integration, development, estimation and application.

*Integration*

Before a cross-modal network model that can integrate different levels of analyses can be created, we must first understand how these different levels of analyses have been typically analyzed within a network analytical framework. While both neuroscience and psychology have been moving from a reductionist approach towards a network perspective, their developments have occurred largely in parallel. Therefore, the first sub-goal of this project was to create an overview of the different conventions in network neuroscience and psychological networks, on which we can base our integration of the different levels. We did so by creating a multidisciplinary team including leading scientists in the field of network neuroscience and graph theory (Dr. Linda Douw) as well as pioneers in the field of psychological network (Prof.dr. Denny Borsboom). Together we reviewed key components of network science in each of the fields: evaluating the concepts, methods and conventions, and their interpretations.

*Development*

Based on the review we must start the development of new methodologies that can bridge the gaps identified in the review. A crucial gap we identified is the timescale on which the data is being acquired. Therefore, we started two research lines where we aim to (i) pool individual networks in network neuroscience to identify commonalities and quantify deviations from common patterns; and (ii) create individual symptom networks based on questionnaire data. For these aims I started to collaborate with Dr. Maarten Marsman to explore the applicability of Bayesian hierarchical modelling and with Prof.dr. Henrik Walter and Dr. Johann Kruschwitz to explore the applicability of kNN networks on symptom data acquired through questionnaires.

*Estimation and application*

Third, parallel to identifying needs for integration and developing state-of-the-art methodologies that allow to start integrating different data sources in cross-modal networks, I have worked on empirical studies to estimate and apply network analyses across modalities. Below, I will outline the methodologies of these applied projects.

*Linking sleep bruxism, insomnia, and anxiety*. This study included N=2251 participants from the Netherlands Sleep Registry who completed questionnaires on sleep bruxism, insomnia, depression, anxiety, smoking frequency, and alcohol and caffeine consumption. Using a series of univariate analyses, multivariate logistic regression, and network analyses we investigated the link between self-reported sleep bruxism, insomnia, and their potential risk factors such as anxiety and depression was examined.

*Behavioural and cognitive treatment targets*. This study included N=128 patients suffering from sleep difficulties who received cognitive therapy (n=65) or behavioral therapy (n=63). Throughout therapy we assessed their insomnia symptomatology as well as behavioral processes, such as bed- and risetime variability, time in bed, and sleep incompatible

behaviors; and cognitive processes, such as worry, dysfunctional beliefs, monitoring for sleep-related threat. Using a series of network analyses we investigated the different points of engagement of both treatments, and, crucially, also the processes along which these changes were brought about.

*Linking mood to dynamic affect trajectories*. This study included N=228 participants who completed at least 20 assessments of affect and depressive complaints over a 9-14 week period during the first COVID-19 wave in 2020. We (i) explored affect trajectories for different evolutions of depressive complaints, (ii) estimated longitudinal multilevel network models to examine the direct interplay between affect and depressive complaints in detail, and (iii) investigated how person-specific network density relates to changes in depressive complaints over time.

## Results and Discussion

*Integrating levels of information: conceptually, theoretically, methodologically*

While network approaches have been increasingly applied to deepen our understanding of the interplay between factors in both neuroscience and psychology, the developments occur mostly in parallel. Consequently, when multiple levels are considered, oftentimes one of the levels is oversimplified. To break this barrier, we must move beyond single level complexity and integrate the levels of neuroscience and psychology, particularly in fields where both levels play a pivotal role, such as in sleep and mood.

To bridge the gap, we have reviewed the conceptual, theoretical, and methodological conventions in network neuroscience and psychopathology networks. Based on these we have proposed three methodologies to start integrating the levels: (a) multilayer networks; (b) integrated networks; and (c) network-based regressor networks, see **figure 2**. Multilayer networks involve combining networks estimated at each level separately, whereas integrated networks involve estimating a single network on the entire variable space. Finally, in network-based regressor networks a network is estimated at one level, after which the network itself is used to link to the variables at the other level.

While these three proposed methodologies form a first step to start linking and developing cross-modal networks, we also identified further gaps for which new methodologies need to be developed. For example, because of time-scale differences in which the data are collected, brain networks are often estimated at the individual level (estimated on high-frequency data), whereas symptom networks are estimated at the group level (estimated on single point cross-sectional group data). The identification of these gaps now forms the basis of the *development* of new methodologies, see below.

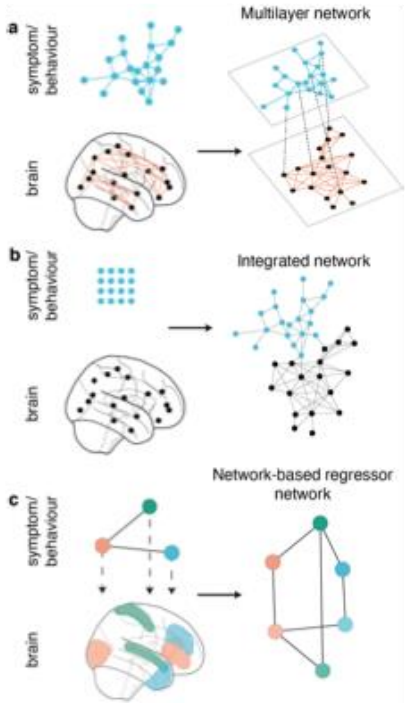


**Figure 2.** Overview of the proposed methodological avenues. a) Multilayer net- works: the symptom/behavior network and brain network are integrated into a multilayer network that contains within- and between-layer links. b) Integrated networks: nodes from behavioral/symptom measures and brain measures are combined into a single network. c) Network-based regressor network: behavior/symptom networks are used to identify brain correlates of each node in the behavioral/symptom network and are subsequently combined in a sin- gle network.

*Development*

By identifying the gaps in creating cross-modal networks, we also developed a new research agenda to start creating this new methodology. In a new collaboration that grew out of my BIAL-funded research we now aim to use a Bayesian hierarchical approach to model the connection between graphical models using random graphs. Critically, this will allow us to bridge the gap between idiographic – i.e., individual – networks and cross-sectional networks. This new framework will allow to integrate networks across modalities and levels of analyses, and to create both individual and group-level networks. As is outlined in the applied projects below, being able to incorporate group-level information as well as individual networks is key in our understanding how biology, cognition, emotion, and behavior interact.

*Estimation and application*

*Linking sleep-bruxism, insomnia, and anxiety*. The link between different biological, psychological, and lifestyle factors is often pivotal to understand how certain moods and behaviors are brought about. In this first applied project, we wanted to move beyond a single framework and focus on creating an integrated account of risk factors.

Using first a series of univariate analysis, akin to an approach that focuses on a single framework or factor, we could reveal that many individual risk factors are indeed related to

sleep-bruxism. However, when taking more factors into account simultaneously, the picture turns out to be more complex. Using network analyses revealed that many of the risk factors themselves are related. Only by analyzing the data using network analysis and creating an integrated approach we could reveal that while self-reported sleep bruxism is not directly related to insomnia, anxiety may act as a bridge factor between these complaints.

Understanding this multivariate 'landscape' of factors allows us to better understand how a plethora of factors interact, providing new opportunities to enhance certain behaviors. For example, now that we revealed anxiety to be a potential bridging factor between sleep bruxism and insomnia, it highlights that when treating sleep-bruxism and insomnia, anxiety management should not be overlooked. This asks for a multidisciplinary and interprofessional collaboration between doctors and dentists.

*Targeting behavioral and cognitive processes*. In this second applied project, we aimed to go beyond static networks and investigate how changes can be brought about in a system of sleep and mood. To understand how better nights may result in better days, we must understand the mechanisms and processes by which sleep and mood interact. Importantly, this system of sleep and mood contains both behavioral as well as cognitive processes.

Crucially, in this project we showed how different elements of the system can be targeted. Through network models we revealed that behavioral interventions of restricting time in bed successfully altered behavioral processes: by decreasing the time in bed, the bed and risetimes stabilized. Over time, these changes in behavioral processes resulted in better sleep: higher sleep efficiency (i.e., the percentage of time spent asleep while in bed), and less problems with waking up too early.

Similarly, by providing cognitive aid the cognitive processes such as worry and dysfunctional beliefs could be targeted. In turn, again, these changes in cognitive processes resulted in a better quality of life. Knowing how different elements of the system can be targeted, provides new ways to enhance the system of sleep and mood through various interventions – both cognitive as well as behavioral, such that we can promote better mood through better sleep.

*Linking mood to dynamic affect trajectories*. While the second applied project incorporated changes over time, all analyses were at the group level. Ultimately, we want to enhance mood and sleep within the individual. In the third project, we therefore focused on understanding individual fluctuations in in mood during the COVID-19 pandemic, which brought about a prolonged period of stress.

In this project we investigated how a perturbation to the system, brought about by COVID-19, would impact mood over time. By understanding the factors that put the system at risk, we also learn about the factors that can stabilize our mood and protect us from stressors. We focused on affect fluctuations across four months during the first wave of the COVID-19 pandemic (March 2020 – June 2020) and found that people whose mood remained stable over this period experienced higher positive affect, showing that affect regulation may be crucial in stabilizing mood.

To explore in what way the dynamics of affect regulation may relate to the development of complaints, we evaluated the individual temporal networks. In these networks we linked the levels of affect fluctuations to the level of depressive complaints and found that there are many and strong relations between the two levels. Crucially, we found a strong correlation

between the density of the person-specific networks over time and their change (aggravation *or* alleviation) in depressive complaints. There thus seems to be a clear link between affect fluctuations and the evolution of mood in times of stress, which may provide new potential leads and opportunities to promote and stabilize mood.

**Conclusion and Recommendations**

In conclusion, the current project led to both methodological and applied innovations. In all projects it became clear that linking biological, cognitive, emotional, and behavioral factors can result in an integrative account of mechanisms and processes. By linking these levels, we thus get a more holistic understanding of sleep and mood by which it provides new opportunities to facilitate better mood through better sleep.

From these projects three clear recommendations can be formulated:

1. First, knowing that the different levels of biology and psychology play an important role in sleep and mood, we should start linking these levels in cross-modal networks that allow us to model the complexity in each of the levels.
2. Second, we must move beyond single frameworks and outcome measures, and include process measures and mechanisms into these network to start unravelling how different factors interact and to learn how certain outcomes - such as better mood - can be promoted.
3. Third, we should investigate these interplays not only at the group, but also at the individual level, requiring new and innovative methods that are currently being developed.