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Computational Analysis of the Role of Epigenetics in Insomnia: A Higher-Order Adaptive Network Model

Sarah Hassouna[1], Jan Treur[1*] and Sophie CF Hendrikse[2]

[1]Vrije Universiteit Amsterdam, Department of Computer Science, Social AI Group, Netherlands

[2]Tilburg University, School of Social and Behavioral Sciences, Department of Methodology and Statistics, Netherlands

ABSTRACT

Insomnia Disorder (ID) is a prevalent stress-related sleep disorder involving burdening symptoms related to emotional disturbances. This paper introduces a higher-order adaptive dynamical system model to explore the potential role of epigenetic mechanisms in the development and persistence of ID. The model examines how epigenetic modifications, particularly in genes related to mechanisms of the sleep-wake regulation and stress response systems, may potentially contribute to the pathology of ID. Results of simulations of the model are reported in this study to underscore the complexity of ID as a dynamic and (mal-)adaptive system of emotion regulation and sleep-wake-regulation processes.

***Corresponding author**

Jan Treur, Vrije Universiteit Amsterdam, Department of Computer Science, Social AI Group, Netherlands.

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Introduction

Insomnia Disorder (ID) is estimated to affect at least 10% of the global adult population. It is the most prevalent sleep disorder and one of the most common neuropsychiatric and mental disorders [1-4]. ID is a relevant public health concern as it is highly burdening, costly and carries substantial morbidity and risk for other physiological and psychiatric disorders, including Major Depressive Disorder (MAD), Generalized Anxiety Disorder (GAD), Posttraumatic Stress Disorder (PTSD), cardiovascular diseases and Alzheimer disease [1,5-7]. ID is stress-related and characterized by difficulties in the initiation or maintenance of sleep and discontentment with the quality or duration of sleep. Although it is natural for most people to experience difficulties and discontentment related to sleep at some moments in their life, especially during contexts of abnormal stress, ID patients differ from normal sleepers encountering the occasional bad night of sleep. Individuals with ID consistently perceive their sleep as nonrestorative and struggle to resume a normal sleeping pattern even during periods without a context of abnormal stress. They suffer from daytime functioning impairments and considerable distress due to a lack of restorative sleep and overnight adaptation of emotional stress. Other ID symptoms include nega-tive associations with sleep, heightened sensitivity to stressful contexts and memories, and symptoms related to anxiety-like behavior. These symptoms and patterns of non-restorative sleep persist over extended periods, despite adequate conditions for normal or restful sleep [1,2,5].

It is crucial to achieve a deeper understanding of the complex etiology, progression, and potential therapies of ID. This significance stems not only from its high prevalence and debilitating symptoms but also from the growing recognition of ID as a substantial influencer, rather than merely a symptom, of psychiatric conditions. Dolsen et al. proposed a transdiagnostic process and bidirectional relationship between ID and the development and persistence of psychiatric disorders [6]. Their research highlighted that cognitive behavioral therapy for insomnia (CBT-I) effectively mitigates symptoms of both ID and other psychiatric disorders in individuals meet-ing diagnostic criteria for both conditions. This lends weight to ID as a significant common factor and transdiagnostic process in psychiatric disorders. Moreover, these findings underscore the importance of a comprehensive understanding and approach to ID because they suggest a potential of ID therapies to also alleviate symptoms of other psychiatric disorders.

Recently, there has been increasing focus on the potential involvement of epigenetic factors in the mechanisms underlying the development and progression of ID. Epigenetic factors refer to mechanisms responding to environmental stimuli, such as stressors, that can cause lasting altera-tions of gene function. Through epigenetic processes, gene expression is affected on a level that surpasses the genetic code. Such changes in gene expression are dynamic and potentially reversible [3]. Considering ID as a mainly epigenetic disorder is a promising avenue, because it could entail that the disorder is epigenetically reversible. A focus on epigenetic influences in ID's development and progression may pave the way for new epigenetic therapeutic methods that could reverse the disorder, and potentially also alleviate symptoms of other psychiatric disorders.

Despite increasing attention and evidence regarding epigenetic mechanisms in ID, a comprehensive model integrating the influence of epigenetics and the dynamic interplay of various biological, psychological, and environmental factors contributing to ID's etiology and persistence re-mains absent. This paper aims to investigate how the interaction of underlying mechanisms and the role of epigenetics in ID can be modeled to address this gap. The paper proposes a higher-order adaptive dynamical system model to explore this question and to analyze the regulation of emotional distress and restorative sleep, considering the influence of epigenetic mechanisms in ID. Furthermore, this paper explores the model while considering the possibilities and mechanisms of potential epigenetically based therapy methods. The higher-order adaptive dynamical system model in this paper is designed based on the Network-Oriented Modelling approach and principles from self-modelling adaptive network models as described by Treur [8,9]. The pro-posed model is meant to provide a flexible framework to test hypotheses regarding IDs underly-ing mechanisms and is intended to serve as an adaptable base for various experimental setups.

In the remainder of this paper, Sections 2 and 3 provide an extensive exploration of the back-ground and underlying mechanisms of ID and their interplay and with epigenetics.Section 4 presents an explanation of the principles used in the model. Section 5 introduces the computational model and Section 6 concludes by presenting simulations resulting from this model and Section 7 a discussion of these findings.

Background for Underlying Mechanisms of ID: Emotion Regulation and Sleep-Wake Regulation

During the 24 hours in a day, an individual generally passes two states, namely the wake state and the sleep state. The mechanisms and alterations between these states are facilitated by a sleep-wake regulation. Insomnia is a stress-related sleep disorder in which this sleep-wake regulation and the restorative function of sleep are disturbed. It is well established that emotional distress and fear are important factors affecting and potentially disrupting sleep [1,10-13]. These factors are also implicated in the development and maintenance of ID. Emotion regulation must therefore be considered as a relevant process in the underlying mechanisms of ID, as the (maladaptive) functioning of emotion regulation processes appear to be highly implicated in the disturbed sleep-wake regulation of ID [1].

Sleep-Wake Regulation

In a healthy functioning sleep-wake regulation, both the sleep- and wake state involve appropriately overlapping and distinct processes to optimally serve their interrelated and discrete functions. During wakefulness a range of cognitive and physiological processes enable an individual to rapidly respond and interact with their environment. This is achieved through generation of the wake state by stimulation of wake systems. These systems include neuronal networks modu-lating excitability or arousal, and the inhibition of sleep-promoting neurons. The wake state is generally assumed to encompass approximately 16 hours of a day, and the remaining 8 hours are encompassed by the sleep-state. Sleep comprises two states cyclically alternating across sleep episodes, these are non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS). REMS is considered the deepest sleep stage as the arousal systems are most sig-nificantly silenced during this period [1,13]. Therefore, evoking an arousal response during REMS normally requires the highest stimulus intensity [13]. This may not be the case in ID. In-dividuals with ID commonly display significantly lower frequency and duration of REMS episodes compared to normal sleepers, while dissimilarities between NREMS measures may not be of significance [1]. This indicates that the initiation and maintenance of REMS is disturbed in ID, and that transitions from REMS to NREMS, from REMS to wakefulness, and from NREMS to the wake state are more frequent and rapid in ID. This suggests that less stimulus intensity is required to evoke rapid transitions and to elicit an arousal response during REMS in ID as the frequency, duration, initiation, and maintenance of this state are fragmented for individuals suffering from the disorder.

A study on the neuro-orchestration of sleep-wake regulation by Sulaman et al. proposed that the initiation and maintenance of the sleep state is facilitated by a de-arousal process [13]. This process entails a gradual reduction of the wake-promoting neuromodulatory tone and vigilance to the external environment. This may be achieved by repetitive pre-sleep behaviors and through proper regulation of socalled wake-on/sleep-off and wake-off/sleep-on neurons in particular brain regions, including the Locus Coeruleus (LC), Basolateral Amygdala (BLA) and the Pre-frontal Cortex (PFC) [1,13].

The process of de-arousal required for sleep, may be disturbed by certain responses following stress exposure, or when an individual remains too highly emotionally responsive to external stimuli. For example, an individual may feel high emotional distress and fear when they experience their environment as unsafe, in this (abnormally distressing) context they may feel the need to remain vigilant to respond adequately to an external threat [1]. Within this context, the de-arousal process required for sleep is suppressed as the generation of wake-systems are per-sistently generated to enable rapid response and interaction with the environment. When the context or environment is indeed abnormally stresfull or unsafe and threatening, this bodily response to the suppress de-arousal process and sleep-state can be advantageous or even necessary for survival. However, ID patients appear to respond in this way even when no threat is involved, suggesting that they are unable to properly regulate the functions of sleep-wake mechanisms in accordance to their current context and environment. This example of sleep-wake dysregulation through suppression of the de-arousal process and the sleep state, can be related to sleep-reactivity. Sleep-reactivity is a term widely referring to sleep disturbances as a response following stress exposure, and it is implicated in the prediction of ID symptom severity [1,10].

In the example, the persistent generation of wake-systems also entails continuous modulation of excitability and arousal. As arousal systems should be extensively silenced or even absent to acquire the deepest sleep stage, REMS will be most affected by this disturbed sleep response caused by the hindrance of the de-arousal process. Maladaptive functioning of this process can result in fragmented or restless REMS, rather than restful REMS, which is commonly perceived in ID patients.

Emotion Regulation

The significance of REMS's contribution to restorative sleep cannot be overstated. The interaction between emotion regulation and REMS is intricate. While REMS depends on mechanisms of emotion regulation to facilitate appropriate levels of emotional responsiveness and arousal, it also aids the proper functioning of emotion regulation by facilitating overnight adaptation when restful.

Restorative Sleep

To experience sleep as restorative, REMS must be restful. The impact on the restorative function of sleep seems to be relatively

less significant for NREMS compared to REMS, as deviations in NREMS do not affect the perception of restorative sleep to the same degree. This may be explained by one important function of REMS related to emotion regulation. During restful REMS emotional distress is neutralized and memory traces of (negative, stressful, and fearful) wake experiences are reprocessed. In this sense, restful REMS aids overnight adaptation and resolution of distress and fear memories [1]. REMS is mostly of significance for memory pro-cessing related to the amygdala. The amygdala is an essential brain region for valence consolidation, fear memory (extinction) and emotional processing [1]. This type of amygdala-related emotion- and memory (re)processing necessitates depotentiation and sleep-dependent synaptic downscaling, pruning and consolidation of new synapses formed during learning [1]. All these factors are influenced by and successful with low levels of arousal. As arousal levels are assumed to be lowest or even absent during restful REMS, it is the favored period for this type of processing [1]. It is plausible that the experience of restorative sleep depends on the success of exactly this processing, which is facilitated by restful REMS. Although REMS is a state of the sleep-wake regulation process, it is interrelated to mechanisms of the emotion regulation process. This interrelatedness is caused by REMS dependence on emotional responsiveness and arousal levels, in determining whether the state is fragmented and restless, or restful and contributive to the restorative functions of sleep.

Stress-Reactivity

Brain regions involved in the emotion regulation process include the amygdala and the PFC. Activation of the amygdala can be considered as the representation of feeling a certain emotion.

When a context or a memory elicits a high emotional feeling, amygdala activity has shown to be correspondingly high [1]. This increased activation can evoke a highly emotional response, which may be described as a disturbed stress response. However, this response can be con-trolled by the PFC which is assumed to function as a suppressor or regulator of emotions and emotional responses. Restful REMS appears to contribute to the suppressing and regulating function of the PFC, by facilitating overnight neutralization and restorative sleep. When REMS is fragmented or restless (as is the case in ID patients) it fails to sufficiently aid the PFC's regulatory functions in decreasing amygdala activity and it may even cause sensitization of the amygdala response [1]. This is confirmed by Van Someren's report on studies observing over-night changes in amygdala responses during emotional experiences through fMRI. The observations occurred while distress was induced via an upsetting stimulus pre- and post-sleep. Signifi-cant discrepancies were found between normal sleepers and highly sleep-reactive participants. In the latter, persistently high activation of the amygdala response was displayed, and sensitiza-tion occurred for those with the most fragmented REMS. This is taken as a result from insufficient occurrence of overnight adaptation [1].

Consequently, the facilitation of restorative sleep is disturbed. Disturbances in sleep in general, and in REMS specifically, can cause emotion dysregulation by increasing the evoked emotional response. This can be related to stress-reactivity. Stress-reactivity is a term widely referring to stress responses following sleep disturbances. Like sleep-reactivity, it is associated with risk of ID onset and persistence [1,10]. Both sleep- and stress-reactivity may independently and jointly predict the severity of ID symptoms, even up to a year [10]. The interaction between the reactivity measures is highly implicated in relation to the prediction of ID symptom severity. This is based on a study by Yoo et. al., which found a significant association between sleep-reactivity and ID symptoms for participants with high stress-reactivity, but not for those with low stress-reactivity [10]. These results not only elucidate that (variances in susceptibility or vulnerability to) stress can underlie insomnia, but they also confirm and suggest that disrupted sleep itself may act as a stressor and perpetuating factor of ID symptoms [1,10].

Thus, through stress-reactivity and REMS fragmentation, sleep-wake dysregulation may affect mechanisms of the emotion regulation process. In this sense, it is plausible to assume a feed-back loop between processes of emotion regulation and sleep-wake regulation in the underlying mechanisms of ID.

Interplay Between Mechanisms for Sleep-Wake Regulation and Emotion Regulation

Results from a study by Van Someren describe that emotional reactivity and altered emotion regulation pose significant risks for ID rather than being mere consequences of it [1]. This supports the assumption of the previous subsection, proposing a feedback loop between emotion regulation and sleep-wake regulation in the underlying mechanisms of ID. Van Someren also proposes that failing to neutralize emotional distress could contribute to the development and persistence of ID [1]. As discussed in the previous subsections, this failure results in REMS disturbance, but it also results from REMS disturbances. Experiencing feelings of distress and fear (memories) and their related brain processing may traverse sleep-wake circuits by activating a stress response, inducing a rapid arousal, and disturbing REMS functioning [1,10,12,13]. Insufficient inhibition of arousal and wake-systems lead to restless or fragmented REMS. This negatively affects the neutralization process, making it potentially maladaptive, resulting in failure of overnight adaptation [1]. This disturbed sleep response, relating to high sleep-reactivity, obstructs (fear) memory reprocessing and overnight emotion regulation, resulting in non-restorative sleep. The associated forms of emotional reactivity, or stress-reactivity, are visible in the amygdala.

Throughout the rest of this paper, ID is assumed to entail the absence of restorative sleep and restful REMS, and the presence of increased emotional responses to stress. The absence of re-storative sleep and restful REMS represent a maladaptive sleep-wake regulation. The underlying mechanisms involved in this sleep-wake dysregulation include increased sleep-reactivity and altered emotion regulation. Non-restorative sleep fails to suppress an increase of stress-reactivity. Stress-reactivity will therefore increasingly interact with sleep-reactivity and exacerbate disturbances in emotion regulation. This process is assumingly involved as the underlying mechanism of excessively high stress response-related ID symptoms, including considerable distress, daytime functioning impairments and anxiety-like behavior.

Insomnia: Epigenetic Regulation of Underlying Mechanisms

ID appears as a maladaptive response to stress in the form of heightened sleep-reactivity and stress-reactivity. As previously mentioned, ID patients differ from good sleepers with an occa-sional bad night, as the persisting disturbed response of ID patients does not require the current presence of a distressing context or unstable environment to elicit the response. This suggests that in ID, stress can have long-term effects on sleep. The effect of stress on sleep can be rephrased as sleep-reactivity. The field of epigenetics may provide a deeper understanding of how these long-term effects are regulated and maintained in ID.

Epigenetics: Explaining Long-Lasting Impact of Stress on Brain Plasticity

In brain activity observations of ID patients, the long-term effects of altered emotion regulation and insufficient overnight adaptations from maladaptive REMS patterns are persistently visible throughout an extensive period of time. Van Someren confirms this in his report on studies showing differences in brain activation patterns between good sleepers and ID patients [1]. While both groups responded to new negative experiences, only ID patients displayed a height-ened limbic response when recalling memories of negative experiences that had occurred in a distant past, even up to decades ago. Individuals with ID responded as if they were encounter-ing the abnormally stressful context of those distant past memories in real-time, even though their current context would not be considered abnormally stressful in general, or to an individual with healthy functioning REMS [1]. This suggests that increased emotional responses to stress are a cause and a long-term effect by failure of overnight adaptation, independently of the amount of time passing after the occurrence of a stressful experience. These results correlate to findings of adverse childhood experiences (ACEs) posing risks for ID development later in life [1,3,11].

The observed brain activation patterns of ID patients are associated with a brain plasticity-related stress response [3]. This response appears disturbed as the patterns do not behave as what would be expected or as what would generally be considered appropriate within the con-text and environment they are situated. Although the effect of stressful events on the brain may be understood by the influence of genetic predispositions, the long-lasting disturbed brain acti-vation patterns and behavior in ID cannot be explained by these predispositions solely [3].

Recent research increasingly suggest that the brain plasticity-related stress response is controlled by epigenetic mechanisms. Therefore, an explanation focused on the influence of epigenetics may provide a more comprehensive understanding of the persisting effects of stress in the de-velopment and perpetuation of ID, including the interplay between genetic and environmental factors [3]. Several studies support the idea of a potential role for epigenetics as underlying factors of ID, including the earlier mentioned study by Van Someren [1]. Palagini et al. [3] reviewed evidence for theories on the influence of epigenetic mechanisms in ID. They support the hypothesis that the development and maintenance of ID may be the result of an epigenet-ically controlled stress response-related gene-environment (G×E) interaction, with a potentially persisting impact on brain plasticity [3]. This hypothesis aids a better understanding of the po-tential risk carried by ACE's to develop ID later in life.

Epigenetic Mechanisms and microRNAs

Following the hypothesis of the previous subsection, ID may be proposed as the result of a stress response-related G×E interaction, that is mainly controlled by epigenetic mechanisms. As discussed in the introduction, considering ID as a mainly epigenetic disorder is promising as it could entail potential epigenetic reversibility of the disorder.

In health and disease, the field of epigenetics aid in an understanding of G×E interactions. The field widely refers to an influence of gene expression or function resulting from molecular or cellular alterations. These alterations are caused by environmental factors or external stimuli, including stressors [3]. Epigenetic mechanisms provoke changes in gene expression or function, without altering the gene- or DNA sequence itself. However, gene expression affected by epigenetic factors are persistently present in cells, even for extensive periods of time following the initiating event [3]. Therefore, epigenetic modifications contribute to a more comprehensive understanding of how stressful experiences, including ACEs, can cause persisting alteration in the adult brain.

MicroRNAs (miRNAs) are RNA molecules that are generally approximated to be 22 nucleotides long. MiRNAs are commonly implicated in epigenetic processes as they function in cellular differentiation and the regulation of gene expression. This is achieved by the miRNA binding to messenger RNA (mRNA) molecules and altering their translation [14]. Consequently, miRNAs may influence a process of alterations related to enzyme production and brain structure. This adaptive process can then be described as an epigenetically controlled process [3,14].

Insomnia: Underlying Mechanisms Epigenetically Controlled by miR-221

Findings from a study by Balakathiresan et al. give reason to believe that the persisting negative effects of stress on sleep in ID, also understood as sleep-reactivity, may be epigenetically controlled under the influence of the microRNA miR-221 [12]. The previous sections elucidated that distressing or fearful experiences and (maladaptive extinction of) their memories negatively affect (REM) sleep [12]. The severity of the effects of these distressing factors varies with individual differences in resilience or vulnerability to stress, related to sleep-reactivity and stress-reactivity [10,12]. The effect of these underlying factors in ID are visible as a brain plasticity-related stress response.

The basolateral amygdala (BLA) is suggested as the most important brain region affecting sleep-reactivity as it is dominant in mediating the effects of stress(full memories) on sleep in general and on REMS specifically [12]. Balakathiresan et al. identified miR-221 in the BLA as an epigenetic factor underlying and regulating its mediating effects of stress on sleep and the formation of memories potentially disrupting future sleep. Upregulation of BLA miR-221 appears to obstruct REMS. This is based on animal studies which found that altered and upregulated expressions of BLA miR-221 in vulnerable participants continuously showed significant reductions in REMS after induced stress, through shock training (ST) and after their memory of the stressful event was triggered through context re-exposure (CTX) [12]. Stress can trigger an increase in the expression of miR-221. This miRNA directly affects levels of the gene coding for stathmin1 (STMN1) and the Fos gene [12]. STMN1 modulates neural transmission and plasticity, affecting interindividual differences in emotion regulation. Elevated levels of (amygdalar) STMN1 are associated with an increase of expressed responses to stress, fear, and anxiety-like behavior, all of which are characteristics of ID symptoms [15,16]. Thus, it is plausible that ID symptoms characterized by such increased stress-responses, may be an effect of elevated STMN1 levels, influenced by miR-221 expressions.

In addition, stathmin-knockout is associated with a decrease of fos-activity in the BLA and an increase of fos-activity in the PFC, an important brain region for stress- and emotion regulation. STMN1-knockout enhances fear extinction and thus reduces the negative effects of a stressor. Reduced negative effects of stress on sleep were also visible in the study by Balakathiresan et al., when the expression of miR-221 was inhibited with an antagomir. The study showed that microinjections of AntagomiR-221 pre-ST can block reductions of REMS even after CTX in vulnerable

participants [12]. This suggests that the negative effects of stress on sleep due to upregulated miR-221expressions, may be prevented by microinjections of AntagomiR-221. However, the study only researched how AntagomiR-221 impacted the effects of stress on sleep prior to potential upregulation of miR-221. Therefore, the study remained inconclusive on evidence for the antagomir's potential to reverse the negative effects once upregulated miR-221 expression had already occurred and resulted in ID symptoms.

Despite this inconclusiveness, it is plausible that AntagomiR-221 not only inhibits expression of miR-221, but also reduces already upregulated expression of the miRNA. Consequently, this reduction could decrease ID symptoms manifested as the negative effects of stress on sleep. For the purpose of illustrating how the reversibility of epigenetically controlled disorders can be modeled, this paper will assume that ID is indeed influenced by miR-221, and that its symptoms are potentially reversible by an epigenetic therapy method via microinjections of AntagomiR-221 inverting upregulated expression of miR-221.

Notable is that Balakathiresan et al. proposed their findings relevant mostly in relation to PTSD [12]. This relevance is assumed as clinical symptoms of PTSD include stress-related sleep disturbances characterized by hyperarousal, fragmented REMS and an increased stress response when memories of negative experiences are triggered. These are the exact same characteristics of ID. As discussed in the introduction, ID has an intricate bidirectional relation with other psychiatric disorders, including PTSD. It appears that the stress-related sleep disturbance that Balakathiresan et al. propose as a PTSD symptom, is actually a description of the stress-related sleep disorder ID, manifested as a common factor and transdiagnostic process related to PTSD. Moreover, Balakathiresan et al. do not study the influence of epigenetics and miR-221 on any other PTSD symptoms beyond the described stress-related sleep disturbance. PTSD is not necessarily present in the study participants and the study objectives and methods are not related to PTSD but to the effects of stress on sleep which are visible as the brain plasticity related stress response of ID. Thus, the relevance of this study does not pertain exclusively to PTSD and may be better related to the development and persistence of ID. Therefore, considering these factors, the findings by Balakathiresan et al. support the hypothesis that epigenetic factors do indeed play a significant role in regulating the effects of stress on sleep, and consequently in the processes underlying the development and maintenance of ID [12]. As altered expressions of BLA miR-221 affect STMN1 and thereby affect how stress influences the sleep-wake regulation in general and REMS specifically, this paper will focus on the influence of miR-221 as a significantly influential epigenetic factor of ID, since dysregulation of REMS and emotional responses to stress are already established as underlying factors in the previous sections.

Adaptive Dynamical Systems Modeled as Adaptive Networks

The underlying mechanisms of ID and the epigenetic processes that regulate it are dynamic. They involve adaptivity on multiple levels and form a higher-order dynamical system. The principles and concepts introduced in [8]. are suitable for the purpose of designing higher-order adaptive dynamical system models. This includes models designed to analyze the dynamics of epigenetics in mental disorders as has been proposed for GAD in Kathusing et al. [17]. This approach makes use of temporal-causal network (TCN) models that can be defined by three types of network characteristics: connectivity characteristics, aggregation characteristics, and timing characteristics. Connectivity characteristics refer to connections and connection weights between the nodes or states of a network. A connection $X \rightarrow Y$ from state X to state Y describes the causal impact that X has on Y, and the connection weight $\boldsymbol{\omega}_{X,Y}$ describes the strength or weight of that impact. Aggregation characteristics refer to combination functions cy, combination function weights $\boldsymbol{\gamma}_{i,Y}$, and combination function parameters $\boldsymbol{\pi}_{i,j,Y}$. For each node Y, $\mathbf{c}_Y$ describes how the causal impacts on Y are aggregated. The timing characteristics refer to the speed factors $\boldsymbol{\eta}_Y$ which describes the speed by which each state Y changes upon aggregated impact. The dynamicity of TCNs is visible through changing activation values of the states or nodes. At time point t, state X has an activation value $X(t)$ which may change over time. Through the causal impact that state X has on another state Y, it affects the activation value $Y(t)$. Based on the network characteristics the following canonical difference equation defines the dynamics of the network states (resembling the format of recurrent neural networks):

$$\boldsymbol{Y(t+\Delta t) = Y(t) + \eta_Y\big[\mathbf{c}_{\pi_{Y,Y}}(\omega_{X_1,Y}X_1(t), \ldots, \omega_{X_k,Y}X_k(t)) - Y(t)\big]\Delta t} \quad (1)$$

Here, state Y receives causal impacts from the incoming connections of states X_1 to X_k.

The model utilizes a software environment which includes a library of 70 basic combination functions applicable to the model design process. The environment and functions are outlined in (Treur, 2020a, Ch. 9). The ID model proposed in this paper uses three of these basic functions; $\mathbf{steponce}_{\alpha,\beta}(V)$, $\mathbf{stepmod}_{\rho,\delta}(V)$, and the advanced logistic sum function $\mathbf{alogistic}_{\sigma,\tau}(V_1, \ldots, V_k)$. The function $\mathbf{alogistic}_{\sigma,\tau}(V_1, \ldots, V_k)$ is applied to all states except those meant as context factors where activity should occur only at specific time points or intervals. To address these exceptions, the functions $\mathbf{steponce}_{\alpha,\beta}(V)$ and $\mathbf{stepmod}_{\rho,\delta}(V)$ are utilized, as these allow for precise control over timing and periodicity. In this model, these functions model the states for context factors labeled as $\mathrm{con}_{\mathrm{sleepdrive}}$, $\mathrm{con}_{\mathrm{abnormalstress}}$, and $\mathrm{con}_{\mathrm{therapy}}$, where activity modulation based on specific timing is crucial and appropriately constrained. The advanced logistic sum function, $\mathbf{alogistic}_{\sigma,\tau}(V_1, \ldots, V_k)$, is widely applied due to its flexibility in setting adjustable parameters for both steepness σ and excitability thresholds τ. This function effectively models the non-linear dynamics and saturation effects often characteristic of stress responses and physiological processes central to ID, which frequently exhibit threshold or ceiling effects. Moreover, $\mathbf{alogistic}_{\sigma,\tau}(V_1, \ldots, V_k)$ is a self-normalizing function, ensuring outputs remain within the 0-1 range. As all states are modeled within a 0-1 range, a normalized scale is used that allows for standardized comparisons of state interactions. The formulas of the used combination functions are described in Table 1. It should be noted that a cut-off at 0 is applied when a negative value is produced by the advanced logistic sum function formula for intended positive values. The software environment executes a set of n difference equations based on (1), where n corresponds to the total number of states in the network, and specific values are applied to Equation (1) based on the network characteristics of each state Y.

Adaptive network characteristics can be achieved by the self-modeling or reification principle introduced in (Treur, 2018; Treur, 2020a), which entails adding a self-model state for the adap-tive characteristic to the network. The model introduced in this paper uses the self-modeling principle for connectivity characteristics in particular. Self-model states $\mathbf{W}_{X,Y}$ are applied to represent adaptive connection weights $\boldsymbol{\omega}_{X,Y}$ by means of the self-modeling principle. This ensures the network's ability to model itself regarding its own connectivity. These connectivity self-model states have incoming

and outgoing connections as any other state. The incoming connections represent the causal impact placed onto them. The outgoing connections from **W** states to others, effectuate casual impact on the concerning affected states. The latter is achieved by applying value $\mathbf{W}_{X,Y}(t)$ for $\boldsymbol{\omega}_{X,Y}$ in Equation (1). If this was applied to all connection weights $\boldsymbol{\omega}_{Xi,Y}$, then Equation (1) results in:

$$\boldsymbol{Y(t+\Delta t) = Y(t) + \eta_Y \left[c_{\pi_Y,Y} (\mathbf{W}_{X_1,Y}(t) X_1(t), \ldots, \mathbf{W}_{X_k,Y}(t) X_k(t)) - Y(t) \right] \Delta t} \quad (2)$$

The network characteristics for the self-model states can themselves be adaptive as well. In that case, the self-modeling principle is applied to the self-model states, and higher-order self-model states are added to the network. If the self-model state $\mathbf{W}_{X,Y}$ has an incoming connection from a context state c, and the weight $\boldsymbol{\omega}_{c,\mathbf{w}_{X,Y}}$ with which c impacts $\mathbf{W}_{X,Y}$ is also adaptive, then the adaptivity of $\boldsymbol{\omega}_{c,\mathbf{w}_{X,Y}}$ can be represented by a second-order self-model state $\mathbf{W}_{c,\mathbf{w}_{X,Y}}$. Iterations of this will be applied to obtain multiple orders of adaptation. The self-model states of each successive order influence the adaptive characteristics of the pathways in the order below, acting as a form of control that can in the end potentially exacerbate or mitigate ID symptoms.

The Introduced Higher-Order Adaptive Network Model

This section introduces a fifth-order adaptive pathway framework to conceptualize the higher-order adaptive dynamical system of interactions between environmental factors, and mental, and biological processes in ID, according to the self-modeling dynamical system network principles described by Treur [8]. The network is designed to model the development and persistence of ID influenced by upregulated expressions of miR-221, and the potential reversibility of ID influenced by a proposed epigenetic therapy method of AntagomiR-221 microinjections, following from the previous sections.

Table 1: The Three Combination Functions Used in Proposed Model for ID

	Notation	Formula	Parameters
Advanced logistic sum	$\mathbf{alogistic}_{\sigma,\tau}(V_1, \ldots, V_k)$	$[\frac{1}{1+e^{-\sigma(V_1+\cdots+V_k-\tau)}} - \frac{1}{1+e^{\sigma\tau}}](1+e^{-\sigma\tau})$	Steepness σ Excitability threshold τ
Steponce	$\mathbf{steponce}_{\alpha,\beta}(V)$	1if $\alpha \le t \le \beta$ 0 else	Time t Start α End β
Stepmod	$\mathbf{stepmod}_{\rho,\delta}(V_1, \ldots, V_k)$	0 if t mod $\rho < \delta$, else 1	Repetition ρ Tipping point δ

The model includes an emotion regulation process based on Treur, Section 3.3 that is linked to sleep-wake regulation processes regarding REMS, restorative sleep, and stress- and sleep-reactivity. It provides a mechanism trying to suppress excessive emotional responses to avoid hindrance of the de-arousal process which would otherwise result in ID as a lack of restful REMS and restorative sleep, exacerbating the stress response. Here, a part of the PFC detecting the presence of undesired emotional distress levels, which as a form of regulation it will try to suppress. The suppressing function of the PFC is aided by a state representing restful REMS, and it will fail when restful REMS is too weak, and stress-reactivity is too strong. This is the case when inhibition of wake-systems is too weak and vigilance and arousal are too high for REMS to neutralize emotional distress and reprocess distressing memories. The initiation of REMS is facilitated by a context state representing sleep-drive following the 16:8 hours structure of the general wake-state, this is orchestrated by the function $\mathbf{stepmod}_{\rho,\delta}(\ldots)$. REMS activation is required to facilitate the restorative sleep state but is negatively impacted by high emotional responses and sleep-reactivity. Restorative sleep is also negatively impacted by sleep-reactivity, but it will suppress stress- and sleep-reactivity when its activation is strong. The mechanism suppressing ID symptoms will fail when the interaction between stress- and sleep-reactivity, and the negative effects of stress on (REM) sleep become too strong. Functioning and connectivity of this mechanism is influenced by the adaptive epigenetic processes. The model uses five levels of adaptation to conceptualize this influence in the form of higher-order self-modeling states. Here, control is exuded over the adaptations impelled by changes in environmental circumstances resulting in alterations in certain pathways. An overview including all states of all levels and their explanations can be found in Table 2 and Table 3.

Kathusing et al. adopted the self-modeling network modeling approach for multilevel adaptive connectivity characteristics as has been developed earlier in [8,18]. to model the evolution of pregnancy and first-trimester disgust [17]. Here, evolutionary processes are broadly imagined as adaptation mechanisms establishing new causal pathways that control existing ones by altering the strength of the causal connections within these pathways. This occurs as a response to shifting environmental conditions, where organisms with more profitable causal pathways are fa-vored, and subsequently dominate the population [17]. In the self-modeling network architecture connection weights in causal pathways are represented by self-model states across subse-quent levels. This resonates with the concept of evolutionary adaptions of causal pathways modulating existing ones [17,18].

In line with this interpretation, Kathusing et al.delineated five adaptation levels which have been adopted here for ID as well:

- **1st order adaptive self-model** The maintenance and strengthening of connections between neurons, modulated by enzymes. Represents adaptive processes in the neuronal circuitry involved in emotion- and sleep-wake regulation
- **2nd order adaptive self-model** Production of the enzyme responsible for the connections involved in the disturbed brain plasticity related stress response in ID. This is modulated by mRNA.
- **3th order adaptive self-model** Production of the mRNA that will incite protein synthesis by conveying genetic information. Its causal pathways affect the causal pathways for the enzyme. This is regulated by expressed genes in the DNA.
- **4th order adaptive self-model** Represents the expression of genes affected by miR-221, here STMN1 with additional associations to Fos are assumed. This modulates the causal pathways for mRNA production.
- **5th order adaptive self-model** Represents miR-221 assumed to be responsible for the regula-tion of STMN1. Its causal pathways affect the causal pathways for STMN1 [17].

Table 2: Explanation of all States Contained Across Five Levels of Adaptation Orders Indicated by Color: Base and First-Order Self-Model Level

State nr	State Name	Biological Concept	Explanation	Level
$X1$	con_{stress}	Normal stress context	Context state for normal stress stimulus s	Base level
$X2$	ss_s	Sensory organ	Sensor state for stimulus s	
$X3$	srs_s	Sensory representation	Sensory representation state for stimulus s	
$X4$	fs_b	Amygdala	Feeling state: person feels stress, fear, and arousal emotions b	
$X5$	ps_b	Emotional response	Emotion state: person prepares for emotional response b, vigilance, arousal, stress	
$X6$	pfc_b	Prefrontal cortex	Regulating state for response b	
$X7$	rem	Restful REMS. Deepest sleep stage lowest/absent arousal levels. Overnight adaptation	Semi-control /REMS state: person enters and completes restful REMS. Aids in regulation of emotional response and feeling. Main contributor to restorative sleep. Negatively affected by high emotional response of fear, stress, arousal, and vigilance and by sleep-reactivity.	
$X8$	slr	Sleep-reactivity	Sleep-reactivity state: person has tendency to follow and react to stress with disturbed sleep, negatively affects REMS and restorative sleep and interacts with stress-reactivity to predict insomnia. Can be reduced by restorative sleep	
$X9$	str	Stress-reactivity	Stress-reactivity state: person has tendency to follow and react to sleep disturbance with stress response, negatively affects emotional stress response and interacts with sleep reactivity in predicting insomnia. Can be reduced by restorative sleep	
$X10$	rslp	Restorative sleep	Restorative sleep state: person experiences sleep as restorative in which fear memories and emotional distressing events are neutralized after overnight adaptation has occured. Positive associations to sleep are formed.	
$X11$	$con_{sleepdrive}$	Sleep drive context	Context state for sleep drive: person feels need to sleep trying to initiate and complete restful REMS	
$X12$	$con_{abnormalstress}$	Abnormal stress context	Context state for abnormal stress stimulus s	
$X13$	$con_{connection}$	Context for connectivity development	Context state for connectivity of neurons in the brain and neuromodulatory tone and circuits involved with emotion- and sleep-wake-regulation. Associated with brain plasticity stress response	First-order Self-mod-el level
$X14$	$\mathbf{W}fs_b,slr$	Connectivity of neurons and states	Self-model state for baselevel connection weight $\boldsymbol{\omega}fs_b,slr$	
$X15$	$\mathbf{W}str,slr$	Connectivity of neurons and states	Self-model state for baselevel connection weight $\boldsymbol{\omega}str,slr$	

Table 3: Explanation of all States Contained Across Five Levels of Adaptation Orders Indi-cated by Color: Second- to Fifth-Order Self-Model Level

State nr	State name	Biological Concept	Explanation	Level
$X16$	con_{enzyme}	Context for enzyme production	Context state enabling enzyme production	Second-order Self-model level
$X17$	$\mathbf{W}_{con_{connection}},\mathbf{W}$	Influence of enzymes re-sponsible for ID, brain plasticity re-lated stress response	Self-model state for first self-modelling level con-nection from conconnection for context to W for Wfsb,slr and Wstr,slr; on a causal pathway from conenzyme	Second-order Self-model level
$X18$	con_{mrna}	Context for mRNA pro-duction	Context sate enabling mRNA production	Third-order Self-model level
$X19$	$\mathbf{W}con_{enzyme},\mathbf{W}con_{connection},\mathbf{W}$	Influence of mRNA re-sponsible for ID, brain plasticity re-lated stress response	Self-model state for the weight of the second self-modelling level connec-tion from con_{enzyme} to $Wcon_{connection}$,W for $\mathbf{W}fs_b$, str to slr; on a causal path-way with a connection from conmrna	
X20	con_{dna}	Context for DNA han-dling	Context state for SMT1 gene	

X21	$\mathbf{W}_{con_{mrna}}, \mathbf{W}_{con_{enzyme}}, \mathbf{W}_{con_{connection}}, \mathbf{W}$	Influence of STMN1	Self-model state for the weight of the third self-modelling level state controlling connectivity in lower orders; on a causal pathway with a connection from con_{dna}	Fourth-order Self-model level
X22	con_{mir221}	Context for epigenetic processes of miR-221	Context state enabling altered expression of epigenetic factor miR-221	
X23	$\mathbf{W}_{con_{da}}, \mathbf{W}_{con_{mrna}}, \mathbf{W}_{con_{enzyme}}, \mathbf{W}_{con_{connection}}, \mathbf{W}$	Influence of miR-221 expression	Self-model state for the weight of the fourth self-modelling level state controlling connectivity in lower orders; on a causal pathway with a connection from con_{mir221}	Fifth-order Self-model level
X24	$con_{therapy}$	Context for epigenetic therapy AntagomiR-221	Context state enabling inhibition and reduction in expression of epigenetic factor miR-221	

Figure 1 presents these levels in a graphical representation of the network model. The upper level (5th order self-model) contains the epigenetic influence of miR-221 expressions exuded onto the next-lower order. This influence in turn causes a dysregulation of operations in the lower levels by the effect of adaptations when this level's working is disturbed due to upregulated miR-221 expressions triggered by (abnormal) stress. Application of the model can be divided into two scenarios. The first would not involve an effect of therapy and only show the effect of upregulated miR-221 expressions in ID development and persistence. This would entail that in Figure 1 contherapy can be disregarded along with its corresponding connections. The second scenario would include the effect of $con_{therapy}$ and consider the state and its corresponding values and connections in Figure 1. This will show downregulation of miR-221 expression following ID developed in the first scenario. The entire model (combination of Scenario 1 and 2) considers the effects of the therapy state, but only activates it via the function $\mathbf{steponce}_{\alpha,\beta}(.)$ after ID has already persisted for a certain amount of time.

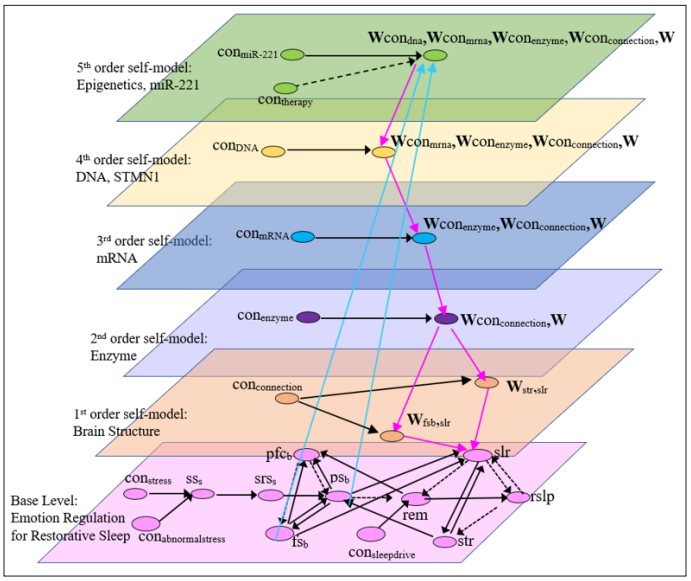

Figure 1: Overview of the network model for development, persistence, and reversibility of ID.

The states of the model are represented by the ovals in Figure 1. The connections between them are indicated by the arrows and the direction of the causal impact by their end. The dotted ar-rows represent a negative connection where the causal impact has a suppressing effect on the impacted state. The solid black arrows represent positive connections. As discussed in Section 2, W-states for connectivity self-modeling states can effectuate causal impacts on the concerning affected states, the pink downward arrows represent these outgoing impacts. The causal incoming impact placed onto them enables the desired dynamics, the blue and black arrows repre-sent these incoming upward or leveled connections. More specifically, different types of states occur in the model, including context states (con), sensor states (ss), sensory representation states (srs), preparation states (ps), feeling states (fs), control states (pfc), semi-control states (rems) and self-model **W**-states. They represent: an external stimulus or contextual environment (con), sensing of the stimulus (ss), sensory/mental representation of stimulus (srs), preparation to express particular response as a body state (ps), feeling particular emotion (fs), regulation or neutralization of particular emotion or response and regulation of restorative function of sleep (pfc, rems). Tables 2 and 3 include a description for all states in more detail, see also the Appendix Section 8.

Results

Simulation Experiments

The dedicated software environment described in was used to illustrate the simulation process of the computational model for the influence of epigenetics in the development, persistence and potential reversibility of ID [8]. Figure 2 shows the process. Here the horizontal axis represents time and the vertical axis activation level. In the 5 colums legend of Figure 3, the left three colums refer to 9 base level states X2 to X10, the fourth column to first-order self-model states X14 and X15 and second-order self-model state X17, and the last column to third-, fourth-, and fifth-order self-model states X19, X21, and X23, respectively.

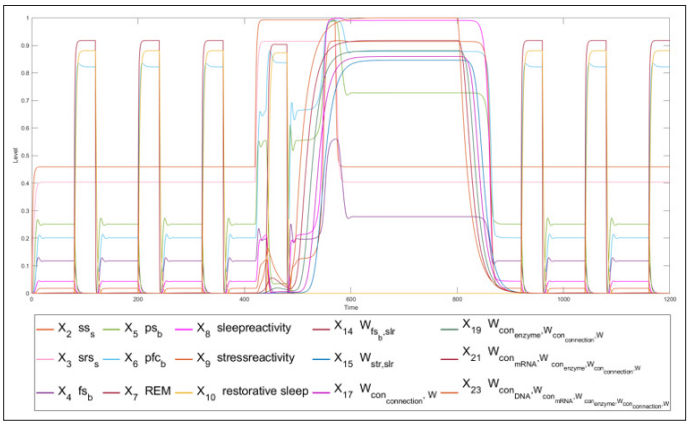

Figure 2: Simulation for the Model of Epigenetics in ID Development, Persistence and Potential Reversibility. The context States are not Depicted.

In the model, a baseline level of stress is introduced by the context state constress which is set to remain stable at 0.5 at all times. This represents the context of a 'normal' stress stimulus which an individual likely encounters on an everyday basis. However, the manner in which an individual responds to such everyday stress stimuli can variate. This variability is visible in the lines representing the states of underlying mechanisms of emotion- and sleep-wake regulation. The lines representing the context states are excluded from Figure 2 to enhance visibility for a de-tailed analysis in the dynamics of relevant underlying mechanisms of ID and variability in re-sponse to stress. Here, only the lines representing states related to mechanisms of the emotion regulation process, sleep-wake regulation process, and the adaptation processes are displayed.

Figure 2 shows that significant disturbances in these processes only begin to occur when the influence of miR-221 and epigenetic processes is exuded. From timepoints 0 – 445 all lines representing the connectivity self-modeling states (and the influence of epigenetic processes) remain stable at value 0. Beyond this timepoint, activation of $\mathbf{W}con_{dna}$,$\mathbf{W}con_{mrna}$,$\mathbf{W}con_{enzyme}$,$\mathbf{W}con_{connection}$,$\mathbf{W}$ is triggered by increased levels of ps_b and fs_b following $con_{abnormalstress}$. This is visible in Figure 3 when t approximates 500. This leads to the observable activation of the **W** states in all orders of adaptation, this involves higher activation levels for genes affected by miR-221, and for mRNA and enzyme production. These increases stabilize around $t = 570$ and $t = 600$ but the levels remain high (all > 0.8). Activation of $\mathbf{W}_{conconnection}$,$\mathbf{W}$ causes an increase in the levels of $\mathbf{W}_{str,slr}$ and $\mathbf{W}_{fs_b,slr}$ and the causal impacts of the affected baselevel states on one another become stronger as their levels also increase. From this point, levels of ps_b, fs_b, pfc_b, str and slr all significantly increase. The negative causal impacts on REMS and restorative sleep become too strong such that after the last REMS and rslp episode ends around $t = 445$, the levels of these states fail to increase again and remain around value 0. As rslp activity remains absent, str levels stay high due to a lack of the normally suppressing impact from rslp. Although pfc_b levels are increased, ps_b and fs_b levels remain excessively high. This indicates that the suppressing and regulatory function of pfc_b is failing due to a lack of aid from REMS and increased levels of ps_b due to increased str. From this point on, the individual behaves according to the disturbed brain plasticity related stress response and displays ID symptoms. This behavior persists even after $con_{abnormalstress}$ ends at $t = 570$. Between timepoints 570 – 800 the levels of all higher-order self-modeling states have stabilized at a high point between 0.78 and 1.0) which entails that the influence of the epigenetic processes remains visible and miR-221 expressions remain highly upregulated. During this period all characteristics of ID are visible; low REMS and rslp levels < 0.005, high str and slr levels > 0.75, relatively high fsb levels > 0.25, compared to < 0.14 prior to $t = 420$, excessive high psb level >0.7 while ss_s and srs_s are around 0.5 as *s* is also at 0.5 with con_{stress}.

Discussion

This paper introduced a higher-order adaptive dynamical system model based on principles described in [8,18]. The fifth-order adaptive self-modeling network is an integrative model as it covers modeling of environmental, biological and mental processes. The model's design is based on an empirical literature research of which the findings are extensively discussed in sec-tions 2-5. The introduced network model was able to effectively simulate the interplay of un-derlying mechanisms in ID while considering the influence of epigenetic factors (related to miR-221 expressions) in ID development, persistence and reversibility. Some other approaches have been proposed in the design of other computational models relating to epigenetic influences in disorders, including the previously mentioned study on GAD [17]. Despite the use of a similar generic multilevel control architecture, currently no other (computational) model has been found in which the factors described in this paper are integrated to model their dynamic and adaptive interplay and influences in ID.

Limitations of this study mostly relate to simplifying assumptions that were made, as is often needed in computational models. The assumptions regarding epigenetic regulation are mostly based on Balakathiresan et al. [12]. As mentioned, this was a study based on animal models and the study methods were applied to rats. Although shared features in brain physiology between these animals and humans exists, the known dissimilarities related to complexity and mediating factors complicate the generalization of these findings. Other simplifying assumptions were made regarding the presence of stress stimuli. The model integrates a rhythm of dedicated times intended for wakefulness and sleep, but it does not apply a similar rhythm for the presence of everyday stress stimuli. Therefore, the levels relating to the context for normal stress, the sensing of that stress stimulus, and the sensory representation of that stimulus, are assumed identical across times intended for both wakefulness and for sleep. An extension of the model could include dynamicity in the constress state or the sss and srss states to further explore the application of such a rhythm. Some known factors related to risk of ID development were excluded, such as the sex of the individual. It has been established that ID is more likely to develop in women [1,3]. In future studies it may be interesting to include this factor.

The model incorporates a negative effect of sleep-reactivity on both REMS and restorative sleep, thereby allowing for the potential possibility that NREMS is also influenced by sleep-reactivity and subsequently impacts restorative sleep. Moreover, this remains the sole instance within the model where NREMS could potentially exert an influence, due to indications in the literature suggesting its less significant role in ID. Opportunities for enhancing the network model in future research may arise with more detailed insights into the specific impacts of both NREMS and REMS regarding a combination of several ID symptoms, including (non)restorative sleep. Additionally, the model could be enhanced by including processes in brain regions beyond the (basolateral) amygdala and PFC. For example, the BDNF levels in the LC have been suggested by Van Someren to be influential in ID development and REMS dysregulation [1]. It may also be interesting to study the influence of other miRNAs, such as miR-132 which has also been mentioned by Palagini et al. and may potentially be implicated in BDNF levels [3].

The model studies adaptation of connectivity related network characteristics. With more detailed insights available, the model could potentially be enhanced by increasing independence in the adaptivity of these network characteristics. Additionally, it may be interesting to model adaptations of other network characteristics as biological, mental, and environmental factors often involve adaptivity of multiple types. Modeling the influence of therapy methods beyond epigenetic regulation, such as CBT-I, may be an interesting addition to the network. As the aim was to model the potential epigenetic reversibility of ID, such therapy methods were excluded from this paper.

Overall, this study aimed to bridge a gap in (computational) modeling of the interrelatedness of operations involved in both emotion regulation and sleep-wake regulation processes in ID. Therefore, this study may have provided valuable insights into (epigenetic regulation of) ID's complex bidirectional relation with other psychiatric disorders as it highlighted the perpetuation of disturbances known to be implicated in both ID and several other psychiatric disorders, in-cluding GAD and PTSD.

The model provides a flexible framework to test hypotheses regarding IDs underlying mechanics and can be adapted for various experimental setups. It can simulate the potential effects of genetic or epigenetic interventions, such as miR-221 modulation, on ID symptoms. Additionally, this framework could guide the design of future empirical studies, such as fMRI or genetic studies, by identifying relevant biologicamarkers and brain regions implicated in ID. Its adaptable structure can incorporate additional processes as empirical knowledge advances, reinforcing its utility.

For the adaptive network modelling approach that was applied, in it has been shown how any smooth adaptive dynamical system can be represented in self-modelling temporal-causal net-work format [9, 19]. So, in line with this and also following the suggestion in Nigg to apply dynamical systems modelling, the self-modelling network modelling approach has been success-fully applied to computationally analyse the role of epigenetics in a variety of disorders, for example, see [17, 20-24]. A six level dynamical system architecture was used as basis, with five orders of control. From these levels, four of them correspond to the control levels (related to DNA, mRNA, enzymes, physiology) distinguished often in biological literature such as [25]. The epigenetic control level to control gene expression was added on top of that and at the lowest level a distinction was made between physiological structure and (mental) process shaped by the physiological structure, following Treur [26]. The importance of such control levels within biology was also emphasized recently from a philosophical perspective in [27,28].

Appendix Detailed Design

To simulate the processes of the network model, it should be executable in the dedicated soft-ware environment MATLAB. To this effect, a detailed representation is designed in terms of role matrices as described in Treur [8]. The full specification of these role matrices can be found in Appendix A. The included role matrices represent a specification of the network characteristics based on the conceptual representation of subsection 5.2 and are structured as follows:

Connectivity characteristics

- **mb:** Base Connectivity
- **Mcw:** Connection Weights **ω**

Aggregation characteristics

- **mcfw:** Combination Function Weights **γ**
- **mcfp:** Combination Function Parametes **π**

Timing characteristics

- **ms:** Speedfactors **η**
- **iv:** Initial Values of the State

In the matrices, each row represents a state X_i. In each row of the role matrices it is indicated which other states from that role affect X_i by the pink cells. For example, in **mb** the incoming connections for the state X_i of that row are effectuated from the states represented in the pink cells. The values affecting X_i are represented by the green cells. For example, the role matrix **mcw** relates to connection weights **ω**, it has already been established that this network characteristic is adaptive in some cases. This entails that **ω** between some states are determined by a value, and some by a self-model state. The green cells in **mcw** indicate the value of the weight for the connection between X_i of that row, and the connected state in that same cell as indicated in **mb** [17]. The (self-model) states X_j modulating the adaptive connection weight between connected states indicated in that same cell in mb, are represented in the pink cells of **mcw** [29-33].

mb	base connectivity	1	2	3	4	5
X_1	con_{stress}	X_1				
X_2	ss_s	X_1	X_{12}			
X_3	srs_s	X_2				
X_4	fs_b	X_5	X_6			
X_5	ps_b	X_3	X_4	X_6	X_9	
X_6	pfc_b	X_4	X_5	X_7		
X_7	rem	X_5	X_8	X_{11}		
X_8	slr	X_4	X_5	X_9	X_{10}	
X_9	str	X_8	X_{10}			
X_{10}	rslp	X_7	X_8			
X_{11}	$con_{sleepdrive}$	X_{11}				
X_{12}	$con_{abnormalstress}$	X_{12}				
X_{13}	$con_{connection}$	X_{13}				
X_{14}	$\mathbf{W}fs_b$,slr	X_{13}				
X_{15}	**W**str,slr	X_{13}				
X_{16}	con_{enzyme}	X_{16}				
X_{17}	$\mathbf{W}_{conconnection}$,**W**	X_{16}				
X_{18}	con_{mrna}	X_{18}				
X_{19}	$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection}$,**W**	X_{18}				

X_{20}	con_{dna}	X_{20}				
X_{21}	$\mathbf{W}_{conmrna}$,$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection}$,$\mathbf{W}$	X_{20}				
X_{22}	con_{mir221}	X_{22}				
X_{23}	$\mathbf{W}_{condna}$,$\mathbf{W}_{conmrna}$,$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection}$,$\mathbf{W}$	X_{23}	X_4	X_5	X_{24}	X_{22}
X_{24}	$con_{therapy}$	X_{24}				

mcw	connection weights	1	2	3	4	5
X_1	con_{stress}	1				
X_2	ss_s	1	1			
X_3	srs_s	1				
X_4	fs_b	1	-0.5			
X_5	ps_b	1	1	-1	1	
X_6	pfc_b	1	1	1		
X_7	rem	-1	-0.5	1		
X_8	slr	X_{14}	1	X_{15}	-1	
X_9	str	1	-0.5			
X_{10}	rslp	1	-0.5			
X_{11}	$con_{sleepdrive}$	1				
X_{12}	$con_{abnormalstress}$	1				
X_{13}	$con_{connection}$	1				
X_{14}	$\mathbf{W}fs_b$,slr	X_{17}				
X_{15}	$\mathbf{W}$str,slr	X_{17}				
X_{16}	con_{enzyme}	1				
X_{17}	$\mathbf{W}_{conconnection}$,$\mathbf{W}$	X_{19}				
X_{18}	con_{mrna}	1				
X_{19}	$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection}$,$\mathbf{W}$	X_{21}				
X_{20}	con_{dna}	1				
X_{21}	$\mathbf{W}_{conmrna}$,$\mathbf{W}_{conenzyme}$, $W_{conconnection}$,$\mathbf{W}$	X_{23}				
X_{22}	con_{mir221}	1				
X_{23}	$\mathbf{W}_{condna}$,$\mathbf{W}_{conmrna}$,$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection}$,$\mathbf{W}$	1	0.5	0.5	-1	1
X_{24}	$con_{therapy}$	1				

mcfw	combination function weights	alogistic	steponce	stepmod
X_1	con_{stress}	1		
X_2	ss_s	1		
X_3	srs_s	1		
X_4	fs_b	1		
X_5	ps_b	1		
X_6	pfc_b	1		
X_7	rem	1		
X_8	slr	1		
X_9	str	1		
X_{10}	rslp	1		
X_{11}	$con_{sleepdrive}$			1
X_{12}	$con_{abnormalstress}$		1	
X_{13}	$con_{connection}$	1		
X_{14}	$\mathbf{W}fs_b$,slr	1		
X_{15}	$\mathbf{W}$str,slr	1		

X_{16}	con_{enzyme}	1		
X_{17}	$\mathbf{W}_{conconnection,W}$	1		
X_{18}	con_{mrna}	1		
X_{19}	$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection,W}$	1		
X_{20}	con_{dna}	1		
X_{21}	$\mathbf{W}_{conmrna,}\mathbf{W}_{conenzyme,}$ $\mathbf{W}_{conconnection,W}$	1		
X_{22}	con_{mir221}	1		
X_{23}	$\mathbf{W}_{condna,}\mathbf{W}_{conmrna,}\mathbf{W}_{conenzyme,}$ $\mathbf{W}_{conconnection,W}$	1		
X_{24}	$con_{therapy}$		1	

mcfp	**combination function parameters**	**alogistic**		**steponce**		**stepmod**	
function		1		2		3	
parameter		**σ**	**τ**	**α**	**β**	**ρ**	**δ**
X_1	con_{stress}	5	0.5				
X_2	ss_s	5	0.5				
X_3	srs_s	5	0.5				
X_4	fs_b	5	0.4				
X_5	ps_b	5	0.5				
X_6	pfc_b	5	0.6				
X_7	rem	5	0.5				
X_8	slr	5	0.8				
X_9	str	5	0.5				
X_{10}	rslp	5	0.5				
X_{11}	$con_{sleepdrive}$					120	80
X_{12}	$con_{abnormalstress}$			420	570		
X_{13}	$con_{connection}$	5	0.5				
X_{14}	$\mathbf{W}_{fsb,slr}$	5	0.5				
X_{15}	$\mathbf{W}_{str,slr}$	5	0.5				
X_{16}	con_{enzyme}	5	0.5				
X_{17}	$\mathbf{W}_{conconnection,W}$	5	0.5				
X_{18}	con_{mrna}	5	0.5				
X_{19}	$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection,W}$	5	0.5				
X_{20}	con_{dna}	5	0.5				
X_{21}	$\mathbf{W}_{conmrna,}\mathbf{W}_{conenzyme,}$ $\mathbf{W}_{conconnection,W}$	5	0.5				
X_{22}	con_{mir221}	5	0.5				
X_{23}	$\mathbf{W}_{condna,}\mathbf{W}_{conmrna,}\mathbf{W}_{conenzyme,}$ $\mathbf{W}_{conconnection,W}$	20	1.5				
X_{24}	$con_{therapy}$			800	950		

ms	speedfactors	1
X_1	con_{stress}	0
X_2	ss_s	0.5
X_3	srs_s	0.5
X_4	fs_b	0.3
X_5	ps_b	0.5
X_6	pfc_b	0.5
X_7	rem	10
X_8	slr	0.5
X_9	str	0.5
X_{10}	rslp	0.5
X_{11}	$con_{sleepdrive}$	2
X_{12}	$con_{abnormalstress}$	2
X_{13}	$con_{connection}$	0
X_{14}	$\mathbf{W}fs_b,slr$	0.1
X_{15}	$\mathbf{W}str,slr$	0.1
X_{16}	con_{enzyme}	0
X_{17}	$\mathbf{W}_{conconnection},\mathbf{W}$	0.1
X_{18}	con_{mrna}	0
X_{19}	$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection},\mathbf{W}$	0.1
X_{20}	con_{dna}	0
X_{21}	$\mathbf{W}_{conmrna},\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection},\mathbf{W}$	0.1
X_{22}	con_{mir221}	0
X_{23}	$\mathbf{W}_{condna},\mathbf{W}_{conmrna},\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection},\mathbf{W}$	0.05
X_{24}	$con_{therapy}$	2

ms	**speedfactors**	**1**
X_1	con_{stress}	0.5
X_2	ss_s	0
X_3	srs_s	0
X_4	fs_b	0
X_5	ps_b	0
X_6	pfc_b	0
X_7	rem	0
X_8	slr	0
X_9	str	0
X_{10}	rslp	0
X_{11}	$con_{sleepdrive}$	0
X_{12}	$con_{abnormalstress}$	0
X_{13}	$con_{connection}$	1
X_{14}	$\mathbf{W}fs_b,slr$	0
X_{15}	$\mathbf{W}str,slr$	0
X_{16}	con_{enzyme}	1
X_{17}	$\mathbf{W}_{conconnection},\mathbf{W}$	0
X_{18}	con_{mrna}	1
X_{19}	$\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection},\mathbf{W}$	0
X_{20}	con_{dna}	1
X_{21}	$\mathbf{W}_{conmrna},\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection},\mathbf{W}$	0
X_{22}	con_{mir221}	1
X_{23}	$\mathbf{W}_{condna},\mathbf{W}_{conmrna},\mathbf{W}_{conenzyme}$, $\mathbf{W}_{conconnection},\mathbf{W}$	0
X_{24}	$con_{therapy}$	0

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