

THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

**The FNDC5/irisin/BDNF axis, as a modulator of
reinforcement learning and mood in health and disease**

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“Nothing is impossible; there are ways that lead to everything, and if we had sufficient will, we should always have sufficient means.”

François VI, duc de La Rochefoucauld

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1 Abbreviations

Akt – protein kinase B

AP – associative pallidum

ApoA1 – apolipoprotein A1

ApoB – apolipoprotein B

BA – bronchial asthma

BAT – brown adipose tissue

BDNF – brain-derived neurotrophic factor

BMI – body mass index

BOLD – blood oxygen level dependent

brite – brown in white

CI – confidence interval

CK – creatine kinase

CNS – central nervous system

COPD – chronic obstructive pulmonary disease

CREB – cAMP response element-binding protein

CRP – C-reactive protein

D3 – dopamine 3 receptor

DA – dopaminergic

DLS – dorsolateral striatum

DMS – dorsomedial striatum

DSM – Diagnostic and Statistical Manual of Mental Disorder

ERK – extracellular signal-related kinase

FEF25-75% – forced expiratory flow between 25% and 75% of forced vital capacity

FEF25-75% % pred – FEF25-75% as a percent of predicted value

FEV1 – forced expiratory volume in 1 second

FEV1% pred – FEV1 as a percent of predicted value

fMRI – functional magnetic resonance imaging

FNDC5 – fibronectin type III domain-containing protein 5

FVC – forced vital capacity

FVC% pred – forced vital capacity as a percent of predicted value

GFR – glomerular filtration rate

GOT – glutamate-oxaloacetate transaminase

GPT – glutamate-pyruvate transaminase

γ GT – gamma-glutamyltransferase

HDL – high-density lipoprotein

HgA1c – hemoglobin A1c

HOMA – homeostatic model assessment

IQR – interquartile range
LDH – lactate dehydrogenase
LDL – low-density lipoprotein
LH – lateral hypothalamus
MEK – mitogen-activated protein kinase
MP – motor pallidum
mTOR – mammalian target of rapamycin
NCD – non-communicable disease
OFC – orbitofrontal cortex
p38 MAPK – p38 mitogen-activated protein kinase
PE – prediction error
PET – positron emission tomography
PFC – prefrontal cortex
PGC1 α – peroxisome proliferator-activated receptor-gamma coactivator 1 α
PI3K – phosphoinositide 3-kinase
PPTgN – pedunculopontine-tegmental nucleus
R_{aw} – airway resistance
RPE – reward prediction error
RR – blood pressure measured according to Riva-Rocci
RV – residual volume
RV% pred – residual volume as a percent of predicted value
RV/TLC% pred – ratio of residual volume to total lung capacity as a percent of predicted value
SD – standard deviation
SGRQ – Saint George’s Respiratory Questionnaire
Sqrt – square root
STN – subthalamic nucleus
sTSH – thyroid-stimulating hormone (determined with a sensitive method)
TLC – total lung capacity
TrkB – tropomyosin-related kinase B
UCP-1 – uncoupling protein 1
VP – ventral pallidum
VS – ventral striatum
VTA – ventral tegmental area
VTA – ventral tegmental area
WAT – white adipose tissue
WHO – World Health Organization

2 Introduction

Unhealthy diet, harmful consumption of alcohol, tobacco use and physical inactivity, are considered as fundamental risk factors for chronic non-communicable diseases (NCDs), e.g. diabetes mellitus, cancer, cardiovascular diseases, and chronic inflammatory lung disease, primarily sources of premature death globally, according to the World Health Organization (WHO) (WHO, 2013; Mitchell et al., 2011).

The need to combat NCDs is clearly undisputable, forcing high-income countries to develop measures to overcome this challenge, a challenge placed in the focus of numerous joint initiatives and international policies including the “Global action plan for the prevention and control of noncommunicable diseases 2013-2020” (WHO, 2013). A central theme of WHO’s said action plan is the paradigm shift that encompasses a road map and a portfolio of policy alternatives, collective implementation of which could cease the increase of obesity and diabetes, as a 25% relative risk reduction is foreseen in terms of premature mortality from diabetes, cardiovascular disease, chronic respiratory disease and cancer.

Moreover, implementation of the global action plan is foreseen to cause a substantial relative reduction in the prevalence of harmful use of alcohol, tobacco use under 15 years of age, and insufficient physical activity by 10%, 30% and 10%, respectively (WHO, 2013). Nevertheless, instead of viewing these elements as risk factors, each may be conceptualized as risk behaviors, a perception underscored by the contemporary finding that behavioral modifications resulting in permanent change of lifestyle are among the most efficacious methods for preventing and halting the progression of major non-communicable diseases (Zsuga et al., 2016a).

Change of behavior is driven by motivation and closely associated reward-related learning and are tightly linked to reinforcement learning paradigms, involving mesocortico- limbic system, as reinforcement learning is the form of learning driven by rewards (Zsuga et al., 2016a). The term limbic system was originally coined to describe cortical structures around the limit (“limbus”) between the cerebral hemispheres and the brainstem. These structures were known together as limbic cortex or limbic lobe (Fig. 1). Later these cortical areas have been linked with the related subcortical components and grouped into the limbic system. Regarding its function, the limbic system is strongly associated with some surrounding three-layered

cortical structures known as paralimbic cortex or mesocortex, together forming the mesocortico-limbic system.

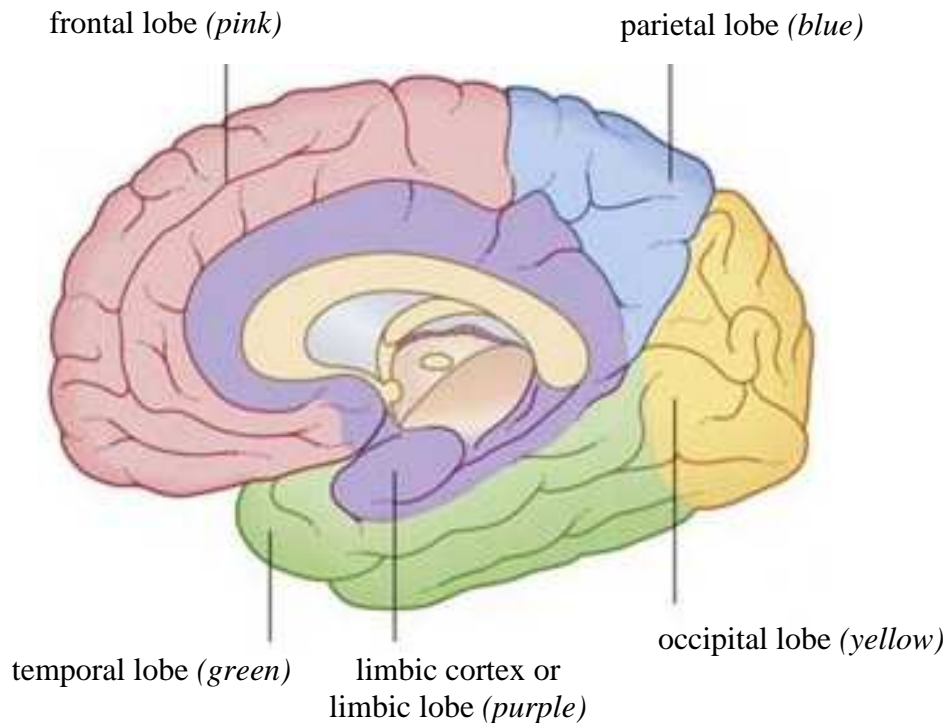


Fig. 1. The limbic cortex seen at the medial side of the right hemisphere of the brain

Altered functioning of reward related mesocortico-limbic structures in the evolution of alcohol and nicotine misuse/abuse is relatively well established by the continuously accumulating body of preclinical and clinical evidence (for an overview refer to (Nutt et al., 2015; Söderpalm & Ericson, 2013)). Recent findings tied the evolution of obesity to mesocortico-limbic dysfunction as attention turned to the ‘hedonic control of eating’ (Saper et al., 2002; Berthoud, 2012; Seeley & Berridge, 2015), and the identification of the complementary phenomenon termed ‘hedonic obesity’. Hedonic obesity is defined as a form of overeating that develops in response to mesocortico-limbic dysfunction, that by inducing hedonic overeating leads to elevated metabolic set-point (Yu et al., 2015). Although, current understanding fails to offer plausible explanation for the evolution of physical inactivity due to mesocortico-limbic dysfunction per se, emerging new factors e.g. the identification of irisin and its downstream mediator brain-derived neurotrophic factor (BDNF), may help elucidating such possible links. Identification of such novel mechanisms may contribute to increased success

rate for achieving sustained lifestyle modification related to physical activity. In the thesis, we will compile evidence in support of the link between altered irisin/BDNF axis and mesocortico-lymbic dysfunction in a clinical population.

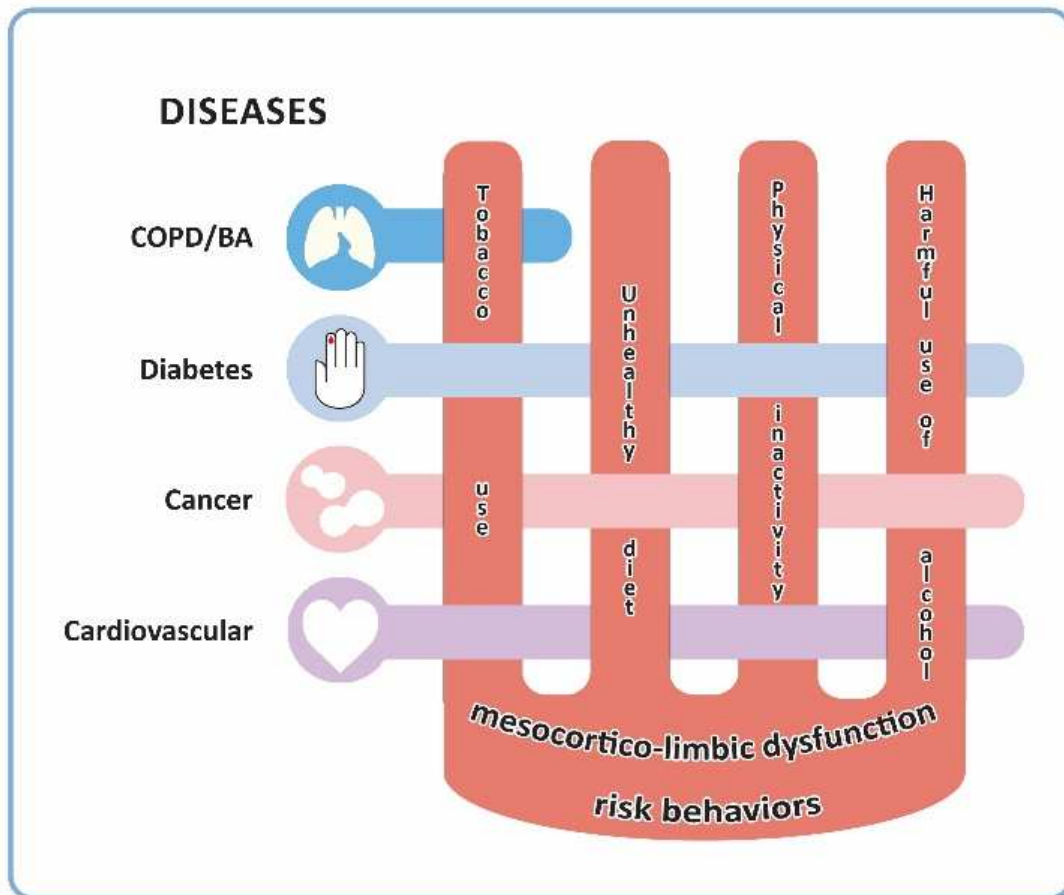


Fig. 2. Dysfunction (or untoward function) of the mesocortico-lymbic system conceptualized as a possible pathognomic factor for risk behaviors underlying major NCDs. Risk behaviors and NCDs are presented in accordance with the infographic compiled by the WHO in the “Global action plan for the prevention and control of noncommunicable diseases 2013-2020” (WHO, 2013). COPD: chronic obstructive pulmonary disease, BA: bronchial asthma. Figure is redrawn from Zsuga et al. (2016a).

Based on these considerations, basic understanding of the neuronal circuitry and its autocrine/paracrine/endocrine modulators is obligatory to develop new diagnostic markers and to discover novel therapeutic targets. During our investigations, we – directly or indirectly – put forward the hypothesis that the common denominator of risk behaviors underlying the most burdening NCDs may be the dysfunction (or untoward function) of the mesocortico-lymbic

system (Fig. 2). This proposition is unique as it provides a novel, common pathomechanism for the evolution of NCDs and as such could have considerable translational implications (Zsuga et al., 2016a).

3 Literature overview

3.1 Reinforcement learning

Reinforcement learning is a concept underlying forms of associative learning, governed by the use of a scalar reward signal (Maia, 2009; Niv, 2009), with learning taking place if expectations are violated. These violations are embodied by prediction errors serving as feedback signals (Rescorla & Wagner, 1972). Stemming from computational accounts, the reinforcement learning paradigm is conceptualized as learning performed by an agent (e.g. the individual) that is interacting with its environment (referred to as a set ‘states’), in an environment that is unknown and uncontrolled by the reinforcement learning agent (Sutton & Barto, 1998). According to this, reinforcement learning processes may be characterized by three agent-related attributes: valuation, policy and use or omission of a model (Sutton & Barto, 1998), with valuation indicating the subjective long term value assigned to states or state-action pairs, policy denoting the set of rules governing action selection and the model of the environment reflecting the agent’s understanding of its environment. It must be noted that value and reward are distinct entities of the reinforcement learning paradigm. Value attribution and policy formation are well embedded in psychological accounts of conditioned behavior: Pavlovian learning for valuation and instrumental learning for action selection. Accordingly reinforcement learning works by utilizing Pavlovian learning to link states and rewards by learning the contingency of neutral state-related stimuli and stimuli predictive of reward, and instrumental learning to optimize action selection in order to maximize the reward obtained long run (Niv & Montague, 2008). Depending on the agent’s approach both accounts can be addressed with or without using the agent’s model of the environment. Accordingly, there are two alternate ways to address reinforcement learning related paradigms: the model-free and the model-based approaches, based on whether the agent attempts to build a model of the external and internal environment or not (Doll et al., 2012) (Table 1).

Panel A	<i>Reinforcement learning: use of scalar value to direct learning</i>	
<i>conditioning paradigm</i>	Pavlovian learning	Instrumental learning
<i>environmental input</i>	unconditioned stimulus (UCS) conditioned stimulus (CS)	stimulus (S)
<i>the agent's reaction to input</i>	unconditioned response (UR) conditioned response (CR)	response (R)
<i>representation of statistical regularities of the environment</i>	yes (associative strength indicating spatiotemporal contiguity)	yes (probability of outcome following a response)*
<i>reward conceptualization</i>	reward value of the UCS	reward value of the outcome (O)
<i>is output contingent on the agent's actions</i>	no	yes
<i>what is learnt</i>	contingency of neutral stimuli and stimuli predictive of reward	optimal response to stimulus to maximize outcome

Panel B	<i>Reinforcement learning: use of scalar value to direct learning</i>			
<i>approach</i>	model-based		model-free	
<i>conditioning paradigm</i>	Pavlovian learning	Instrumental learning	Pavlovian learning	Instrumental learning
<i>is there a model</i>	"world model" (e.g. transition and reward functions) constructed		no attempt to construct world model	
<i>what is learnt by direct experience</i>	the model (transition and reward functions)		value function	value function and policy
<i>what is updated during learning</i>	the model (transition and reward functions)		cached state values	cached state-action values
<i>how is the update done?</i>	by learning (e.g. supervised learning)		using prediction error obtained from direct experience and learning rate	
<i>are making predictions possible?</i>	yes		yes	
<i>outcome of predictions</i>	estimation of reward in a given state	estimation of reward in given state, using given policy	estimation of state value	estimation of state-action value
<i>is optimization possible?</i>	no	yes	no	yes
<i>output of optimization</i>	none	max cumulated sum of reward over the long-term⁺	none	max cumulated sum of reward over the long-term⁺
<i>are forward-looking simulations possible?</i>	yes	yes	no	no
<i>outcome of forward-looking simulation</i>	identify maximal reward within the state-space	identify optimal policy to obtain maximal reward	none	none

Table 1. The learning paradigms of Pavlovian and instrumental conditioning may be interpreted within the computational reinforcement learning framework, as in both cases learning is governed by the scalar value of reward. As accounts of reinforcement learning, both Pavlovian learning and instrumental learning may be approached using concepts of model-based and model-free learning, leading to distinct set of assumptions. (* usually, instrumental learning paradigms are deterministic, + These are also denoted as estimation of reward in a given state, using a given policy or estimation of state-action value, in model-based and model-free instrumental learning, respectively.)

Interesting to note at this point that recent investigations pertaining the functional organization of the striatum seem to reflect a division similar to that of the reinforcement learning agent, with model-based instrumental learning, model-free instrumental learning and

Pavlovian learning being linked to the dorsomedial (DMS), dorsolateral (DLS) and ventral striatum (VS), and their relating cortico-striatal-thalamo-cortical loops, respectively (Balleine et al., 2008; Daw et al., 2005; Maia, 2009; Yin & Knowlton, 2006) (Fig. 3). Additionally, while both the value and policy function of reinforcement agents have been clearly linked to behavioral accounts of learning, there exists no uniform concept pertaining the neurobiological underpinnings of what sort of model does the brain use for model-based reinforcement learning accounts.

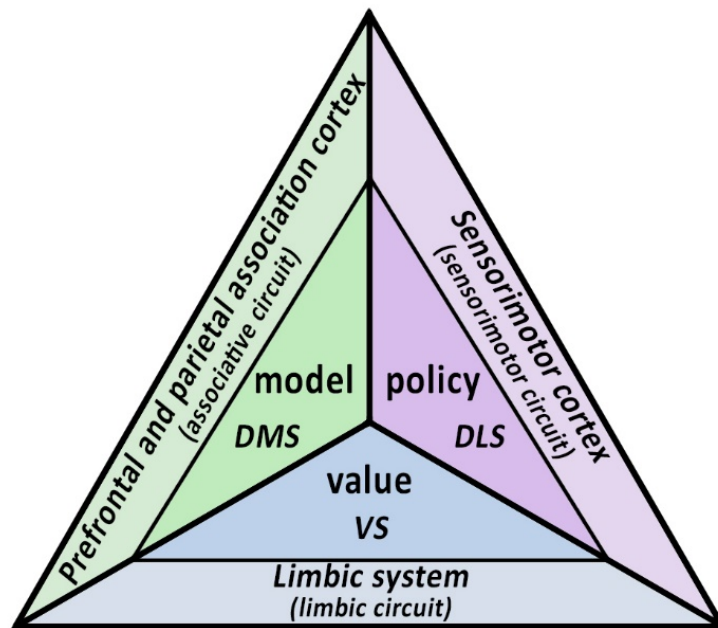


Fig. 3. Functional organization of the striatum (and relating cortico-striatal circuits) interpreted using the attributes characteristic of reinforcement learning agents: value, policy and model. We posit that the ventral striatum functions as the value function component of the agent and that the model used by the reinforcement agent is that produced by the default network encompassing the limbic and associative circuit.

3.1.1 Model-free approach of reinforcement learning

Model-free approaches such as temporal difference learning (or its variants e.g. the actor-critic model, SARSA a policy- and Q-learning a value-iteration method) work by making predictions about the future value of states (in Pavlovian learning) or state-action pairs (instrumental learning) based on direct interaction with the environment e.g. using experience

to sample the environment (Sutton & Barto, 1998; Glimcher, 2011; Pennartz et al., 2011). Accordingly model-free reinforcement learning uses a simple state space and values obtained are specific for a given state (McDannald et al., 2011). Model-free learning is governed by the utility of a stimulus (Pavlovian learning) or outcome (instrumental learning) with respect to its predicted cumulative future value discounted as a function of time (Doll et al., 2012), embodied by the reward prediction error (Schultz et al., 1997). Summarizing, orthodox thinking implies that model-free learning is based on experience, driven by prediction errors and takes place in a simple state.

Compelling evidence from varying fields of neuroscience depicted dopaminergic neurons of the mesocortico-limbic system as candidate neural substrates for model-free information processing. Indeed, to date the most elaborate framework accounting for the role of dopaminergic (DA) neurons in reinforcement learning is the RPE hypothesis (Colombo, 2014). Accordingly, phasic DA neuronal activity is triggered by either unexpected reward (Covey et al., 2014; Fiorillo, 2013; Fiorillo et al., 2014; Goto et al., 2007), or sensory signals for unexpected rewards (Schultz et al., 1997). The difference between the predicted and actual value of rewards are depicted yielding a response pattern that is in alignment with a model-free appetitive RPE (Cooper et al., 2014; D'Ardenne et al., 2008; Fiorillo, 2013; Schultz et al., 1997). Dopaminergic neurons emanating from the VTA and pars compacta substantiae nigrae project to the VS, forming the key neuronal pathway of the mesocortico-limbic circuit. (Additionally, VTA DA neurons project to the amygdala, hippocampus and the orbitofrontal cortex (OFC) and dorsal striatum (Grace et al., 2007; Kelley & Berridge, 2002)).

The most salient activity of DA neurons is burst firing that causes a transient high amplitude release of dopamine into the synaptic cleft. In fact burst firing of VTA DA neurons has been shown to confer an activation pattern in the VS that is both necessary and sufficient for use of an RPE system (Delgado et al., 2008; Garrison et al., 2013; Glimcher & Fehr, 2013; Glimcher, 2011; Niv, 2009). Corroborating this proposition, of the several neural substrates proposed to be involved in the computation of dopamine-associated RPE signals, only the VS - conceived as the receiver of RPE signal emitted by the VTA - met axiomatic proof congruent with temporal difference learning models (O'Doherty et al., 2004). Nonetheless other candidates (also richly innervated by dopaminergic neurons) such as the OFC showed intermediate results, while the anterior cingulate cortex violated the assumptions of consistent prize ordering and consistent lottery ordering (Caplin et al., 2010; Glimcher, 2011); failing to meet the axiomatic criteria.

To account for learning, RPE serves as plasticity-modulating teaching signal that governs future behavior in order to maximize predicted future reward and consequently minimize RPE (Schultz, 1998; Wise, 2005). During learning the dopamine teaching signal is transferred from the unconditioned primary reinforcer to its preceding sensory cue in a way that allows for the back-propagation of the teaching signal so reward may be predicted at the earliest time possible (Glimcher, 2011; Schultz et al., 1997; Schultz, 2007). The causal link between dopamine neuron reward predicted signaling and cue-reward learning was recently established in behaving rats using temporally precise neuron specific optogenetic tools that mimic prediction error (Steinberg et al., 2013).

Burst generation of VTA DA neurons depend on intact synaptic inputs, (Paladini & Roeper, 2014) as the presence of glutaminergic synaptic drive from the subthalamic nucleus (STN) and laterodorsal tegmentum gated glutaminergic and cholinergic activity of the pedunculopontine-tegmental nucleus (PPTgN) (Floresco et al., 2003; Mena-Segovia & Bolam, 2011) are prerequisites for burst firing to occur. The PPTgN offers one of the strongest excitatory drives to the VTA (Kobayashi & Okada, 2007; Okada et al., 2009). The afferent connectivity of the PPTgN posits that this structure may receive information pertaining to the expected value and actual value attributes of the reward. Signals used for the computation of expected values may emanate from the orbitofrontal cortex (Simmons & Richmond, 2008; Tremblay & Schultz, 1999), prefrontal cortex, or the striatum while actual value related signals may be derived from the lateral hypothalamus, respectively (Kobayashi & Okada, 2007; Okada et al., 2009) (Fig. 4).

Summarizing, according to the reward prediction error hypothesis discrepancy between actual and expected reward following a cue is embodied by the phasic dopamine signal (Schultz et al., 1997; Schultz, 2007). Merging this hypothesis with the reinforcement learning framework posits that the reward prediction error signal produced by the VTA dopaminergic neurons is neural substrate of the prediction error attribute of model-free reinforcement learning.

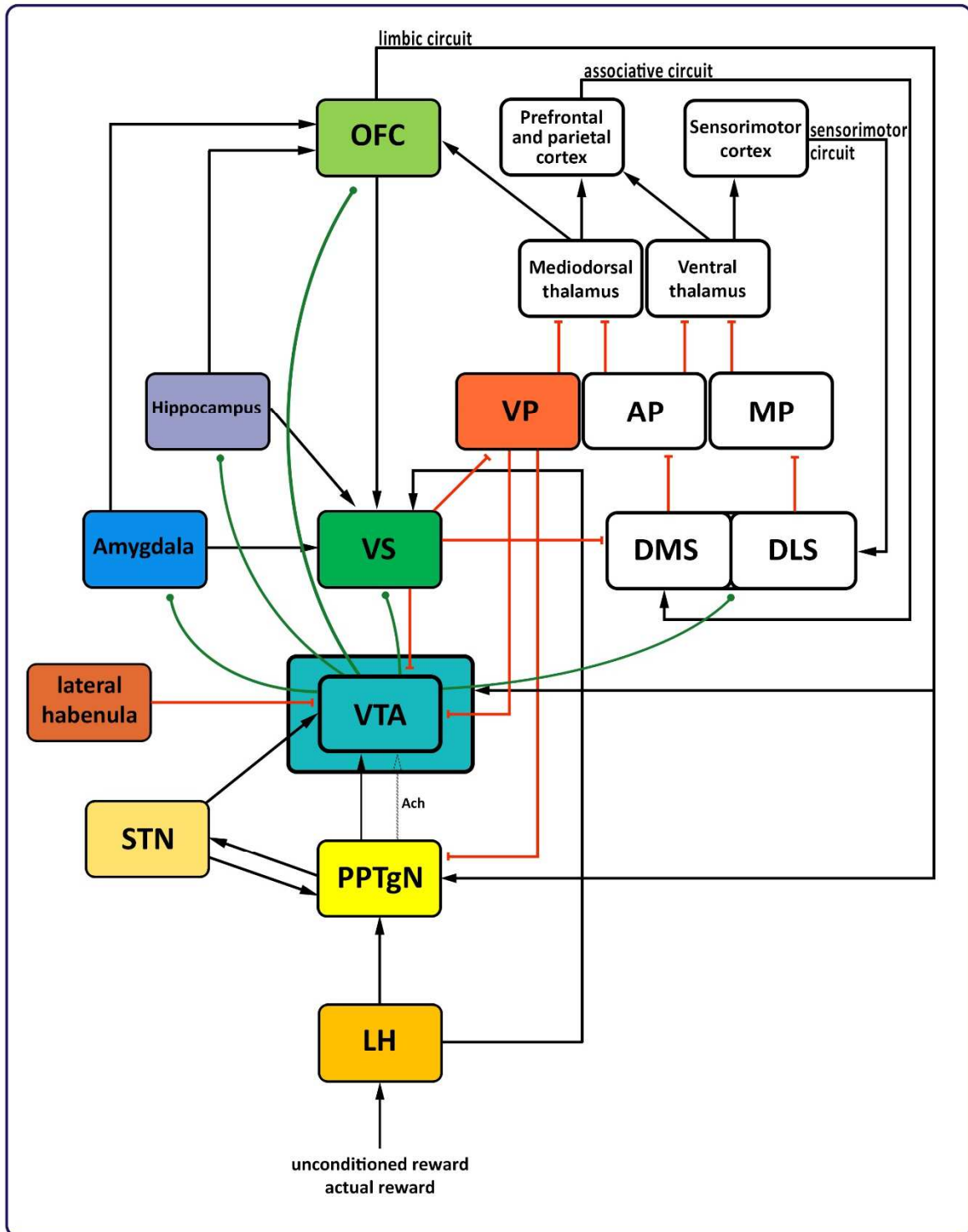


Fig. 4. Neurobiological correlates of model-free and model-based reinforcement learning. The key neuronal pathway in the mesocortico-limbic system is the dopaminergic system originating from the VTA/ substantia nigra pars compacta innervating the VS. The function of VTA DA neurons is fundamentally determined by its afferentation as at baseline, as approximately 50% are inactivated by GABA-ergic inhibition (red lines). Burst firing, perceived as the key signal

for generating RPE may ensue if the population of active DA neurons (e.g. those that show tonic spike activity) are further stimulated by afferent excitatory (glutamatergic and cholinergic) input (glutamatergic and cholinergic input are indicated by solid and dotted black lines, respectively). Population activity is indicated by the concentric boxes, with the smaller area relating to a smaller population activity. Please note, the GABA-ergic, and glutamatergic influence on decreasing and increasing population activity, respectively. The VS integrates glutamatergic inputs of the hippocampus, amygdala and OFC and regulates the activity of VTA by modifying the GABA-ergic inhibition through the ventral pallidum (VP). DA VTA efferents innervate VS, amygdala, hippocampus and the OFC and thus may contribute to both model-free- and model-based reinforcement learning by providing dopamine, the plasticity-modulating teaching signal needed for inducing long-term potentiation (the green dots indicate the place of learning). Distinct cortico-striatal circuits centering the VS, dorsomedial and dorsolateral striatum (e.g. the limbic-, associative- and sensorimotor circuits, respectively) are also indicated with a schematic representation of their functional connectivity. Abbreviations: associative pallidum (AP) lateral hypothalamus (LH), motor pallidum (MP), ventral pallidum (VP), green line: dopaminergic innervations (plasticity inducing), red line: GABA-ergic innervations (inhibitory), solid black arrow: glutamatergic innervations (excitatory), dotted black arrow (cholinergic). (See text for a more elaborate discussion.)

Emergence of a competing account conceptualizing the role of phasic dopamine must be noted at this point. It comes from Berridge and colleagues, who put forward the idea that processes associated with reward should be teased apart into the three psychological components, ‘wanting’ e.g. incentive salience or motivational incentive of a cue, ‘liking’ e.g. the hedonic value of a cue and reward learning by means of associative learning (Berridge, 2012). Hence, this theory attributes incentive (motivational) value to cues changing the extent they are ‘wanted’ (thus cues may become more or less ‘wanted’ (Berridge, 2007). This hypothesis gives an alternative interpretation for the phasic release of dopamine in the mesocortico-limbic system by suggesting that rather than coding hedonic attribute, it codes incentive salience of cues (Berridge, 2007; Berridge & Robinson, 1998). Therefore, incentive salience is defined as attribution of motivational value by Pavlovian-guided learning, to a formerly neutral representation of a cue (conditioned stimulus) to bring about a more attractive and ‘wanted’ cue/stimulus (Zhang et al., 2009).

3.1.2 Model-based approach of reinforcement learning

The fundamental lemma of model-based approaches is the model built to represent the internal and external environment e.g. of distinct states encompassing rewards (described by the reward function), their connections and probabilities governing state transitions (characterized by the transition function) (Glascher et al., 2010; Niv & Montague, 2008; Niv, 2009). Model-based methods use the knowledge of sequential contingencies describing state transitions and the reward function for either making predictions pertaining to future rewards, or planning e.g. use of the model for making forward-looking mental simulations relating to actual or imagined states (Pavlovian learning) or state-action pairs (instrumental learning) (Glascher et al., 2010; Solway & Botvinick, 2012; Wilson et al., 2014). By running serial computations concerning the immediate consequences of state transitions (Pavlovian learning) and/or action sequences (instrumental learning) the utility of a state (Pavlovian learning) or state-action pair (instrumental learning) is obtained indirectly based on the model (Daw et al., 2005).

There are numerous reports dealing with the involvement of specific brain structures in model-based reinforcement learning, however propositions concerning the unambiguous neurobiological underpinning of the model seem to be missing. In the following section utilizing the proactive brain concept we elaborate that the brain's default network is the entity building and continuously updating the model used by model-based reinforcement learning. In addition, we will show that several components of the default network (e.g. the hippocampus, the amygdala and the OFC) have been linked to model-based reinforcement learning, thus it is convenient to suggest that the model constructed by the default network is accessed by the reinforcement learning system (both by Pavlovian and instrumental learning) to allow model-based computations.

3.2 The proactive brain concept

The concept of proactive brain provides a framework for understanding how the brain makes predictions (Bar, 2004, 2007, 2009; Barrett & Bar, 2009; Kveraga et al., 2007; Lebrecht et al., 2012; Tal & Bar, 2014). In focus of this theory stands the proposition that the brain in its default mode is continuously making predictions by means of associations driven by external

gist information obtained from sensory stimuli or alternatively by thought mobilizing relevant memories. These associations as elemental building blocks of thought enable taking advantage of frequent trends in the environment to help interpret and anticipate immediate future events therefore help cope with uncertainty, resolve ambiguity, generate reward-related perceptions, and govern action selection (Bar, 2004; Barrett & Bar, 2009), as these predictions offer information pertaining to what to expect in a given environment. Accordingly, one of the key functions of the default network (as indicated by its overlap with contextual associative areas (Bar et al., 2007; Bar, 2009)) is to organize typical arrangements of the environment into context frames that contain typical, generic representations such as the probable objects clustered together, their relations and affective and reward value and offer a set of expectations that can govern attention and action selection (Bar, 2004, 2007). The structure of context frames enables pattern activation in associative memory e.g. automatic co-activations based on feature similarity, spatiotemporal contiguity.

To fully appreciate how context frames contribute to predictions (or formation of expectations), another momentum of the proactive brain must be introduced- analogies (Bar, 2007, 2009; Bar & Neta, 2008). Upon encountering a novel situation initial processing of information is done by extracting minimally analyzed information e.g. gist, via quick computation of poorly processed data with the aim of determining whether a situation has relevant affective and motivational meaning (e.g. is it rewarding?). This rudimentary information is used to form an analogy based on perceptual, semantic, or affective feature similarity. This analogy will be used to activate the most relevant context frame and it will be used to formulate what is expected (pertaining to the identity and affective-motivational features of stimuli). By forming analogies and mobilizing context frames, online computations may be performed for action selection as subsequent associative activation of analogy derived information can be used to predict what else likely to be present in a given context, what is the most rewarding action to take. This information is readily accessible as a result of prior learning. Thus, by organizing the external world into context frames, information pertaining to valence and reward value of stimuli is accessible in a way that it may assist making predictions facilitating action selection for maximizing reward (Bar, 2007; Tal & Bar, 2014).

3.3 Modulation of the reward circuitry: putative role of the adipomyokine irisin

Additional to understanding the neuronal circuitry governing reinforcement learning, the quest for identifying novel humoral factors, e.g. possible modulators of the neurobiological function must also be pursued. Recently, emergence of a new class of muscle-derived peptides and cytokines led to skeletal muscle being acknowledged as an endocrine organ (Pedersen et al., 2007; Pedersen & Febbraio, 2012). This discovery yielded an array of new mediators that in addition to their effect in the periphery may have central effects as well. Myokines, are peptides expressed, synthesized and released by muscle to produce their effect in an endocrine, paracrine or autocrine fashion. They are typified based on their function, e.g. their involvement in metabolic, angiogenic or myogenic processes (Yoon et al., 2012). Recently, a subclass of myokines, contraction-regulated myokines, stirred substantial interest due to their potential ability to explain the beneficial effects of exercise, based on their presumed role in mediating the interaction between skeletal muscle, brain and adipose tissue (Pedersen & Febbraio, 2012).

A key phenomenon involved in the interplay between muscle-fat-brain is adipocyte browning (Contreras et al., 2015). Traditionally, differentiation of brown adipose tissue (BAT) and white adipose tissue (WAT) is done based on their role in energy homeostasis and developmental origin. The two types of adipose tissues have somewhat opposing role as WAT is primarily the organ for storing energy to enable prolonged survival upon calorie deprivation, and BAT fuels energy dissipation by means of non-shivering thermogenesis. Expression pattern of the key protein underlying thermogenic activity, mitochondrial uncoupling protein UCP-1, is in alignment with this as it is high and low in BAT, and WAT, respectively (Cannon & Nedergaard, 2004). Nevertheless, lately beige or brite (brown in white) adipocytes were discovered, as an intermediate form (Seale et al., 2008; Ishibashi & Seale, 2010). Brite adipocytes develop from cell lines phenotypically similar to WAT and are reliably identified in anatomical sites characteristic of WAT. Conversely, their baseline expression of UCP1 is low. Nonetheless, upon activation these brite adipocytes switch to energy dissipating mode from energy storage, paralleled by increase of UCP-1 expression and other phenotypic changes rendering these activated brite cells to resemble BAT. According to contemporary thinking it may be that human BAT adipocytes are in fact mostly brite adipocytes (Wu et al., 2012). Elucidation of the molecular determinants underlying adipocyte browning is expected to lead to the identification of new therapeutic targets and diagnostic markers with high utility for

combatting the risk factors for major NCDs (Contreras et al., 2015). Of the numerous factors known to be relevant for adipocyte browning, irisin, a contraction-regulated myokine, rose substantial attention with this respect, due to its elaborate central and peripheral effects (Lee et al., 2014; Chen et al., 2015).

Irisin was discovered by Boström and colleagues in mice and humans (Boström et al., 2012). It is a highly conservative polypeptide (12 kDa) with its amino acid sequence showing 100% homology in most mammals, reflecting highly conserved function (Roca-Rivada et al., 2013). Irisin is released by proteolysis from the transmembrane fibronectin type III domain-containing 5 protein (FNDC5). FNDC5 expression is regulated by the transcriptional co-activator, peroxisome proliferator-activated receptor-gamma coactivator protein-1 α (PGC1 α), a known regulator of oxidative processes in BAT (Phillips et al., 2014). Expression of both FNDC5 and PGC1 α are positively correlated with physical activity and with each other, evidenced by their decreased and increased expression in response to sedentary lifestyle or sustained physical training, respectively (Handschin & Spiegelman, 2008; Lecker et al., 2012). Irisin is released into the circulation following proteolytic cleavage of FNDC5. Although most abundant in skeletal muscle, FNDC5/irisin expression is present in other tissues as well, including the adipose tissue, (hence irisin is an adipokine too) (Roca-Rivada et al., 2013; Novelle et al., 2013), the rectum, the tongue, and the brain (Huh et al., 2012).

The main effect of irisin is to activate thermogenesis and coupled oxygen consumption of adipocytes (Phillips et al., 2014) by inducing WAT browning in specified regions (Boström et al., 2012). Previously, recombinant irisin's beneficial influence was shown in mice as parallel to the upregulation of thermogenic genes (UCP-1 and PGC1 α), an effect possibly mediated by p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-related kinase (ERK) signalization, decrease of body weight and improvement of glucose homeostasis was seen (Zhang et al., 2014). Moreover, Kristof and colleagues demonstrated irisin's ability to induce brite differentiation of human subcutaneous WAT, using Laser-scanning cytometry (Kristóf et al., 2015). On these foundations, irisin's putative ability to influence obesity and connected metabolic diseases like insulin resistance, Type II diabetes and polycystic ovarium syndrome has been put forward, however presently data are inconsistent (Chen et al., 2015; Huh et al., 2012).

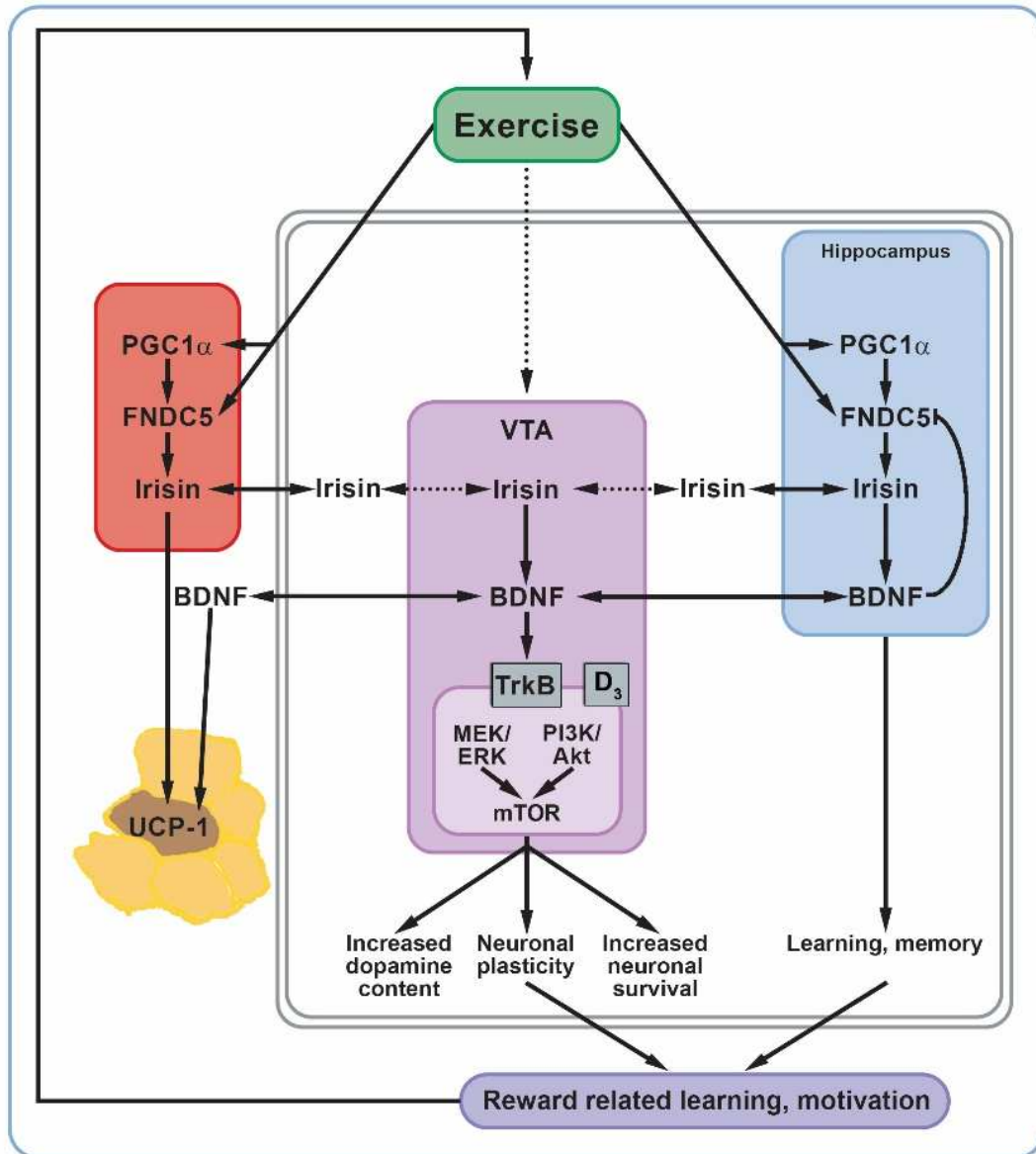


Fig. 5. The contribution of physical activity to the alteration of the irisin-BDNF axis, reinforcement learning and motivation. Physical activity induces expression of both FND5 (parent molecule of irisin) and its upstream regulator PGC1 α . Following proteolysis, irisin is released in the periphery (most abundantly from skeletal muscle, red box) and from certain brain areas (e.g.: hippocampus) involved in reinforcement learning. Once in the peripheral circulation, irisin induces adipocyte browning by the expression of UCP-1 in adipose tissue. Central effect of irisin is seen due to irisin's ability to cross the blood-brain barrier, and its expression in the CNS. This central effect is to upregulate BDNF expression in the hippocampus and the VTA. BDNF also crosses the blood-brain barrier, thus BDNF formed in the brain can exert effects in the periphery e.g. adipocytes. Increase of irisin levels induces BDNF expression in the CNS, which by TrkB receptor activation of dopaminergic neurons in the VTA, is able to modulate dopamine content, plasticity and neuronal survival, causing a

change of reward-related learning and motivation. The significant interplay between these molecular signaling paths is underscored by findings that BDNF has the ability to inhibit FNDC5 expression (Wrann et al., 2013), and that BDNF liberated from the CNS may induce expression of UCP-1 and related browning in peripheral adipocytes (Cao et al., 2011). It may be noted that signalization of TrkB and D3 dopamine receptors overlap. Dotted lines indicate connections suggested by our group. Abbreviations: Akt: protein kinase B, BDNF: brain-derived neurotrophic factor, CNS: central nervous system, D3: dopamine 3 receptor, ERK: extracellular signal-related kinase, FNDC5: fibronectin type III domain-containing protein 5, MEK: mitogen-activated protein kinase, mTOR: mammalian target of rapamycin, PGC1 α : peroxisome proliferator-activated receptor-gamma coactivator 1 α , PI3K: phosphoinositide 3-kinase, UCP-1: uncoupling protein 1, TrkB: tropomyosin-related kinase B, VTA: ventral tegmental area. Figure is redrawn from Zsuga et al. (2016a).

Additional to irisin's role as a link between skeletal muscle and adipose tissue, its effect in the central nervous system (CNS) is also being acknowledged (Fig. 5). FNDC5 mRNA was isolated from distinct structures linked to reinforcement learning processes e.g. the hippocampus (model-based learning), and midbrain (model-free learning) in rodents (Phillips et al., 2014). Likewise, corroborating evidence was offered when endurance exercise was shown to elevate hippocampal FNDC5 expression in mice (Wrann et al., 2013). Furthermore, it should be noted that irisin produced in the periphery readily crosses the blood-brain barrier (Phillips et al., 2014). Additional indirect evidence is provided in support of the link between exercise and altered PGC1 α /FNDC5 axis by a preclinical study performed in mice. Brain and muscle mitochondrial biogenesis was characterized by quantifying several markers (e.g. PGC1 α), after an 8-weeks long endurance training program. Compared to their sedentary controls, significant increase of the PGC1 α level was shown in mice undergoing exercise-training, both in the muscle and the brain e.g. in certain CNS structures specifically linked to reinforcement learning (e.g. the frontal lobe, the hippocampus and the midbrain) (Steiner et al., 2011). Moreover, the observation that FNDC5 expression is decreased in PGC1 α $-/-$ mice reflects PGC1 α 's ability to induce neuronal FNDC5 expression, similar to that shown in skeletal muscle (Wrann et al., 2013).

The most relevant central effect of neuronal FNDC5/irisin regarding its contribution to reinforcement learning processes may be its effect to induce BDNF expression in relevant brain areas. Forced hippocampal expression of FNDC5, for example resulted in BDNF expression, and conversely, parallel to the increase of irisin's level in the systemic circulation led to

increased hippocampal BDNF expression. Moreover, alteration of the expression of FNDC5 by RNAi, small noncoding RNA transcripts, regulators of mRNA expression-mediated knockdown in cortical neurons, resulted in a parallel reduction of cortical BDNF expression (Wrann et al., 2013).

3.4 BDNF, a link between irisin and mesocortico-limbic system

BDNF, a neurotrophin that has a substantial role regarding the plasticity of the CNS (Chao et al., 2006) modulates neurotransmitter, especially serotonin and dopamine release (Bahi & Dreyer, 2013). Hence, decrease of BDNF level alters synaptic strength (Huang et al., 2008), as BDNF induces long-term potentiation, an integral process for reinforcement-learning, thus consequently influences the process of behavioral modification (Yan et al., 2005). Furthermore, recent advancements pointed to BDNF as a probable mediator for cognition-enhancement developed upon intermittent fasting and exercise (Marosi & Mattson, 2014). Results show that voluntary aerobic exercise boosts cognitive functioning parallel to elevating serum BDNF levels both in rodents and humans (Griffin et al., 2011; Vaynmann et al., 2004; Kobilko et al., 2011). Upregulation of BDNF levels is seen as a consequence of peripheral upregulation of FNDC5 and resulting increase of irisin in the peripheral circulation in response to exercise, as well as the due to direct neuronal upregulation of FNDC5. (Wrann et al., 2013).

BDNF synthesis is present both in the CNS (e.g. VTA, the hippocampus) and in the periphery (e.g. organs like the skeletal muscle, liver and adipose tissue) (Marosi & Mattson, 2014). Hence, the pattern of expression for BDNF is similar to that of FNDC5. Following its synthesis, pre-pro-BDNF is released into the circulation as pro-BDNF (to be converted into BDNF in the plasma) or as BDNF (the active form). BDNF similarly to irisin is also able to cross the blood-brain barrier. BDNF has a specific high affinity receptor, the tropomyosin-related kinase B (TrkB), a tyrosine kinase receptor (Marosi & Mattson, 2014) (Fig. 4).

The link between mesocortico-limbic function and BDNF is well established as BDNF is expressed (Yan et al., 2005) and has direct influence on neuronal circuits activated by reinforcement learning and related reward-processing (Nees et al., 2015). BDNF's role concerning the development of the dopaminergic system is underscored by its efficacy as a trophic factor in human and rat mesencephalic dopaminergic neuron cultures, indicated by increase of neuronal survival and elevation of neuronal tyrosine hydroxylase and dopamine

content (Yan et al., 2005). Lately, presence of microRNAs, specifically microRNA124a were shown in VTA dopaminergic neurons, with the ability of modify the expression of BDNF, neuronal plasticity and survival (Bahi & Dreyer, 2013; Chandrasekar & Dreyer, 2009) (Fig. 4).

Previous findings show the expression of TrkB receptors by mesencephalic dopaminergic neurons, hence making these neurons susceptible to the endocrine/paracrine and autocrine effects of BDNF (Numan & Seroogy, 1999). Upon activation by BDNF, TrkB receptors activate distinct signalization pathways like the phosphoinositide 3-kinase –Akt and MEK/ERK pathways (Chen & Russo-Neustadt, 2005). These two signalization pathways are shared by the dopamine 3 (D3) receptor (Collo et al., 2014). Moreover, presynaptic D3 receptor expression of VTA dopaminergic neurons is responsive of BDNF levels (Guillin et al., 2003; Jeanblanc et al., 2006) as following D3 receptor stimulation, these receptors will mediate dopaminergic structural plasticity by phosphorylating MEK/ERK and PI3/Akt/mTOR paths, paths that are controlled by BDNF as well (Collo et al., 2014). Moreover, the D3 receptor agonist quinpirole was shown to increase soma size and number, length of primary dendrites, an effect potentially inhibited by D3 receptor antagonists (Collo et al., 2014).

The most robust clinical exemplar underscoring BDNF's involvement in the function of the mesocortico-limbic system comes from substance abuse studies. The hallmark of substance abuse disorders is the alteration or untoward function of the mesocortico-limbic system (Collo et al., 2014; Covey et al., 2014). Chronic drug abuse leads to increased BDNF levels in the VTA and in agreement with this, infusion of BDNF into the mesencephalon causes psychomotor agitation and drug seeking behavior typical of drug addiction (Bolaños & Nestler, 2004). Previously, Vargas-Perez and colleagues have elegantly shown, that BDNF could induce the switch between the healthy and drug-dependent motivational state, an effect that relies on dopamine's rewarding attribute. When they assessed BDNF's ability to influence the neurobiological substrates underlying opioid reward, they showed BDNF's ability to cause this transition in a dopamine dependent manner, an effect that could be blocked by the dopamine receptor antagonist alpha-flupenthixol (Vargas-Perez et al., 2009). Conversely, the val66met single nucleotide polymorphism of BDNF was shown to influence reward processing by altering the activity of relevant neurotransmitters in addition to altering neural response to reward and alcohol-related risk phenotypes (Nees et al., 2015).

Summarizing the above-mentioned findings, we propose that the exercise-related myokine irisin is a possible modulator of reinforcement learning related phenomena by

modulating mesocortico-limbic processes such as reward learning and motivation as a function of altered BDNF's effect in reward-related structures, e.g. VTA and hippocampus.

3.5 Mood disturbance and the reinforcement learning paradigm

Motivation and allied reward-related processes are often conceptualized using the reinforcement learning theorem, tied closely to the mesocortico-limbic system (Zsuga et al., 2016b; Maia, 2009). Several disorders have been mapped onto the reinforcement learning paradigm including depression, with distinct attributes of value-based decision making being altered. For example, higher discounting rates for delayed rewards reflective of hopelessness and unwillingness to invest in the future was shown in major depressive disorder (Pulcu et al., 2014). In a different study, anhedonia, one of the cardinal symptoms of major depressive disorder, was associated with diminished primary sensitivity to rewards (Huys et al., 2013). Accordingly, the dysfunction of VTA - VS axis have been specifically associated with anhedonia and anergy, also characteristic of depression (Nestler & Carlezon, 2006).

Summarizing, it may be proposed that change of reward processing in mood disorders may be accompanied by alteration of the irisin/BDNF axis.

3.6 Mood disturbance, a highly co-morbid disorder of COPD

Chronic inflammatory pulmonary disease (COPD), by profoundly impacting the patient's quality of life, poses great socio-economic burden for individual patients, their families and society (Mathers & Loncar, 2006; Uchmanowicz et al., 2016). COPD primarily worsens quality of life by developing chronic, progressive dyspnea and consequent limitation of physical activity (Ding et al., 2017). Moreover, co-existing mental health problems show higher prevalence in COPD patients than in the general population (Uchmanowicz et al., 2016; Hanania et al., 2011), with depression and anxiety being present in approximately 20-40% and 30-50% of COPD cases, respectively (Uchmanowicz et al., 2016; Hanania et al., 2011; Mikkelsen et al., 2004; Ng et al., 2007; Ouellette & Lavoie, 2017). Disturbance of mood not only causes disability per se, but changes the course of the disease by altering how patients experience and manage their disease thus worsening their

functional and health status (Hanania et al., 2011; Hynninen, 2007). Therefore, the quest to elucidate the potential mechanisms underlying mood disturbances in COPD is ever so pressing.

Starting from these considerations we set out to investigate the significant predictors of mood disturbance, with special focus on the role serum irisin and BDNF play in a cohort of patients suffering from COPD, a disease associated with mental health problems including depressive symptoms.

4 Goals

During our investigations, we – directly or indirectly – put forward the hypothesis that the common denominator of risk behaviors underlying the most burdening NCDs may be the dysfunction (or untoward function) of the mesocortico-limbic system and consequent alteration of the reinforcement learning system and that a number of humoral factors appear to play a significant role in its evolution. According to this our aims were:

1. To develop a unified, integrated model for reinforcement learning that has the ability to account for the model-based and model-free accounts of reinforcement learning
2. To offer a neurobiological substrate for the model used by the model-based reinforcement learning system.
3. To clinically validate the hypothesis that humoral mediators, such as irisin and BDNF, can contribute to the development of disorders e.g. mood disorders in which the reinforcement learning paradigm has been previously described to be altered.

5 Materials and methods

5.1 Conceptualization

Based on theoretical premises we conceptualized a model that links together concepts of reinforcement learning (e.g. both Pavlovian and instrumental learning), model-based and model-free accounts by utilizing functional anatomical considerations, concepts of machine learning (e.g. the reinforcement learning agent) and the theoretical framework of ‘proactive brain’ deploying the brain’s default network. The merit of the resultant concept termed “proactive model of reinforcement learning” is that it gives rise to several testable hypotheses and offers a representational architecture carrying clinical implications. The current work is deeply rooted in the conceptual and experimental findings of others, cited throughout the thesis.

5.2 Study design for investigating the COPD patients

This investigation was designed in agreement with the STROBE statement for cross-sectional studies (von Elm et al., 2014) and is in line with the principles established by the Declaration of Helsinki. Approval of the Ethical Committee of the University of Debrecen (DEOEC RKEB/IKEB 3632-2012) was obtained in advance. Informed consent was obtained from each participant.

In this study, data of our COPD cohort (described previously in Tajti et al., 2017) have been further analyzed. Briefly, every COPD patient, attending the outpatient unit of the Department of Pulmonology (University of Debrecen) between September 1, 2012 and October 15, 2013 for the management of COPD, were screened by attending pulmonologists, who were unaware of the research hypothesis and study protocol. Patients suffering from any acute inflammatory disease over the preceding one month and those having benign or malignant tumors in their case history were excluded. Patients meeting the entry criteria were referred to the study nurse who explained the details of the study and obtained informed consent. Every patient referred by the pulmonologists consented to study participation. Overall, 74 COPD patients were recruited. At the time of inclusion, patients were managed for COPD according to the relevant Hungarian practice guideline (COPD irányelv, 2009) and the GOLD initiative

(Vestbo et al., 2013). Airway limitation was defined using the lower limit of normal (Celi et al., 2004; Swanney et al., 2008; Nathel et al., 2007). Patients received therapy at the time of inclusion as clinically warranted. Whole-body plethysmography was performed for every patient to obtain lung function parameters. Demographic, anthropometric, anamnestic, laboratory and quality of life data were also acquired. Cumulative measure of smoking exposure was described by pack-years (accounted for both past and current smoking exposure). To assess disease-specific quality of life, the official Hungarian version of Saint George's Respiratory Questionnaire (SGRQ) (Meguro et al., 2007) was used with the permission of the proprietor (Paul Jones, University of London, London, UK).

5.3 Pulmonary function testing

Whole-body plethysmography was performed according to the ATS/ERS criteria (Miller et al., 2005; Wanger et al., 2005) with Piston whole-body plethysmograph (PDT-111/p, Piston Medical, Budapest, Hungary) equipped with automatic body temperature- and pressure-saturated (BTPS) correction, furthermore with full automatic calibration and leakage test. Plethysmography was performed while patients were receiving long-term therapy for COPD. The best of three technically sound maneuvers was selected in case of each participant. Regarding resistance curves, at least two separate and technically appropriate measurements were performed (each measurement consists recordings of at least 5 resistance loops) and results were accepted only if these were the same for both measurements. Of the lung function parameters provided by the whole-body plethysmography, the following data proved to be interesting in the present study: airway resistance (R_{aw}), forced expiratory volume in 1 second (FEV1), FEV1 as a percent of predicted value (FEV1% pred), forced vital capacity (FVC) as a percent of predicted value (FVC% pred), forced expiratory flow between 25% and 75% of FVC (FEF25-75%), FEF25-75% as a percent of predicted value (FEF25-75% % pred), residual volume (RV) as a percent of predicted value (RV% pred), ratio of RV to total lung capacity (TLC) as a percent of predicted value (RV/TLC% pred). For the statistical analysis, parameters showing Gaussian distribution were used in their raw forms, whereas those not normally distributed were appropriately transformed to obtain normal distribution.

5.4 Blood samples and routine laboratory tests

Blood samples were obtained in the morning of the examination, after an overnight fast. Routine laboratory investigations were performed by the Department of Laboratory Medicine (University of Debrecen) following their standard procedures. Serum or plasma samples were used to characterize carbohydrate homeostasis (glucose, insulin, hemoglobin A1c (HgA1c)), lipid homeostasis (total cholesterol, triglyceride, low-density lipoprotein (LDL) -cholesterol, high-density lipoprotein (HDL) -cholesterol, lipoprotein(a), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), kidney function (glomerular filtration rate (GFR), urea, creatinine), liver function (glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), gamma-glutamyltransferase (γ GT)), status of skeletal muscles (creatine kinase (CK), lactate dehydrogenase (LDH)), thyroid-stimulating hormone-sensitive (sTSH) and systemic inflammation (C-reactive protein (CRP), procalcitonin, fibrinogen). From glucose and insulin concentrations, homeostatic model assessment (HOMA) index was calculated as described previously. (Zsuga et al., 2007) Serum samples used to determine irisin and BDNF were frozen within 60 minutes and stored at -80 °C until further analysis.

5.5 Determination of serum irisin and BDNF

Serum BDNF levels were measured compliant with the manufacturer's instructions (Sigma-Aldrich, MO, USA). In short, standards and samples (diluted 100-fold) were administered into 96-well microplates coated with anti-BDNF monoclonal antibody and incubated overnight at 4 °C. Next, plates were washed 4 times, then 100 μ l biotinylated anti-human BDNF Detector Antibody was added to each well and incubated with gentle shaking for 1 hour. Afterwards, the wells were washed and 100 μ l HRP-Streptavidin solution was added to each well, followed by a 45-minute long incubation period at room temperature with gentle shaking. Samples were washed again, then 100 μ l TMB One-Step Substrate Reagent was added to each well and incubation was undertaken for 30 minutes to induce a color reaction. The reaction was stopped with manufacturer-supplied stop solution. The absorbance at 450 nm was measured immediately with an automated microplate reader. All measurements were performed in duplicate. The detection limit for BDNF was less than 80 pg/ml.

Serum irisin levels were assayed according to the manufacturer's instructions using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Phoenix Pharmaceuticals, Burlingame, CA, USA). Briefly, 50 μ l of standard or sample (diluted 2 times), 25 μ l primary antibody and 25 μ l biotinylated peptide was added to each well, followed by a 2-hour long incubation period at room temperature. The plates were then washed four times and 100 μ l/well SA-HRP solution was added and incubated at room temperature for 1 hour. After washing, 100 μ l/well of substrate solution was added followed by incubation for 1 hour, after which the reaction was terminated with 100 μ l/well of 2 N HCl. Absorbance was read immediately at 450 nm. According to the manufacturer, the irisin standard curve was linear from 1.34 to 29.0 ng/ml, and the detection limit was 1.34 ng/ml.

A standard curve showing linear relationship between optical density and concentration of irisin as well as BDNF were obtained with each plate. For the stratification of the final multiple regression model, serum BDNF levels were dichotomized according to their median value.

5.6 St. George's Respiratory Questionnaire (SGRQ)

The official Hungarian version of SGRQ validated for a 1-month recall period was used according to the SGRQ manual supplied by the proprietor (Jones et al., 1991). SGRQ quantifies health impairment with three component scores and one total score. The Symptoms score characterizes the patients' perception of their recent respiratory problems in terms of their effect, frequency and severity; Activity score quantifies the impairment in daily physical activity; while the Impacts score characterizes a wide array of disturbances related to the psycho-social function. Importantly, Impacts score also strongly correlates with disturbances of mood (e.g. depression). The Total score sums up the significance of the disease on overall health status. Scores are provided as a percentage, thus 100% indicates the worst and 0% represents the best subjective health status. Differences in scores were considered clinically meaningful if they exceeded 4 percent points (Jones, 2005). Patients filled out the questionnaire by means of supervised self-administration. Two independent raters recorded data by diligently following data entry guidelines, and scoring was done using the score calculation algorithm provided by the developer of the SGRQ (Ferrer et al., 2002). Inter-rater variability assessed by Spearman correlation was 0.99 ($p < 0.001$), 0.988 ($p < 0.001$), 0.999 ($p < 0.001$) and 0.999

($p < 0.001$) for the Symptoms, Activity, Impacts and Total scores of SGRQ, respectively. Both raters were blinded to patients' irisin and BDNF levels. For statistical analysis, the mean of scores was computed.

5.7 Statistical analysis

Disturbances of mood were quantified with the Impacts score reflective of mood disorders and overall psycho-social dysfunction.

The mean of the Impacts score was used as cutoff for dichotomization of the COPD cohort, so patients with Impacts score $< 32.65\%$ were put into the lower Impacts score group ($n=40$), while patients with Impacts score $\geq 32.65\%$ formed the higher Impacts score group ($n=34$), corresponding to less or more pronounced mood disturbances, respectively.

Normality of continuous variables was checked by the Shapiro-Wilk test. For variables following Gaussian distribution, two datasets were compared using Student's t-test, while Mann-Whitney U test was carried out for those not showing normal distribution. Frequencies were compared with Pearson's χ^2 test.

The correlation of mood disturbance and serum irisin concentration was established using Spearman's correlation. The relationship between mood disturbance and serum irisin level was further investigated with simple as well as multiple linear regression. To ensure normal distribution of variables for these analyses, CK, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, ApoA1, ApoB, insulin, HgA1c, sTSH, HOMA index, FEF25-75%, RV, RV% pred were log-transformed, furthermore square root of disease duration, reciprocal of irisin and reciprocal of square of glucose concentration were computed.

Simple linear regression was carried out with traditional confounding factors (age, gender, height, disease duration in years), lung function parameters and routine laboratory parameters obtained from the serum or plasma samples. Missing data were omitted. To eliminate effects of potential confounders, multiple linear regression modeling was performed. First, the least parsimonious multiple model was compiled including all significant regressors identified by means of simple linear regression and a priori variables (age and gender). Variables were introduced into the initial multiple model simultaneously, then factors not contributing significantly to the model were deleted (except for the a priori variables). The final

model contained (in addition to the a priori parameters) FEV1% pred, body mass index, weight and (log) triglyceride levels. Furthermore, the final model was stratified with respect to BDNF levels. Heteroskedasticity and goodness of fit for the model was assessed by Cook-Weisberg and Ramsey test.

Statistical analysis was performed with Stata 13.0 software (Stata Corporation). Values are given as mean \pm SD or median (with the interquartile range: IQR), and regression coefficients are presented with their 95% confidence interval (CI).

6 Results

6.1 The proactive model of reinforcement learning

Based on the results of conceptualization we offer a model that links together concepts of reinforcement learning (e.g. both Pavlovian and instrumental learning), model-based and model-free accounts by utilizing functional anatomical considerations, concepts of machine learning (e.g. the reinforcement learning agent) and the theoretical framework of ‘proactive brain’ deploying the brain’s default network.

The proactive model of reinforcement learning posits that the model-free and model-based reinforcement learning are complementary and strongly interacting forms of reinforcement learning given the two-way interaction between the distinct structures of each system. On one hand the canonical output of the model-free system, involving the pedunculopontine-tegmental nucleus (PPTgN), and the ventral tegmental area (VTA), the reward prediction error (RPE) is delivered to several model-based structures e.g. the amygdala, the hippocampus and the OFC to serve as a plasticity modulating signal that is prerequisite for learning. On the other hand, the proactive model of reinforcement learning suggests that OFC after integrating distinct reward attributes incorporates these into context frames and as a result emit information about expected reward as a function of glutaminergic input for the model-free structures PPTgN and VTA, as well as the VS. Given that the OFC has strong connections with the VTA (Grace et al., 2007) and its afferent PPTgN (Okada et al., 2009), structures relevant for dopaminergic burst firing, the OFC may offer modulatory input that further interferes with the model-free system. Hence the ventral striatum assumes a central integrative role as according to our model it computes the value function component of the reinforcement learning agent by integrating model-free and model-based inputs about rewards in a way that value is computed, hence the VS supplies value information for both types of reinforcement learning paradigms, e.g. Pavlovian and instrumental learning.) Furthermore, we suggest that the model used by the model-based system is a function of the default network with the amygdala, hippocampus and the orbitofrontal cortex assuming specific reward-related roles. The default network functions in a way that allows future-oriented predictions and planning by forming associations and related context frames. The amygdala couples with VS to code stimulus-outcome contingencies. The hippocampus couples with VS to code context-outcome

contingences while the orbitofrontal cortex (OFC) is driven by hippocampus and amygdala to integrate reward-related information into context frames thus OFC will provide information about expected rewards.

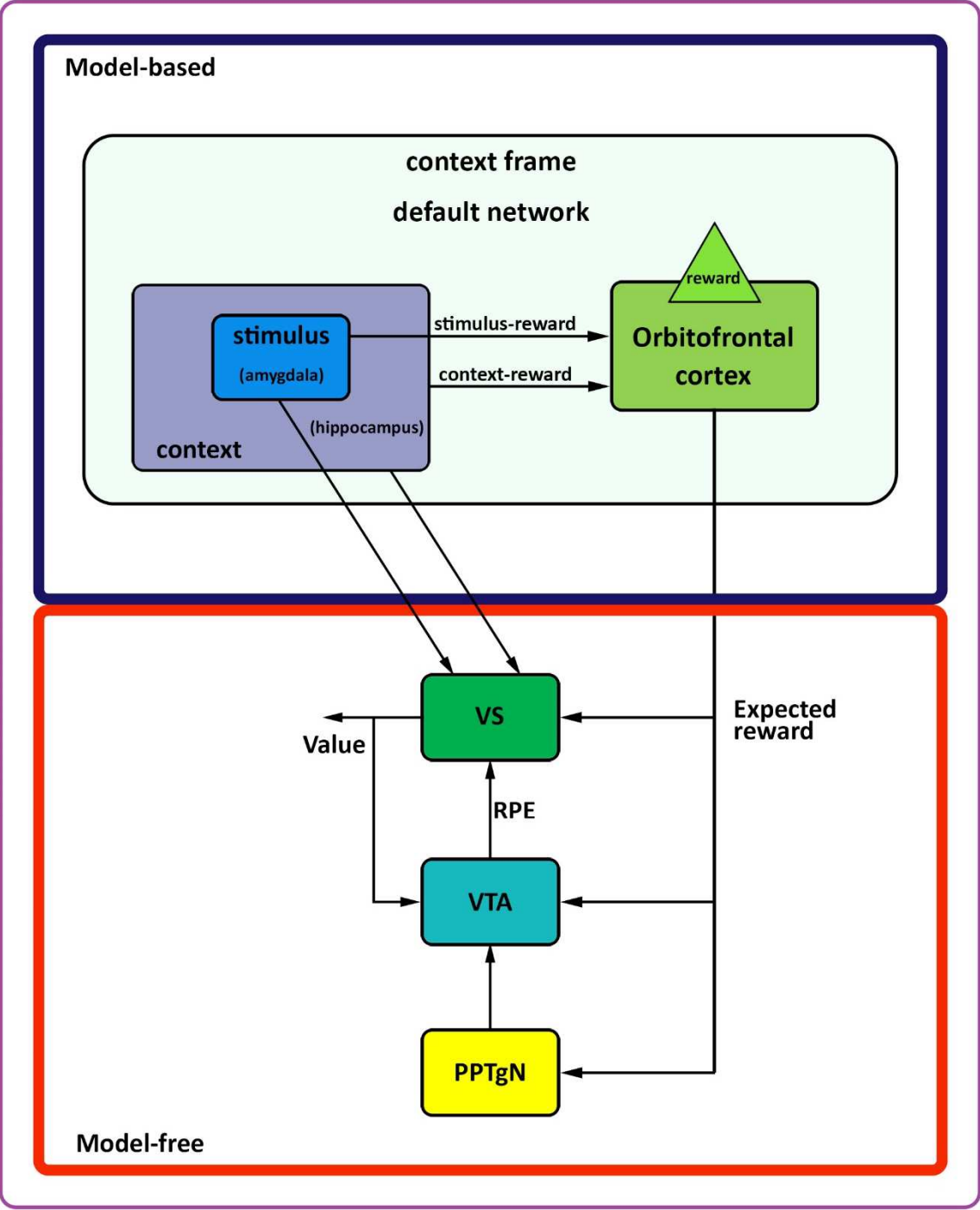


Fig. 6. The proactive model of reinforcement learning. The ventral striatum assumes the value function component of the reinforcement learning agent by integrating model-free (reward-prediction error related) and model-based (expected reward related) inputs to compute value.

Based on the proactive brain concept the model-based system deploys the default network to compile context frames that function as a model of the environment upon which reinforcement-learning based computations may be performed. Furthermore components of the default network, the amygdala, the hippocampus and the orbitofrontal cortex assume specific reward-related roles that converge on the VS. The model-free system involves pedunclopontine-tegmental nucleus, the ventral tegmental area and the VS that together compute reward prediction error. Given that the OFC has strong connections with the VTA, and its afferent PPTgN, the OFC may offer modulatory input that further interferes with the model-free system. Summarizing the expected reward information provided by the OFC is sent to the model-free system, in a way that the VS may integrate model-based reward information with the model-free reward prediction errors to compute the value signal emitted by the VS.

Summarizing the default mode network compiles context frames from which information relating to the expected reward may be extracted by the OFC. This expected reward signal emitted by the OFC as a function of glutaminergic efferents gets fed back to the model-free system. Since the VS is a receiver of both the OFC derived model-based reward information and the model-free reward prediction error signal it has the ability to compute and emit the value signal that is the central attribute of reinforcement learning (Fig. 6).

My contribution to the development of the proactive model of reinforcement learning, I participated in processing of the literature and the compilation of the model. Furthermore, I drafted and finalized Table 1 and drafted Figures 2 to 6.

6.2 The impact of BDNF and irisin on mood disturbance in COPD

6.2.1 COPD patient population

The baseline characteristics of our COPD patient cohort was detailed previously (Tajti et al., 2017). Demographic, anthropometric characteristics, medication history, pulmonary function and disease specific health impairment measures are summarized in Table 2.

Parameters

Age (years)	62.15±9.70	Cholesterol (mmol/L)	5.30 (4.00-6.30)
Gender (female/male)	27/47	LDL-C (mmol/L)	3.10 (2.60-3.70)
Smoker	25/74 (33.8%)	HDL-C (mmol/L)	1.40 (1.20-1.80)
Smoking (pack-years)	20.00 (5.25-33.75)	Triglyceride (mmol/L)	1.35 (1.00-2.00)
Smoking (years)	10.00 (0.00-33.00)	CRP (mg/L)	2.00 (1.21-4.00)
Diabetes present	13/74 (17.6%)	Fibrinogen (g/L)	3.67 (3.25-4.00)
Dyslipidemia present	26/74 (35.1%)	Procalcitonin (µg/L)	0.00 (0.00-0.00)
Hypertension present	43/74 (58.1%)	SGRQ Symptoms score	32.66 (13.64-58.28)
Disease duration (years)	5.00 (3.00-10.00)	SGRQ Impacts score	29.64 (15.44-49.79)
Waist (cm)	101.99±14.31	SGRQ Activity score	57.32 (47.24-72.08)
Weight (kg)	79.71±17.12	SGRQ Total score	41.08±20.99
Height (m)	1.68±0.094	FEV1 (L/s)	1.86±0.72
BMI (kg/m ²)	28.19±5.09	FEV1% pred	66.54±20.29
Irisin (ng/ml)	7.22 (6.63-8.10)	FEF25-75% (L/s)	1.18 (0.65-1.81)
BDNF (ng/ml)	345.6 (294.20-387.90)	FEF25-75% % pred	35.50 (24.00-55.00)
CK (U/L)	101.00 (74.00-139.00)	RV/TLC	54.45±10.08
LDH (U/L)	208.62±34.98	RV/TLC% pred	139.97±21.27
Glucose (mmol/L)	5.00 (4.20-5.80)	FVC (L)	2.75 (2.23-3.39)
Insulin (mU/L)	8.95 (5.55-16.50)	FVC% pred	82.54±17.44
HgA1C (%)	5.70 (5.50-6.10)	R _{aw} (kPa·s/L)	0.27 (0.22-0.42)
HOMA index	2.14 (1.14-4.67)		

Table 2. Main characteristics of the whole COPD cohort (n=74). Data are presented as mean±SD or median (IQR) unless otherwise stated.

6.2.2 Comparison of patients with respect to mood disturbance

The two groups of COPD patients, dichotomized with respect to the mean of Impacts score, proved to be homogenous regarding most of the parameters investigated. Nevertheless, in the group with higher Impacts score (showing more pronounced impairment of mood), dyslipidemia and hypertension (as anamnestic data) were more frequent, serum LDL cholesterol, serum irisin, FEV1% pred and FVC% pred were significantly lower, while serum glucose was significantly higher than the corresponding values in the group with lower Impacts score (showing less despair) (Table 3).

<i>Parameters</i>	<i>Lower Impacts score</i>	<i>Higher Impacts score</i>	<i>p</i>
Age (years)	62.75±9.15	61.44±10.40	0.567
Gender (female/male)	12/28	15/19	0.209
Smoker	13/40 (32,5%)	12/34 (35.3%)	0.800
Smoking (pack-years)	19 (2.25-33)	20 (8.8-37.5)	0.227
Smoking (years)	5.50 (0.00-30.00)	12.50 (0.00-38.00)	0.460
Diabetes present	5/40 (12.5%)	8/34 (23.5%)	0.214
Dyslipidemia present	9/40 (22.5%)	17/34 (50.0%)	0.017
Hypertension present	18/40 (45.0%)	25/34 (73.5%)	0.013
RR systolic (mmHg)	135.45±15.34	137.70±16.60	0.545
RR diastolic (mmHg)	83.00±14.62	81.65±13.60	0.683
Prior AMI	4/40 (10.0%)	5/34 (14.7%)	0.538
Prior stroke (n/y)	0/40 (0%)	1/34 (2.9%)	0.275
Disease duration (years)	5.00 (3.00-8.00)	6.00 (3.00-10.00)	0.301
Waist (cm)	101.11±13.04	103.02±15.81	0.570
Weight (kg)	78.77±15.41	80.81±19.13	0.617
Height (m)	1.70±0.94	1.65±0.10	0.110
BMI (kg/m ²)	27.29±4.25	29.25±5.82	0.103
Irisin (ng/ml)	7.37 (6.99-8.12)	6.85 (6.49-7.99)	0.030
BDNF (ng/ml)	347.55 (316.10-413.60)	343.15 (292.00-377.90)	0.400
Urea (mmol/L)	5.31±1.30	5.31±1.47	0.995
Creatinine (µmol/L)	69.50 (57.50-81.50)	72.00 (61.00-80.00)	0.840
GFR (mL/min/1.73m ²)	90.00 (81.50-91.00)	91.00 (80.00-91.00)	0.920
GOT (U/L)	20.00 (16.00-24.00)	19.00 (15.00-22.00)	0.384
GPT (U/L)	20.50 (14.50-29.50)	1.00 (13.00-21.00)	0.102
γGT (U/L)	32.50 (19.50-49.00)	32.50(20.00-47.00)	0.724
CK (U/L)	101.50 (77.50-138.50)	93.50 (73.00-147.00)	0.640
LDH (U/L)	207.55±36.08	209.88±34.12	0.780
Glucose (mmol/L)	4.08 (4.00-5.50)	5.30 (4.70-6.60)	0.015
Insulin (mU/L)	7.50 (5.30-13.50)	9.45 (5.90-22.40)	0.243
HgA1c (%)	5.70 (5.45-6.00)	5.70 (5.50-6.20)	0.550
HOMA index	1.48 (1.00-3.38)	2.35 (1.46-5.92)	0.092
Cholesterol (mmol/L)	5.70 (4.00-6.30)	5.00 (4.00-5.80)	0.112
LDL-C (mmol/L)	3.25 (2.65-4.00)	2.80 (2.40-3.30)	0.030
HDL-C (mmol/L)	1.45 (1.20-1.80)	1.35 (1.00-1.80)	0.570
Triglyceride (mmol/L)	1.35 (0.95-1.95)	1.35 (1.00-2.00)	0.691
CRP (mg/L)	1.90 (0.85-3.65)	2.60 (1.50-7.00)	0.060
Fibrinogen (g/L)	3.63 (3.13-4.00)	3.69 (3.33-4.00)	0.543
Procalcitonin (µg/L)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.360
sTSH (mU/L)	1.36 (0.84-2.00)	1.12 (0.78-1.43)	0.216
FEV1% pred	71.37±19.26	60.85±20.25	0.025
FVC% pred	86.3±16.92	78.12±17.25	0.043

Table 3. Main characteristics of two groups of the COPD cohort dichotomized according to mood disturbances indicated by the Impacts score. Patients in the lower and higher Impacts score group had smaller and higher (or equal) Impacts score than (or to) 32.65%, the mean Impacts score of the whole cohort, respectively. Data are presented as mean±SD or median

(IQR), unless otherwise stated. Differences between the two groups were considered significant at $p < 0.05$ (indicated in bold).

6.2.3 Associations among SGRQ's Impacts score, serum irisin and BDNF levels

Upon assessing the correlation between the Impacts score and reciprocal of irisin, we found a significant positive correlation in the whole COPD cohort (Spearman correlation coefficient: 0.26, $p = 0.02$; Fig. 7), in agreement with the finding that the irisin concentration was smaller in the higher Impacts score group (Table 3). This correlation became stronger (and remained almost statistically significant) in the stratum with lower BDNF level, while it was weaker (and non-significant) in the stratum with higher BDNF (Spearman correlation coefficient: 0.32 and 0.22, $p = 0.055$ and $p = 0.19$, respectively).

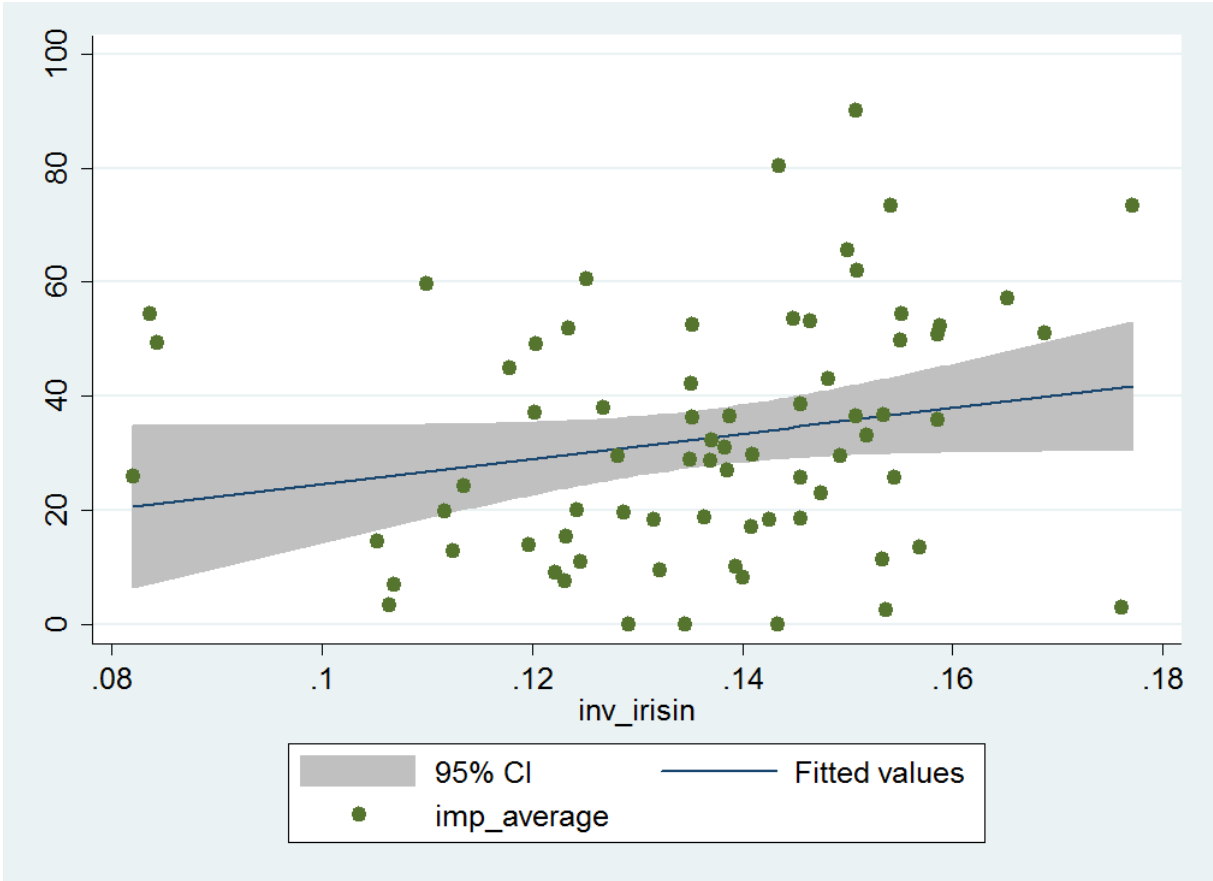


Fig. 7. Correlation of mood disturbance (characterized by the Impacts score of SGRQ) and reciprocal of serum irisin concentration in the whole data set ($n = 74$). The x-axis shows the

reciprocal of serum irisin level (in ng/ml), while the y-axis denotes the Impacts score of SGRQ. The blue line shows the fitted line to the data points (represented by the green dots), while the grey zone indicates the 95% CI.

When the relationship between the Impacts score and reciprocal of serum irisin level was analyzed with simple linear regression, the regression coefficient failed to reach statistical significance ($p=0.08$) (Table 4).

<i>Parameter</i>	<i>Coefficient (95% CI)</i>	<i>p</i>
<i>Simple linear regression of reciprocal of irisin</i>		
Waist circumference	0.00045 (0.00015, 0.00075)	0.004
Weight	0.00027 (0.00002, 0.00052)	0.036
Reciprocal of glucose square	-0.31 (-0.56, -0.06)	0.014
Log HgA1c	0.043 (0.008, 0.077)	0.016
Urea	0.0035 (0.00027, 0.0068)	0.034
LDH	-0.00014 (-0.00026, $-9.94 \cdot 10^{-6}$)	0.035
Log triglyceride	0.011 (0.0033, 0.019)	0.006
Log HDL cholesterol	-0.022 (-0.035, -0.008)	0.002
FVC	0.0061 (0.00084, 0.011)	0.024
FEV1	0.0068 (0.0006, 0.013)	0.032
RV/TLC% pred	-0.0023 (-0.00043, -0.00002)	0.03
<i>Simple linear regression of Impacts score</i>		
Height	-57.86 (-109.01, -6.65)	0.027
Sqrt disease duration	5.52 (0.89, 9.58)	0.019
Reciprocal of glucose square	-369.63 (-635.69, -103.58)	0.007
Log HgA1c	44.97 (7.58, 82.37)	0.019
CRP	0.95 (0.19, 1.72)	0.015
Log cholesterol	-21.41 (-39.21, -3.61)	0.019
Log LDL cholesterol	-15.56 (-28.7, -2.42)	0.021
Log HOMA index	5.82 (1.29, 10.56)	0.012
BMI	1.16 (0.23, 2.1)	0.016
Log sTSH	-9.89 (-17.35, -2.43)	0.01
FVC	-10.04 (-15.36, -4.73)	<0.001
FVC% pred	-0.39 (-0.66, -0.12)	0.005
FEV1	-12.24 (-18.5, -5.99)	<0.001
FEV1% pred	-0.38 (-0.61, -0.15)	0.001
FEF25-75%	-7.01 (-12.96, -1.06)	0.022
Log FEF25-75% % pred	-9.45 (-17.91, -1)	0.029
RV/TLC	0.62 (0.15, 1.08)	0.01
RV/TLC% pred	0.34 (0.12, 0.55)	0.03

Table 4. Significant predictors of reciprocal of serum irisin level and Impacts score of SGRQ determined with simple linear regression for the whole COPD cohort (n=74). Regression coefficient values are presented with their 95% CI.

However, after adjusting for all significant predictors and a priori determinants by means of multiple linear regression, the Impacts score and reciprocal of irisin showed a strong, significant, positive association (β : 419.97; CI: 204.31, 635.63; $p < 0.001$) (Table 5). This association became even more distinct among patients with lower BDNF levels (β : 434.11; CI: 166.17, 702.05; $p = 0.002$), while a considerably weaker and statistically non-significant association was present in case of patients with higher BDNF concentrations (β : 373.49; CI: -74.91, 821.88; $p = 0.10$). All three models were significant ($p < 0.001$, $p = 0.001$, $p = 0.009$). The Cook-Weisberg test showed no heteroskedasticity for the full model and strata with lower and higher BDNF ($p = 0.92$, $p = 0.67$ and $p = 0.82$, respectively). Furthermore, all three models showed good fit reflected by the locally weighted scatterplot smoothing (Fig. 8) as well as by the Ramsey test ($p = 0.82$; $p = 0.53$ and $p = 0.79$ for the whole data set and strata with lower and higher BDNF, respectively).

<i>Parameter</i>	<i>Coefficient (95% CI)</i>	<i>P</i>
<i>Whole cohort</i>		
Reciprocal of irisin	419.97(204.31, 635.63)	0.000
Age	-0.42(-0.85, 0.01)	0.053
Gender	0.45(-9.92, 10.83)	0.931
FEV1% pred	-0.52(-0.71, -0.32)	0.000
BMI	3.68(2.01, 5.34)	0.000
Log triglyceride	-8.70(-16.38, -1.02)	0.027
Weight	-0.78(-1.31, -0.25)	0.004
<i>Lower BDNF stratum</i>		
Reciprocal of irisin	434.11(166.17, 702.05)	0.002
Age	-0.39(-0.94, 0.16)	0.160
Gender	-3.87(-23.46, 15.72)	0.689
FEV1% pred	-0.50(-0.76, -0.23)	0.001
BMI	3.45(0.49, 6.42)	0.024
Log triglyceride	-11.91(-22.31, -1.50)	0.026
Weight	-0.58(-1.60, 0.43)	0.250
<i>Higher BDNF stratum</i>		
Reciprocal of irisin	373.49(-74.91, 821.88)	0.099
Age	-0.49(-1.38, 0.40)	0.269
Gender	1.19(-15.55, 17.94)	0.885
FEV1% pred	-0.56(-0.93, -0.19)	0.004
BMI	3.70(1.25, 6.15)	0.005
Log triglyceride	-4.62(-18.32, 9.07)	0.494
Weight	-0.83(-1.59, -0.07)	0.033

Table 5. Multiple linear regression model for the SGRQ's Impacts score of the whole COPD cohort and its strata with respect to the median BDNF level. Regression coefficient values are presented with their 95% CI. The initial model for the multiple linear regression analysis consisted of the significant parameters provided by the simple linear regression and the relevant a priori identified parameters (age, gender).

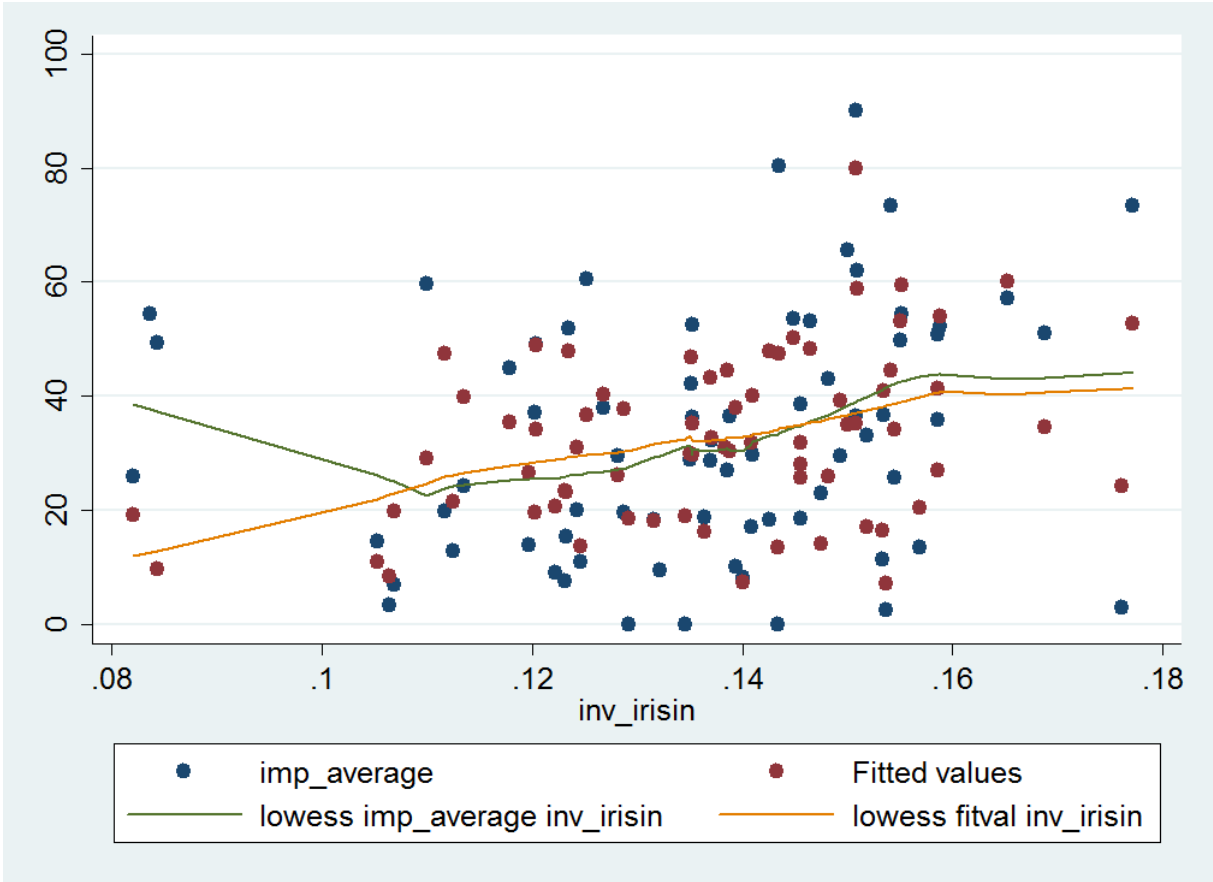


Fig. 8. The model describing the correlation between the Impacts score of SGRQ and reciprocal of serum irisin concentration in the whole data set (n=74). The x-axis shows the reciprocal of serum irisin concentration (in ng/ml), whereas the y-axis denotes the Impacts score of SGRQ. The blue and red dots indicate the raw and fitted values obtained by multiple linear regression, respectively. The green and orange lines indicate the curves fitted to the raw data and to data provided by multiple linear regression. Fitting was done by locally weighted scatterplot smoothing (lowess).

Based on the final multiple linear regression model (built for the Impacts score), body mass index, log triglyceride and body weight were significantly associated with mood

disturbances among COPD patients. In addition, severity of airflow limitation, characterized by FEV1% pred, showed a significant negative association with the Impacts score (β : -0.52; CI: -0.71, -0.32; $p < 0.001$) (Table 5).

My contribution to the investigation of the link between the alteration of the irisin/BDNF axis and mood in COPD patients includes drafting the study protocol, data processing and cleaning, interpretation of results, drafting the manuscript.

7 Discussion

7.1 Interpretation of the model in terms of contemporary findings

In the first section of the discussion, we compile evidence supporting this integrative framework, using the proactive model of reinforcement learning as a scaffold to organize relevant literature to overview the core structures underlying model-free and model-based reinforcement learning. To account for the neurobiological link between model-free and model-based reinforcement learning we overview the network of brain nuclei (e.g. nuclei and their afferent and efferent connectivity) surrounding the mesocortico-limbic dopaminergic system. Finally, we present data corresponding to prior propositions implicating the possible link between model-free and model-based reinforcement learning and we make some speculative assumptions utilizing the proactive brain concept about how the brain's default network serves as the model for the environment used in model-based reinforcement learning.

7.1.1 Default network for building a model of the environment

The term default network was coined by Gusnard and Raichle (Gusnard & Raichle, 2001) to describe the phenomenon of decreasing brain activity seen in response to cognitive tasks as opposed to the heightened metabolic activity encountered in the same areas upon passive mental states (e.g. when left to think undisturbed). The core regions associated with this network include the ventro-medial and ventro-lateral prefrontal cortex (including the OFC), the posterior cingular/retrosplenial cortex, the inferior parietal lobule, the lateral temporal cortex, the hippocampal formation (including the entorhinal and the parahippocampal cortex) and the amygdala (Amft et al., 2014; Buckner et al., 2008), hence mainly cortical association and memory-related areas are included while sensory and motor cortices are spared. This network is defined based on structures that co-activate, have functional correlation with each other and are directly or indirectly connected by anatomic projections. The connection of the default network with striatal reward pathways has also been established, in fact there is evidence for the default network supporting goal-directed simulations (Schacter et al., 2012).

The function of the default network was disentangled by critical evaluation of varying paradigms it is associated with, such as contextual associations, navigational and spatial processing, affective decision-making, emotional and self-referential processing, autobiographical memory, social interacting, mental state attribution, thinking about one's own future, mind-wandering and daydreaming (Andrews-Hanna et al., 2010; Bar, 2007). Based on the ubiquity of its involvement in these mental processes, the default network was proposed to have an essential, adaptive function. Recently the proactive brain concept has attributed an integrative function to the default network based on the elaborate overlap seen between the contextual associative network and that the default network (e.g. that the default network continuously creates and updates the model of the environment by means of generating contextual associations) (Bar, 2007, 2009). In accordance with this, other conceptualizations posit that the default network is associated with remembering real past experiences and simulating alternate future ones. Furthermore, recent fMRI evidence shows that constructing alternative outcomes to past experiences is also a function of the default network (Van Hoeck et al., 2013) to the extent that some argue that such mental simulations are core processes for future-oriented thinking (Schacter et al., 2012). In fact, several groups have come to the conclusion that the most important function of the default network is to offer a foundation for predicting the future by utilizing imagined scenarios, and to enable the flexible combination of components of past experiences into the simulation of novel future events to ensure proper adaptation (Schacter et al., 2012). In our view, the model used by model-based reinforcement learning is the result of the default network's (and the overlapping contextual associative areas') continuous effort to organize the environment into context frames, in a way that association-based predictions may be formed. Hence this function pertains to the use of a model in reinforcement learning for the purpose of planning and optimizing policy in a way to maximize the sum of future discounted reward. (The following subsections will overview the component structures of the default network that are involved in reward-related processes used in model-based learning.)

7.1.2 Model-based Pavlovian learning: amygdala-VS computes stimulus-reward contingencies

Intact amygdala function is necessary for delivering reward-related information about discrete stimulus. The amygdala is highly important for extracting the affective properties of a

stimulus and as such assumes a central role in processing those aspects that are in agreement with actual goals. In other words amygdala responds to motivationally relevant information with relevance indicating the congruence of the affective component of the stimulus and goal (Cunningham et al., 2010). Therefore the activity in the amygdala is enhanced in cases when the valence of the stimulus is congruent with the goal or outcome (reward or punishment), a phenomenon called affective flexibility. Thus, the amygdala modulates perceptual, attentional and autonomic processes mandatory for efficient coping (Cunningham et al., 2008). The integrity and proper functioning of the amygdala (as a contributing element of limbic corticostriatal circuit) is important in storing the stimulus-reward information (Everitt et al., 1999) and the associative activation of the expected outcome (reward) in the presence of a predictive (affective) cue is based on the activation of cue selective neurons in the amygdala (Saddoris et al., 2005). Summarizing amygdala signaling is important for extracting biologically relevant information from the environment including reward-related perceptions, appraisal of negative and positive emotional stimuli in a self-relevant environment (Amft et al., 2014).

7.1.3 Model-based Pavlovian learning: hippocampus-VS compute context-reward contingencies

The hippocampus is postulated to be a key in contextual learning as its role in encoding and remembering contexts is well described (Everitt et al., 1999; Maren et al., 2013). This was robustly corroborated by a recent interventional study using non-invasive electromagnetic stimulation of cortico-hippocampal networks in which associative memory performance was selectively enhanced, parallel to the increase of connectivity in stimulated cortico-hippocampal areas (Wang et al., 2014). The hippocampus is able to encode the spatial properties of the environment. Moreover, hippocampus encodes interoceptive contexts (such as hunger, thirst and timing) and accordingly is able to influence motivated behavior by integrating information about internal and external state related information into response-outcome relationships (Davidson et al., 2010; Kennedy & Shapiro, 2009). Furthermore, Lansink and colleagues (2009) have demonstrated that VS-hippocampal connections have a role in learning place-reward associations, as during task performance and replay of spatial and motivational information during sleep showed specific temporal (hippocampus → VS) ordering while simultaneously recording the activity of relevant neuronal ensembles. The authors concluded that this finding

may be indicative of memory consolidation relating to spatial information pertaining rewards (Lansink et al., 2009). The possible contribution of the hippocampus to model-based reinforcement learning has been postulated by accounts which give evidence for hippocampal representation of anticipated future states (van der Meer et al., 2010), and that these representations reflect the statistics of the environment (Bornstein & Daw, 2012), properties inherent of model-based systems. These findings are corroborated by hippocampal lesion studies where hippocampal damage was linked to deficits in forming and storing contextual representations (Kennedy & Shapiro, 2004; Kennedy & Shapiro, 2009). Other relevant structures for context processing include the ventromedial prefrontal cortex (PFC), the anterior insula, and the anterior cingulate cortex (Maren et al., 2013).

7.1.4 Model-based Pavlovian learning: the function of OFC in the integration of reward-related attributes into default-network derived context-frames

We propose that OFC is a likely candidate for integrating stimulus-reward and context-reward information (coming from the integration of amygdala and hippocampal input) in a way that reward-related information (spatio-temporal, affective, motivational attributes) are integrated into context frames yielded by the function of the default network. As a result the OFC provides expected reward information to its downstream structures the PPTgN, VTA and VS. This assumption rests on several grounds. First the afferent connectivity of OFC differs from that of the surrounding prefrontal areas, as it receives multimodal sensory input, and afferentation from the anterior cingulate cortex, the dorsolateral prefrontal cortex, the hippocampus, the amygdala and the VS (Wilson et al., 2014) (structures also known to be part of the default network). Accordingly, the OFC is a heterogeneous associative area that integrates external and internal information in order to embed multimodal representations in a spatio-temporal context reflecting the monetary and affective value of stimuli (Barrett & Bar, 2009). Its efferents are highly intertwined with structures of the reward systems as its glutaminergic neural outflow targets the VS, the VTA, and the PPTgN (Cho et al., 2015; Kable & Glimcher, 2007; Okada et al., 2009), structures canonical for model-free learning (e.g. VS, VTA and PPTgN) (Fig. 6). A role for OFC in driving reinforcement learning may be proposed based on the fact that it is embedded in distinct circuits related to outcome-specific and value-based behaviors (McDannald et al., 2011), behaviors that depend on instrumental learning and Pavlovian learning, respectively. Concordantly, several lines of evidence corroborates, the role

of the OFC in model-based learning, as reward value signals were shown to be localized to this area in Pavlovian valuation as well as devaluation tasks (Doll et al., 2012).

Second, several groups proposed that the OFC carries information about the expected rewards (Hikosaka & Watanabe, 2000; Okada et al., 2009; Roesch & Olson, 2004; Simmons & Richmond, 2008). In fact, the OFC is one of the few areas of the brain that captures a conjoint history of choices and rewards, and is involved in assigning a value to stimuli thus carries a representation of reward-expectation (McDannald et al., 2011; Noonan et al., 2010) (a parameter used as input for computing RPE). Based on functional studies the OFC has been proposed to contribute to the generation of subject-specific reward value in the form of a single common currency (e.g. irrespective of the disparate nature of the reward, OFC activation parametrically correlated with attributed value) (Levy & Glimcher, 2012; Padoa-Schioppa & Assad, 2006) and linking this reward value to preceding actions (Tsuchida et al., 2010; Walton et al., 2010). Previously OFC was thought to store these learnt value signals, but recently it was proposed that the OFC computes these values on-line (e.g. in a model-based way), allowing for flexible economic decision making (Padoa-Schioppa, 2011). Furthermore the OFC is capable of generating predictions pertaining to outcome expectancies extracted from sensory properties, context, environmental cues and general affective information (Cardinal et al., 2002).

Thirdly in a competing account the group of Schoenbaum has elegantly provided robust evidence that albeit the OFC is essential for normal error signaling of the VTA, rather than signaling expected values per se, the OFC signals state information (Schoenbaum et al., 2009; Takahashi et al., 2011; Wilson et al., 2014). According to their framework the OFC integrates cortical and subcortical multisensory perceptual input with memory about prior stimuli, actions and rewards to determine the so called ‘current state map’ – an abstraction of available information relevant for to the current situation as positioned on a “cognitive map” of the task (Wilson et al., 2014), note the resemblance between ‘current state map’ and context frames of Barrett and Bar (see above). They have shown that the OFC contributes to the computation of error signals by dopamine neurons (in a reward learning task), by modulating the firing of VTA DA neurons via OFC input carrying ‘current state’ information. This effect was most profound in tasks where disambiguation of perceptually similar states based on internally rather than externally available information was needed to realize that the contingencies changed leading to different outcomes (Wilson et al., 2014).

7.1.5 Ventral striatum: the role of value function component of reinforcement learning agent in the integration of model-based (reward-related) and model-free (RPE) inputs

A key nucleus of the mesocortico-limbic system is the ventral striatum. The neural underpinnings of reward hypothesis postulate a central role for dopaminergic mesolimbic pathways with ventral striatum receiving dopaminergic afferents from the ventral tegmental area and the substantia nigra while offering GABA-ergic efferents through the ventral pallidum (Zhang et al., 2009), the limbic final common pathway for mesocortico-limbic processing of many rewards (Smith et al., 2009). Based on previous experimental data and theoretical propositions the VS is a key structure for model-free reinforcement learning as it is perceived as a receiver of RPE signal. Studies using fMRI have shown that blood oxygen level dependent (BOLD) signaling in the VS is reflective of RPE (O'Doherty et al., 2004). Considering the fact that BOLD signal correlates with dendritic input (Logothetis, 2003), this phenomenon also suggests that VS is a receiver of RPE. Additionally fast-scan cyclic voltammetry measures of dopamine in the VS have shown that burst firing of VTA dopaminergic neurons release dopamine in the VS in a way that is quantitatively characteristic of a prediction error signaling (Niv & Montague, 2008).

Model-based inferences to the function of VS may be deduced upon the considering the connectivity of VS; showing abundant glutaminergic afferentation rising from the hippocampus, the amygdala and the OFC (Goto & Grace, 2008; Grace et al., 2007; Kelley & Berridge, 2002; Paladini & Roeper, 2014). Based on these considerations we suggest the strong interconnection of model-free and model-based learning processes based on the functional connectivity of the VS, as the VS - a likely candidate for computing value - receives input from the dopaminergic neurons of the VTA/ substantia nigra pars compacta (in the form of reward prediction error emitted by model-free account) as well as the hippocampus, amygdala and orbitofrontal cortex (offering reward-related input from the model-based account).

The functional anatomy of VS reflects this integrative function, as one of the main roles of VTA DA neurons is modulation of the model-based afferent inputs of the VS. Prior research have shown that increase of burst firing rate of VTA DA neurons facilitates limbic input from amygdala and hippocampus (Goto & Grace, 2008). On the other hand, increasing tonic spike firing of DA neurons attenuates, whereas decrease in tonic VTA DA afferentation facilitates OFC input in VS (Goto & Grace, 2005).

Summarizing it may be said that the VS integrates these varying afferent inputs, and serves as the value function component of the reinforcement learning agent by emitting a value signal that encompasses both reward-related signals and RPE, provided by model-based and model-free inferences, respectively. This proposition is supported by unit recordings in rats that failed to reflect reward prediction error coding in the VS. Instead it was suggested that the dopaminergic signal emitted by the VTA is transformed by ventral striatal processing in a way that it results in a value signal (van der Meer et al., 2011). Indeed there are reports depicting the source of the value signal emitted by the VS; as ramping neurons were shown to increase their firing rate in anticipation of rewards showing a pattern reflective of temporal discounting of future value (Khamassi et al., 2008; van der Meer et al., 2011). Actor-critic accounts of model-free learning are also congruent with this proposition that the VS computes value of states, as the function of the critic (known for computing value of states or state-actions pairs and using this value to update the actor's function) is often confined to the VS (van der Meer et al., 2011).

7.2 Antecedents of our integrative model on the relationship between reward-related processes and motivation in the mesocortico-limbic system

Our proposition is that model-free and model-based reinforcement learning are linked via the integrative function of the VS as the value function component of reinforcement learning for utilizing the proactive brain concept serves as a framework for organizing hippocampal, amygdala and OFC functioning into a 'model', by use of which model-based reinforcement learning paradigms may be interpreted.

Possible support for the default network's ability to offer a model upon which model-based reinforcement-learning related computations are performed comes from a recent fMRI study, showing the co-operation of the default network and reward-processing regions in generating simulations of desired future outcomes to facilitate decision-making about future goals. The authors interpreted their finding as evidence for the involvement of the default network in goal directed episodic simulations that may help with selecting the most beneficial long-term goals (Gerlach et al., 2014).

Furthermore there have been several accounts stretching model-free approaches to include some elements of models encompassing the internal/external state, and previously unanticipated crosstalk or integration of these systems were also postulated by several groups

(Daw et al., 2011; Doll et al., 2012; Glascher et al., 2010; Takahashi et al., 2011). Our concept that model-based learning depends on input to the OFC from the amygdala (stimulus-based information) and the hippocampus (contextual information) is further corroborated by findings of others showing that lesions of the prelimbic cortex (Coutureau & Killcross, 2003), the basolateral amygdala (Blundell et al., 2003) and the OFC (Izquierdo et al., 2004) seem to interfere with model-based learning (Daw et al., 2005).

Daw and colleagues have proposed two competing but presumably complementary systems underlying reinforcement learning and action selection. In their work they have proposed a model-free component deploying dopaminergic striatal loops and a model-based component attributed to prefrontal cortical loops that work parallel and in competition using a Bayesian principle of arbitration for optimizing computational simplicity (model-free approach) and flexible and statistically efficient use of experience (model-based approach). The authors propose that these two systems must interact based on computational considerations and suggest that the role for dopamine in model-based learning should be elucidated (Daw et al., 2005).

Modeling data obtained by implementation of a probabilistic sequential Markov decision task, Glascher and colleagues (Glascher et al., 2010) were able to identify distinct neural signatures for model-free and model-based reinforcement learning in the form of RPE confined to the VS and state-prediction error (SPE) localized to the superior parietal lobule and the lateral PFC. The authors concluded that the lateral PFC contributes toward a model-based reinforcement learning account by integrating learning signals from several sources.

Likewise the reward structural learning hypothesis incorporates the value of expected reward based on momentary external event information and internal state derived reward structure representation corresponding to classical RPE and an entity reflecting environmental reward structure, respectively (this latter could correspond to Glascher's state prediction error signal) (Nakahara & Hikosaka, 2012).

The concept of Schoenbaum's group provides further support for our 'proactive' model of reinforcement learning as they have shown that prefrontal representations contribute to the so-called cached values underlying dopaminergic errors (e.g. RPE), facilitating the iteration of more accurate values, by enabling downstream structures to incorporate information about distinct states and the transitions between them, by mobilizing on both stimulus-bound external and internally inferred information (Morris et al., 2006; Wilson et al., 2014). Thus the OFC modifies behavior when reward configurations change, by updating associative representations

in other brain areas. They showed that the OFC contributes information necessary for calculating the teaching signal for RPE that drives learning, in a way that OFC does not signal the RPE per se rather it might contribute to it by signaling information (e.g. state information) about the expected outcome value. This proposition is underlined by OFC's necessity for reversal learning and further underscored by some lesion studies that showed that disruption of OFC hinders behavioral flexibility upon changes in the environment (e.g. changes of contingencies) (Schoenbaum et al., 2009) (but see also for Rudebeck and Murray, for discordant findings (Rudebeck & Murray, 2008)). Our account is somewhat similar, yet there are considerable differences. By building on the idea that the network of brain nuclei centered on the VS belong to circuits representative of model-free (PPTgN-VTA-VS) and model-based (amygdala-VS, hippocampus-VS, OFC-VS, OFC-amygdala, OFC-hippocampus) learning we deduce that the two learning systems interact. In addition by integrating the proactive brain concept deploying the default network of the brain we offer a framework for understanding the model constructed by the brain. Furthermore, using the proactive brain concept for conceptualization of how the brain uses analogies to mobilize associations for the sake of making predictions, we have proposed that this model may be accessed by model-based reinforcement learning systems (e.g. both model-based Pavlovian and instrumental learning runs simulations on the model constantly being constructed by the default network). Furthermore we have discussed that in addition to the default network's function as a whole, some of its components (e.g. the hippocampus, the orbitofrontal cortex and the amygdala) have already shown to be involved in model-based learning processes.

Corroborating, others have found that change limited to reward identity, but not its scalar value, also changes the 'RPE' signal, a change also dependent on intact OFC functioning (McDannald et al., 2011). The authors have interpreted their findings by concluding that temporal difference learning models should be modified in a way that in addition to general scalar value, access to the internal model of the environment must be integrated when expectations are calculated (McDannald et al., 2011). In line with these propositions, Doll and colleagues have shown (Doll et al., 2009) that top-down rule based inferences coming from cortical (e.g. prefrontal or hippocampal) areas introduce an instruction-based bias onto the model-free learning system, a bias that overrides model-free reinforcement learning based predictions (Doll et al., 2009).

Moreover, it was implicated that only part of the VS derived RPE correlates is due to dopaminergic activation and residual signaling relates to afferent inputs coming from neural

substrates depicted in model-based learning (e.g. amygdala, hippocampus, OFC) (Doll et al., 2012). This proposition fits well with our integrative framework as detailed above. Substantiating evidence came from an elegant fMRI study using a multistep decision task to attest for model-free and model-based influences in human learning showing that the brain combines the strategies for temporal difference and model-based valuations in a way the VS RPE signal reflects both types of valuations parallel to choice behaviors. This implies that RPE previously considered as a hallmark for model-free learning may be altered by information provided by both model-free and model-based systems (Daw et al., 2011).

Further corroborating evidence may come from a competing account coined incentive salience by Berridge that offers a different psychological content for burst firing of DA neurons that convey onto the VS. According to his concept reward associated processes are conceptualized using three psychological components e.g. liking (the hedonic value of a cue), reward learning by means of associative learning and incentive salience e.g. ‘wanting’ (motivational incentive of a cue) (Berridge, 2007; Berridge, 2012; Dayan & Berridge, 2014). Incentive salience is the Pavlovian-guided attribution of motivational value to a previously reward-related neutral representation of a cue (conditioned stimulus) resulting in a more attractive and ‘wanted’ cue/stimulus. Based on the computational model for incentive salience, Zhang and colleagues noted that the incentive salience value of a cue is the net of (associative-learning) derived prior knowledge concerning the relationship between the cue and the reward (unconditioned stimulus), and of the neurobiological environment pertaining to the actual state the cue is encountered in (e.g. the context). As such incentive salience is proposed to be dynamically generated by mesocortico-limbic systems upon each encounter/re-encounter of the reward stimulus, updating the stored knowledge about the cue-reward association using the information obtained from the surroundings. This latter process enables the modulation of the motivational value (the incentive salience) of a cue by changes in the neurobiological surroundings without further learning as it accounts for the differences in the state of mesocortico-limbic circuits (Dayan & Berridge, 2014; Zhang et al., 2009).

Summarizing, we offered an integrative account, ‘proactive’ model of reinforcement learning, to conceptualize model-free and model-based reinforcement learning by laying out a set of propositions. Also we articulate that the brain’s default network underlies modeling the environment in a way that it may be accessed by structures involved in model-based learning. Accordingly the neurobiological connectivity of the DA reward system (e.g. VTA-VS) was overviewed with the aim of accentuating its centrality with respect to afferentation by the

amygdala, hippocampus and OFC. To account for making prediction-based analogies for elucidating what is expected the concept of proactive brain was elaborated in light of the brain's default network function. We theorized that the orbitofrontal cortex offers an input for computing the reward expectations by integrating reward information into context frames developed as a function of the default network and forwards this information to the model-free reinforcement learning structures, and as a result RPE and model-based reward expectations are combined to yield the value signal in the VS.

7.3 The relationship between irisin, BDNF and mood in COPD patients

The main finding of this study is that the reciprocal of serum irisin level shows significant positive correlation with the Impacts score of SGRQ in COPD patients. Thus, more pronounced disturbance of mood (indicated by higher Impacts score) is accompanied by lower irisin levels. This effect has proven even more prominent among patients with lower BDNF levels but become non-significant in patients possessing higher BDNF concentrations. Analysis by means of multiple linear regression that corrects for possible confounders has confirmed the significant association between Impacts score and serum irisin, furthermore revealed four other significant determinants of Impacts score: BMI, weight, triglyceride level and FEV1% pred, an index of the severity of airflow limitation in COPD (Vestbo et al., 2013).

Several studies have corroborating evidence for the relationship between markers of disease severity and BMI. Recently, the COPDGene investigators analyzed the data of 3631 spirometry-confirmed COPD patients obtained from a multicenter prospective cohort study. The investigators found significant association between obesity, characterized by higher BMI and worse outcomes including poorer quality of life, dyspnea and reduced 6-minute walk distance. Furthermore, greater odds for acute exacerbations was observed, independent of the presence of comorbidities (Lambert et al., 2017). Furthermore, Ho and colleagues have also reported significant correlation between FEV1% (FEV1/FVC) and BMI (Spearman's correlation coefficient 0.255, $p < 0.01$) (Ho et al., 2015). In another study, the influence of metabolic syndrome and its components on the 5-year mortality was assessed in COPD. The authors found that 100 mg/dL increase of plasma triglyceride concentration increases the probability of death over the 5 years by 39% (translating into a hazard ratio of 1.39, CI: 1.06, 1.83) (Tanni et al., 2015). This finding corroborates our result that log triglyceride levels

significantly associated with the Impacts score in our final multiple linear regression model (Table 5). Moreover, the possibility for a common pathomechanism of COPD and depressive disorders was also suggested based on the results of an interventional study. Patients were enrolled in a complex exercise program (2 hours per day, 5 days per week, for 6 weeks) supervised by physiotherapists and lung specialists. At follow-up, improvement of depressive symptoms paralleled by significant reduction of BMI was reported in the subgroup of patients showing signs of depression at baseline (Catalfo et al., 2016). These findings could be explained by our proposition that exercise-induced increase of irisin levels may simultaneously induce white adipocyte browning and consequent weight loss and enhance mood via activation of the BDNF pathway in specific brain areas (e.g. hippocampus, ventral tegmental area) involved in affective disorders.

Prognostic value of FEV1% pred regarding population level clinical outcomes is acknowledged by the “Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2017 report” (Vogelmeier et al., 2017). FEV1% pred is also predictive of health status and the rate of exacerbations in COPD and it is closely interconnected with alteration of mood and psychosocial function (Celli et al., 2004). The significant inverse relationship between Impacts score and FEV1% pred is also in line with previous findings. Significant negative correlation between FEV1% pred and all component (Symptoms, Impacts, Activity) and the total score of SGRQ was previously described in a cohort of Hispanic smokers (Diaz et al., 2016). Similarly, in another study, significant negative correlation between FEV1% pred and the Total score was described in a sample of severe COPD patients ($r=-0.4$, $p<0.001$) (Welling et al., 2015). In a double-blind placebo-controlled study designed to assess the benefits of the fixed combination inhaler fluticasone propionate and salmeterol versus placebo, the longitudinal analysis of data for 4951 COPD patients showed significant negative correlation regarding the change in SGRQ scores and FEV1 during the 3 years of the study in all treatment arms, combined (Jones et al., 2011). Previously, we also found a significant negative correlation between the Total SGRQ score and FEV1% pred (Tajti et al., 2017).

Our present analysis showed a very strong positive association between the Impacts score reflective of depressive mood disturbances in COPD and the reciprocal of serum irisin (Table 5) that was substantially more remarkable in the stratum with BDNF levels lower than the sample median. In addition to reciprocal of irisin, regression coefficients remained significant for FEV1% pred, BMI and log triglyceride in the stratum with lower BDNF levels.

However, only FEV1% pred, BMI and weight showed significant contribution to the final model in the stratum with higher BDNF levels (Table 5). These results suggest the presence of an interaction between serum irisin and serum BDNF levels regarding their influence on Impacts score and they underscore our previous hypothesis that serum irisin may exert a peripheral effect reflected by the alteration of metabolic parameters (BMI, weight and serum triglyceride levels) and a central effect related to mood and motivation based on BDNF's action.

The role of BDNF in depressive disorders has been articulated by the neurotrophic hypothesis of depression. According to this, depression is based on neurotrophin deficiency of the limbic system, an effect that may be reversed by long-term administration of antidepressants (Dumas et al., 1997; Jeon & Kim, 2016). This hypothesis is closely linked to the neural plasticity hypothesis which postulates that environmental factors (e.g. stress) cause dysfunction of signal transduction cascades involved in neuronal adaptation and plasticity. A candidate pathway is that containing BDNF-cAMP response element-binding protein (CREB), a transcription factor (Jeon & Kim, 2016).

Change of BDNF plasma levels as well as tissue levels from post mortem biopsies of hippocampus have been described in depressed patients (Jeon & Kim, 2016). Furthermore, the cause-effect relationship between BDNF and major depressive disorder was established by a case-control study nested in a cohort of 1276 women aged 75 to 84 years. Using incident cases and controls over the four-year observation period, the authors concluded that BDNF is a state marker of major depressive disease based on the longitudinal decrease of serum BDNF levels in this cohort (Ihara et al., 2016). Corroborating evidence from a systemic review and meta-analysis of twenty publications including 1504 participants, furthermore showed significant correlation between changes of BDNF level and depression score as well as significant increases of BDNF levels accompanied therapy with antidepressants (Brunoni et al., 2008). Nevertheless, it should be noted that, despite the accumulating preclinical and clinical evidence, there are some controversies related to the role BDNF plays in the evolution of depression, as inconsistent observations questioning this hypothesis were also reported (Kheirouri et al., 2016; Groves, 2007). However, these discrepancies may stem from the methodologic differences like variance of patient populations, sample size, treatment schedules, disease severity and assessment tools quantifying disease severity (Kheirouri et al., 2016).

To the best of our knowledge, this is the first time that the irisin-BDNF axis was assessed with respect to its possible influence on mood disturbances in COPD patients. The ability of exercise to induce BDNF expression in the hippocampus via induction of the FNDC5/irisin

pathway has been reported previously in mice (Wrann et al., 2013). Our present results seem to support these findings in humans for the first time.

Limited number of reports deal with the alteration of serum irisin and BDNF levels in COPD patients. Irisin levels were shown to be lower in COPD patients than in controls (31.6 (IQR: 22.7-40.4) ng/ml and 50.7 (IQR: 39.3-65.8) ng/ml, respectively; $p < 0.001$) (Ijiri et al., 2015). This tendency was present even when patients were divided into subgroups with respect to the level of physical activity: in patients with lower physical activity, serum irisin levels were 23.1 (IQR: 17.3-27.0) ng/ml and 39.6 (IQR: 36.0-43.7) ng/ml in COPD and control patients, respectively (Ijiri et al., 2015). Others reported comparable irisin levels of 26.3 (IQR: 22.6-32.4) ng/ml, 53.7 (IQR: 46.7-62.8) ng/ml, 58.5 (42.8-78.9) ng/ml in smokers with and without COPD, and in non-smoking individuals, respectively (Kureya et al., 2016). While the serum BDNF levels measured in our study are higher than those in the study of Stoll and colleagues that included COPD patients (Stoll et al., 2012), they are within the magnitude measured in other studies involving healthy individuals and other patient populations. The reported serum BDNF levels span over five orders of magnitude, ranging from 0.005 ng/ml to 280 ng/ml (Ihara et al., 2016; Kheirouri et al., 2016; Jacoby et al., 2016; Failla et al., 2016), depending on the use of different ELISA kits.

A possible limitation of the present study comes from its design (cross-sectional study) limiting the possibility to draw cause and effect conclusions. Due diligence was exercised to counterbalance the effect of possible confounders by using multiple linear regression to account for their effect. Characterizing disturbance of mood by the Impacts component score of the SGRQ may also be viewed as a possible shortcoming. Identification of depression based on DSM 5 may prove to be challenging as accompanying somatic symptoms could be secondary to either depression or COPD (Catalfo et al., 2016). Furthermore, utility of certain diagnostic instruments, e.g. hospital anxiety and depression scale, has been questioned with respect to their accuracy in COPD patients (Chuang et al., 2016). Nevertheless, strong correlation between the Impacts score and depression has been described previously (Jones et al., 1992; Hynninen et al., 2007), allowing us to propose that irisin is a possible link between both metabolic disturbances and affective changes. The absence of post-bronchodilator whole-body plethysmography may also be viewed as a limitation, however, as previously described (Tajti et al., 2017), this patient population has been included in a COPD management program for a median of 5 (IQR: 3-10) years, hence patients already received bronchodilator therapy and were asked to take their medications as usual in the morning of the examinations. Thus, the current

results should be interpreted as on-treatment results. Summarizing, future prospective studies are needed to further underscore the propositions laid out in our current work. Nevertheless, this investigation has several merits like the relatively large clinical patient sample, the use of special tools (whole-body plethysmography and SGRQ, a validated disease-specific questionnaire), furthermore the stringent data analysis resulting in powerful findings.

In summary, we have found a significant inverse relationship between severity of mood disturbance and serum irisin levels among COPD patients. The fact that this correlation was considerably more influential among patients with BDNF levels below the sample median further supports the possibility that, in COPD, irisin links deterioration of mood to the central effects of BDNF exerted in areas closely associated with reward-related processes involved in the evolution of depression. Furthermore, our findings have a possible practical implication as the efficacy of disease management programs have been shown to depend greatly on the patients' ability to utilize personal resources like motivation to alter behavior and willingness to set new goals (Effing et al., 2014). Non-adherence to standard care is very frequent among COPD patients reaching about 70% (Ding et al., 2017). Considering these aspects, a further consequence of altered irisin-BDNF axis (and downstream processes including mesocortico-limbic dysfunction) may be the impairment of reward related motivation, preventing change of behavior needed for COPD management and causing lack of efficacy of disease management programs. Future interventional studies investigating the potential beneficial effect of endurance training tailored to the needs of COPD patients with respect to change of irisin-BDNF levels as well as mood and motivation are needed to further support this notion.

8 New findings

1. The proactive model of reinforcement learning was developed a novel, integrative framework that accounts for the interaction between model-free and model-based reinforcement learning.

2. Using this new model, the proactive model of reinforcement learning a neurobiological substrate was pinpointed for the model used by model-based reinforcement learning; e.g. it was proposed that this model develops as the result of the continuous function of the default network.

3. Starting from the integrative model to link mood disorder to reinforcement learning it was shown that humoral modulation of reinforcement learning associated neuronal structures, by altered irisin/BDNF may underlie the mood disturbances accompanying COPD.

9 Summary

Interventions focusing on the prevention and treatment of chronic non-communicable diseases are on rise. An integrative theoretical framework, the proactive model of reinforcement learning is proposed as it may contribute to understanding the etiopathogenesis of certain risk behaviors leading to NCDs.

The proactive model of reinforcement learning posits that based on the connectivity of structures attributed to model-based and model-free account, the two approaches for solving the reinforcement learning problems are closely linked and interact. On one hand based on the functional connectivity of VS, model-free and model based RL systems center on the VS that by integrating model-free signals (received as reward prediction error) and model-based reward related input to compute the main substrate of reinforcement learning the value signal. The proactive model of reinforcement learning also offers a neurobiological substrate for the model utilized by model-based reinforcement learning by suggesting that the default network showing extensive functional overlap with contextual associative areas functions in a way that the environment is continuously organized into context frames enabling the formulation of analogy-based association that are turned into predictions of what to expect.

Additional to the neural inferences humoral factors are also important, with irisin, a contraction-regulated myokine formed primarily in skeletal muscle but also in the brain and its downstream mediator BDNF possibly assuming a role. Starting from this we set out to elucidate the possible alteration of the irisin/BDNF axis in a clinical population who suffer from mood disorder, a disorder known to be linked with alteration of the reinforcement learning paradigm in a cohort of COPD patients. Case history, laboratory parameters, serum irisin and BDNF, pulmonary function and disease-specific quality of life (SGRQ) were determined in a cohort of COPD patients (n=74). Simple and then multiple linear regression was used to evaluate data.

We found that mood disturbances are associated with lower serum irisin levels (SGRQ's Impacts score and reciprocal of irisin showed a strong positive association; β : 419.97; CI: 204.31, 635.63; $p < 0.001$). This association was even stronger among patients in the lower 50% of BDNF levels (β : 434.11; CI: 166.17, 702.05; $p = 0.002$), while it became weaker for patients in the higher 50% of BDNF concentrations (β : 373.49; CI: -74.91, 821.88; $p = 0.1$). These results suggest that irisin exerts beneficial effect on mood in COPD patients, possibly by inducing the expression of BDNF in brain areas associated with reward-related processes involved in by depression. Future interventional studies are needed, nevertheless.

10 Összefoglalás

A magas átlagos jövedelemmel jellemezhető társadalmakban egyre nagyobb jelentőségűek a krónikus nem fertőző betegségek, melyek háttérében a WHO négy alapvető rizikómagatartást azonosított: dohányzás, egészségtelen étrend, elégtelen testmozgás és káros mértékű alkoholfogyasztás. Feltételeztük, hogy ezek mind az agy ősi viselkedésszabályozó rendszerének kóros (és/vagy civilizált körülmények között célszerűtlenné vált) funkciójára vezethetők vissza, ezért első célkitűzésünk egy új modell kidolgozása volt a mesocortico-limbikus rendszer működésére („a megerősítéses tanulás proaktív modellje”).

A megerősítéses tanulás egyik formája ún. modell-alapú, a másik modell-független. Az általunk kifejlesztett koncepció, a megerősítéses tanulás proaktív modellje a modell-alapú és modell-független idegi struktúrák konnektivitására alapozva felveti, hogy a megerősítéses tanulás középpontjában álló probléma megoldása a két rendszer interakciójának eredményeként jön létre. A ventralis striatum (VS) funkcionális konnektivitása arra utal, hogy a VS központi szerepet játszik mind a modell-alapú, mind a modell-független megerősítéses tanulásban. A megerősítéses tanulás proaktív modellje a modell-alapú tanulást meghatározó modell létrejöttét a kontextuális asszociációs területekkel nagyfokú átfedést mutató ún. agyi alaphálózat működésének tulajdonítja. Modellünk kiemelt szerepet feltételez az orbitofrontalis cortexnek (OFC) a modell-alapú és modell-független működés összehangolásában azáltal, hogy az OFC-nek tulajdonítja a jutalommal kapcsolatos információk integrálását a kontextuális keretbe. Az OFC ennek eredményeként generálhatja a várható jutalmat, ami glutaminerg pályákon keresztül érheti el a modell-független rendszert.

Mivel a hangulati életet alapvetően befolyásoló megerősítéses tanulás neuronális szabályozása mellett fontos szerepet játszik a humorális reguláció is, 74 COPD-vel kezelt beteg adatait egyszerű és összetett lineáris regresszióval elemezve megvizsgáltuk a szérum irisin és brain-derived neurotrophic factor (BDNF) koncentrációjának összefüggését a betegek szubjektív életminőségével. Mintánkban a Saint George's Respiratory Questionnaire (SGRQ) életminőségi tesztben a hangulatzavar kvantifikálására használt Hatás pontszám és az irisin-szint között szignifikáns fordított kapcsolatot találtunk, ami erősebb volt az alacsonyabb BDNF-szinttel rendelkező betegek körében, míg gyengébbnek mutatkozott a magasabb BDNF-szintűeknél. A fentiek alapján felvethető, hogy az irisin kedvező hatást gyakorol a hangulatra COPD-s betegek körében, vélhetően azáltal, hogy indukálja a BDNF expresszióját a megerősítéses tanulás szempontjából releváns agyi struktúrákban.

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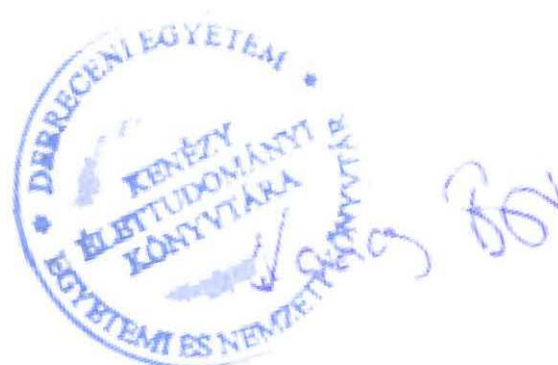


Registry number: DEENK/166/2017.PL
Subject: PhD Publikációs Lista

Candidate: Csaba Papp
Neptun ID: EKCKVB
Doctoral School: Doctoral School of Health Sciences

List of publications related to the dissertation

1. **Papp, C.**, Pák, K., Erdei, T., Juhász, B., Seres, I., Szentpéteri, A., Kardos, L., Szilasi, M., Gesztelyi, R., Zsuga, J.: Alteration of the irisin / brain-derived neurotrophic factor axis contributes to disturbance of mood in chronic obstructive pulmonary disease patients. *Int. J. Chronic Obstr. Pulm. Dis.* "Accepted by Publisher", 2017.
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3. Zsuga, J., Erdei, T., Szabó, K., Lampé, N., **Papp, C.**, Pinter, Á., Szentmiklósi, J. A., Juhász, B., Szilvássy, Z., Gesztelyi, R.: Methodical Challenges and a Possible Resolution in the Assessment of Receptor Reserve for Adenosine, an Agonist with Short Half-Life. *Molecules*. 22 (5), 839-855, 2017.
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Total IF of journals (all publications): 18,463

Total IF of journals (publications related to the dissertation): 5,736

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

01 June, 2017



12 Key words

Model-free reinforcement learning, model-based reinforcement learning, proactive brain, default network, proactive model of reinforcement learning, irisin, BDNF, SGRQ, whole-body plethysmography, COPD

13 Kulcsszavak

Modell-független megerősítéses tanulás, modell-alapú megerősítéses tanulás, proaktív agy, agyi alaphálózat, a megerősítéses tanulás proaktív modellje, irisin, BDNF, SGRQ, teljesest-pletizmográfia, COPD

14 Acknowledgements

This research was supported by the Hungarian Brain Research Program (**KTIA_13_NAP-A-V/2**), the Scientific Research Grant of the Hungarian Foundation for Pulmonology (awarded in 2015), the Ministry for National Economy (**GINOP-2.3.2-15-2016-00062** and **AGR-PIAC-13-1-2013-0008**). Writing the thesis was supported by the Ministry for National Economy (**GINOP-2.3.2-15-2016-00005**).

15 Appendix