THE MIND Bulletin on Mind-Body Medicine Research

Editorial

Personalized and One Medicine Coming Together

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In an earlier publication (see for detailed information and references [1]), we highlighted the contributions of new genetic and bioinformatics tools to the development of personalized medicine. We also considered how these developments might be used to accelerate advances and reduce healthcare costs based on the principles of One Medicine.

Personalized medicine focuses on the development and application of therapeutic strategies that are tailored to specific patient characteristics. One successful example of this direction is trastuzumab, which is a humanized monoclonal antibody used to treat patients diagnosed with advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancers. Similarly, cetuximab and panitumumab are monoclonal antibody drugs that have been approved by the United States Food and Drug Administration as targeted treatment of epidermal growth factor-(EGFR) positive metastatic colon cancers. While the introduction of these and related drugs has created a virtual revolution in clinical care, future development of personalized therapies will depend on increased knowledge and understanding of the unique features of each patient and each disease. Ongoing advances will rely on comparatively new and highly sophisticated methods used to explore genome sequences and gene expression both in health and disease states. Among these is whole genome sequencing (WGS), which is a process used to elucidate the sequence and chromosomal localization of the ~3 billion nucleotide pairs in the human genome. While the first near-complete human genome sequence was reported in 2004, several more recent methodologic advances, including whole exome sequencing and single nucleotide polymorphism (SNP) genotyping, have served to advance the field and accelerate discovery. As a group, these tools can be used to identify genetic variation (e.g., polymorphisms and potentially-damaging mutations) and thus may aid in the diagnosis and discovery of genetic diseases and their associated risks. These tools were originally quite time-consuming and prohibitively expensive to perform which precluded their use in routine clinical practice. However, in recent years, some inroads have been made toward using genomic information collected by these methods to develop personalized strategies that address the needs and concerns of physicians and patients.

While WGS and related techniques can provide information on gene structure and sequence, in some cases it may be more critical to evaluate patterns of gene expression. For example, cancers are now frequently classified based on their gene expression patterns rather than their location or tissue of origin. Microarray and RNA sequencing (RNAseq) are two techniques that have been used to

evaluate gene expression in specific target cells and tissues. Microarray analysis relies on the quantitative evaluation and interpretation of binding interactions between cellular RNA isolated from target cells of interest and short fragments of nucleic acid sequences (probes) affixed to a surface. This technique has broad application beyond gene expression and is already in clinical use as a means to diagnose viral infections via unbiased detection of viral DNA or RNA genomes. By contrast, RNAseq is a more open-ended and flexible method for evaluating gene expression, as it can be used for simultaneous identification of both characterized and as yet uncharacterized transcripts from multiple sources (e.g., the numerous bacterial species that constitute the human gut microbiome). Both microarray and RNAseq generate vast amounts of data that require complex statistical evaluation by highly skilled bioinformaticians to generate patterns and clusters useful for further consideration. This has led and will continue to lead to new and more effective and specific therapies for cancer treatment.

While RNAseq remains primarily a research technique at this time, it will eventually enter the mainstream and will be used for clinical decision-making. Thus, physicians will need training so that they will have a clear understanding of this method and thus be capable of interpreting its outcomes.

Given the numerous anthropological, genealogical, and forensic applications of this technology, it is perhaps not surprising that most of the clinical emphasis has been placed on efforts to understand genomic variation and disease-associated gene expression patterns in humans. Thus, while other mammalian genomes have been fully sequenced, the clinical use of personalized strategies in veterinary medicine remains limited. Based on the principles of One Medicine, which is a field that focuses on diagnoses and therapeutic strategies that may be shared by human and veterinary medicine, an improved understanding of genetic variation and its relationship to disease processes in other mammalian species may be an overlooked source of critical clinical information. As a first principle, it is critical to recognize that cellular metabolic and biochemical pathways, growth factors, and signaling mechanisms are similar, if not identical, across many mammalian species. Thus, it is certainly not surprising to find that many diseases (e.g., cancer, diabetes, and arthritis) are frequently diagnosed in both human and animal species.

Future developments in the field of One Medicine will rest on our understanding of conformational matching. Many of our previous publications have highlighted the nature and evolution of structurally-matched ligand-receptor pairs. Based on this principle, we understand that variations will only be tolerated if they can be accommodated within pre-existing patterns. These constraints lead to the overall conservation of critical pathways while permitting the development of novel modalities (e.g., improved cognition).

Finally, recognition and application of the principles of One Medicine may ultimately serve to reduce healthcare costs. Toward this end, we will need to identify methods that facilitate the “retro-matching” of genomic and gene expression data to appropriate clinical pathologies. These and related strategies may provide us with cross-species information that predicts outcomes and adverse events. Taken one step further, genomic and gene expression data from plant species may ultimately be used to understand human nutrition and food intolerance based on our understanding of shared signaling pathways and conformational matching principles. Increased computing capacity and new developments in bioinformatics techniques will ultimately increase the economic feasibility of these directions. Similarly, healthcare costs will be reduced once personalized treatments have been developed that can be used for similar indications in both human and veterinary medicine.

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Research

Mobility Coupled with Motivation Promotes Survival: The Evolution of Cognition as an Adaptive Strategy

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In a recent publication [1], we present the hypothesis of an evolutionary and functional relationship between the occurrence and use of the catecholamine dopamine (DA) as a neurotransmitter (messenger)—particularly in invertebrates—and the catecholamines epinephrine (EP) and norepinephrine (NE), messengers that are found only in vertebrates. Interestingly, both are also involved in pathways leading to the production of endogenous morphine, another messenger substance. We assume that the use of EP/NE as messengers represents an evolutionary advantage and adaptation process, whereby this "metabolite" (its biochemical intermediates) is only used "in retrospect" as a neurotransmitter (evolutionary "retrofitting"); on the way to greater mobility, with a need to expand data storage (memory, cognition) within the scope of this expanded radius, additional messengers were needed. Moreover, challenges and "stress" coming with increased mobility (e.g., entering unfamiliar environments) had to be successfully met to ensure survival. The same applies to the synthesis of morphine, which is formed from tyramine and tyrosine via DA (mediated by enzymes that also interact with EP/NE) so that morphine can be chemically classified as an "end product" of a DA-opiate cascade. Morphine's functional importance is the downregulation and termination of a motivational sequence from wanting (appetite) to avoiding (avoidance) to relaxation/quiescence (assertion).

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Personalized Medicine and Personalized Health Promotion Based on Motivation and Reward Proceedings

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As the number of patients with lifestyle-related chronic diseases continues to increase worldwide [1], the need for personalized medicine is growing. At the same time, the development and implementation of prevention and health promotion interventions to help individuals change their health behaviors is becoming increasingly important. While personalized medicine focuses on the development and application of therapeutic strategies tailored to specific patient characteristics, such as specific antibodies, personalized health promotion focuses on specific patient lifestyle characteristics, such as diet, exercise and relaxation behaviors (or stress management). Thus, supporting patients change specific negative health behaviors that they perform on a regular basis is the focus of contemporary health promotion. Examples of tools with this objective include technological applications such as fitness trackers that connect to mobile phone apps and suggest behaviors based on the measurement (e.g., walking more steps the next day). However, these technological advances are often available to clients before their effectiveness has been examined in research studies. In addition, the development of health behavior change techniques often occurs without an adequate theoretical basis about the psychological or neurobiological processes involved in health behavior change. This imposes the risk of decreasing patient engagement over time because extrinsic motivational incentives are not strong enough to build sustained engagement.

To better understand patients' engagement in health behavior change processes, in [2], we have analyzed the role of motivation and reward proceedings at different stages of behavior change processes. Our analysis is based on the triad of motivation and reward mechanisms, which include approach motivation (wanting) with its associated reward pleasure, aversive motivation (avoiding) with its associated reward relief, and assertion motivation (non-wanting) with its associated reward quiescence. In our Model of Engagement (Figure 1), individuals first proceed from being unaware of the benefits of a particular behavior change to becoming aware of the benefits. At these first two stages, individuals are not engaged in a health behavior change process (non-engagement). Once they begin contemplating changing their behavior and move to the planning stage, they become motivationally engaged. The transition to the initiation stage, where the new behavior is performed for the first time and then continually performed until the new behavior is maintained (has become a habit), is characterized by executive engagement. Motivation and reward proceedings play distinct roles ate these stages. During non-engagement, assertive motivation is active because no need to change behavior is yet considered relevant. Parasympathetic activity and the release of endogenous opiates, oxytocin and related neurotransmitters are involved. During contemplation, planning, initiation and continued action, an individual progresses in response to appetitive motivational stimuli or appetitive motivational goals (see [2] for a distinction between stimulus-driven behavior and goal-directed behavior), involving, for example, the mesocortical dopamine pathway in the frontal cortex. An alternative to appetitive motivational salience is aversive motivational salience, which can lead to the same behavioral outcomes. However, because of the negative emotions involved (e.g., fear), appetitive motivational salience is preferred. In fact, repeated activation of appetitive motivational salience can lead to other positive resources [3], i.e., an upward spiral of positive emotions. At the maintenance stage, individuals are steered by assertive motivational salience, i.e., the desire to maintain the new status quo. This phase is characterized by the involvement of the hippocampus, which stores memories of past affect (rewards) from specific behaviors

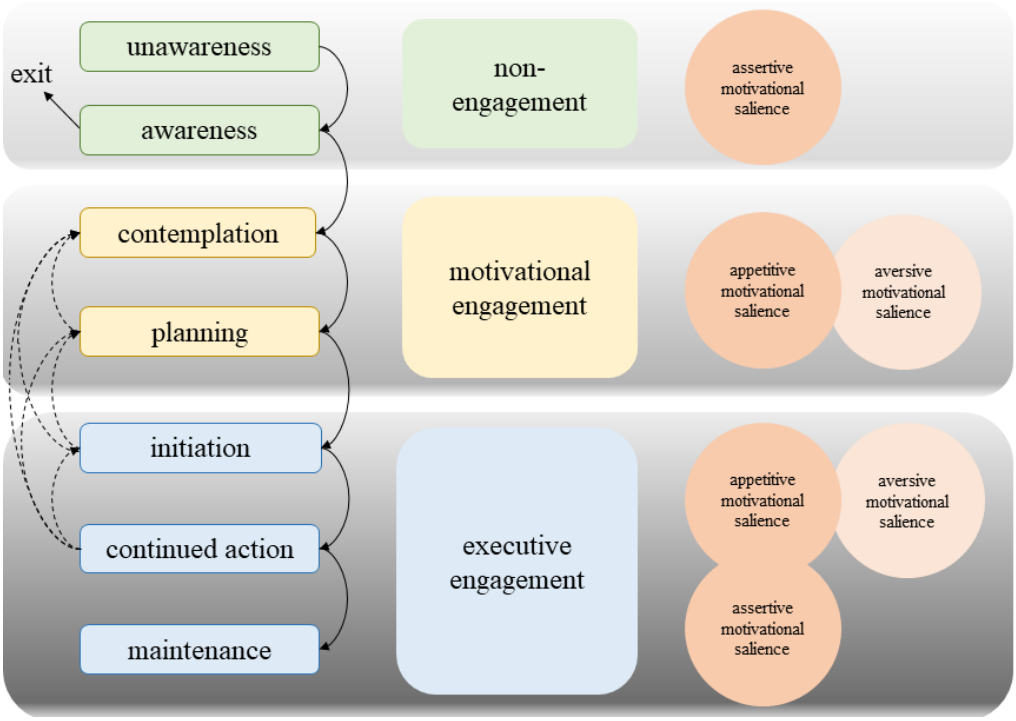

Figure 1: Model of Engagement (adapted from [1]).

By applying motivational interviewing or other tools, it is possible to determine which stage of a particular health behavior change process an individual currently is at and what is needed to progress to another stage. For example, imagine a person who regularly watches Netflix series for relaxation in the evening and has just learned that breath awareness meditation leads to a physiologically better relaxation response. This person has just moved from the unawareness stage to the awareness stage. To progress to the contemplation stage, motivational cues are needed that activate appetitive motivational salience and thereby make the new behavior more attractive. This motivational cue could be the information that by replacing one episode per day by a meditation session, the person might sleep better at night and thus experience increased sense of well-being. Various behavior change techniques can be chosen to convey this information, such as a nudging technique like social comparison (e.g., showing a short movie about a person who meditates and sleeps well at night), or a facilitating technique such as providing a flyer with an explanation (e.g., in a patient counseling session). Such behavior change techniques increase reward expectancy and are therefore likely to support lasting health behavior change when applied according to an individual's current type of engagement.

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Combining App-based Behavioral Support with Electronic Nicotine Delivery System Devices for Smoking Cessation

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Worldwide, tobacco use causes over 7 million deaths annually [1]. As of 2022, over 35% of Germans report current use of cigarettes. Approximately 38% of current smokers report wanting to quit smoking [2]. However, about 80% of individuals who attempt to quit smoking without support relapse within a month; only 3% remain abstinent six months later [3]. Treatment methods outlined in medical guidelines are rarely used, and both the effectiveness of and adherence to these interventions remain low [4,5], necessitating the development of novel and effective smoking cessation methods.

Electronic nicotine delivery systems (ENDS) have been found to be more effective in helping smokers quit than recommended cessation methods [6]. Their effectiveness can be further increased if coupled with a behavioral support component [7]. These findings highlight the need for smoking intervention efforts that target the physical as well as the psychological mechanisms of nicotine dependence. Recognizing the importance of holistic approaches to smoking cessation, the Berlin-based startup company Sanos Group developed an integrated smoking cessation intervention (‘nuumi’). The smoking cessation program is accessible via a smartphone app, thus allowing users to personalize their intervention experience by having control over the place and time they wish to interact with the app [8]. Additionally, digitalized interventions allow for further personalization of health-related information by tailoring content to users’ needs, e.g. via personalized text messages [9].

Nuumi offers an app-based behavioral support consisting of video and audio recordings and interactive exercises, coupled with a bluetooth-supported ENDS device. The behavioral support consists of the digitalized content of a health promotion course developed by Tobias Esch; the course framework is described elsewhere [10]. The digitalized course features content derived from four areas, including Behavior, Exercise, Relaxation, and Nutrition (BERN). In order to meet the specific needs of smokers motivated to quit, the course content has been tailored to help individuals overcome barriers frequently encountered during smoking cessation attempts. For example, smokers report greater stress levels relative to nonsmokers, and one of the most frequently reported reasons for continued smoking is the management of stress and negative emotions [11,12]. Stress and negative emotions can even increase during withdrawal [13], creating a barrier to successful smoking cessation [14]. App content and exercises draw from Mind-Body Medicine-based techniques designed to foster social, psychological, behavioral, and spiritual wellbeing [15] and decrease negative emotions including depressive symptoms, anxiety, and stress [16,17]. Nuumi users learn to effectively manage stress and negative emotions and learn to apply coping strategies when experiencing withdrawal symptoms. Instead of taking a one-size-fits-all approach, nuumi provides the opportunity of using the exercises to reflect on one’s own smoking history, identify individuals and situations that serve as triggers for cigarette cravings, and to recognize which individuals in one’s environment serve as an effective source of social support during one’s smoking cessation process.

Simultaneously, users are asked to substitute an ENDS device equipped with a nicotine-containing liquid solution for their tobacco cigarettes. Over a period of several weeks, participants are provided with pods containing gradually decreasing concentrations of nicotine. Reducing nicotine content in tobacco products has been suggested to lead to a reduction of reinforcing effects, and a subsequent decrease in positive sensations typically associated with nicotine self-administration, both of which are key factors of nicotine dependence [18].

The scientific evaluation will be conducted by principal investigator Tobias Esch and his team of research associates including Cosima Hoetger and Helen Schiek at the Institute for Integrative Health Care and Health Promotion at Witten/Herdecke University. In early 2023, a two-arm parallel randomized controlled trial will be conducted among a sample of current tobacco cigarette smokers (n=250) who self-report having smoked more than 9 cigarettes per day for a period of at least 12 months, who are deemed to be dependent on nicotine as indexed by a score of >3 on the Fagerström test for Cigarette Dependence, and who are motivated to quit. Participants will be randomized to either an intervention group or a control group. While the intervention group will be given access to nuumi (i.e., app plus ENDS device), the control group will receive self-help cessation support consisting of a pamphlet provided by the German Federal Center for Health Education and a supply of

nicotine patches. Biochemically verified abstinence, as indexed by saliva cotinine and carbon monoxide testing results will serve as the primary outcome. Secondary outcomes will include, but not be limited to, self-reported one-week point prevalence abstinence at six-month follow-up, treatment adherence, cravings, health-related quality of life, mindfulness, and perceived stress. If found to be effective, nuumi could constitute a cost-effective and convenient smoking cessation method for smokers motivated to quit. Long-term, nuumi could contribute to decreasing the risk of smoking-related morbidity and mortality.

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Mind-Body Exercise Corner

Breath Awareness Meditation

Breath awareness meditation is a type of meditation that involves focusing on the breath as a way to quiet the mind and bring greater awareness to the present moment. It is a simple and effective practice that can be done by anyone, anywhere, at any time.

To practice breath awareness meditation, find a comfortable and upright seated position, with your spine straight and your feet planted on the ground. Begin by closing your eyes and taking a few deep breaths, allowing yourself to fully relax and let go of any tension in the body.

Then, bring your attention to the sensation of the breath as it moves in and out of the body. Notice the sensation of the breath as it enters the nostrils, fills the chest, and expands the belly. Notice the coolness of the air as it enters the body, and the warmth as it leaves.

As you focus on the breath, your mind will inevitably wander. When this happens, gently redirect your attention back to the breath. Do not judge or criticize yourself for being distracted. Simply acknowledge the thought and return to the breath.

Breath awareness meditation can be practiced for as little as a few minutes at a time, and can be gradually increased as you become more comfortable with the practice. It is a powerful tool for cultivating mindfulness, reducing stress and anxiety, and promoting overall well-being.

The Mind-Body Medicine Research Council

Exploring the Details of Body and Mind That Account for a Healthy Life in an Uncertain World

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Pandemic, war, climate change, artificial intelligence – Our world and our lives are full of challenges that require a high level of psychological resistance and coping. Since the mind and the body are interconnected, it is important to develop, implement, evaluate and understand measures at both levels for a healthy and thriving society.

The Mind-Body Medicine Research Council (MBMRC) aims to analyze these aspects in their details. The MBMRC is hosted by the Institute for Integrative Health Care and Health Promotion (IGVF), Faculty of Health/School of Medicine at Witten/Herdecke University, Germany. The institute focuses its attention on improving primary health care and increasing the effectiveness of health promotion efforts for patients. While the implications of our research findings certainly contribute to improving health outcomes at the population level, our focus remains on the individual and their personal resources as well as the pathways through which protective (salutogenetic) factors – including, but not limited to, resilience, self-efficacy, self-care and -healing, and the motivation to improve one's personal health behaviors – can be activated and strengthened.

For this, we apply basic and applied sciences, from neurobiology to general health research, including integrative as well as Mind-Body Medicine (MBM). Tobias Esch, a university professor, researcher, and physician, serves as the institute's director and has founded the university's outpatient clinic in general medicine, thus closing the gap between rigorous research and patient-focused practice, and ensuring that the research conducted remains clinically relevant to patients.

Our research efforts are driven by a team of researchers and health care practitioners from a wide spectrum of disciplines who work closely and effectively with one another. Witnessing the successful fusion of research and practice at the institute has led us to pursue additional and similarly fruitful collaborations.

In this endeavor, we seek to uncover life processes involved in healthy living and longevity, including molecular and neurobiological aspects, as well as the applied sciences of MBM. In order to deepen and expand as well as for internationalization in this area, our institute has created the MBMRC composed of outstanding scientists and research affiliates, who contribute their respective expertise in specific and complementary ways to the institute.

The timeliness of this Council and its educational and research mission also may be ascertained by the stressful times we all find ourselves (pandemics, global warming etc.). Thus, as a body, the Council hopes to alleviate the associated stress of our time by generating knowledge in medical research and disseminating it to our communities. The mind, in particular, is the harvester of both internal and external stimuli, which can be harnessed for health and longevity.

At the present time, the Council consists of the following members:

Tobias Esch, M.D. (Co-Chair)
George B. Stefano, Ph.D. (Co-Chair)
Maren M. Michaelsen, Dr. rer. oec. (Project Lead)

How to become a member of MBMRC

As the MBMRC has just been founded, the number of members is yet small. In the future, the council aims to invite outstanding researchers in the field of Mind-Body Medicine to become MBMRC members. Membership implies no fee.

Call for Papers / Events

- **Special Issue „Neurobiological Aspects of Motivation and Positive Mood" in *Biology* (IF: 5,2)**

  The Special Issue on "Neurobiological Aspects of Motivation and Positive Mood" in the journal *Biology* is being edited by Tobias Esch and Maren M. Michaelsen from Witten/Herdecke University, Germany, and Gregory Fricchione from Harvard Medical School, USA. More information of the special issue is available on:

  www.mdpi.com/journal/biology/special_issues/T2AUK5D697

  The submission deadline is 15 September 2023.

- **Conference "The Science of Tai Chi & Qigong as whole-person health – Advancing the Integration of Mind-Body Practices in Contemporary Health Care"**, Boston, USA, Sept 18-19, 2023

  The Call for Abstracts and Call for Sessions will open in February 2023.

  www.oshersciencecoftcq.org

Recent publications of MBMRC members

Altmann, N., Scheer, L. & Esch, T. (2022). Digitale Kommunikation in der Praxis: Chancen, Risiken, Tipps und Tools. In M. Henningsen, P. Stachwitz, S. Fahimi-Weber, B. Afzali & N. Altmann (Hrsg.), *Die digitale Arztpraxis: Technik, Tools und Tipps zur Umsetzung.* Medizinisch Wissenschaftliche Verlagsgesellschaft.

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