Accepted Manuscript

Title: Conceptual endophentoypes: A strategy to advance the impact of psychoneuroendocrinology in precision medicine

Authors: Dirk Hellhammer, Gunther Meinlschmidt, Jens C. Pruessner

PII: S0306-4530(17)31499-3
DOI: https://doi.org/10.1016/j.psyneuen.2017.12.009
Reference: PNEC 3787

To appear in:

Received date: 9-11-2017
Revised date: 18-12-2017
Accepted date: 19-12-2017

Please cite this article as: { https://doi.org/

Conceptual Endophentoypes: A Strategy to Advance the Impact of Psychoneuroendocrinology in Precision Medicine

Dirk Hellhammer[a,1], Gunther Meinlschmidt[b,c,d,1,*], Jens C Pruessner[e,1]

[1]Authors in alphabetical order; all authors contributed equally

Affiliations:

[a]Department of Psychology, University of Trier, D-54286 Trier, Germany, Email: hellhamm@uni-trier.de

[b]Department of Psychosomatic Medicine, Faculty of Medicine, University of Basel and University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland, Email: gunther.meinlschmidt@unibas.ch

[c]Division of Clinical Psychology and Epidemiology, Department of Psychology, University of Basel, Missionsstrasse 60/62, CH-4055 Basel, Switzerland

[d]Division of Clinical Psychology and Cognitive Behavioral Therapy, International Psychoanalytic University, Stromstrasse 1, D-10555 Berlin, Germany

[e]Department of Psychology, University of Konstanz, D-78457 Konstanz, Germany, Email: jens.pruessner@uni-konstanz.de

[*]Correspondence to: Gunther Meinlschmidt, gunther.meinlschmidt@unibas.ch; Department of Psychosomatic Medicine, University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland, Phone: ++41 61 265 53 17

Word Count (text body only): 10,674

Graphical abstract: 1

Number of Figures (in color online only): 3

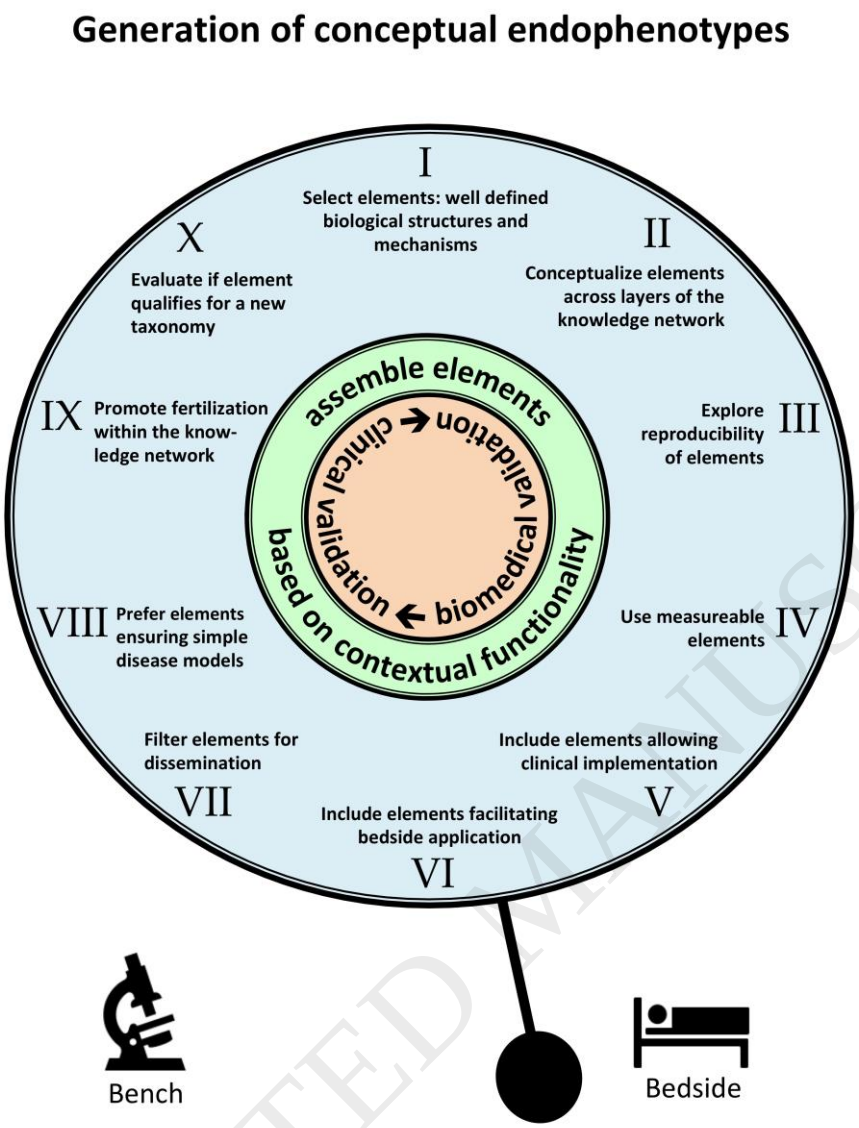
Number of Tables: 0

Short title: Conceptual endophenotypes in psychoneuroendocrinology

Revised version for submission as invited viewpoint to

Psychoneuroendocrinology

Graphical abstract



Highlights

- We introduce a new translational strategy based on conceptual endophenotypes (CEs).
- This CE-strategy aims at identifying subtypes for targeted treatments.
- CEs are iteratively developed and validated, linking research and clinical evidence.
- The CE-approach is exemplified for stress related disorders.

Abstract

Psychobiological research has generated a tremendous amount of findings on the psychological, neuroendocrine, molecular and environmental processes that are directly relevant for mental and physical health, but have overwhelmed our capacity to meaningfully absorb, integrate, and utilize this knowledge base. Here, we reflect about suitable strategies to improve the translational success of psychoneuroendocrinological research in the era of precision medicine.

Following a strategy advocated by the National Research Council and the tradition of endophenotype-based research, we advance here a new approach, termed “conceptual endophenotypes”. We define the contextual and formal criteria of conceptual endophenotypes, outline criteria for filtering and selecting information, and describe how conceptual endophenotypes can be validated and implemented at the bedside. As proof-of-concept, we describe some of our findings from research that has adopted this approach in the context of stress-related disorders.

We argue that conceptual endophenotypes engineer a bridge between the bench and the bedside. This approach readily lends itself to being continuously developed and implemented. Recent methodological advances, including digital phenotyping, machine learning, grassroots collaboration, and a learning healthcare system, may accelerate the development and implementation of this conceptual endophenotype approach.

Keywords: biomarker; personalized medicine; precision medicine; precision psychiatry; Research Domain Criteria (RDoC); Neuropattern.

1. Introduction

Over the past several decades, psychobiological research has generated a tremendous wealth of findings on the psychological, neuroendocrine, molecular and environmental

processes implicated in mental and physical health. However, to date little progress has been made in the translation and application of these findings into clinical practice. This chiasm between the bench and bedside has motivated our interest in conceptualizing and implementing suitable strategies to improve the translational success of psychoneuroendocrinological research in this current era of precision medicine.

Precision Medicine has been described as the provision of “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentation.” Inherent in this concept is the goal of improving clinical outcomes for individual patients (Jameson and Longo, 2015). In a landmark paper entitled “Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease”, the US National Research Council (National Research Council, 2011) formulated its vision of precision medicine, defining a new taxonomy that links multi-parameter molecular, clinical, and environmental data with health outcomes in a dynamic, iterative fashion.

Referring to the NRC report, Krishnan (2015) recently commented on the role of this strategy for precision psychiatry: “Psychiatric research has entered, just like the rest of medicine, an inflection point where the data deluge is beginning to overwhelm our capacity to absorb, integrate, and utilize knowledge. The growth of data-intensive biology and information technology developments have generated an exciting opportunity to improve the diagnosis and management of disease by developing a knowledge network, and a new taxonomy, that integrates biological and clinical information with outcome data to improve the lives of patients. The compelling need is to improve the link between biology and the patient with their treatment and outcome.” Krishnan compared the NRC approach with common taxonomies (e.g., the Diagnostic and Statistical Manual of Mental Disorders; DSM) and the Research Domain Criteria (RDoC) of the National Institute of Mental Health (NIMH). As

proposed by the NRC, he views a “knowledge network” (defined below in Section 2) as a prerequisite for understanding the biology and underlying causes of psychiatric diseases, and for successfully discriminating subgroups for a new taxonomy.

This paper aims to identify strategies for how psychobiological research can best improve precision medicine. We first review how the NRC strategy fits with RDoC, endophenotypes, and other approaches of basic research in mood disorders. Next, using the example of mood disorders, we demonstrate how strategies generating endophenotypes may best be suited to add to the strategy, advocated by the NRC. Generalizing from that analysis, we argue that most biomedical research data are essentially presented in a theoretical framework, loosely based on a broad set of hypotheses and psychobiological concepts. Thus, we introduce in section 4 the term ‘conceptual endophenotype” as a new and explicit conceptual strategy to improve clinical applicability. We then define the contextual and formal criteria of conceptual endophenotypes, and discuss how they can be validated and implemented at the bedside.

Finally, we describe research findings that have successfully adopted the latter strategy in the context of the psychoneuroendocrinology of stress-related disorders. We conclude by arguing that conceptual endophenotypes can be continuously developed and easily implemented in clinical care, thereby facilitating personalized diagnostic and therapeutic treatments in a stepwise manner.

2. Identifying patient subtypes in Precision Medicine

The NRC paper arguing for a new taxonomy of disease offers an elaborate and innovative strategy for advancing precision medicine (National Research Council, 2011): The long-term goal of the new taxonomy is to facilitate personalized diagnostic and treatment. The new taxonomy is based on an underlying “Information Commons” and a “Knowledge Network”. The Information Commons refer to available data that link individual molecular and biological information to patient demographic characteristics. These data are then proposed to be made widely available to other researchers in what is called a ‘Knowledge Network’ and a ‘New Taxonomy’. The ‘Knowledge Network’ adds value to these data by integrating them with evolving knowledge of fundamental biological processes. Here, the patient is characterized not only through signs and symptoms, but also by specific measures of the genome, epigenome, microbiome, exposome, and any other types of data that are available. In other words, the characterization of any given patient across these different ‘layers’ of the knowledge network provides (or establishes) the basis for determining an individual subtype. Upon validation, each new disease or disease subtype contributes to a new taxonomy, which then engenders more accurate diagnosis and targeted treatment for improved health (see Figure 1).

Insert Figure 1 around here

These subtypes map on to the theoretical framework of the endophenotype concept. The endophenotype approach has led to a re-evaluation of the relationship between nature and nurture (Gottesman and Hanson, 2005). Given the profound implications of the movement towards the development of endophenotypes, we discuss below, in Section 3, whether and how such an approach could contribute to the development of a new taxonomy of disease subtypes in a knowledge network, as proposed by the NRC.

Need for hypotheses and concepts

The NRC articulated the expectation that layers of the knowledge network would be continuously updated through new biomedical research and observational studies during the normal course of clinical care. They stated researchers can “propose hypotheses about the importance of various inter-and intra-layer connections that contribute to disease origin, severity, or progression, or that support the sub-classification of particular diseases into those with different molecular mechanisms, prognoses, and/or treatments, and these ideas then could be tested in an attempt to establish their validity, reproducibility, and robustness.” (p. 14) Thus, the NRC approach advocates the development and testing of hypotheses with an explicit focus on the improvement of personalized diagnosis and treatment. In addition to generating data-based subtypes, such approaches would be expected to first generate “conceptual subtypes”, which may be particularly useful in the context of complex diseases such as mental disorders. However, the NRC did not provide a detailed example of this proposed approach, leaving it unresolved as to how this validation process would contribute to the development of knowledge networks.

With respect to endophenotypes, Turetsky et al. (2007) suggest “candidates” that reflect a “discrete and well-understood neurobiological mechanism that is both informative for the pathophysiology of a disorder and indicative of the action of a limited number of genes” (p. 70). When considering this criterion, it is apparent that one can start by identifying a relevant biological mechanism before classifying a phenomenon as an endophenotype, or one can start by classifying a phenomenon as an endophenotype, with the identification of the relevant biological or other mechanisms to follow. Taking the latter route, Prendes-Alvarez and Nemeroff (2016) recently published a review discussing how endophenotypes could contribute to personalized medicine in the prediction of an individual’s vulnerability for mood

disorders. They expect that about a dozen or so currently-identified genetic variants could provide knowledge about mechanisms, which then could inform diagnosis, treatment and prognosis, and foster the development of novel blood-based tests (Yu et al., 2016).

In another paper, Alhajiji and Nemeroff (2015) described their vision of personalized medicine in the context of mood disorders. Like the approach formulated by the NRC, they argue such a vision should integrate “genetic information, epigenetic characteristics, biomarkers, environmental exposures, and clinical signs and symptoms to predict disease susceptibility, establish an accurate diagnosis, and predict the response to specific treatments“ (p. 395). Thus, the authors suggested going beyond endophenotypes to integrate all available individual characteristics, personal history and biomarkers into the clinical approach for optimizing diagnosis, treatment, and prevention. This approach satisfies the NRC criteria for a knowledge network: constructing a common knowledge network for mood disorders as an effective platform for integrating and comparing data across different studies is likely to facilitate research on subtype discovery.

In sum, the currently available strategies attempt to integrate multiple levels of information from biological and non-biological data, including genetics, epigenetics, neuroimaging and environmental factors, including family and personal history (e.g., exposure to adversity in early life). Depending on the individual approach, specific measures are integrated into the decision process, and they guide clinical decisions in the context of mood disorders. However, most research studies to date have been predominantly driven by a diverse set of concepts and hypotheses that are not grounded in an overarching theoretical model, and their findings need to be validated and replicated before they can be incorporated into standard clinical practice.

Challenges for implementation of research in clinical reality

The vision of establishing a unified knowledge network in precision medicine, especially in disciplines addressing mental disorders, is challenged by reality of the situation on the ground, in so far as its implementation in health care is concerned.

The RDoC have their own classification framework, as summarized by Cuthbert (2014): This "framework for psychopathology research intended to explicate specific aspects of functional impairment by studying relevant brain-behavior relationships, in contrast to the current heterogeneous categories of mental disorders defined by various groupings of symptoms. Endophenotypes fit naturally into the RDoC context since they are typically conceived to be closer to fundamental neural and psychological mechanisms than more abstracted disorder categories. Consequently, the genomic aspects of endophenotypes take on a particular significance for understanding genetic risk architectures in such an approach to psychopathology." Cuthbert further notes the RDoC approach takes into account the fact that "the vast majority of research grant applications are limited to a single disorder and exclude any patients with comorbid diagnoses. The difficulty is that the current categorical nosology has become the *de facto* criterion for evaluating research grant applications, journal publications, and treatment development". Grant applications that embody a non-DSM approach are seldom reviewed favorably because there is no accepted alternative standard to reflect other research approaches that might be based upon emerging findings in neuroscience and behavioral science. This is precisely the problem the NIMH tried to address when initiating RDoC. RDoC's core aim is to "free investigators from the contemporary nosological hegemony of the grant-review system and encourage studies based on neuroscience and specific aspects of functioning that can lead to new diagnostic and treatment innovations." (p. 1205).

Basic research may also contribute in a meaningful manner to elucidate associations among measures in the knowledge network. Hand in hand, both biomedical and clinical research can foster the growth of the knowledge network (see Figure 1). Thus far, most measures related to RDoC and basic research have been only weakly linked to clinical practice. While RDoC likely improves knowledge about psychopathology, it is still unclear how the respective domains and dimensions contribute to a new taxonomy, and, more importantly, how this translates into improved personalized treatment (Kozak and Cuthbert, 2016; Patrick and Hajcak, 2016). Clearly, what is missing here is a systematic integration into a common knowledge network of mental disorders.

By definition, the goal of precision medicine is to improve the clinical outcome of an individual patient. However, clinical studies in the area of mental disorders typically refer to taxonomies that do not meet, or only weakly meet, the criteria of a knowledge network, as proposed by the NRC. Even when they help discriminate subgroups, the unavailability of measures from other layers makes it difficult to detect associations within a knowledge network. Biomarkers derived from such studies are often diverse and only correlational in nature. For example, with respect to depression, they predominantly refer to functional systems in the brain that are known to be centrally involved in depressive disorders, such as the hypothalamic-pituitary-adrenal axis (HPA), the serotonergic, and the noradrenergic systems. Interestingly, although this research documented multiple associations among the measures of these systems across all layers of the NRC knowledge network, so far, only a few of them have qualified as discriminators of subgroup specific endophenotypes that could provide personalized clinical applications (e.g. Ozomaro et al., 2013).

Clearly, all these challenges need to be considered carefully to enable the scientific community to contribute to personalized medicine. Below, we discuss how best these issues could be addressed, and which criteria would need to be fulfilled to incorporate research data

into a knowledge network to systematically develop a new taxonomy.

3. Endophenotypes

The term ‘endophenotype’ originates from the work of John and Lewis (1966), who were forced to come up with a new term to describe the specific structural arrangement of genes in the absence of genetic change. In their original work on drosophila, they noticed inversions and translocations happened more frequently in specific geographic locations, making it likely to be intentional. As neither of the terms ‘genotype’ nor ‘phenotype’ could adequately capture this observation, they coined the term ‘endophenotype’ to refer to indiscernible changes within the individual.

Several years later, Gottesman & Shields (1973; 1972) extended the meaning of the term by arguing that the chromosomal arrangement, and as such, the endophenotype, affected the reproducibility and the survivability of the species; thus they were making a link between the occurrence of a specific endophenotype and likelihood of pathology. They also specified what constitutes an endophenotype by stating it must be an internal feature, identified through a biochemical test or through use of a microscope, after formulation of a specific hypothesis. Buchsbaum and Heier (1983), and also Reus (1982) and Loosen (1983) introduced the idea of using biological variables as independent variables in clinical studies, thus shifting the focus from looking for biological patterns associated with specific diseases to looking for disease associated with specific biological patterns. Although these authors did not use the term ‘endophenotypes’, their approach is much in line with the core idea of what a endophenotype represents. Unfortunately, this approach was not followed systematically by other authors, and remained rare. Eventually, the term endophenotype was extended to the psychopathology domain, and by the NIH to their Research Domain Criteria.

Miller and Rockstroh (2013) argued the extension of the endophenotype concept to the psychopathology domain served to “identify the genes that contribute to psychopathology”

and to “identify the mechanisms by which genetic inputs translate into biological and psychological processes (including psychopathology) manifest in the phenotype.” The implicit assumption here is that a limited number of genes underlie the production of endophenotypes. This makes it easier to conceptualize and understand disease, although recent studies contest this notion and suggest endophenotypes can be complex phenomena (Kendler and Neale, 2010; White and Gottesman, 2012). However, the basic idea remains valid that it might be more straightforward to work with clearly identified psychological and biological processes rather than with a complex disorder. Miller and Rockstroh summarized close to five decades of work on endophenotypes by stating that they are useful for the understanding of the origins of mental disorders, that they support a transdiagnostic perspective on mental disorders, and that their multivariate, multilevel approach encourages a welcome change from the formulation of a single causal chain.

Over the ensuing years these original formulations have further evolved to allow for the conceptualization of endophenotypes which not rely entirely on genetic or biological factors; this does not mean that genes or biology don't play a role, but what is measured might not need to be directly associated with a genetic or biological factor. Examples of this notion include the idea that a personality profile can be an endophenotype; that a cognitive test can have greater predictive power than an underlying biological state; or that, as reported by Mazhari and colleagues (2011), eye movements might be a valid marker to aid in the diagnosis of schizophrenia. These examples thus suggest that behavioral measures can be linked to, and part of, the endophenotype concept.

In their 2015 paper, Alhajiji and Nemeroff supported previous extensions of the conception of endophenotypes by stating that they can serve as important clinical tools in personalized medicine, but that in contrast to biomarkers, they are always stable both in the presence or absence of disease. Thus, differences could exist prior to the onset of disease, and

endophenotypes could also be considered as 'risk markers', and not only 'disease markers.' They reiterated the view that endophenotypes need not necessarily be biological, but could also be cognitive or behavioral. Several other extensions of the endophenotype concept have occurred: Gandal et al. (2016) suggested that endophenotypes might be factors that translate genes into disease mechanisms; Gur et al. (2007) introduced the term neurocognitive endophenotypes; Joober (2013) pointed out that the term 'intermediate phenotype' as introduced and referred to by Rasetti and Weinberger (2011) is simply the concept of endophenotypes in disguise; and Shah (2016) finally introduced the term 'dynamic endophenotype', referring to the frequently progressive nature of biomarker changes over the course of mental illness development. All this goes to show that the concept has remained popular, and that there is considerable momentum behind the research into the contribution of endophenotypes to psychopathology.

An underlying assumption remains that while a specific disorder – or one of its specific or unspecific component parts or symptoms – may have a neurobiological correlate, it is actually *caused* by a specific neurobiological pattern, termed an 'endophenotype'. The assumption of causality is generally problematic. However, setting aside assumptions of causality, endophenotypes could become important concepts in the understanding of complex diseases, and their use might contribute to a better understanding of disease variants and progression. The basic assumption here is that at least a significant proportion of the heterogeneity in the pathophysiology of complex disorders can be understood when applying the concept of endophenotypes. Phenomenologically identical or at least similar disease forms may have different genetic origins.

To summarize, the concept of endophenotypes has seen substantial expansions since its origin. The introduction and use of the endophenotype concept represents the first systematic attempt to develop a biologically oriented framework of mental disorders. Many

researchers have tried to identify neurobiological variables that are readily accessible and might differentiate between health and disease states (‘biomarkers’). Endophenotypes were believed to be characterized by stable neurobiological patterns that are distinct between individuals and may correlate with disease risk. Despite the various nuances in the development of this concept over these past 5 decades, what has remained consistent is the notion that endophenotypes can provide simpler and more stable clues than single *biomarkers or genetic variants alone*, and *are better suited to* bridge the gap between genes and disease. Moreover, endophenotypes are believed to be heritable (expected to run within families) and state independent (stable). The term endophenotype has garnered considerable attention, but is limited by its explicit or implicit link to genetic variation, hampering its application in precision psychiatry and necessitating a broader and more embracing conceptualization.

4. Conceptual Endophenotypes

As outlined above, there remains a wide chiasm between bench and bedside, between basic biomedical research and clinical practice in the field of stress-related mental and physical disorders, and there is virtually no indication of a reduction of this 'translation' gap despite the remarkable research advances over recent years. Therefore, more than ever, fostering the translation of findings from basic and clinical neuroscience to clinical practice is of paramount importance. Yet, attaining this goal has been challenging.

As discussed above, approaches that aim to reduce this 'translation gap' or 'translation chiasm' have included the endophenotype concept and RDoC. They share a simplified classical nosology (DSM; International Statistical Classification of Diseases and Related Health Problems, ICD) to put more basic entities at the core of scientific inquiry, focusing on dimensionally conceptualized physiological characteristics and mental functions, respectively.

We now proceed to propose and introduce a new strategy to improve clinical application of research-based knowledge, namely, the 'conceptual endophenotype' approach. Consistent with the endophenotype and RDoC tradition, the 'conceptual endophenotype' approach also *refers to* clinical nosology, yet it introduces some new concepts and features: First, it puts at its core a conceptual understanding of psychobiological systems, including the recognition of their functional role within an environmental context (and theories of etiopathology that emanate from this recognition), to structure clinically-relevant information and knowledge. Second, it emphasizes the role of information and insight generated through clinical practice ('at the bedside') for the process of structuring and selecting information and knowledge. And third, it applies formal criteria to improve clinical utility during the discovery phase itself (cf., Westfall et al., 2007).

In the following, we first address the suitability of the NRC concept of information commons and knowledge network as the fountain of information in laying the groundwork for the conceptual endophenotype approach. Next, we define and characterize conceptual endophenotypes and describe how they are generated and validated. Finally, we summarize the approach and provide a vision for future research.

Information commons and knowledge network

The NRC highlighted the need to employ an information commons, in which data derived from patient populations are made broadly available for research (National Research Council, 2011). This approach was in line with early efforts and initiatives, such as the Psychiatric Genomics Consortium (Sullivan, 2010), and the past years have seen substantial activities to establish study populations of increasing size, sometimes aiming at more than a million individuals, such as the *All of Us* research program, a cornerstone of the U.S. precision medicine initiative (Collins and Varmus, 2015) (see https://allofus.nih.gov/about/about-all-us-research-program). However, information accumulated in this information commons does not necessarily have to originate from one or only a few large-scale studies. Notably, bottom-up research activities have been advocated as a promising strategy (National Research Council, 2011) to contribute to the information commons: The information commons may be fueled by observational studies, conducted during the normal course of clinical care or during the daily lives of subjects or via biomedical research studies. We suggest expanding the scope of these sources of information commons, and we advocate the inclusion of single-case studies, one-person trials, and other observations ‘at the bedside’ as another valuable source in fueling the information commons (Schork, 2015). Notably, the latter is in line with a recently-suggested Clinical Information

Commons (CIC) that aggregates clinical data and biological samples derived from routine clinical care (Mandl and Bourgeois, 2017). In sum, the information commons shall be informed by evidence from studies of different types and sizes, including basic biomedical studies, clinical trials, and observational studies, as well as by evidence derived from single-case studies and other observations 'at the bedside.'

The resulting information commons spans a variety of levels, including the genome, epigenome, microbiome, exposome, clinical signs and symptoms, and other types of patient data (National Research Council, 2011). Making sense of these data by highlighting their inter-connectedness and integrating them with knowledge of fundamental processes is what constitutes the 'knowledge network' (Krishnan, 2015; National Research Council, 2011).

However, while this approach is appealing, it poses major challenges: Data that can potentially fuel the information commons are i) vast, as indicated by the already more than 27 million entries covered just by PubMed; ii) continuously growing, with an estimated annual scientific output growth rate of 8 – 9 percent (Bornmann and Mutz, 2015), equating to a doubling of scientific output roughly every nine years; iii) highly variable with respect to their reproducibility (Goodman et al., 2016); iv) often difficult to access, as indicated by the struggle to establish data sharing as standard practice in clinical trials (Goodman et al., 2016; Strom et al., 2016; Taichman et al., 2017); and v) often entirely inaccessible, for example, when it comes to data and knowledge accumulated by the millions of clinicians working around the globe. Consequently, in order to successfully apply the 'information commons and knowledge network' to improve clinical practice, we advocate an approach that provides i) a filter and structure to select and organize information that will drive and improve clinical practice, and ii) an efficient and multi-layered process to validate the filtered and structured information, in order to enhance and ensure its clinical utility. Additionally, we need new ways to systematically improve the manner in which information originating from clinical practice

can add to the information commons and knowledge network (cf., Chekroud, 2017; Mandl and Bourgeois, 2017), but this discussion goes beyond the scope of this article.

Definition and generation of conceptual endophenotypes

The 'conceptual endophenotype' concept represents the cornerstone of our approach to addressing the challenges (discussed above) regarding how best to filter and select the most pertinent evidence from the information commons and knowledge network that could potentially impact and improve clinical practice. We present an overall framework that can be adapted/specified for any subgroup of complex disorders (for example, as explicated below in Section 5 for stress-related disorders).

Initiatives such as RDoC aim to classify mental disorders using dimensions of observable behavior and their neurobiological correlates, and provide a framework for psychopathology research to explicate specific aspects of functional impairment by studying relevant brain-behavior relationships (Cuthbert, 2014). This approach is consistent with the endophenotype concept (Gottesman and Gould, 2003), since both are typically conceived to be closer to fundamental neural and psychological mechanisms than more abstract disorder categories (Cuthbert, 2014). Yet, if the gain in understanding fundamental neural and psychological mechanisms is restricted to a descriptive level, it may come at a substantial cost. In our view, simply abandoning specific ways of trying to establish a valid nosology (Faucher and Goyer, 2015) does not bring us closer to an appreciation of the clinical value of research findings, but instead leaves clinicians in the dark with respect to the question how to best use the rapidly expanding 'information commons and knowledge network.'

Following an initial period of enthusiasm, skepticism is now growing regarding the actual value of initiatives such as RDoC, with recent calls for rigorous and empirical scrutiny (see, e.g., https://www.nimh.nih.gov/about/director/messages/2017/the-future-of-rdoc.shtml). Indeed, empirical evidence does not always favor the new approaches, as indicated by a meta-analysis finding no support for the endophenotype concept being better than the classical approach using diagnostic categories outlined in standard classification systems, in elucidating associations with mental health-related genetic variation (Flint and Munafo, 2007). Assertions that RDoC will "develop a better understanding of how biology codes for and constrains cognitions and behavior" (Insel and Cuthbert, 2009) have not yet been substantiated, and it remains unclear whether they will ever be so.

We question whether simply following the path of theoretical reductionism (Kozak and Cuthbert, 2016) and dismissing ICD or DSM standards (and replacing them with dimensional core mental functions) will lead to the desired goals. Instead, we suggest that establishing theoretical frameworks, including hypotheses and concepts, will facilitate better organization of biomedical research data, thereby structuring the information commons and turning it from an information cloud into a knowledge network.

Consequently, we need to *i*) better recognize conceptual dimensions underlying new systematizations (Wakefield, 2014); *ii*) move beyond the theoretical models underlying new approaches such as RDoC (Glannon, 2015); *iii)* expand beyond the brain system level and include data derived from the individual, first person perspective (Bracken et al., 2012; Glannon, 2015; Keshavan and Ongur, 2014); and *iv*) adopt an iterative approach, alternating between conceptual constructs and clinical data (Carroll, 2015).

How can this be achieved? At the conceptual dimension, it has been emphasized that mental functions (thought process and content, mood, emotional regulation, reality orientation,

perception, *etc*.) are comprehensible only in their social context (Tandon et al., 2015). We suggest that this is not only true with regard to mental functions, but also for psychobiological systems. Indeed, several perspectives have been formulated as starting points to theoretically conceptualize psychobiological information in a clinically relevant way, such as neuroanatomical, neurophysiological and evolutionary perspectives (Gray, 1987; Hellhammer, 1983; Hess, 1960; McEwen et al., 2015; Panksepp, 2006; Stephan, 1975).

Thus, we propose to focus on structures that constitute clinically relevant systems within the brain, and, where appropriate, the pathways that enable cross talk between the brain and peripheral organs (Hellhammer and Hellhammer, 2008), and to then conceptualize them in terms of their 'contextual functionality'.

We define 'contextual functionality' as the purpose of a psychobiological system with its constitutive elements in the context of its environmental milieu. The milieu, in turn, is described by its phylogenetic and ontogenetic history, current features, adaptational demands, and is ideally identified through exposome approaches (Rauh and Margolis, 2016; Wild, 2012). We provide examples of such contextual functionalities below, consistent with von Wright's nomenclature (Tuomela, 1976; Von Wright, 1971).

We suggest that adopting this perspective of contextual functionality of psychobiological systems may constitute a focus back on what matters most. It adds a more Aristotelian approach, with greater teleological understanding, as compared to the more Galilean approach with causal understanding that continues to dominate the biomedical field. This is in line with the original understanding of psychiatry and psychobiology as it was brought forward by one the founders of psychobiological research, Adolf Meyer, who became one of the key drivers of modern psychiatry in North America. He successfully put forward the notion that to understand mental disorders, one must bring together the study of the patient's

current behavior, the patient's biographic origin, and its physiology (Lidz, 1966). This is further in accordance with calls for a rapprochement between Galilean and Aristotelian approaches in the field of mental health (Lilienfeld and Treadway, 2016). Taking contextual functionality into account is one way of addressing the important aspect of complexity related to stress-related disorders, because mental disorders emerge at the interface between the complex brain and the even more complex world in which we live (Maj, 2016b).

We propose that this 'contextual functionality' perspective constitutes the guiding principle for the identification of 'conceptual endophenotypes'. Expanding on the concept developed by Maj (2016b), we suggest that 'conceptual endophenotypes' should not be mistaken for 'disease entities'. Instead, we propose that 'conceptual endophenotypes' are patterns of observable signs, symptoms or phenomena, as well as related physiological and biological processes, that draw from the different levels of the information commons and knowledge network outlined above (cf. the network theory of mental disorders, Borsboom, 2017). This approach also is consistent with previous approaches that have aimed to better integrate findings across multiple levels of observation (Andrews et al., 2013) in order to make brain-behavior research more clinically relevant (Tandon et al., 2015).

We believe it is relevant to formulate conceptual endophenotypes as patterns of the above-mentioned elements (signs, symptoms, phenomena, and biological measures) to gain a holistic understanding. If we restricted 'contextual functionality' to each of the single elements that collectively constitute a conceptual endophenotype, we might miss the overall pattern. This would be similar to the RDoC approach that tries to break down – or even replace – mental disorders by the description of multiple basic dimensions of mental phenomena. Notably, a given element may have a different meaning and reflect a different underlying pathogenetic process as a function of the overall context within which it emerges (cf. Maj, 2016a). Therefore, contextual functionality cannot be divided in terms of individual elements,

but represents the context with respect to the overall pattern of relatedness of underlying elements. This assumption is testable, and it has an important implication: When using content from the information commons and knowledge network, it is crucial to account for the functional context of this content (data). For example, brain activity signatures that occur in conjunction with signs of exhaustion could vary considerably as a function of context. If they occur in the context of current high energetic demand, they may be very different from when they occur in the context of recovery following high energetic demand. Notably, we need to guard against the risk of circular reasoning: the contextual functionality underlying conceptual endophenotypes cannot be inferred from the same studies that served to identify their individual elements (signs, symptoms, phenomena, or biological measures).

To derive conceptual endophenotypes, we require specific strategies. We suggest a combination of three approaches. First, as starting point to construct a conceptual endophenotype, we suggest beginning from established knowledge about discrete brain systems and their contextual functionality. Second, to identify the elements that constitute the conceptual endophenotype, we assemble: *i*) elements functionally linked to each other within the same level of information, such as neuroendocrinology, *ii*) elements that co-vary across different levels of information, and *iii*) elements co-emerging in the relevant functional context. Third, we enter the iterative process: At the beginning, the conceptual endophenotypes are temporary assumptions that have the status of meta-level descriptions (Hellhammer and Hellhammer, 2008). The process then iterates between the fields of basic biomedical science and clinical practice (see Figure 2), in line with recommendations that the translational endeavor should be a two-way street (Tandon et al., 2015). This iteration serves two goals: First, the conceptual endophenotype is evaluated in terms of its validity and clinical utility. Second, the conceptual endophenotype is refined and enriched by absorbing, integrating, and utilizing new information and knowledge (Krishnan, 2015).

Notably, current discovery pipelines involve the clinical aspect at a late stage during this process. In contrast, our strategy incorporates the clinical bedside at a much earlier stage of the process. This often provides to the clinician a tool to conceptualize the clinical situation of a specific patient from a psychobiological perspective, allowing the implementation of an unbiased intervention, as opposed to one based on intuitive reasoning alone. In sum, and based on the considerations outlined above, we define 'conceptual endophenotypes' as follows:

> *A conceptual endophenotype consists of a pattern of empirically accessible elements, integrating measures from different layers (psychological, biological, symptomatic), based on a common conceptual model of their contextual functionality, and being informed and supported by iteratively conducted basic, applied, and patient-oriented research, as well as by clinical evidence.*
>
> *The value of a conceptual endophenotype is determined by the fit of its conceptualization across layers (conceptual value), its ability to integrate and concurrently stimulate clinical and research evidence (translational value), its potential to improve health care (clinical value), and its potential to advance knowledge through emerging new findings (prospective value).*

Thus, the application of conceptual endophenotypes links clinical practice with basic, applied, and patient-oriented research, allowing for personalized diagnosis and treatment of potentially complex (stress-related) conditions, thereby drawing on and informing scientific evidence and progress.

Of note, the adoption of a psychobiological perspective does not, in and of itself, address the conceptual challenge of distinguishing disorder from normality (cf. Wakefield, 2014). Hence, in order to apply conceptual endophenotypes, there is a need for an applicable disease

model. We propose several (non-exhaustive) types of disease models based on conceptual endophenotypes: *i*) a more general or persistent dysfunction within the conceptual endophenotype, with some symptoms originating early during the individual's development, *ii*) a more temporary dysfunction within the conceptual endophenotype, most likely triggered by acute events or circumstances, and *iii*) an apparently normal and well coordinated conceptual endophenotype, however activated excessively or inappropriately out of context.

To align conceptual endophenotypes with 'information commons' and the 'knowledge network', there is need for some structured process to act as a filter between these entities. There have been previous suggestions to systematically evaluate potential candidates, such as the mathematical 'endophenotype ranking value' that supports an automated, high-throughput way of ranking potential endophenotypes based on heritability parameters as a way to support the development of biologically-based nosologies (Glahn et al., 2014). Another approach includes specific selection criteria that potential biological features should fulfill, such as the formulation by Pine and Leibenluft (2015) that stresses the need to prioritize biomarkers that not only predict course or treatment outcome but provide substantial insights into mechanisms.

We propose here a filter consisting of a cascade of criteria that are used to select elements from the information commons and knowledge network that meaningfully inform the conceptual endophenotype approach. Notably, integrating new evidence should occur within an iterative process, in line with recommendations to shape and refine constructs and units of analysis and to create algorithms for adding new discoveries (Elmer et al., 2016). The filtering criteria we propose include the following:

1. Selection: The focus should be on well-defined biological structures and mechanisms, known to be closely associated with mental and physical health.
2. Conceptualization: There should be sufficient information about the element to allow conceptualization across the layers of the knowledge network.

3. Reproducibility: There should be evidence of reproducibility of the information and knowledge that forms the basis for each element within the conceptual endophenotype, ideally based on meta-analysis (Ioannidis, 2017a; Sweeney et al., 2017).
4. Measurability: The elements should be measurable, with (diagnostic) instruments exhibiting sufficient performance criteria.
5. Implementation: Inclusion of the element should improve the implementation of the conceptual endophenotype in the clinical context. Preferably, instruments to assess an element should aim to be applicable in the regular clinical context (diagnostic routine).
6. Application: Inclusion of the element should improve the application of the conceptual endophenotype in clinical practice.
7. Dissemination: Inclusion of the element should improve dissemination of the conceptual endophenotype in clinical practice.
8. Parsimony: Simplicity is a virtue and the key criterion for evaluating and choosing scientific theories; simpler theories should be preferred to more complex ones, given that all other things are equal (the principle of scientific parsimony, or ‘Occam’s razor’). We propose that elements should be selected that favor the retention of parsimony of the conceptual endophenotype, such that improvements in clinical utility outweigh the increase in complexity.
9. Fertility: Conceptual endophenotypes are not only fueled by the information commons and knowledge network, but they can also be considered contributing to the knowledge network themselves. So, it is advisable to include elements that increase the potential of a conceptual endophenotype to fertilize basic and applied biomedical and other research, by making a significant contribution to the knowledge network.
10. Clinical validity: Last, but not least, inclusion of an element should improve the validity of a conceptual endophenotype by demonstrating that its clinical application reduces intangible costs, and preferably also direct and indirect costs.

Validation of conceptual endophenotypes

Once elements of the information commons and knowledge network have been chosen using the above strategies, and a conceptual endophenotype has been developed, it needs to be validated. The validation effort is absolutely critical, given the rapidly growing evidence of non reproducibility of a substantial proportion of published research findings (Ioannidis, 2017a). Ensuring validity is even more important within an approach that puts conceptualization at its core, as it has been noted that validating concepts is more challenging than validating empirical findings (Ioannidis, 2017b). Here we suggest an iterative approach (see Figure 2) consisting of three loops. Notably, the conceptual endophenotype approach requires balancing the need of ensuring reproducibility against the need of incorporating new findings (cf., Elmer et al., 2016). Establishing an efficient process to validate reproducibility and utility of conceptual endophenotypes for making clinically relevant distinctions (e.g., prognosis or selection of treatment) is consistent with recommendations by the NRC to develop a new taxonomy of disease (National Research Council, 2011).

The three loops that constitute the validation approach are:

1. Initial validation loop: This loop aims at assessing the degree of convergence across levels of information that constitutes the conceptual endophenotype. This is achieved by using appropriate statistical analysis in clinical or general population samples (Goodman et al., 2017; Schork, 2015), and this acts as an initial quality control to inform the decision-making process regarding whether or not a particular conceptual endophenotype should be further scrutinized.

2. Biomedical validation loop: This loop aims at assessing the biomedical validity of a conceptual endophenotype. This is achieved by controlled experiments to test specific predictions that emanate from the conceptual endophenotype.
3. Clinical validation loop: This loop aims at assessing the clinical validity of a conceptual endophenotype. This is achieved, first, by observational studies during standard care, and second, by clinical trials that assess the clinical outcomes of the application of the proposed conceptual endophenotype.

Insert Figure 2 around here

It has been stated that “for several decades now the biomedical research community has pursued a narrative positing that a combination of ever-deeper knowledge of subcellular biology, especially genetics, coupled with information technology will lead to transformative improvements in health care and human health” (Joyner et al., 2016), yet there has been little evidence to date regarding the success of this approach (Joyner et al., 2016). We hope that our proposed conceptual endophenotype approach will provide a new platform for imaginative research that is truly innovative and is not constrained by the current narrative (Joyner et al., 2016), while, at the same time, is closely related to the current biomedical research venture (by drawing from biomedical evidence that is present in the information commons and knowledge network).

Taken together, we suggest the bench and bedside can be effectively bridged by conceptual endophenotypes that are derived from elements filtered out of the information commons and knowledge network fueled both by research and clinical evidence. The development and refinement of conceptual endophenotypes continuously benefits from concurrently mining the

knowledge network and evaluating the validity and clinical utility at the bedside, as exemplified below.

5. Conceptual endophenotypes of the stress response network

Stress is a popular research topic in psychoneuroendocrinology. Today, a vast knowledge base is available about brain systems that constitute the stress response network and their contextual functionality (e.g., overviews in Baum and Contrada, 2010; Chrousos and Kino, 2007, 2009; McEwen, 1998; Steptoe et al., 2010). However, this knowledge base has infrequently or only anecdotally been applied in the precision medicine approach to stress related disorders, *including depression, somatoform and anxiety disorder*s. We suggest that the time has come to systematically translate this knowledge to develop conceptual endophenotypes and evaluate their clinical validity.

In accordance with the criteria discussed above, a first essential step is the selection of well-defined biological structures and mechanisms that are closely implicated in stress-related disorders, and that can be conceptualized in terms of their contextual function across the layers of the knowledge network. Preferably, such conceptual endophenotypes also should be embedded in a disease model that will facilitate translation at the bedside.

One such example of a comprehensive approach is the allostatic model proposed by Bruce McEwen (2017c). His influential work on brain mechanisms underlying the stress response network addresses the issue of contextual functionality across the various layers of the knowledge network and illustrates the relevance of genetic, epigenetic, and cellular effects (McEwen, 2017a) of social and developmental processes. In addition, studies about the allostatic load construct highlight autonomic, endocrine and immune processes, which are

functionally connected and involved in the etiopathology of stress-related disorders (McEwen, 2017b).

McEwen and Getz (2013) have asserted that “high-tech personalized medicine based on detailed bio-molecular mapping, monitoring and tailored drug-interventions holds promise only as part of a wider, socio-culturally informed approach to the person”. The question, then, is which strategies may best be suited to translate that complex knowledge to the bedside and to precision medicine. Notably, McEwen´s disease model of allostatic load is a complex clinical construct, characterized by the cumulative impact of multiple biological regulatory systems. To better differentiate causal pathways to diseases, Buckwalter et al. (2016) recently introduced a more refined strategy, selecting biomarkers from five physiological systems (neuroendocrine, cardiovascular/respiratory, immune and metabolic), as well as anthropometric status. They developed a computational model allowing discrimination of nine different allostatic load profiles, each of which relate to specific health outcomes such as diabetes, cardiovascular disorders, and the metabolic syndrome. This work represents an important advance and indicates that the allostatic load construct can be differentiated and more effectively measured and modeled to provide a promising starting point in the effort to reduce the gap between basic research and clinical application (Wiley et al., 2016). A dissection of the different elements of the allostatic load model into conceptual endophenotypes may facilitate their clinical application. For example, glutamatergic neurons play a key role in McEwen´s model, and they are relevant for the development and treatment of stress-related disorders (McEwen et al., 2010). The characterization of these neurons and their contextual functionality within the knowledge network may aid in the development of conceptual endophenotypes that identify subgroups of stress-related disorders.

The construction of a knowledge network of stress-related disorders would include several conceptual endophenotypes, for example those addressing the crosstalk between the central

nervous system (Haroon et al., 2012; Rohleder, 2014) or the role of inflammation induced depression and sickness behavior (Dantzer et al., 2011), or those pathways participating in metabolic diseases (Rasgon and McEwen, 2016), or psychoses (Pruessner et al., 2017). One can expect that such a growing knowledge network will generate conceptual endophenotypes, which could be used and further developed by peers, and will become increasingly relevant for targeted treatments in multiple stress-related disorders.

Neuropattern: an initial effort to develop and test conceptual endophenotypes in the context of stress-related disorders.

Several challenges impede the goal of precision medicine to provide personalized interventions for stress-related disorders. Psychobiological stress research is very heterogeneous; it has not yet been systematically integrated into a common knowledge network; and it is hampered by nosological, regulatory, and administrative demands at the bedside. Clinical research often is limited to patients with only a single disorder (as categorized by DSM or ICD criteria) and explicitly excludes patients with comorbidity, and also by its selection of a narrow range of psychobiological measures.

The ambitious goal for precision medicine in the context of stress-related disorders is its implementation at the bedside. Both biomedical and clinical research seem to neglect one decisive and critical issue: while patients enrolled in clinical research studies are studied by specialists, approximately 70 to 90% of all depressed patients are first treated by primary care physicians, and only 10% are referred to psychiatrists (Kessler et al., 2002; Mühlenfeld, 2005). Notably, in about half of these patients, the primary care physicians initially do not diagnose mental disorders. Thus, one critical question is whether and how precision medicine initiatives for mental health could even make a connection with this patient

population of individuals with mood disorders but who have not been diagnosed as such.

Although the practice of the primary care physician is a major target for the implementation of stress medicine, primary care physicians have drifted away from participation in scientific inquiry due to “high demands for clinical practice productivity” (Khanna et al., 2009). In addition, low funding priorities for family medicine (Lucan et al., 2009; Lucan et al., 2008) deter applied translational research in this important area. To address this situation, we proposed a new, exploratory strategy that is based on conceptual endophenotypes and can be readily implemented in outpatient care. Introduced in 1999, we named this strategy “Neuropattern”. Meanwhile, more than 1000 patients have been treated according to the latest version of Neuropattern. We defined 13 conceptual endophenotypes of the stress response network, described in more detail by Hellhammer and Hellhammer (2008) and Hellhammer et al. (2012). The aim was to improve personalized treatment of stress-related physical and mental disorders.

The Neuropattern strategy had to address several challenges in the treatment of outpatients:

- First, a primary care physician in Germany sees an average of 58 patients per day, and spends about 3 minutes with each of them (Wittchen and Pieper, 2006). These figures are likely similar in other developed countries. Thus, primary care physicians do not have sufficient time to elicit and analyze the biological, psychological and social determinants of affective and somatic symptom disorders. A translational diagnostic tool is unlikely to gain acceptance if it requires additional time from the physician.
- Second, the primary care physician can only prescribe on-label drugs. Neuropattern can be used to choose the best option among available drugs as evidenced by individual dysregulations of conceptual endophenotypes.

- Third, the primary care physician and outpatient care setting will likely lack a number of features typically available in research settings. They will not have:
    - individual access to technologies like brain imaging. Thus, patients who have used the Neuropattern diagnostics system have typically been required to collect most of their own data, which, obviously, limits the kinds of biological measures that can be obtained;
    - sufficient expert knowledge, given that stress-related disorders are multi-factorial in nature, and it is unreasonable to expect a primary care practitioner to possess the required capabilities for diagnosis and personalized treatment;
    - the ability to make the optimal choice of psychopharmacological agents. On-label prescriptions of these drugs require using ICD diagnostic criteria, but these may not map on to distinct (conceptual) endophenotypes.

In order for Neuropattern to be used, a system had to be developed to provide its findings and treatment recommendations to patients and their physicians in an easily comprehensible manner, and preferably embedded in a disease model. Accounting and cost compensation for Neuropattern's use had to meet contractual services by the respective insurance companies.

Also, given that a patient using Neuropattern is required to self-collect much of her or his own data, the biological measures that could be included represented a compromise between optimal scientific standards and practical applicability. Preferably, biological data should represent both activity and reactivity measures of stress-responsive systems. Thus, Neuropattern was designed to assess salivary endocrine and autonomic measures under basal and challenge conditions (e.g., after awakening). A low-dose dexamethasone test was also implemented. Signs and symptoms were obtained by a standardized interview of the

patients medical history of the primary care physician and the Patient Health Questionnaire (PHQ, Gräfe et al., 2004).

Development of the Neuropattern diagnostic tool

As discussed earlier, the information commons contains a large amount of material related to the tremendous complexity of mechanisms underlying stress-related disorders across all layers of the knowledge network. For our selection of conceptual endophenotypes, we decided to focus solely on measures of the interface in the crosstalk between the brain and peripheral systems under stressful conditions, e.g. the HPA axis, autonomic nervous system, and selected components of the central nervous system, namely the locus caeruleus–noradrenergic (NE) and the dorsal raphe–serotonergic (5-hydroxytryptaminergic, 5-HT) systems. These systems were selected because they are clinically important modulators of stress-related disorders such as depressive, anxiety and somatic symptom disorders, and they constitute the main targets for currently-available psychopharmacological agents. Notably, our conceptualization does not yet include some other important players of the stress response network, such as metabolic and immunological processes (Dallman and Hellhammer, 2011).

Thus far, we have defined 13 distinct conceptual endophenotypes. They reflect the following dysregulations:

- Ergotropic dysregulations: hyperreactivity, hyper- and hypoactivity of norepinephrine neurons originating from the locus caeruleus, sympathetic hyperactivity and hyperreactivity. Ergotropy refers to catecholaminergic/sympathetic functions associated with arousal, mental or physical work, and alertness (Hess, 1925, 1962; Klingmann and

Hellhammer, 2008)

- Trophotropic dysregulations: hyperreactivity and hypoactivity of serotonergic neurons from the dorsal raphe nucleus. Trophotropy refers primarily to central and parasympathetic functions that underlie regeneration, recovery, and protection against stress overload (Hellhammer and Klingmann, 2008; Hess, 1925, 1962).
- Glandotropic dysregulations: hyperactivity, hyperreactivity and hypoactivity of hypothalamic CRF and CRF/AVP neurons, elevated and diminished cortisol release from the adrenals, and glucocorticoid receptor resistance. Glandotropy refers to the activity of the different central and peripheral components of the HPA axis that are associated with mobilization of energy, prevention of an disinhibited stress response, and psychological states such as anticipation, worry, lack of control, and ego involvement (Fries, 2008; Pütz, 2008).

The terms for these three biological systems were selected to reflect their functional roles, since these functions are complex and are regulated by multiple other neurobiological processes (Hellhammer, 2008; McEwen, 2000, 2017b). The idea was to first focus on these three functional systems, and then to systematically build up (in a bottom-up manner) and to scrutinize their interplay and dependencies.

The 13 conceptual endophenotypes were operationalized as distinct patterns of associations among and across specific biological, psychological, and symptomatology measures from information commons and own research data (as exemplified in more detail in Box 1). Interactions among these patterns were also considered. With respect to the exposome, exposure to various forms of adversity over the entire life course (with a particular emphasis on the pre- and postnatal periods of development) is assessed using standardized self-report measures (PHQ, Gräfe et al., 2004; NPQ-PSQ; Hero, 2013).

Currently, saliva-based measures of genetic and epigenetic characteristics are being analyzed to investigate their potential for use in Neuropattern. For example, there is preliminary evidence that certain haplotypes of the mineralocorticoid receptor are evident in only 1 of the 13 conceptual endophenotypes (CRF-hypoactivity) (Kumsta et al., 2015). Thus, Neuropattern may allow an early identification of a disease subgroup that reflects the effects of central biological processes on stress pathology.

Disease model

Once Neuropattern diagnostics have been performed, results are provided to the patient and the treating physician. The physician receives a medical report, highlighting the patient-specific dysregulations of the stress response network, their relationship to patient-specific pathology, and personalized pharmacological and/or psychotherapeutic treatment recommendations (see Box 2). The patient receives the same information, but in an abbreviated and simpler manner, illustrated by a “stress triangle” that illustrates her or his personal dysregulations of the glandotropic, ergotropic and trophotropic systems (see Figure 3). These results are illustrated as positions in the normal, upper, or lower range on the glandotropic, ergotropic, and trophotropic columns, respectively. The stress triangle connects these three positions. The patient is provided advice about currently-available treatment strategies to re-balance the stress-triangle. Thus, the stress triangle represents the diagnostic end point from which personalized indications for treatment are derived. An effectivel communication with the patient is essential for compliance and treatment success.

Insert Figure 3 around here

Validation

For Neuropattern to pass a biomedical and clinical validation loop, observational data are employed that indicates whether and which specific conceptual endophenotypes are relevant for clinical studies. In the second step, exploratory clinical studies are conducted to determine whether the application of Neuropattern produces a greater reduction of intangible (e.g. symptom severity, improved wellbeing) and/or direct and indirect costs than current clinical practice. For Neuropattern, a cost reduction has been demonstrated in randomized clinical trials in outpatients (Näher, 2015) and inpatients of two hospitals (Bruhn, 2014; Hero et al., 2012), as well as in a workplace study for prevention of stress related disorders (Contreras et al., under review). In a third step, RCTs focus on those specific conceptual endophenotypes that have been shown to be reproducible and efficacious in predicting personalized therapeutic success. In a fourth step, additional biomedical research should be conducted to improve the characterization of the conceptual endophenotype across the layers of the knowledge network, and to test its value as an endophenotype, which eventually defines a subgroup for improved personalized interventions.

The biomedical validation loop primarily uses the data pool from the above-described studies to evaluate the biological, psychological, and symptomatology-related variables of a given conceptual endophenotype for subtyping of patients, and also as predictors of therapeutic outcome. Moreover, hypothesized patterns of associations among and between these variables are tested for reliability. The association of measures of the exposome (e.g., exposure to adversity in early life) is also investigated here.

Our initial experiences with Neuropattern in three exploratory clinical studies in patients with diagnosed stress-related disorders show moderate, positive and encouraging effects on symptom severity, perceived stress, and quality of life. In the additional workplace study, employees who felt stressed had the opportunity to use Neuropattern via their family physician. Here, primary care providers diagnosed 17% of participants with neurasthenia/burnout and other disorders potentially associated with stress, including sleep disorders, pain, gastrointestinal complaints, hypertension, tinnitus, and hearing loss. In 35% of participants they did not find any evidence of stress-related pathology. Neuropattern exhibited greater sensitivity in detecting stress-related disorders (65% qualified for a Neuropattern diagnosis, and 22% for a sub-threshold stage of stress pathology) as compared to the 17% figure by the primary care physicians. This early detection of stress pathology and its potential causes, along with the individual disease model (stress triangle), provided the opportunity for personalized prevention and intervention, which, in turn, was associated with a reduction of stress symptoms and improvement in quality of life.

In each of these three clinical studies, we note that approximately 60 to 70% of each study population had different constellations of our conceptual endophenotypes. The small group sizes made it difficult to perform statistical analyses on subgroups with one or more conceptual endophenotypes. Our largest study population was the outpatient study (N = 560) (Näher, 2015); here positive effects over a 12-month follow-up period were observed in patients in the CRF-hyperreactivity and serotonin hyperreactivity endophenotypes, two patterns that are closely related to the behavioral stress response. Some of these patients responded remarkably well to personalized treatment recommendations, while others did not respond at all. In light of this heterogeneity, both single case studies and larger patient studies are necessary to validate and further develop these conceptual endophenotypes. Our disease model aided patients in reaching a more comprehensive understanding of their

individual vulnerability for stress-related disorders, and thereby facilitating the acceptance of behavioral interventions to prevent and/or cope with the effects of stress.

In sum, these initial experiences with Neuropattern in the context of the four explorative studies have been encouraging (Hero et al., 2012; Bruhn, 2014; Naeher, 2015; Contreras et al., submitted). Neuropattern appears to become an appropriate translational tool to use knowledge about the stress response network to detect and prevent or treat stress-related pathology. This enterprise is an iterative approach in terms of structural demands at the bedside, the diversity of patients' histories, comorbidities, etc., thereby stimulating a continuous development of the system. Furthermore, we anticipate that Neuropattern will facilitate basic research on the genetic and epigenetic determinants of these endophenotypes, as exemplified by the study on the haplotypes of the mineralocorticoid receptor and the CRF-hypoactivity endophenotype (Kumsta et al., 2015). We also anticipate that other recent technological advances (e.g., sensor technologies) will improve collection of autonomic and behavioral measures. Digital phenotyping may offer a promising approach (Insel, 2017). On that basis, we need to further develop our current personalized self-help modules to allow an early interception and treatment of stress-related disorders. We advocate that the deployment of the conceptual endophenotype approach should not await the discovery of traditional endophenotypes but instead use a stepwise conceptual approach that learns from each application. Here, we agree with Goethe (1829) "Knowing is not enough; we must apply. Willing is not enough; we must do". Notably, the United States National Academy of Sciences has chosen this quotation as its mission statement.

Box 1:

Example: Development of CRF-related glandotropic conceptual endophenotypes

1. Information commons suggest that CRF and CRF/AVP neurons in the hypothalamus respond to acute and chronic stress and play an important role in the stress response network (Schulkin, 2017). CRF effects on the release of glucocorticoids and the autonomic nervous system can be classically conditioned (Kreutz et al., 1992), suggesting that they are responsive to psychological stimuli.

2. We consider salivary cortisol concentration a reasonable indirect biomarker of the activity and reactivity of these neurons under healthy (Hellhammer et al., 2009) and clinical conditions (Zorn et al., 2017). The associations of salivary cortisol with clinical symptoms vary in the context of hypo- and hyperactivity and the hyperreactivity of the pituitary-adrenal axis.

3. Using the information contained in the above two points, we conceptualized three endophenotypes and characterized each of them through a specific pattern of psychological, biological and symptomatology measures (Fries, 2008; Pütz, 2008). In addition, we conceptualized two non-CRF triggered endophenotypes, namely cortisol-hypoactivity and glucocorticoid receptor resistance.

4. Across a knowledge network, the three CRF-related conceptual endophenotypes are linked with:

a. symptomatology such as general anxiety, major depression and somatoform disorders

b. environmental conditions (early adversity, acute and chronic stressors)

c. characteristic behavioral, psychological and social variables

d. biological (genetic, epigenetic, metabolic, neuroendocrine, immunological, autonomic)

measures

5. Many basic research studies were performed to test the reliability and validity of these measures. The results and new information from information commons were used to continuously develop the respective patterns.

6. In addition to psychotherapeutic treatments, on label pharmacological interventions are available to normalize CRF-hyperactivity in major depression (e.g. mirtazapine, trimipramine), CRF-hyperreactivity in general anxiety disorders and/or depression (e.g. buspirone, tricyclic antidepressants), and CRF-hypoactivity in atypical depression (sertraline, MAOI). Exploratory clinical studies were performed to validate psychological and pharmacological treatment effects

7. Limitations in information commons included the reproducibility of study data and absence of meta-analyses. In addition, animal models on CRF-receptors did not translate readily to the human situation (Spierling and Zorrilla, 2017).

Box 2:

Example: Case study

Patient: Male, 44 years age, participant in a clinical trial (Bruhn, 2014).

Diagnoses according to ICD 10: moderate depressive episode (F32.1), panic disorder (F41.0), somatoform disorder (F45.1), burnout state (Z73.0), tinnitus (H93.1), restless-legs-syndrome (G25.8).

Medical history: gastritis/ulcus pepticum, osteoporosis/osteopenia, back pain, joint pain, migraine, tinnitus, transient ischaemic attack, sleep disorder.

Treatments: The patient previously responded well to psychotherapy and benserazid, modestly to mirtazapine and agomelatine, but not to physiotherapy and dietary changes. Stressors: the patient suffered from chronic work stress in his own company.

Neuropattern: The patient fulfilled criteria for:

- *norepinephrine-hyperactivity,* mainly related to panic attacks and pain
- followed by *norepinephrine hypoactivity,* promoting burnout and somatic poststress symptoms
- *serotonin hypoactivity,* mainly related to depressivity, impulsivity, and sleep disorders
- followed by *serotonin hyperreactivity,* mainly related to conservation-withdrawal behavior

- *glucocorticoid receptor resistance***,** mainly related to pain disorders and sickness behavior

Disease model: chronic stress triggered a hyperactivity of the dorsal noradrenergic system, resulting in a depletion of norepinephrine stores. In addition, low serotonergic activity caused a hyper-responsivity of serotonergic receptors. Finally, chronic stress dampened the sensitivity of glucocorticoid receptors on lymphocytes, thus weakening cortisol functions. In the stress triangle, the initial states are indexed by ergotropy in the upper, and trophotropy and glandotropy in the lower range (see Figure 3B).

Treatment: We recommended psychotherapy and replacement of agomelatin by doxepine, which seemed better suited to normalize the dysregulations of the stress triangle. Within a week the patient recovered and could be discharged from the hospital.

6. Conclusion

The field of psychoneuroendocrinology has the potential to make a substantial contribution towards the precision medicine initiative, particularly in the areas of physical and mental disorders. However, the information commons contain a pool of very diverse, heterogeneous, and multi-faceted research data. We agree with Krishnan (Krishnan, 2015) that we urgently need a knowledge network to absorb, integrate, and utilize this knowledge. This could provide the basis for a new taxonomy to improve the diagnosis, prevention, early interception and treatment of mental and stress-related physical diseases. We propose that the 'conceptual endophenotype' concept is particularly suitable for integrating biological, psychological, social and environmental measures in knowledge networks.

What is unclear, at this point, is the best approach to filter, select and weigh all the different information in order to arrive at the best possible individual-level prediction. That is, how can all the information be optimally utilized within the framework of a knowledge network?

We suggest that data first need to be embedded into a theoretical biological framework across the various different layers of a knowledge network. This may best be accomplished by defining clusters of data into conceptual endophenotypes, in order to discriminate patient subgroups using this new taxonomy. Once defined, such conceptual endophenotypes can serve as temporary tools at the bedside. They would then have to pass both a clinical and a biomedical validation loop. If they exhibit robustness and replicability in discriminating subgroups, they may be adopted as the basis for a new taxonomy.

In line with the traditional evidence-based medicine (EBM) approach that is based on evidence from populations, we have provided first evidence for the clinical usefulness of the

conceptual endophenotype approach, as exemplified by Neuropattern above. It has been pointed out that such a traditional EBM approach is hardly reconcilable with the precision medicine approach (Tonelli and Shirts, 2017). Instead, it has been argued that “precision medicine demands case-based reasoning, in which the relevant particulars of the individual patient must be elucidated and incorporated into clinical assessments and decisions” (Tonelli and Shirts, 2017). Of note, there are first indicators for a shift in regulatory epistemology, accepting mechanistic information as actionable knowledge (Tonelli and Shirts, 2017). We anticipate that future developments of both, the conceptual endophenotype and the EBM approaches are mutually related. Further, recent methodological advances, such as machine learning (Iniesta et al., 2016), may reconcile both, the particulars of the individual patient and EBM at a population level, based on strong mechanistic reasoning.

The ultimate fruition of the conceptual endophenotype approach will require the establishment of an infrastructure to *a*) develop and maintain a knowledge network by continuously analyzing and adapting new data (Eisenberg and Pellmar, 2000) (see https://www.nimh.nih.gov/about/director/messages/2017/computational-neuroscience-deciphering-the-complex-brain.shtml), and *b*) develop grass-roots collaborations between researchers across the globe working on the same problems (Mainen et al., 2016; Silbersweig and Loscalzo, 2017); and *c*) implement a learning healthcare system (Addie et al., 2016; Angus, 2015; Greene et al., 2012) that also provides for the rapid and efficient dissemination of advances (Chambers et al., 2016; Dahabreh and Kent, 2014), particularly in the context of primary health care (Edwards et al., 2017).

Acknowledgements

We greatly appreciate valuable comments and feedback from Dres Juliane Hellhammer, Marita Pruessner, Arthur Stone, Marion Tegethoff, and Pathik Wadhwa.

Contributions and conflict of interests

Conflict of interests: none. DH and GM have been acting as consultant for Janssen Research & Development, LLC. DH is offering Neuropattern diagnostics in his private practice; cost compensation is provided by the patients' insurance companies. Daacro, the company of his wife, offers Neuropattern as a tool for clinical research studies.

All authors have made substantial contributions to (1) the conception of the manuscript, (2) drafting the article and revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector. GM discloses funding from the National Research Foundation of Korea (NRF) within the Global Research Network Program (under project no. 2013S1A2A2035364) and from the Swiss National Science Foundation (under project no. 100014_135328).

The funding sources had no role in conception of the manuscript; in the writing of the report; and in the decision to submit the paper for publication.

References

Addie, S., Olson, S., Beachy, S.H., Roundtable on Translating Genomic-Based Research for Health, Board on Health Sciences Policy; Health and Medicine Division, National Academies of Sciences, E., and Medicine,, 2016. Applying an Implementation Science Approach to Genomic Medicine: Workshop Summary. The National Academies Press, Washington (DC).

Alhajji, L., Nemeroff, C.B., 2015. Personalized Medicine and Mood Disorders. Psychiatr Clin North Am 38, 395-403.

Andrews, J., Ali, N., Pruessner, J.C., 2013. Reflections on the interaction of psychogenic stress systems in humans: the stress coherence/compensation model. Psychoneuroendocrinology 38, 947-961.

Angus, D.C., 2015. Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems? JAMA 314, 767-768.

Baum, A., Contrada, R., 2010. The handbook of stress science: Biology, psychology, and health. Springer Publishing Company.

Bornmann, L., Mutz, R., 2015. Growth rates of modern science: A bibliometric analysis based on the number of publications and cited references. Journal of the Association for Information Science and Technology 66, 2215-2222.

Borsboom, D., 2017. A network theory of mental disorders. World Psychiatry 16, 5-13.

Bracken, P., Thomas, P., Timimi, S., Asen, E., Behr, G., Beuster, C., Bhunnoo, S., Browne, I., Chhina, N., Double, D., Downer, S., Evans, C., Fernando, S., Garland, M.R., Hopkins, W., Huws, R., Johnson, B., Martindale, B., Middleton, H., Moldavsky, D., Moncrieff, J., Mullins, S., Nelki, J., Pizzo, M., Rodger, J., Smyth, M., Summerfield, D., Wallace, J., Yeomans, D., 2012. Psychiatry beyond the current paradigm. Br J Psychiatry 201, 430-434.

Bruhn, K., 2014. Optimierung der Depressionsbehandlung durch die Neuropattern - Diagnostik. Shaker, Herzogenrath.

Buchsbaum, M.S., Haier, R.J., 1983. Psychopathology: biological approaches. Annu Rev Psychol 34, 401-430.

Buckwalter, J.G., Castellani, B., McEwen, B., Karlamangla, A.S., Rizzo, A.A., John, B., O'Donnell, K., Seeman, T., 2016. Allostatic Load as a Complex Clinical Construct: A Case-Based Computational Modeling Approach. Complexity 21, 291-306.

Carroll, B.J., 2015. Clinical science and biomarkers: against RDoC. Acta Psychiatr Scand 132, 423-424.

Chambers, D.A., Feero, W.G., Khoury, M.J., 2016. Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System: A New Model for Biomedical Research. JAMA 315, 1941-1942.

Chekroud, A.M., 2017. Bigger Data, Harder Questions-Opportunities Throughout Mental Health Care. JAMA Psychiatry.

Chrousos, G.P., Kino, T., 2007. Glucocorticoid action networks and complex psychiatric and/or somatic disorders. Stress 10, 213-219.

Chrousos, G.P., Kino, T., 2009. Glucocorticoid signaling in the cell. Expanding clinical implications to complex human behavioral and somatic disorders. Ann N Y Acad Sci 1179, 153-166.

Collins, F.S., Varmus, H., 2015. A new initiative on precision medicine. N Engl J Med 372, 793-795.

Contreras, C., Hellhammer, J., Gerhards, F., Hellhammer, D.H., under review. Translational Stress Medicine In Personalized Workplace Health Promotion - A Pilot Study. Journal of Occupational Health Psychology.

Cuthbert, B.N., 2014. Translating intermediate phenotypes to psychopathology: the NIMH Research Domain Criteria. Psychophysiology 51, 1205-1206.

Dahabreh, I.J., Kent, D.M., 2014. Can the learning health care system be educated with observational data? JAMA 312, 129-130.

Dallman, M.F., Hellhammer, D., 2011. Regulation of the hypothalamo-pituitaryadrenal axis, chronic stress, and energy: the role of brain networks, in: Contrada, R.J., Baum, A. (Eds.), The handbook of stress science: Biology, psychology, and health. Springer, New York, pp. 11-36.

Dantzer, R., O'Connor, J.C., Lawson, M.A., Kelley, K.W., 2011. Inflammation-associated depression: from serotonin to kynurenine. Psychoneuroendocrinology 36, 426-436.

Edwards, S.T., Dorr, D.A., Landon, B.E., 2017. Can Personalized Care Planning Improve Primary Care? JAMA 318, 25-26.

Eisenberg, L., Pellmar, T.C., 2000. Bridging disciplines in the brain, behavioral, and clinical sciences. National Academies Press.

Elmer, G.I., Brown, P.L., Shepard, P.D., 2016. Engaging Research Domain Criteria (RDoC): Neurocircuitry in Search of Meaning. Schizophr Bull 42, 1090-1095.

Faucher, L., Goyer, S., 2015. RDoC: Thinking outside the DSM box without falling into a reductionist trap, The DSM-5 in Perspective. Springer, pp. 199-224.

Flint, J., Munafo, M.R., 2007. The endophenotype concept in psychiatric genetics. Psychol Med 37, 163-180.

Fries, E., 2008. Hypocortisolemic Disorders, in: Hellhammer, D.H., Hellhammer, J. (Eds.), Stress. The Brain-Body Connection. Karger, Basel, pp. 60-77.

Gandal, M.J., Leppa, V., Won, H., Parikshak, N.N., Geschwind, D.H., 2016. The road to precision psychiatry: translating genetics into disease mechanisms. Nat Neurosci 19, 1397-1407.

Glahn, D.C., Knowles, E.E., McKay, D.R., Sprooten, E., Raventos, H., Blangero, J., Gottesman, II, Almasy, L., 2014. Arguments for the sake of endophenotypes: examining common misconceptions about the use of endophenotypes in psychiatric genetics. Am J Med Genet B Neuropsychiatr Genet 165B, 122-130.

Glannon, W., 2015. Research domain criteria: a final paradigm for psychiatry? Front Hum Neurosci 9, 488.

Goethe, J.W., 1829. Wilhelm Meisters Wanderjahre, Gesamtausgabe 1981, von Wiese B. (Ed) ed. C.H. Beck, München.

Goodman, S.N., Fanelli, D., Ioannidis, J.P., 2016. What does research reproducibility mean? Science Translational Medicine 8, 341ps312-341ps312.

Goodman, S.N., Schneeweiss, S., Baiocchi, M., 2017. Using Design Thinking to Differentiate Useful From Misleading Evidence in Observational Research. JAMA 317, 705-707.

Gottesman, II, Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 160, 636-645.

Gottesman, II, Hanson, D.R., 2005. Human development: biological and genetic processes. Annu Rev Psychol 56, 263-286.

Gottesman, II, Shields, J., 1973. Genetic theorizing and schizophrenia. Br J Psychiatry 122, 15-30.

Gottesman, I.I., Shields, J., 1972. Schizophrenia and genetics: A twin study vantage point. Academic Press, New York.

Gräfe, K., Zipfel, S., Herzog, W., Löwe, B., 2004. Screening psychischer Störungen mit dem "Gesundheitsfragebogen für Patienten (PHQ-D)". Diagnostica 50, 171-181.

Gray, J.A., 1987. The psychology of fear and stress. Cambridge University Press, Cambridge.

Greene, S.M., Reid, R.J., Larson, E.B., 2012. Implementing the learning health system: from concept to action. Ann Intern Med 157, 207-210.

Gur, R.E., Calkins, M.E., Gur, R.C., Horan, W.P., Nuechterlein, K.H., Seidman, L.J., Stone, W.S., 2007. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. Schizophr Bull 33, 49-68.

Haroon, E., Raison, C.L., Miller, A.H., 2012. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 37, 137-162.

Hellhammer, D., 1983. Gerhin und Verhalten: Eine anwendungsorientierte Einführung in die Psychobiologie. Aschendorff, Münster.

Hellhammer, D., Hero, T., Gerhards, F., Hellhammer, J., 2012. Neuropattern: a new translational tool to detect and treat stress pathology I. Strategical consideration. Stress 15, 479-487.

Hellhammer, D.H., 2008. Principles of the Crosstalk between Brain and Body – Glandotropy, Ergotropy, and Trophotropy, in: Hellhammer, D.H., Hellhammer, J. (Eds.), Stress. The Brain-Body Connection. Karger, Basel, pp. 21-38.

Hellhammer, D.H., Hellhammer, J., 2008. Stress. The Brain-Body Connection, Key Issues in Mental Health. Karger, Basel.

Hellhammer, D.H., Klingmann, P.O., 2008. Serotonergic and Parasympathetic Disorders, in: Hellhammer, D.H., Hellhammer, J. (Eds.), Stress. The Brain-Body Connection. Karger, Basel, pp. 91-105.

Hellhammer, D.H., Wust, S., Kudielka, B.M., 2009. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology 34, 163-171.

Hero, T., 2013. The Neuropattern Pre-/Postnatal Stress Questionnaire (NPQ-PSQ). A New Tool to Assess Pre- and Postnatal Adversity (First Edition). Shaker, Herzogenrath.

Hero, T., Gerhards, F., Thiart, H., Hellhammer, D.H., Linden, M., 2012. Neuropattern: a new translational tool to detect and treat stress pathology. II. The Teltow study. Stress 15, 488-494.

Hess, W., 1960. Die physiologischen Grundlagen der Psychosomatik. Klinische Wochenschrift 38, 1228-1228.

Hess, W.R., 1925. Ueber die Wechselbeziehungen zwischen psychischen und vegetativen Funktionen. Schweiz Arch Neurol Psychiatr 16, 36-55.

Hess, W.R., 1962. Die physiologischen Grundlagen der Psychosomatik. Deut Med Wochenschr 86, 3-8.

Iniesta, R., Stahl, D., McGuffin, P., 2016. Machine learning, statistical learning and the future of biological research in psychiatry. Psychol Med 46, 2455-2465.

Insel, T.R., 2017. Digital Phenotyping: Technology for a New Science of Behavior. JAMA 318, 1215-1216.

Insel, T.R., Cuthbert, B.N., 2009. Endophenotypes: bridging genomic complexity and disorder heterogeneity. Biol Psychiatry 66, 988-989.

Ioannidis, J.P., 2017a. Acknowledging and Overcoming Nonreproducibility in Basic and Preclinical Research. JAMA 317, 1019-1020.

Ioannidis, J.P.A., 2017b. The Reproducibility Wars: Successful, Unsuccessful, Uninterpretable, Exact, Conceptual, Triangulated, Contested Replication. Clin Chem 63, 943-945.

Jameson, J.L., Longo, D.L., 2015. Precision medicine--personalized, problematic, and promising. N Engl J Med 372, 2229-2234.

John, B., Lewis, K.R., 1966. Chromosome variability and geographic distribution in insects. Science 152, 711-721.

Joober, R., 2013. On the simple and the complex in psychiatry, with reference to DSM 5 and research domain criteria. J Psychiatry Neurosci 38, 148-151.

Joyner, M.J., Paneth, N., Ioannidis, J.P., 2016. What Happens When Underperforming Big Ideas in Research Become Entrenched? JAMA 316, 1355-1356.

Kendler, K.S., Neale, M.C., 2010. Endophenotype: a conceptual analysis. Mol Psychiatry 15, 789-797.

Keshavan, M.S., Ongur, D., 2014. The journey from RDC/DSM diagnoses toward RDoC dimensions. World Psychiatry 13, 44-46.

Kessler, D., Bennewith, O., Lewis, G., Sharp, D., 2002. Detection of depression and anxiety in primary care: follow up study. BMJ 325, 1016-1017.

Khanna, N., Nesbitt, L., Roghmann, M.C., Tacket, C., 2009. Translation of clinical research into practice: defining the clinician scientist. Fam Med 41, 440-443.

Klingmann, P.O., Hellhammer, D.H., 2008. Noradrenergic and Sympathetic Disorders, in: Hellhammer, D.H., Hellhammer, J. (Eds.), Stress. The Brain-Body Connection. Karger, Basel, pp. 78-90.

Kozak, M.J., Cuthbert, B.N., 2016. The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. Psychophysiology 53, 286-297.

Kreutz, M., Hellhammer, D., Murison, R., Vetter, H., Krause, U., Lehnert, H., 1992. Pavlovian conditioning of corticotropin-releasing factor-induced increase of blood pressure and corticosterone secretion in the rat. Acta Physiol Scand 145, 59-63.

Krishnan, R.R., 2015. A knowledge network for a dynamic taxonomy of psychiatric disease. Dialogues in Clinical Neuroscience 17, 79.

Kumsta, R., Kliegel, D., de Kloet, E.R., de Rijk, R.H., Linden, M., Hellhammer, D.H., 2015. Evidence for an association between mineralocorticoid receptor gene haplotypes and psychobiological measures of atypical depression. Psychoneuroendocrinology 61, 14.

Lidz, T., 1966. Adolf Meyer and the development of American psychiatry. Am J Psychiatry 123, 320-332.

Lilienfeld, S.O., Treadway, M.T., 2016. Clashing Diagnostic Approaches: DSM-ICD Versus RDoC. Annu Rev Clin Psychol 12, 435-463.

Loosen, P.T., Kistler, K., Prange, A.J., Jr., 1983. Use of TSH response to TRH as an independent variable. Am J Psychiatry 140, 700-703.

Lucan, S.C., Barg, F.K., Bazemore, A.W., Phillips, R.L., Jr., 2009. Family medicine, the NIH, and the medical-research roadmap: perspectives from inside the NIH. Fam Med 41, 188-196.

Lucan, S.C., Phillips, R.L., Jr., Bazemore, A.W., 2008. Off the roadmap? Family medicine's grant funding and committee representation at NIH. Ann Fam Med 6, 534-542.

Mainen, Z.F., Hausser, M., Pouget, A., 2016. A better way to crack the brain. Nature 539, 159-161.

Maj, M., 2016a. Narrowing the gap between ICD/DSM and RDoC constructs: possible steps and caveats. World Psychiatry 15, 193-194.

Maj, M., 2016b. The need for a conceptual framework in psychiatry acknowledging complexity while avoiding defeatism. World Psychiatry 15, 1-2.

Mandl, K.D., Bourgeois, F.T., 2017. The Evolution of Patient Diagnosis: From Art to Digital Data-Driven Science. JAMA.

Mazhari, S., Price, G., Dragovic, M., Waters, F.A., Clissa, P., Jablensky, A., 2011. Revisiting the suitability of antisaccade performance as an endophenotype in schizophrenia. Brain Cogn 77, 223-230.

McEwen, B.S., 1998. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 840, 33-44.

McEwen, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108-124.

McEwen, B.S., 2017a. Allostasis and the Epigenetics of Brain and Body Health Over the Life Course: The Brain on Stress. JAMA Psychiatry 74, 551-552.
McEwen, B.S., 2017b. Epigenetic Interactions and the Brain-Body Communication. Psychother Psychosom 86, 1-4.
McEwen, B.S., 2017c. Neurobiological and Systemic Effects of Chronic Stress. Chronic Stress (Thousand Oaks) 1.
McEwen, B.S., Bowles, N.P., Gray, J.D., Hill, M.N., Hunter, R.G., Karatsoreos, I.N., Nasca, C., 2015. Mechanisms of stress in the brain. Nat Neurosci 18, 1353-1363.
McEwen, B.S., Chattarji, S., Diamond, D.M., Jay, T.M., Reagan, L.P., Svenningsson, P., Fuchs, E., 2010. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol Psychiatry 15, 237-249.
McEwen, B.S., Getz, L., 2013. Lifetime experiences, the brain and personalized medicine: an integrative perspective. Metabolism 62 Suppl 1, S20-26.
Miller, G.A., Rockstroh, B., 2013. Endophenotypes in psychopathology research: where do we stand? Annu Rev Clin Psychol 9, 177-213.
Mühlenfeld, H.-M., 2005. Wann und wie sollten wir intervenieren. Der Nervenarzt 5, 48-51.
Näher, K.L., 2015. Exploration von Therapieverläufen in Beobachtungsstudien: Prädiktoren für Veränderungen im Verlauf einer Therapie und Subgruppenidentifikation in messwiederholten Daten, Applied Mathematics. Fachhochschule Koblenz, Remagen.
National Research Council, 2011. Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease. National Academies Press, Washington.
Ozomaro, U., Wahlestedt, C., Nemeroff, C.B., 2013. Personalized medicine in psychiatry: problems and promises. BMC Med 11, 132.
Panksepp, J., 2006. Emotional endophenotypes in evolutionary psychiatry. Progress in Neuro-Psychopharmacology and Biological Psychiatry 30, 774-784.
Patrick, C.J., Hajcak, G., 2016. RDoC: Translating promise into progress. Psychophysiology 53, 415-424.
Pine, D.S., Leibenluft, E., 2015. Biomarkers With a Mechanistic Focus. JAMA Psychiatry 72, 633-634.
Prendes-Alvarez, S., Nemeroff, C.B., 2016. Personalized medicine: Prediction of disease vulnerability in mood disorders. Neurosci Lett.
Pruessner, M., Cullen, A.E., Aas, M., Walker, E.F., 2017. The neural diathesis-stress model of schizophrenia revisited: An update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci Biobehav Rev 73, 191-218.
Pütz, P., 2008. Hypercortisolemic Disorders, in: Hellhammer, D.H., Hellhammer, J. (Eds.), Stress. The Brain-Body Connection. Karger, Basel, pp. 39-59.
Rasetti, R., Weinberger, D.R., 2011. Intermediate phenotypes in psychiatric disorders. Curr Opin Genet Dev 21, 340-348.
Rasgon, N.L., McEwen, B.S., 2016. Insulin resistance-a missing link no more. Mol Psychiatry 21, 1648-1652.
Rauh, V.A., Margolis, A.E., 2016. Research Review: Environmental exposures, neurodevelopment, and child mental health – new paradigms for the study of brain and behavioral effects. Journal of Child Psychology and Psychiatry 57, 775-793.
Reus, V.I., Joseph, M.S., Dallman, M.F., 1982. ACTH levels after the dexamethasone suppression test in depression. N Engl J Med 306, 238-239.
Rohleder, N., 2014. Stimulation of systemic low-grade inflammation by psychosocial stress. Psychosom Med 76, 181-189.
Schork, N.J., 2015. Personalized medicine: Time for one-person trials. Nature 520, 609-611.

Schulkin, J., 2017. The CRF Signal: Uncovering an Information Molecule. Oxford University Press, Oxford.
Shah, J.L., Chakravarty, M.M., Joober, R., Lepage, M., 2016. Dynamic endophenotypes and longitudinal trajectories: capturing changing aspects of development in early psychosis. J Psychiatry Neurosci 41, 148-151.
Silbersweig, D., Loscalzo, J., 2017. Precision Psychiatry Meets Network Medicine: Network Psychiatry. JAMA Psychiatry 74, 665-666.
Spierling, S.R., Zorrilla, E.P., 2017. Don't stress about CRF: assessing the translational failures of CRF1antagonists. Psychopharmacology (Berl) 234, 1467-1481.
Stephan, H., 1975. Allocortex. Springer Berlin Heidelberg.
Steptoe, A., Freedland, K., Jennings, J.R., 2010. Handbook of behavioral medicine. Springer.
Strom, B.L., Buyse, M.E., Hughes, J., Knoppers, B.M., 2016. Data Sharing — Is the Juice Worth the Squeeze? New England Journal of Medicine 375, 1608-1609.
Sullivan, P.F., 2010. The psychiatric GWAS consortium: big science comes to psychiatry. Neuron 68, 182-186.
Sweeney, T.E., Haynes, W.A., Vallania, F., Ioannidis, J.P., Khatri, P., 2017. Methods to increase reproducibility in differential gene expression via meta-analysis. Nucleic Acids Res 45, e1.
Taichman, D.B., Sahni, P., Pinborg, A., Peiperl, L., Laine, C., James, A., Hong, S.T., Haileamlak, A., Gollogly, L., Godlee, F., Frizelle, F.A., Florenzano, F., Drazen, J.M., Bauchner, H., Baethge, C., Backus, J., 2017. Data Sharing Statements for Clinical Trials - A Requirement of the International Committee of Medical Journal Editors. N Engl J Med 376, 2277-2279.
Tandon, R., Rankupalli, B., Suryadevara, U., Thornton, J., 2015. Psychiatry is a clinical neuroscience, but how do we move the field? Asian journal of psychiatry 17, 135-137.
Tonelli, M.R., Shirts, B.H., 2017. Knowledge for precision medicine: Mechanistic reasoning and methodological pluralism. JAMA.
Tuomela, R., 1976. Explanation and Understanding of Human Behavior, in: Manninen, J., Tuomela, R. (Eds.), Essays on Explanation and Understanding: Studies in the Foundations of Humanities and Social Sciences. Springer Netherlands, Dordrecht, pp. 183-205.
Turetsky, B.I., Calkins, M.E., Light, G.A., Olincy, A., Radant, A.D., Swerdlow, N.R., 2007. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophr Bull 33, 69-94.
Von Wright, G., 1971. Understanding and Explanation. Cornell University Press, New York.
Wakefield, J.C., 2014. Wittgenstein's nightmare: why the RDoC grid needs a conceptual dimension. World Psychiatry 13, 38-40.
Westfall, J.M., Mold, J., Fagnan, L., 2007. Practice-based research--"Blue Highways" on the NIH roadmap. JAMA 297, 403-406.
White, T., Gottesman, I., 2012. Brain connectivity and gyrification as endophenotypes for schizophrenia: weight of the evidence. Curr Top Med Chem 12, 2393-2403.
Wild, C.P., 2012. The exposome: from concept to utility. Int J Epidemiol 41, 24-32.
Wiley, J.F., Gruenewald, T.L., Karlamangla, A.S., Seeman, T.E., 2016. Modeling Multisystem Physiological Dysregulation. Psychosom Med 78, 290-301.
Wittchen, H.U., Pieper, L., 2006. Schwerpunkt: Diabetes und Herz-Kreislauferkrankungen beim Hausarzt – Die Detect-Studie. . Die Ersatzkasse 7, 260-263.
Yu, J.S., Xue, A.Y., Redei, E.E., Bagheri, N., 2016. A support vector machine model provides an accurate transcript-level-based diagnostic for major depressive disorder. Transl Psychiatry 6, e931.

Zorn, J.V., Schur, R.R., Boks, M.P., Kahn, R.S., Joels, M., Vinkers, C.H., 2017. Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. Psychoneuroendocrinology 77, 25-36.

Figure legends

Figure 1. “Information Commons” with “Knowledge Network” including data of evolving knowledge of fundamental biological processes (reprinted with permission; Copyright © 2011, National Academy of Sciences).

Figure 2. Construction of a conceptual endophenotypes through three approaches. We suggest beginning from established knowledge on discrete brain systems and their contextual functionality. To then identify the conceptual endophenotype, elements functionally linked to each other within the same level of information are assembled, together with elements that co-vary across different levels of information, and elements co-emerging in the relevant functional context. This then leads to an iterative process between the field of (biomedical) science and clinical practice.

Figure 3. Depiction of the Neuropattern ‘stress-triangle’. Panel A: the triangle in an equilibrium state at medium level. Panel B: the triangle in a disequilibrium state at medium level. Panel C: the triangle in a disequilibrium state at upward-shifted level.