International Journal of Methods in Psychiatric Research
Int. J. Methods Psychiatr. Res. 23(Suppl. 1): 28–40 (2014)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/mpr.1409

The need for a behavioural science focus in research on mental health and mental disorders

HANS-ULRICH WITTCHEN,[1] SUSANNE KNAPPE,[1] GERHARD ANDERSSON,[2,3] RICARDO ARAYA,[4] ROSA M. BANOS RIVERA,[5] MICHAEL BARKHAM,[6] PER BECH,[7] TOM BECKERS,[8,9] THOMAS BERGER,[10] MATTHIAS BERKING,[11] CARMEN BERROCAL,[12] CHRISTINA BOTELLA,[13] PER CARLBRING,[14] GUY CHOUINARD,[15] FRANCESC COLOM,[16] CLAUDIO CSILLAG,[7] PIM CUJIPERS,[17,18,19,20] DANIEL DAVID,[21,22] PAUL M.G. EMMELKAMP,[9] CECILIA A. ESSAU,[23] GIOVANNI A. FAVA,[24] THOMAS GOSCHKE,[25] DIRK HERMANS,[26] STEFAN G. HOFMANN,[27] WOLFGANG LUTZ,[28] PETER MURIS,[29] THOMAS H. OLLENDICK,[30] FILIP RAES,[26] WINFRIED RIEF,[11] HELEEN RIPER,[17,18,31] ELIANA TOSSANI,[24] SASKIA VAN DER OORD,[26,32] BRAM VERVLIET,[26] JOSEP M. HARO[33,34,35] & GUNTER SCHUMANN[36,37]

1 Institute of Clinical Psychology and Psychotherapy, Center for Clinical Epidemiology and Longitudinal Studies (CELOS), Technische Universität Dresden, Dresden, Germany
2 Department of Behavioural Sciences and Learning, Swedish Institute for Disability Research, Linköping University, Linköping, Sweden
3 Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden
4 Academic Unit of Psychiatry, School of Social and Community Medicine, University of Bristol, Bristol, UK
5 University of Valencia, Valencia, Spain
6 Centre for Psychological Services Research, Department of Psychology, University of Sheffield, Sheffield, UK
7 Psychiatric Research Unit, Mental Health Centre North Zealand, University of Copenhagen, Hillerod, Denmark
8 Department of Psychology, KU Leuven, Leuven, Belgium
9 Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands
10 Department of Clinical Psychology and Psychotherapy, University of Bern, Bern, Switzerland
11 Institute of Clinical Psychology and Psychotherapy, University of Marburg, Marburg, Germany
12 PAIDI Research Group on Epidemiology and Psychometrics in Health and Behavioural Sciences, University of Malaga, Malaga, Spain
13 Jaume I University, Castellón, Spain
14 Department of Psychology, Stockholm University, Stockholm, Sweden
15 Department of Psychiatry, Saint Antoine Hospital, EA 3522, Centre de Recherches Psychanalyse, Médecine et Société (CRPMS), Paris, France
16 Psychoeducation and Psychological Treatments Area, Barcelona Bipolar Disorders Unit, IDIBAPS-CIBERSAM, Institute of Neurosciences, Hospital Clinic, Barcelona, Spain
17 Department of Clinical Psychology, VU University Amsterdam, Amsterdam, The Netherlands
18 EMGO Institute for Health and Care Research, VU University Amsterdam, Amsterdam, The Netherlands
19 VU University Medical Centre, Amsterdam, The Netherlands
20 Leuphana University, Lüneburg, Germany
21 Department of Clinical Psychology and Psychotherapy; Mount Sinai School of Medicine, Babes-Bolyai University, Cluj-Napoca, Romania

22 Department of Oncological Sciences, New York, USA
23 University of Roehampton, London, UK
24 Laboratory of Psychosomatics and Clinimetrics, Department of Psychology, University of Bologna, Bologna, Italy
25 Department of Psychology, Technische Universität Dresden, Dresden, Germany
26 KU Leuven, Leuven, Belgium
27 Department of Psychology, Boston University, Boston, MA, USA
28 Department of Psychology, University of Trier, Trier, Germany
29 Maastricht University, Maastricht, The Netherlands
30 Virginia Tech University, Blacksburg, VA, USA
31 Department of Psychiatry, VU University Medical Centre, Amsterdam, The Netherlands
32 University of Amsterdam, Amsterdam, The Netherlands
33 Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain
34 Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, Sant Boi de LLobregat, Barcelona, Spain
35 Universitat de Barcelona, Barcelona, Spain
36 Institute of Psychiatry, King's College London, London, UK
37 MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Key words
behaviour change, agenda, psychology, mental health, health behaviour, mental disorder, personalized medicine, translation

Correspondence
Hans-Ulrich Wittchen, Institute of Clinical Psychology and Psychotherapy and Centre of Clinical Epidemiology and Longitudinal Studies (CELOS), Technische Universität Dresden, Chemnitzer Str. 46, 01187 Dresden, Germany.
Telephone (+49) 351-463-36983
Fax (+49) 351-463- 36984
Email: wittchen@psychologie.tu-dresden.de

Abstract

Psychology as a science offers an enormous diversity of theories, principles, and methodological approaches to understand mental health, abnormal functions and behaviours and mental disorders. A selected overview of the scope, current topics as well as strength and gaps in Psychological Science may help to depict the advances needed to inform future research agendas specifically on mental health and mental disorders. From an integrative psychological perspective, most maladaptive health behaviours and mental disorders can be conceptualized as the result of developmental dysfunctions of psychological functions and processes as well as neurobiological and genetic processes that interact with the environment. The paper presents and discusses an integrative translational model, linking basic and experimental research with clinical research as well as population-based prospective-longitudinal studies. This model provides a conceptual framework to identify how individual vulnerabilities interact with environment over time, and promote critical behaviours that might act as proximal risk factors for ill-health and mental disorders. Within the models framework, such improved knowledge is also expected to better delineate targeted preventive and therapeutic interventions that prevent further escalation in early stages before the full disorder and further complications thereof develop. In contrast to conventional "personalized medicine" that typically targets individual (genetic) variation of patients who already have developed a disease to improve medical treatment, the proposed framework model, linked to a concerted funding programme of the "Science of Behaviour Change", carries the promise of improved diagnosis, treatment and prevention of health-risk behaviour constellations as well as mental disorders.

The challenge

What determines the onset and progression of mental disorders such as substance disorders, eating disorders and anxiety disorders? What drives humans to develop and to maintain health-risk behaviours such as harmful drinking and eating or smoking? Why are many individuals able to control their substance use or eating behaviours while others develop a persistent maladaptive

behavioural pattern ultimately leading to dependence or obesity, consequential disease and disability, and eventually a loss of control over their life? Why are many people able to cope with traumatic stress and anxiety, while others develop increasingly severe avoidance behaviour resulting in anxiety disorders and their sequelae such as helplessness and depression? What are the critical trajectories from maladaptive behaviours to (mental) disorders as defined in classificatory diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (APA, 2000, 2013) or the International Classification of Diseases (ICD) (WHO, 1991)? Can we modify critical developmental pathways by directly targeting such mechanisms?

From a psychological and cognitive-affective neuroscience perspective, such health-risk behaviours and mental disorders can be conceptualized as the procedural and developmental outcome of complex interactions of individual genetic predispositions with the environment and as neurobiological, psychological and social processes within "personal biographies". The brain as the essential target structure is shaped by genetic factors, development, environment and experience in multiple, highly complex and probably individual ways. All human actions including adaptive and dysfunctional decision-making involved in health-risk behaviour and common mental disorders are the result of complex interactions between (i) higher cognitive processes such as the anticipation of long-term consequences, the regulation of emotional impulses and the inhibition of habitual responses in favour of long-term goals, (ii) complementary forms of learning and memory, and (iii) basic emotional, reward-related, and motivational processes. Health-risk behaviours as well as mental disorders also provide indirect evidence for latent shared mechanisms. They share many behavioural, cognitive and physiological features suggesting the existence of similar etiological mechanisms, such as the "continued making of maladaptive choices even in the face of the desire to make a different choice" as a defining diagnostic criterion (APA, 2000), they frequently "bundle together", start predominantly early in life and escalate temporally in similar patterns.

From a broader neuroscience perspective, mental disorders can be conceptualized as insufficiently understood dysfunctions in basic psychological processes as well as "perturbations" in brain functions at the cell and systems level. The former processes can be conceived of as being centrally involved in the behavioural, cognitive-affective and somatic symptoms currently used to define mental disorders. The latter "perturbations" can broadly be described as various types of dysfunction in complex structural and functional neural circuits for information processing. Appropriate experimental psychological paradigms in combination with brain imaging methods, supplemented by molecular and biochemical analyses, allow examining the complex, plastic interactions and the connectivity of brain regions for different functions.

We still lack complete maps of such human circuitry dysfunctions. For many conditions though, candidate models exist and serve as a starting point (e.g. addictive behaviours – involvement of reward circuitries, i.e. Koob and Le Moal, 2001; fear and anxiety disorders – abnormalities of the amygdala-based fear circuitry, i.e. Shin and Liberzon, 2010). Corresponding candidate mechanisms at the behavioural level include aspects of cognitive control and volition, emotion regulation, meta-cognition, and decision-related processes, such as evaluation, risk perception and temporal discounting. However, the diagnostic specificity, moderating or even causal role of such highly complex "circuitry perturbations" in the evolution of mental disorders and persistent health-risk behaviours and associated clinical behavioural syndromes (e.g. adipositas, obesity) remains unclear.

Core questions and critical domains

Despite impressive achievements we still lack answers to core questions:

(i) How do complementary cognitive, affective, and motivational systems *interact dynamically*, which proximal and distal variables (e.g. acute or chronic stress) modulate *patterns of interactions* among these systems, and how do stable patterns of systems interactions evolve as a result of genetic variation, developmental change, and learning?
(ii) Which mechanisms underlie transitions from adaptive cognitive-behavioural patterns into maladaptive patterns of persistent health-risk behaviours or mental disorders? Are there critical developmental windows of vulnerability? Are cognitive dysfunctions (e.g. impaired volitional control) simply "constitutive markers" or generalizable causal disease factors?
(iii) How can effective change of dysfunctional behaviour patterns be induced and maintained by targeting such mechanisms?

One promising way to address such questions is to conceptualize mental disorders as maladaptive developmental processes, that reflect complex interactions of individual genetic predispositions with environments within "personal biographies" of psychological dispositions, associated with characteristic changes in neural systems and circuitries. One might also hypothesize that processes responsible for the development of health-risk behaviours and the shaping of respective vulnerabilities can be conceptualized on the same

theoretical grounds and that both unique and cross-cutting pathways and mechanisms exist. Such an approach offers the opportunity of addressing core questions; however such an endeavour involves addressing a number of critical issues:

- *Cognitive-affective factors and processes involved in human action*: There is a need for concerted efforts to examine experimentally the neurocognitive mechanisms underlying human behaviour and for example decision-making. This includes better knowledge of cognitive systems (Schumann *et al.*, 2013), including modulating influences (i.e. stress) and developmental (see later) trajectories of adaptive and maladaptive patterns, such as of decision-making and action control, in non-clinical and clinical populations (see Goschke, 2014).
- *Developmental mechanisms and pathways*: Mental disorders and health risk behaviours must be conceptualized as occurring on multiple timescales and thus as "developmental" in a broad sense. The concerted growth of regulatory mechanisms in early ages is a prerequisite for adaptive behaviour and sustained mental health. The brain's developmental plasticity in early ages along with prospective-longitudinal evidence that the onset of most common mental disorders is centred in relatively small, predominantly early time windows in the lifespan (Kessler *et al.*, 2005; Beesdo-Baum and Knappe, 2012) renders a developmental psychological perspective essential. Further, determinants and modifiers of (mal-)adaptation might arise from genetic/epigenetic factors as well as from gene–environment interactions, all intersecting at the level of functional and structural neurobiological functioning during development, progressing from early prenatal and postnatal stages throughout the lifespan.
- *Stress and environment*: There is overwhelming evidence that conditions of traumatic and chronic stress can significantly change the structure and functioning of brain circuits and significantly impact gene expression and translation. Such plastic changes in peripheral physiology and neural activity are linked to adverse health outcome in many animal disease models. Characteristic differences in neurotransmitter systems, immune systems functions, and peripheral endocrine patterns follow stress exposition. Very likely, acute and chronic stress affects the developmental trajectory of health-risk behaviours also in humans. Use of cutting-edge psychoneuroendocrine methodology will help to understand the complex interaction patterns of stress and ill-health behaviour in children, adolescents, and adults. Innovative methods to measure "stress" will propel our understanding of the mechanisms leading to health-risk behaviour and resulting morbidity.
- *Computational and other modelling approaches* (e.g. trajectory, latent growth modelling) are central for modelling complex interactions in order to reduce the enormous complexity, because there are no simple "causal" relationships. There is a lack of explicit (e.g. computational or connectional) models of the mechanisms and dynamics of developmental change, which are needed to understand how non-linear interactions among component processes on different levels of analysis give rise to emergent properties (e.g. non-linear developmental trajectories; critical periods; stable patterns of dysfunctional regulation).
- *Associated "reductionistic" mechanistic basic research* is needed ultimately to identify and examine the nature of critical systems characteristics and putative causal mechanisms. This means that such an overall strategy needs to be supplemented by stringent mechanistic behavioural and biological experiments, where necessary also in animals and cells. This applies to interactions of putative components within neural cells, cell systems and circuitries, within different psychological processes and between neural circuitry and psychological processes. Skilful data integration and modelling (systems biology, computational neuroscience) can help to reduce complexity so that specific hypotheses become testable in concrete biological or behavioural models, which in turn can feedback into the research design.
- *Epidemiology and population genetics*: Clinical samples have only limited value for investigating potentially causal interactions in many conditions. This is not only due to the fact that subjects sampled from clinical populations are typically suffering for many years, but also due to confounding by selection bias, treatment effects and the presence of comorbid conditions, that might have developed as a consequence of prior clinical conditions. They also provide little information about normal and adaptive processes, protective factors or preventive targets, this limiting their value when it comes to identifying protective factors and resilience. Use of the full range of options provided by descriptive and causal analytic epidemiologic approaches to define cases/patients in all stages, as well as population genetics and developmental psychology to define developmentally sensitive, prospective cohorts of relevant phenotypes and genotypes are thus mandatory to identify developmental and symptom pathways as well as their critical trajectories.
- *Clinical, treatment and translational perspective*: Identifying the potentially causal or mediating role of such processes and interactions over time promises a better understanding of when, how and why the evolved mechanisms might fail or become dysfunctional. Such insight can be seen as a precondition for testing

similarities and differences in the evolution of specific behaviours and syndromes and their malleability. More importantly, such improved understanding also provides the opportunity to identify potentially more promising targets of intervention that aim less to modify common symptoms, but rather directly to allow modification of underlying core vulnerabilities as well as core dysfunctional aetiological factors. This might have tremendous potential, for example with regard to optimizing targets as well as form and dose of cognitive-behavioural intervention in patients as well as preventive efforts.

- *Symptom progression models and an integrative translational public health perspective*: From such an integrative translational perspective existing "symptom progression models" are at least of great heuristic value (Figure 1). Such existing descriptive models, though imperfect and still largely speculative, assume a systematic evolution of symptoms from initially transient to more persistent and pronounced expressions, seen as the result of critical interactions of vulnerabilities with environmental and experiential influences and their dysfunctional processing in developmentally sensitive periods.

What might be the most promising targets?

Descriptive and empirically sound models are instrumental to define starting points, for example with regard to the questions: What are putative core dysfunctional process targets? What are the most critical trajectories in the developmental pattern? What is the most promising and feasible strategy to modify the progression trajectories from early preclinical signs to clinically significant expressions. Such targeted strategy has the potential of not only improving existing and deriving novel interventions that could be adapted too early, in preclinical (preventive) as well as in advanced clinical stages, but they have also two evident additional advances. First, such an approach is likely to enhance the public health utility (benefits) of research, because there is the premise that such early targeted intervention will be associated with a higher probability of reducing substantially the future burden. Second, this strategy will at least partially avoid the traditional "translational hurdles" of the conventional approach (see Figure 2). Procedural developmental modelling in representative samples of low and high risk subjects, as well as of clinical groups, is required to identify:

(a) the determinants of critical trajectories (e.g. adaptive- to maladaptive, non-clinical to clinical),

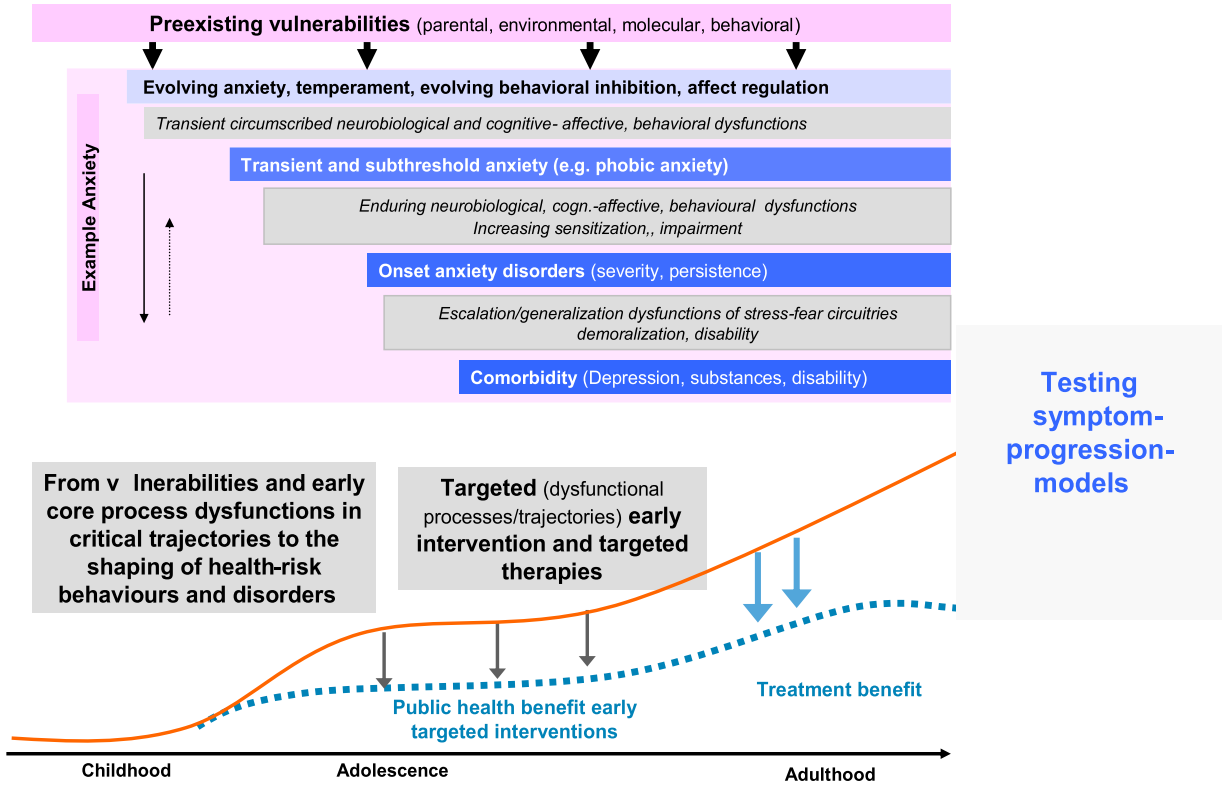

Figure 1. Examples for symptom progression models.

Int. J. Methods Psychiatr. Res. 23(Suppl. 1): 28–40 (2014). DOI: 10.1002/mpr

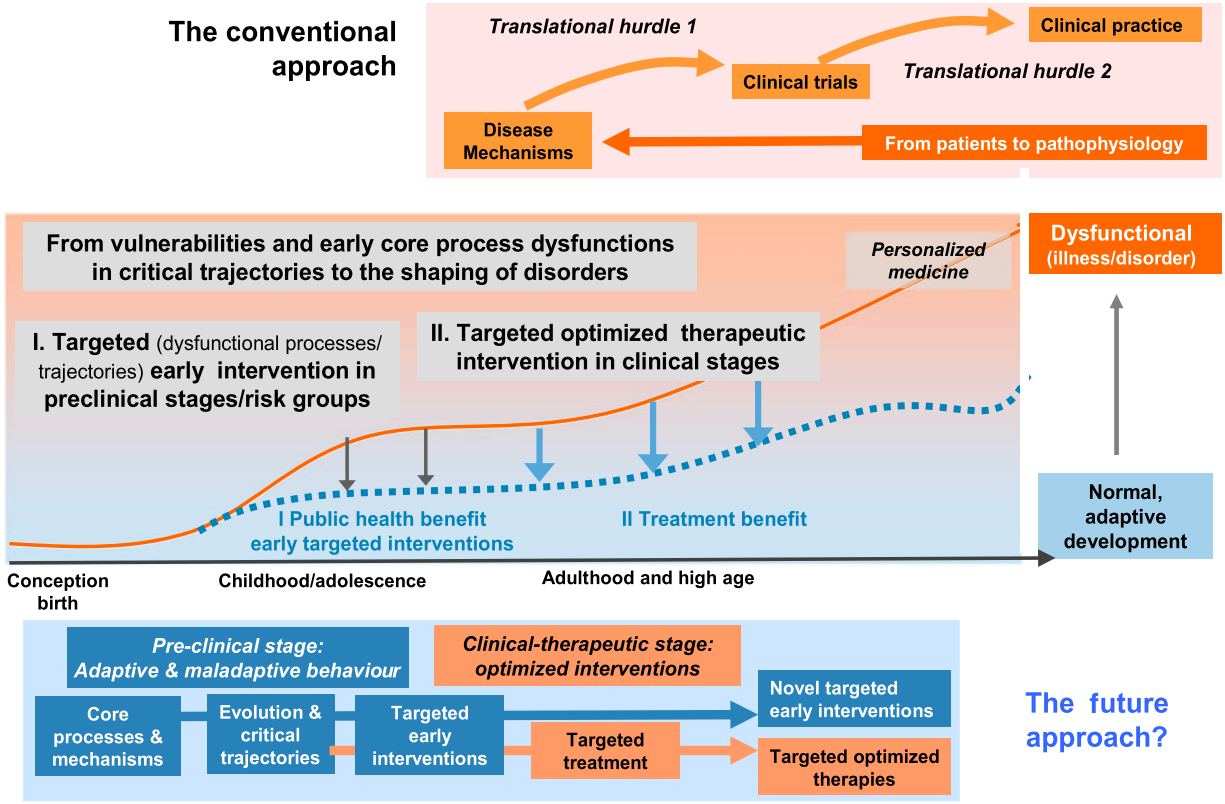

Figure 2. The conceptual framework for translation in clinical research.

(b) specific and cross-cutting processes,
(c) novel "targeted" interventions.

It further carries the potential of greater research synergies across disciplinary boundaries, and adds considerable public health and translational utility, beyond major impact on diagnosis and treatment.

As displayed in Figure 2, such a strategy requires an iterative transdisciplinary multi-method approach in samples and cohorts starting already at conception, respectively (very) young age across to old age. More precisely, this strategy involves:

(i) Elucidating the "normative" (adaptive) expressions of psychological functions and processes, their neurobiological, molecular and genetic substrates, and their interaction by developmental stage in well-defined "normal" populations with theory-driven, tailored task paradigms.
(ii) Modelling pathways and system interactions both at a structural (e.g. latent trait and growth; reduction of complexity, "higher order constructs") and a "mechanistic" level (e.g. circuitry processes, computational neuroscience).
(iii) Validating, challenging and improving the derived models by basic science experiments (e.g. cells, animal models) to derive improved models for further testing (e.g. systems biology).
(iv) Incorporating individual and contextual factors to determine how functions, processes and circuitries are developmentally influenced by learning, plasticity, emotional traits, and stress.
(v) Applying the derived models in defined risk cohorts to examine how, why, when and where system components are affected and prospectively associated with increased risk for onset.
(vi) Testing how and to which degree these dysfunctions can be altered by interventions.

In the following, we provide four examples of how such a strategy might be translated into concrete research action.

Examples for a translational agenda

Core topic A: Stress, fear, avoidance and anxiety disorders

Fear and its anticipation (anxiety) and avoidance can be conceptualized as normal emotional states comprising a typical pattern of cognitive, affective, behavioural and physiological

responses. Anxiety as a basic emotional state, reaction or trait plays a significant role in many critical health behaviours, such as avoidance (withdrawal), smoking, drinking, drug abuse or restrictive eating and plays an increasingly recognized role in the pathogenesis of many clinical conditions.

Anxiety disorders, such as Panic Disorder, Agoraphobia, Generalized Anxiety Disorder, Social Anxiety Disorder, Specific Phobias, Post-traumatic Stress-Disorder (PTSD) and Obsessive-Compulsive Disorder (OCD) (according to ICD-10 and DSM-IV) comprise a large group of phenotypically remarkably different disorders, all of which, however, share "anxiety" as a core defining feature and process in both the initiation as well as the maintenance of the disorder over time. Cutting edge epidemiological research of natural developmental pathways has shown that the onset of anxiety disorders is linked to relatively narrow, particularly sensitive developmental periods, typically in childhood/adolescence. Such studies have also shown that anxiety and anxiety disorders (i) may be best conceptualized dimensionally, for example with regard to frequency, severity and persistence, and (ii) that anxiety disorders tend to co-occur over the lifespan and are highly comorbid, with both, other "internalizing" (like depression) disorders and with externalizing disorders (i.e. substance disorders) (for an overview, see Beesdo *et al.*, 2009). Sophisticated longitudinal "symptom progression models" suggest various common escalating pathways in their pathogenic expression, also involving the occurrence of other, temporally secondary conditions such as depression, highlighting in particular the detrimental effects of avoidance.

Avoidance behaviour of external and internal triggers for anxiety is believed to be mainly responsible for the progression and maintenance of anxiety disorders (Koerner and Fracalanza, 2012). From a cognitive-behavioural perspective, avoidance decreases the probability of extinction, respectively relearning as well as the establishment of alternative behaviours. Changing avoidance behaviour is considered to be central goal in the prevention and treatment of stress, fear and anxiety spectrum disorders. Referring to psychological, cognitive-affective neuroscience and neurobiological research it has been proposed that based on shared psychological, environmental and neurobiological factors and processes, the disorders might be better called "*Stress-induced and Fear Circuitry Disorders*", emphasizing the critical interaction of environmental and stress factors and dysfunctions in neural circuitries as a core feature (i.e. OCD: frontal-striate cognitive circuits; panic and phobias: abnormalities of the amygdala-based fear circuitry; PTSD: amygdala, medial prefrontal cortex, hippocampus) (Craske *et al.*, 2009). Evidence for and the utility of this conceptualization, however, is still lacking.

Cognitive-behavioural therapies (CBTs) are considered to be first-line treatments for these disorders (Olatunji *et al.*, 2010). Despite the existence of various heuristical models, it is not known why, when and how which components of CBT are essential in promoting behaviour change. The neurobiological and particular fear-circuitry underpinnings of this method remain unclear. Improved understanding of such processes might have tremendous implications not only in improving treatment by optimizing the formal and content structure of CBT, but also for targeted prevention of anxiety-related reactions and behaviours, before the full syndrome is expressed clinically. Due to the heterogeneity of CBT approaches and its many, though variable, ingredients the core mechanisms of action of CBT remain unclear. Recent critical research appraisals have suggested highly promising strategies to identify the core mechanisms of action with the promise of deriving improved targeted and specifically tailored interventions (Wittchen and Gloster, 2009) targeting directly dysfunctions in preclinical/clinical stages of various fear/anxiety disorders.

Core research questions regarding basic mechanisms and systems interaction concerning fear and anxiety might be:

(i) In what way are patterns of interaction between complementary systems involved in reward-based learning, motivation, and executive control different in predromal and clinical anxiety conditions? In what way is their modulation altered by emotions and stress?
(ii) How do neural circuits interact with psychological mechanisms and behaviour? Do they differ by anxiety type, developmental stage, and severity?
(iii) What is the specific role of fear circuitries and in amygdale, medial prefrontal cortex, insula, and hippocampal regions in particular? What other circuitary systems are involved?
(iv) Do abnormalities identified represent acquired signs of the disorders (correlate, marker of severity) or vulnerability or even (causal) risk factors that increase the risk of developing the disorders? (e.g. can we demonstrate that amygdala hyper-responsivity occurs before the onset of specific phobia or social anxiety disorder or OCD or PTSD?)
(v) Which behavioural and molecular factors influence such patterns and processes, and which environmental (experiential, stress) factors are relevant in the interactions arising?

Core research questions regarding mechanisms of action of CBT are:

(i) What are the active core components of CBT (e.g. cognitive versus behavioural-exposure) as well as their mechanisms of action (e.g. activation of relearning and neural plasticity)?

Int. J. Methods Psychiatr. Res. 23(Suppl. 1): 28–40 (2014). DOI: 10.1002/mpr

(ii) What are the core endophenotypes with good, respectively poor response to various drug and behavioural therapies, to advance knowledge about individualized treatment strategies?

Core topic B: Addictive behaviours and addiction

Addiction is a complex phenomenon. Causes can be identified from many perspectives. All perspectives have some, though limited explanatory power and all seem to provide, though limited, contributions to pragmatic therapeutic interventions. One central feature is that harmful substance use and substance use disorders are associated with impairments of cognitive control. Addiction (i.e. dependence according to DSM-IV-TR, APA, 2000) at its clinical most severe expression is operationally defined as the "continued making of maladaptive choices of behaviours, even in the face of the explicitly stated desire and decision to make a different choice" (APA, 2000) as well as a loss of control over how and when the substance is consumed (i.e. to continue smoking and drinking, despite recognition of severe negative consequences). Addictive drugs are hypothesized to drive maladaptive decision-making through pharmacological interactions with neurophysiological mechanisms evolved for normal learning systems. However, how these interactions drive maladaptive decision-making remains yet to be determined. Adolescence as a period of growth, exploration, change and neurocognitive and affective maturation, is the core risk period for initial (first) use of and experiences with psychotropic substances such as alcohol and nicotine (Merikangas *et al.*, 2010; Behrendt *et al.*, 2008). There is a need to identify, with a view to potential interventions, why almost 20% of adolescents develop a dysfunctional substance use pattern or even dependence – while 80% will not – and derive targeted interventions from this examination.

The profound neuron-adaptive and neurotoxic effects of chronic dependent use on dopaminergic, serotonergic, opiod and GABA-ergic systems and on pre-frontal and limbic circuitry involved in affective learning is well documented (Le Moal and Koob, 2007). The question, however, which behavioural, cognitive-affective and neurobiological factors are responsible for the initiation and the trajectories from experimental, to regular, harmful and dependent use, and vice versa, remains unanswered. A series of hypotheses have been proposed that might account for this failure. These range from genetic mechanisms, over pharmacological interactions with neurophysiologic mechanisms evolved for normal learning systems to dysfunctional interactions between normal learning systems and the reward distribution of behaviours. Strong indications suggest that a compromised interaction of brain systems involved in motivation, cognitive control and executive functions, as well as basic motivational-affective systems involved in the implicit processing of rewards, incentives and emotional cues are of core relevance. Neuroimaging studies revealed, for example, functional differences in lateral and prefrontal and orbitrofrontal cortices in tasks requiring cognitive control (Paulus *et al.*, 2002). Specifically, substance abusers showed reduced recruitment of control and less neural activity in the anterior cingulated cortex following response conflicts and errors, suggesting dysfunctional interaction between anterior cingulated cortex (conflict monitoring) and lateral prefrontal cortex (involved top-down control). During adolescence, critical maturation processes in these motivational and executive neurocircuitries are believed to result in increased susceptibility for substance abuse. Numerous theories have been developed, focusing on planned and habitual decision-making, ranging from acute drug effects on homeostasis to allostatic alterations of set points to executive dysfunctions to increased habitual drug intake.

Strategically intermediate and long-term objectives might build on novel theoretical unified perspectives for addiction as "vulnerabilities" in established "decision-making systems" (Redish *et al.*, 2008) and extensions thereof (e.g. temporal difference reinforcement learning). These acknowledge interactions between a planning and a habit system associated with different characteristics and key anatomical structures. This can be based on a set of theoretical targets with associated vulnerabilities and experimental assessment areas (e.g. vulnerability: reward-based processing – pharmacological access to reward signal drives the return to those signals, or vulnerability "impulsivity – unwillingness to weigh future events leads to impulsive choices). This theoretical and conceptual framework can be used as a starting point to adapt existing standard paradigms addressing such vulnerabilities specifically to our research questions.

Core topic C: Development of adaptive and maladaptive mechanisms and modulators of decision-making and behavioural control (see also Goschke, 2014)

Many mental health problems and mental disorders refer to "maladaptive behaviours" such as overeating (as in obesity) or harmful substance use (like in addictive disorders). They are often described metaphorically as instances of "weakness of will" or lack of "willpower". While such folk-psychological concepts describe the fact

that individuals often persist with maladaptive behaviour despite being aware of adverse long-term consequences, they provide no explanations of the psychological and neurobiological mechanisms underlying decisions and actions in situations involving conflicts between long-term (e.g. health-related) goals and strong competing motivational and habitual tendencies. In recent years, the combination of sophisticated behavioural tasks with advanced neuroimaging methods has yielded new insights into mechanisms underlying (i) incentive motivation, (ii) reward-based learning, (iii) habit formation, and (iv) "higher" executive control processes (e.g. anticipation of long-term consequences, prospective memory, emotion regulation, response inhibition). Importantly, research indicates that prefrontal brain regions critically involved in executive control do not form a unitary "central executive", but are interconnected with and strongly modulated by systems mediating emotions, reward, and stress. Moreover, research on implicit evaluation and motivation indicates that conscious decisions can dissociate from automatic affective reactions and motivations. Thus, understanding how motivation, learning, and executive control systems interact dynamically and how those interactions develop is a critical precondition for improved models of maladaptive (health-injuring) behaviours and mechanisms underlying enduring behavioural change. The emerging field of (developmental) computational neuroscience is of critical importance for deriving explicit models of how non-linear interactions in neural systems on different levels of analysis give rise to emergent properties such as stage-like transitions and critical periods in the development of chronic dysfunctional regulation patterns (cf. McClelland and Vallabha, 2009). However, despite impressive recent progress, core questions of an integrative account of adaptive and maladaptive behaviour remain unresolved:

(i) how habitual, motivational, affective, and executive control systems *interact dynamically* and how this interaction is modulated by proximal and distal variables (e.g. acute/chronic stress)
(ii) how stable patterns of interactions between motivational, emotional and executive-control systems evolve as a result of the interplay of learning, development, and genetic variation, and how inter-individual differences in intra-individual change patterns emerge
(iii) which mechanisms underlie the transition from adaptive goal-directed behaviour into dysfunctional regulation patterns leading to maladaptive behavioural choice
(iv) whether behavioural change and adaptive (e.g. health-promoting) behaviour can best be supported by strengthening *volitional* functions (e.g. the ability to maintain intentions in the face of competing habits or emotional temptations) or by enhancing *motivational* incentives associated with long-term goals (or whether both aspects need to be targeted).

Such research may then be able to address (i) how patterns of interaction between systems involved in reward-based learning, motivation, and executive control, (ii) give rise to (mal-)adaptive behavioural decisions, (iii) are modulated by emotions and stress, and (iv) develop during adolescence.

Core topic D: Eating, eating disorders and neurometabolic conditions

The neurobiology and the adaptive and maladaptive cognitive-affective regulation of eating disorders (e.g. anorexia, bulimia, binge eating) and related conditions (picky eating, neurometabolic conditions, such as obesity) requires investigation from preclinical to clinical expressions as well as the consideration of other complex factors (e.g. perceived stress, stress regulation, environment, anxiety/depression) contributing to its dysregulation. There are common neurobiological and neurocognitive regulation mechanisms shared by eating behaviour, addictions and internalizing disorders (Mercer and Bird, 2012). The common denominator of these conditions is "a persistent disturbance of eating behaviour or behaviour intended to control weight and eating" (First and Tasman, 2010). Examination of common and specific psychological, neurological and circuitry dysfunctions across various forms of syndromes and disorders and in different stages of expression/developmental stage may help to derive improved models and novel therapeutic targets and approaches.

For example, the discovery of leptin and ghrelin has led to a new understanding of the neurobiology of eating behaviour and the neural circuits and mechanisms that underlie appetite (Pandit *et al.*, 2012). Many established genetic links with human obesity reflect mutations in specific elements of those pathways known from rodent studies [e.g. mutations that affect proopiomelanocortin (POMC) signalling]. The motivation to eat competes with other motivations, e.g. the motivation to reproduce. These processes are integrated by a complex, highly conserved neural circuitry – the reward *sy*stem (Nogueiras *et al.*, 2012). Its key elements are the mesolimbic dopamine neurons in the ventral segmental area (VTA) that project to the nucleus accumbens (NAcc), where the target cells include cholinergic, GABAergic and opioid-containing

Int. J. Methods Psychiatr. Res. 23(Suppl. 1): 28–40 (2014). DOI: 10.1002/mpr

cells. The reward system is a target for both, natural (such as food and sex) and artificial rewards (such as drugs of abuse and alcohol). Leptin and ghrelin reflect the nutritional state or food ingestion and modulate signals in the reward system. The reward circuitry also underlies addictive behaviours, including nicotine (a cholinergic agonist), endocannabinoids, and opiates. These "short circuit" the reward system, resulting in accelerated reward seeking behaviour. Epigenetic mechanisms regulate mRNA and protein expression, modifying the HPA homeostasis and stress response. Evidence suggests that environmental factors (e.g. maternal care, alcohol, smoking, nutrition) can change epigenetic patterns. The present obesity epidemic and the increase in eating disorders (Wittchen *et al.*, 2011) indicate that the aforementioned homeostatic mechanisms can be easily overridden.

Anorexia nervosa (AN) is often associated with a wide range of symptoms and comorbid conditions, some of which are secondary to starvation. Multiple candidate mechanisms have been proposed with symptom and diagnostic relevance. In addition to multiple nutrition- and stress-related endocrine mechanism (i.e. ghrelin, leptin, HPA), results from genetic, CSF and PET studies indicate that dopamine dysfunction, particularly in striatal circuits, might contribute to altered reward and affect, decision-making and executive control, as well as excessive motor movements and decreased food ingestion in subjects with AN. fMRI studies suggested that AN patients may have a reward-circuit-based abnormality (localized in the ventral striatum) which may be related to difficulties discriminating between positive and negative feedback (Wagner *et al.*, 2007). Instead, patients seem to recruit compensatory "cognitive control" regions such as the DLPFC and the parietal cortex. Converging evidence for other eating disorders and related phenomena (bulimia, binge eating, picky eating) are currently lacking. It is likely that the interactions of genetic with environmental/experimental and developmental factors are involved in the dysfunctions ultimately observed in clinical stages. However the specific role of executive control process dysfunctions in this disorder remains unclear.

A key stage in the progression to obesity appears to be the development of leptin resistance – insensitivity to the effects of leptin that would, in a normal individual, suppress appetite (Pandit *et al.*, 2012). This is analogous to insulin resistance (type 2 diabetes), and is not easily reversed. This might reflect a dysfunction of the reward circuitry. So, when leptin resistance develops in the homeostatic circuitry controlling appetite, does a similar resistance develop in the reward circuitry – meaning that food is rewarding independently of energy balance? This mechanism includes several components such as, but not limited to, neurometabolic and neuroendocrine changes and stress-induced alterations of homeostatic regulation, triggered by modern lifestyle on the basis of an existing genetic predisposition. Importantly, it corroborates the notion that eating disorders and obesity exhibit a striking shared biology with anxiety and addictive behaviour.

Against this background, it seems promising to identify the shared and syndrome-specific vulnerabilities and developmental processes for dysfunctional eating, eating disorders and neurometabolic conditions by examining:

(i) maladaptions and moderating factors in decision-making and action control and their control in the evolution of transient and persistent dysfunctional eating behaviours and disorders
(ii) the role and interaction of peripheral and central mechanisms of catecholaminergic dysregulation, behaviour and its crosstalk with metabolic pathways and interactions between endocrine signals (leptin, ghrelin, HPA axis), epigenetic patterns, reward and other circuitries as well as cognitive control in various at risk, subclinical and clinical groups
(iii) to conduct basic science research into the structure and process of neurometabolic and catecholaminergic perturbations, including molecular and mouse models
(iv) and to examine syndrome-specific and -shared processes and mechanisms involved in the development of dysfunctional eating behaviour, eating disorders as well as metabolic conditions.

This perspective allows exploration and testing of preventive and therapeutic intervention strategies and components that target novel shared signalling pathways as well as individualized targets.

Conclusion

In this paper we emphasized that in order to make major progress in mental health research and mental disorders we need to rethink our current fragmented research strategies towards a broader behavioural science focus, instead of narrower and fragmented cognitive or neurobiological perspectives. Using four examples of behavioural problems and related mental disorders, the goals and challenges to be met are depicted in Table 1. The well known translational barriers can only be overcome when segregated research approaches are combined in a concerted, interdisciplinary action, linking biological, psychological and social sciences within a developmental framework. Our proposal refers in this context to similar conceptual frameworks such as the one proposed by the NIH (NIH, 2009) or the NIMH Working Group on

Table 1. Goals and challenges for selected behavioural problems and related mental disorders

Goals	Challenges (advances needed to meet these goals)
Stress, fear, avoidance and anxiety disorders	(i) Despite the existence of various heuristical models, it is not known why, when and how which components of cognitive behavioural therapy (CBT) are essential in promoting behaviour change. (ii) The neurobiological and particular fear-circuitry underpinnings of this method remain unclear. (iii) Improved understanding of such processes might have tremendous implications not only in improving treatment by optimizing the formal and content structure of CBT, but also for targeted prevention of anxiety-related reactions and behaviours, before the full syndrome is expressed clinically.
Addictive behaviours and addiction	Strategically intermediate and long-term objectives might build on novel theoretical unified perspectives for addiction as "vulnerabilities" in established "decision-making systems" (Redish *et al.*, 2008) and extensions thereof (e.g. temporal difference reinforcement learning).
Analysis of the development of adaptive and maladaptive mechanisms and modulators of decision-making and behavioural control	(i) How habitual, motivational, affective, and executive control systems interact dynamically and how this interaction is modulated by proximal and distal variables (e.g. acute/chronic stress). (ii) How stable patterns of interactions between motivational, emotional and executive-control systems evolve as a result of the interplay of learning, development, and genetic variation, and how inter-individual differences in intra-individual change patterns emerge. (iii) Which mechanisms underlie the transition from adaptive goal-directed behaviour into dysfunctional regulation patterns leading to maladaptive behavioural choice. (iv) Whether behavioural change and adaptive (e.g. health-promoting) behaviour can best be supported by strengthening volitional functions (e.g. the ability to maintain intentions in the face of competing habits or emotional temptations) or by enhancing motivational incentives associated with long-term goals (or whether both aspects need to be targeted).
Eating, eating disorders and neurometabolic conditions	(i) Examination of common and specific psychological, neurological and circuitry dysfunctions across various forms of syndromes and disorders and in different stages of expression/developmental stage may help to derive improved models and novel therapeutic targets and approaches. (ii) Despite multiple candidate mechanisms having been proposed with symptom and diagnostic relevance for anorexia nervosa, evidence for other eating disorders and related phenomena is lacking. (iii) It remains yet to be determined whether leptin resistance develops in the homeostatic circuitry controlling appetite, and thereby, a similar resistance develops in the reward circuitry. If so, food may serve as a rewarding stimulus, independently of energy balance, and alteration of these mechanisms may facilitate understanding of obesity.

Int. J. Methods Psychiatr. Res. 23(Suppl. 1): 28–40 (2014). DOI: 10.1002/mpr

Child and Adolescent Mental Health (NAMHC, 2008) highlighting the critical developmental transition points across the lifespan in order to link basic science findings with clinical and social aspects. Most solutions to the complex problems of mental health require the synthesis of knowledge and methods across various disciplines. However, past barriers have made true interdisciplinary approaches rare exceptions (Pellmar and Eisenberg, 2000). The fragmentation and "disciplinary insularity" of the mental health research field needs to be overcome by linkages among relevant biological, psychological, social and clinical approaches. Thus, only a concerted trans-disciplinary effort will be able to adequately address the full scope of mental health, involving behavioural, clinical and neurosciences concepts using a multi-level, multi-measurement approach.

Acknowledgements

This article was generated as part of the activities of a group of leading European experts on psychological research and intervention, in order to provide an assessment of the state-of-the-art of research in different domains, identifying major advances and promising methods and pointing out gaps and problems which ought to be addressed in future research. A similar critical appraisal with partly similar conclusions is concurrently provided elsewhere (Schumann *et al.*, 2013) by the ROAMER work group "Biomedical research" (ROAMER, 2013). Experts in both work groups have been selected for their academic excellence and for their competence in the different units of analysis needed to comprehensively characterize particular symptom domains. Their contributions do not aim to be systematic reviews of the field but rather provide a well-informed opinion of the authors involved. They also do not represent official statements of the ROAMER consortium, but are meant to inform the discussion on psychological research and intervention in mental disorders among interested stakeholders, including researchers, clinicians and funding bodies. Recommendations made in this supplement will undergo a discussion and selection process within the ROAMER consortium, and contribute to a final roadmap, which integrates all aspects of mental health research. We thus hope to provide an informed and comprehensive overview of the current state of psychological research in mental health, as well as the challenges and advances ahead of us.

Declaration of interest statement

The authors have no competing interests.

References

American Psychiatric Association (APA). (2000) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), 4th edition, Arlington, VA, American Psychiatric Association.

American Psychiatric Association (APA). (2013) Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Arlington, VA, American Psychiatric Publishing.

Beesdo K., Knappe S., Pine D.S. (2009) Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Psychiatric Clinics of North America*, **32**, 483–524, DOI: 10.1016/j.psc.2009.06.002

Beesdo-Baum K., Knappe S. (2012) Developmental epidemiology of anxiety disorders. *Child & Adolescent Psychiatric Clinic of North America*, **21**(3), 457–478, DOI: 10.1016/j.chc.2012.05.001

Behrendt S., Wittchen H.-U., Höfler M., Lieb R., Low N.C.P., Rehm J. (2008) Risk and speed of transitions to first alcohol dependence symptoms in adolescents: a 10-year longitudinal community study in Germany. *Addiction*, **103**, 1638–1647.

Craske M.G., Rauch S.L., Ursano R., Prenoveau J., Pine D.S., Zinbarg R.E. (2009) DSM V anxiety, obsessive-compulsive spectrum, posttraumatic, and dissociative disorders work group literature review: what is an anxiety disorder? *Depression and Anxiety*, **26**, 1066–1085, DOI: 10.1002/da.20633

First M.B., Tasman A. (2010) Clinical Guide to the Diagnosis and Treatment of Mental Disorders, (pp. 57–63), New York, John Wiley & Sons.

Goschke T. (2014). Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps, and needs in current research. *International Journal of Methods in Psychiatric Research*, **23** (Suppl.1), 41–57.

Kessler R.C., Berglund P., Demler O., Jin R., Merikangas K.R., Walters E.E. (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives in General Psychiatry*, **62**, 593–602, DOI: 10.1001/archpsyc.62.6.593

Koerner N., Fracalanza K. (2012) The role of anxiety control strategies in imaginal exposure. In Neudeck P., Wittchen H.-U. (eds) Exposure Therapy: Rethinking the Model – Refining the Method, pp. 197–216, New York, Springer.

Koob G.F., Le Moal M. (2001) Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, **24**, 97–129, DOI: 10.1016/S0893-133X(00)00195-0

Le Moal M., Koob G.F. (2007) Drug addiction: pathways to the disease and pathophysiological perspectives. *European Neuropsychopharmacology*, **17**, 377–393, DOI: 10.1016/j.euroneuro.2006.10.006

McClelland J.L., Vallabha G. (2009) Connectionist models of development: mechanistic dynamical models with emergent dynamical properties. In Spencer J.P., Thomas M.S.C., McClelland J.L. (eds) Toward a unified theory of development: connectionism and dynamic systems theory re-considered, pp. 3–24, New York, Oxford University Press.

Mercer J.G., Bird S.P. (2012) NeuroFAST – the integrated neurobiology of food intake, addiction and stress. *Obesity Facts*, **5**(2), 293–297.

Merikangas K.R., He J.-P., Burstein M., Swanson S. A., Avenevoli S., Cui L., Benjet C., Georgiades K., Swendson J. (2010) Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication-Adolescent Supplement (NCS-A). *Journal of the American Academy of Child and Adolescent Psychiatry*, **49**(10), 980–989.

National Advisory Mental Health Council (NAMHC). (2008) Transformative Neurodevelopmental Research in Mental Illness, Washington, DC, NIMH.

National Institute of Health (NIH). (2009) NIH Science of Behavior Change Meeting Report, 15–16 June 2009. http://commonfund.nih.gov/behaviorchange/meetings/sobc062012/index.aspx. accessed August 14, 2013.

Nogueiras R., Romero-Picó A., Vazquez M.J., Novelle M.G., López M., Diéguez C. (2012) The Opioid system and food intake: homeostatic and hedonic mechanisms. *Obesity Facts*, **5**(2), 196–207.

Olatunji B.O., Cisler J.M., Deacon B.J. (2010) Efficacy of cognitive behavioural therapy for anxiety disorders: a review of meta-analytic findings. *Psychiatric Clinics of North America*, **33**(3), 557–577.

Pandit R., Mercer J.G., Overduin, J., la Fleur S.E., Adan R.A.H. (2012) Dietary factors affect food reward and motivation to eat. *Obesity Facts*, **5** (2), 221–242.

Paulus M.P., Hozack N.E., Zauscher B.E., Frank L., Brown G.G., Braff D.L., Schukit M.A. (2002) Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology*, **26**(1), 53–63.

Pellmar T.C., Eisenberg L. (2000) Bridging Disciplines in the Brain, Behavioral, and Clinical Sciences, Washington, DC, IOM/The National Academies Press.

Redish A.D., Jensen S., Johnson A. (2008) A unified framework for addiction: vulnerabilities in the decision process. *Behavioral and Brain Sciences*, **31**(4), 415–487.

ROAMER (Roadmap for Mental Health Research in Europe). (2013) http://www.roamer-mh.org [1 May 2013].

Schumann G., Binder E., Holte A., de Kloet E.R., Odegaard K.J., Robbins T.W., Walker-Tilley T.R., Brown V.J., Buitelaar J., Ciccocioppo R., Cools R., Escera C., Fleischhacker W., Flor H., Flor H., Frith C.D., Heinz A., Johnsen E., Kirschbaum C., Klingberg T., Lesch K.-P., Lewis S., Maier W., Mann K., Martinot J.-L., Meyer-Lindenberg A., Müller C.P., Müller W.E., Nutt D.J., Persico A., Perugi G., Pessiglione M., Preuss U.W., Roiser J., Rossini P.M., Rybakowski J.K., Sandi C., Stephan K.E., Undurraga J., Vieta E., van der Wee N., Wykes T., Haro J.M., Wittchen H.-U. (in press) Stratified medicine for mental disorders. *European Neuropsychopharmacology*. DOI: org/10.1016/j.euroneuro.2013.09.010 e-pub ahead of print.

Shin L.M., Liberzon I. (2010) The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, **35**, 169–191, DOI: 10.1038/npp.2009.83

Wagner A., Aizenstein H., Venkatraman V.K., Fudge J., May J.C., Mazurkewicz L., Frank G.K., Bailer U.F., Fischer L., Nguyen V., Carter C., Putnam K., Kaye W.H. (2007) Altered reward processing in women recovered from anorexia nervosa. *American Journal of Psychiatry*, **164**(12), 1842–1849, DOI: 10.1176/appi.ajp.2007.07040575

Wittchen H.-U., Gloster A.T. (2009) Developments in the treatment and diagnosis of anxiety disorders. *Psychiatric Clinics of North America*, **32**(3), xiii–xix.

Wittchen H.-U., Jacobi F., Rehm J., Gustavsson A., Svensson M., Jönsson B., Olesen J., Allgulander C., Alonso J., Faravelli C., Fratiglioni L., Jennum P., Lieb R., Maercker A., van Os J., Preisig M., Salvador-Carulla L., Simon R., Steinhausen H.C. (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, **21**(9), 655–679, DOI: 10.1016/j.euroneuro.2011.07.018

World Health Organization (WHO). (1991) Tenth Revision of the International Classification of Diseases Chapter V (F): Mental and Behavioral Disorders (including disorders of psychological development). Clinical Descriptions and Diagnostic Guidelines, Geneva, WHO.

Int. J. Methods Psychiatr. Res. 23(Suppl. 1): 28–40 (2014). DOI: 10.1002/mpr