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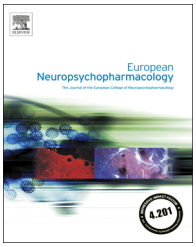

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REVIEW

Stratified medicine for mental disorders ☆

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Abstract
There is recognition that biomedical research into the causes of mental disorders and their treatment needs to adopt new approaches to research. Novel biomedical techniques have advanced our understanding of how the brain develops and is shaped by behaviour and environment. This has led to the advent of stratified medicine, which translates advances in basic research by targeting aetiological mechanisms underlying mental disorder. The resulting increase in diagnostic precision and targeted treatments may provide a window of opportunity to address the large public health burden, and individual suffering associated with mental disorders. While mental health and mental disorders have significant representation in the "health, demographic change and wellbeing" challenge identified in Horizon 2020, the framework

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programme for research and innovation of the European Commission (2014–2020), and in national funding agencies, clear advice on a potential strategy for mental health research investment is needed. The development of such a strategy is supported by the EC-funded "Roadmap for Mental Health Research" (ROAMER) which will provide recommendations for a European mental health research strategy integrating the areas of biomedicine, psychology, public health well being, research integration and structuring, and stakeholder participation. Leading experts on biomedical research on mental disorders have provided an assessment of the state of the art in core psychopathological domains, including arousal and stress regulation, affect, cognition social processes, comorbidity and pharmacotherapy. They have identified major advances and promising methods and pointed out gaps to be addressed in order to achieve the promise of a stratified medicine for mental disorders.

1. Introduction

The worldwide disease burden (DALY) of mental disorders among non-communicable diseases is 28% (Prince et al., 2007) and the cost of mental disorders in Europe in 2010 was €523.3 billion (Gustavsson et al., 2011). This is a severe public health problem, which requires urgent action. There is of course recognition of the need for action in this area. President Obama recently announced BRAIN (Brain Research through Advancing Innovative Neurotechnologies) and the EU month of the Brain in May 2013 facilitated discussions on investments in scientific excellence as well as strategies to improve patient benefit and disease prevention. The mental health disorder challenge has significant representation in the "health, demographic change and wellbeing" challenge identified in "Horizon 2020" the framework programme for research and innovation of the European Commission (2014–2020) (European Commission, 2013), as well in research strategies by national funding agencies.

In the scientific community there is widening recognition that biomedical research into the causes of mental disorders and their treatment needs to develop novel paradigms and improved psychopharmacological targets to reduce the size and burden of mental disorders in the 21st century. Recent neurobiological techniques involving neuroimaging, neuropsychology, neurobiology and -omics (Anon, 2010; Meyer-Lindenberg, 2010) have tremendously advanced our understanding of brain development and function, including our knowledge of how cognition, affect and behaviour relate to brain circuitry. Based on this progress stratified medicine, an approach which uses genetic and/or endophenotypic measures to allow more precise diagnostics and better targeting of treatments (Owen et al., 2013), has emerged. Stratified medicine for mental disorders aims to identify somatic, cognitive, affective, motor and social-behaviour domains defined by associated, potentially common, aetiological neural mechanisms (see examples in Schumann et al., 2010a; Robbins et al., 2012). This is in contrast to existing diagnostic criteria which are usually based on patient report, observation and duration of symptoms and do not incorporate biological or neuropsychological markers (Kapur et al., 2012).

Given that many of the biological and psychological findings are present across disorders, exclusive reliance on current diagnostic classification might be an obstacle for improved aetiological research. It may also hinder the search for improved future classificatory principles. Aetiology-based research cutting across diagnostic boundaries may be a critical step towards overcoming what some view as "therapeutic stagnation in psychiatry" and provide patient benefit and reduce the public health burden. These "transdiagnostic" strategies need to take into account the close relation of psychological and biomedical research in basic and clinical mental health research. They may offer a new and rational path for the development of a stratified psychiatry.

A key element is the concerted effort supported by academic researchers, representatives from pharmaceutical industry, regulatory authorities (Broich et al., 2011) and funding bodies to use and expand our knowledge of the (neuro-)biology of behaviours and functions. The identification and validation of translational behavioural and physiological (biomarker) assays, experimental perturbations, *in vitro* and *in vivo* tools, experimental medicine in volunteers and patients and reverse translation as well as neuropsychiatric drug discovery are too multifaceted for any one academic or industrial concern to tackle alone. They also require a range of modifications in regulatory authorities. The European Commission (EC) has recognised the requirement for more intensive public–private collaboration in neuropsychiatric research. EC-funded research projects also facilitate networks among the private sector, academia, regulatory, patient-advocacy groups and other stakeholders. As part of the Innovative Medicines Initiative Joint Undertaking, the EU is supporting several projects, which investigate the biological mechanisms of mental disorders.

To further develop and expand these efforts a strategy for mental health research investment is required. The development of such a research strategy is supported by the EC-funded "Roadmap for Mental Health Research" (ROAMER, 2013). This project will create an integrated and participatory roadmap for mental health research in Europe. It is structured in several work packages, namely 'Structuring of research capacity, infrastructures, capacity building & funding strategies'; 'Biomedical research'; 'Psychological research and treatments'; 'Social and economic aspects'; 'Public health research'; 'Well-being'; 'Analysis of geographic, clinical, multi-disciplinary and life course integration'; 'Stakeholder involvement'; 'Promotion and dissemination'; and 'Translation into Roadmaps'. The ROAMER initiative is aligned with the Horizon 2020 programme and its three pillars of excellent science; industrial leadership and

competitiveness; and responding to societal challenges (see: Proposal for a COUNCIL DECISION. Establishing the Specific Programme Implementing Horizon 2020 – The Framework Programme for Research and Innovation [2014–2020]). It is highly participatory with involvement of all key stakeholders (patients, industry, funding organisations and policy makers) to ensure that its recommendations are socially relevant as well as scientifically excellent. All ROAMER work packages have a similar methodology of a critical appraisal using experts and state-of-the-art reviews. These suggestions will be considered by the scientific community as well as by stakeholder groups. Their likely costs and chances of impact on mental health burdens and the European agenda of competitiveness, growth and jobs will be assessed. The final recommendations will balance the priority levels of each of the identified potential gaps in research.

The ROAMER workpackage on "Biomedical Research" involves biomedical researchers on mental disorders who have engaged with a group of leading experts to provide an assessment of the state of the art of biomedical research, identify major advances and promising methods and point out gaps that ought to be addressed in future research. Recognising the constraints of the current diagnostic classification systems the members of the workpackage decided to structure their assessment on behavioural domains relevant for psychopathology. This strategy is consistent with similar decisions in the NIMH's Research Domain Criteria (RDoC) initiative (Insel et al., 2010) and proposes a two dimensional matrix structure with several "Research Domains" (and sub-domains), which are selected to provide comprehensive coverage of human behaviour. The domains include negative and positive valences, cognitive systems, systems for social processes, and arousal and regulatory systems. The second dimension of the matrix is comprised of "Units of Analysis", which includes genes molecules, cells, circuits, physiology, behaviour, self-reports and paradigms. A similiar approach was used by the workpackage on "psychological research and treatments".

Experts were selected by the workpackage members for their academic excellence and competence in the research domains and the different units of analysis. Their contributions are not systematic reviews but rather provide a well-informed opinion of the authors involved. They do not represent official ROAMER consortium statements but contribute to the comprehensive and participatory approach of ROAMER. A description of the methods and the gaps and advances of the whole ROAMER consortium can be found on ⟨http://www.roamer-mh.org/⟩. The workpackage on "psy chological research and treatments" also produced a set of position statements presenting views and perspectives on the scope, current topics, strength and gaps in Psychological Science. These statements aim to delineate advances needed to inform future research agendas specifically on the understanding of psychological (mental), developmental and neurobiological processes and the psychological treat ment of maladaptive health behaviours and mental disor ders (Wittchen et al. 2013).

While RDoC provides a compelling theoretical advantage, it became evident in the course of the project, that from a clinical perspective there is an incomplete fit between behavioural domains on the one hand and psychopathological criteria on the other hand. More refined behavioural characterizations may better capture clinically relevant psychopathology. Further challenges for this framework are the integration of epidemiological evidence, such as the importance of environmental influences and life span symptoms and a developmental perspective. These are just some of the conceptual problems necessary to be tackled if a biologically based classification of psychiatric disorders is to become of clinical significance, and of benefit to patients. Nevertheless, RDoC is a useful framework to focus our minds on the type of biomedical research necessary to identify and target specific biological processes underlying psychopathology, and to translate it into transformative clinical studies capable of alleviating the public health burden posed by mental disorders. At the same time we acknowledge the continued need to appreciate classical psychopathology and current diagnostic conventions for diagnosing mental disorders, last not least to provide appropriate linkage to current clinical practice standards and current knowledge.

2. Arousal and stress regulatory systems

Arousal and stress systems are crucial for adaptation, resilience and health, but if these systems are dysregulated the vulnerability to psychiatric disorders is enhanced. In recent years, it is better understood how the mediators of these systems can change their action from protective to harmful. In addition to these novel insights into the action mechanism, it is also recognised that vulnerability and resilience are adaptations to the outcome of (adverse) experiences at critical times during brain development and maturation. At the root of this notion are newly discovered mechanisms explaining the interaction of experience-related factors with genetic and environmental inputs that underlies emotional expression and cognitive function for better and for worse. Arousal and stress power these gene × environmental interactions in which the balance between factors that activate and suppress the processing of stressful information, respectively, is crucial for the mechanism of resilience and vulnerability. Here, major advances and gaps are identified in our current knowledge of arousal and stress regulation that highlight possible causal treatment strategy's directed towards preventing the precipitation of psychiatric disorders or promoting mechanisms of resilience present in the disordered brain.

2.1. Definition

Arousal is defined as a state of being conscious, awake and alert, which is required for information processing underlying all cognitive functions and emotional expressions. According to an operational definition (Pfaff et al., 2007), an animal or human with higher generalised arousal shows greater sensory alertness and enhanced mobility, and is more reactive emotionally. Arousal is crucial for motivating various behaviours including sexual activity, exercise, the anticipation of a reward, and coping with stressful experiences.

Stress is defined "as a composite multidimensional construct in which three components interact: (i) the input, when a stimulus, the stressor, is perceived and appraised,

(ii) the processing of stressful information, and (iii) the output, or stress response. The three components interact via complex self-regulating feedback loops that are initiated by a stressor which is any change in the environment that disturbs homoeostasis (Levine, 2005)." The goal of the stress response is to restore homoeostasis through behavioural and physiological adaptations. The original definition by Hans Selye was extended from a psychological perspective, because the individual usually spends considerably more time to anticipate a stressor – either real or imagined – than actually suffering from it.

Arousal not necessarily causes a stress response, but the reaction to a stressor is always preceded and accompanied by arousal, particularly in cases of an adverse experience. The most arousing and stressful condition is a situation of uncertainty where there is no or ambiguous information, poor predictability of upcoming events and lack of controllability during the stressful experience, but with a fearful anticipation of worry and other cognitive-emotional representations of inability to cope. The impact of such a stressor, that is usually chronic and repetitive, is modulated by a variety of factors such as personality traits, self-esteem, sense of safety, social rank and social support or combinations of these psychosocial contexts (Lazarus, 2006; Fink, 2007; Taylor, 2010a; Koolhaas et al., 2011).

An organism incapable to launch a stress response will succumb and die. Alternatively, if an organism is unable to turn off its stress response vulnerability to disease is enhanced. A dysregulated stress response is not restricted to a single organ, but rather affects the coordination between cells, tissues, organs, systems and behaviour. Vulnerability is enhanced when this coordination becomes compromised. Hence for understanding the relationship between stress and disease it is essential to understand the functioning of circuitry in the brain that help appraise, cope and adapt to environmental stressors.

2.2. State-of-the-art

2.2.1. Organisation of arousal and stress systems

Arousal and stress are distinct, but partial overlapping constructs. What distinguishes arousal and stress is their biological substrate. If novel sensory input is perceived, it produces an alarm reaction that is initially processed by the nucleus gigantocellularis of the brain stem causing generalised arousal by enhanced activity of ascending excitatory pathways (Csete and Doyle, 2004). Arousal governs activation of the reticular activating system in the brain stem, the sympathetic nervous system and the neuroendocrine system. Arousal, caused by glutamate-enhanced excitability, is modulated by the classical neurotransmitter systems and by neuropeptides that induce behavioural and physiological activations characterised by increased attention, alertness and vigilance.

Novel adverse signals are evaluated by processing the information in the limbic-cortical circuitry. If the outcome of the appraisal process in these circuits is interpreted as a threat to integrity, the individual attempts to cope with the stressor by initiating physiological responses for defence and mobilisation of energy and to execute behaviours that facilitate adaptation. Bodily influences are integrated in the central stress circuitry as well and signals of the immune, cardiovascular–kidney, gastro-intestinal and metabolic system affect brain function either directly or via the nervus vagus. The stressful information from body and brain converges with inputs from various neural networks such as the arousing brain stem neurons from the locus coeruleus, and feeds into relay stations: e.g the amygdala complex and the hypothalamic paraventricular nucleus (PVN) (Herman et al., 2003).

2.2.1.1. Limbic – cortical circuits. The amygdala generates emotionally loaded information, which is labelled in time, place and context while processed in e.g. the hippocampal formation (Eichenbaum et al., 2007). In mutual feedback and feedforward loops the amygdala and hippocampus communicate with frontal brain regions, notably the mesolimbic – cortical DA pathways of reward and adversity, and the prefrontal cortex of which subregions are involved in specific higher cognitive functions, as well as mood, affect, emotional and stress regulation (Grace, 2010).

All this information converges in the PVN, which organises the autonomous and neuroendocrine responses to stressors, i.e. the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, that ultimately feedback to the limbic and arousal circuitry. These limbic-cortical circuits show during and in the aftermath of the stressful experience a profound functional and structural adaptation that is regulated by neural and hormonal factors by modulating molecular signalling pathways. A new science is emerging dedicated to calibrate and monitor these adaptive changes as indices of vulnerability, resilience and energy expenditure. This is the science of allostasis and allostatic load (McEwen and Gianaros, 2011).

2.2.2. Temporal organisation

Arousal and stress regulatory systems operate in distinct temporal domains:

2.2.2.1. Basal rhythm and sleep/wake states. The parasympathetic nervous system is dominant in the resting state, at a time that the arousal and stress systems operate in a basal state of activity. The latter systems display circadian rhythms controlled by the circadian clock in the suprachiasmatic nucleus entrained by the diurnal light-dark cycle. Moreover, the HPA-axis shows hourly ultradian pulses, particularly of cortisol. These cortisol pulses vary in amplitude over the circadian cycle (Lightman and Conway-Campbell, 2010) with highest amplitude at the circadian peak. The organisation and pattern as reflected in the pulse amplitude and frequency of the ultradian rhythm can vary in spikes depending on the psychological and physical condition of the individual.

It is thought that the pulsatile rhythm enables synchronization and coordination of daily activities and sleep-related events. In the elderly, the organisation of the ultradian rhythm disappears and becomes desorganized which explains why old individuals may have compromised sleep- and daily activity patterns. Also the ultradian and circadian rhythms provide a basis for the threshold and sensitivity of the stress system: the magnitude and nature of the behavioural and physiological stress response varies depending on the phase of the hourly cortisol pulse (Sarabdjitsingh et al. 2010).

2.2.2.2. Response to stressors. The stress-induced HPA-axis activity has two modes of operation that can be separated in distinct temporal domains: a fast activation

representing primary defence reactions, which are then slowly dampened to prevent these initial reactions from overshooting and becoming damaging themselves (Sapolsky, 2000; Joëls and Baram, 2009). Overall the fast and slow domains of the stress reaction aim to defend the integrity of the organism and to restore homoeostasis. While doing so the systems operate in concert to facilitate activation and to promote adaptation and recovery, and to store the experience in the memory in preparation of a future experience. The energy required to maintain the balance between activation and adaptation contributes to the allostatic load.

How the HPA-axis is activated by stressors is well-documented. The stressor activates through multiple innervating pathways the PVN neuropeptide secreting cells that produce a cocktail of CRH, vasopressin, angiotensin II (and from elsewhere other neuropeptides such as e.g. PACAP and oxytocin) and are released in the portal vessel system to activate the synthesis and release of proopiomelanocortin (POMC) peptides including the endorphins and melanocortins. ACTH stimulates the adrenal cortex to secrete the glucocorticoids cortisol and corticosterone, which feedback precisely on the limbic-cortical circuits that have generated the initial stress reaction. This action exerted by a single glucocorticoid hormone has an enormous diversity, which depends in its pattern on temporal, contextual and site-specific factors.

2.2.3. Chronic stress and vulnerability to psychiatric disorders

If coping fails repeatedly the reaction to the stressful situation is reinforced and adaptation may occur to the chronic stress condition. Selye indicated this General Adaptation Syndrome as the 'resistance' phase that slowly develops over a period of weeks after the initial stress (alarm) reaction. Upon chronification this may ultimately culminate in the exhaustion phase characterised by breakdown of adaptation. McEwen calls the adaptation to stress 'allostasis' meaning that in the context of the organism-wide stress response the brain has the capacity to maintain homoeostasis through changes in circuits, synaptic structure and function, and behaviour. The cost of allostasis is termed 'allostatic load', a term that describes the individual's state or 'stress' during Selye's resistance phase.

In such a chronic stress condition profound changes take place in the stress system. Chronic stress produces in basal state desynchronization of circadian cycles and sleep-wake states, and evokes REM sleep abnormalities that accompany depression and other psychiatric disorders. An elevated sympathetic tone and activation at inappropriate times is one aspect. A flattened circadian and ultradian pattern of HPA-axis activity caused by an enhanced magnitude of cortisol pulses at the trough is then a characteristic feature of the dysregulated neuroendocrine stress activity of a severely depressed individual (Holsboer and Ising, 2010).

2.2.3.1. Structural plasticity. The functional and structural plasticity of limbic circuitry allows adaptation to either excessive or inadequate cortisol responses. In response to chronic stressors the apical dendrites of neurons in the hippocampus CA3 region and areas of the prefrontal cortex atrophy (McEwen and Gianaros, 2011). At the same time the dendritic organisation of neurons of the basolateral amygdala and orbitofrontal cortex become hypertrophic.

Chronic stress also affects the fate and embedding of newborn neurons into circuitry of the hippocampal dentate gyrus and discrete regions of the olfactory brain, a process that was shown to produce functional changes (Fitzsimons et al., 2013). The organisation and function of the newly build circuitry is therefore affected by stress, while other studies have demonstrated enhanced neurogenesis after antidepressants. Yet, even though small circuit changes can have profound consequences, the function of neurogenesis in psychiatric disorders, if any, still needs to be elucidated.

2.2.3.2. Resistance and hypersensitivity. During chronic stress the balance changes between the central CRH drive and the cortisol feedback potential, i.e. the actual setpoint of the HPA-axis regulation. The drive depends on the sensitivity of the stress system which is also under control of cortisol. When either resistance or hypersensitivity to cortisol develops one way or the other, the rest of the body and brain is exposed to aberrant levels of the circulating hormone. Thus, in case of elevated cortisol levels due to feedback resistance, immune function is suppressed, the bones are osteoporotic and a cardio-metabolic syndrome may develop that is hazardous for physical health. This further aggravates changes taking place in the brain. Likewise if too little cortisol is circulating the glucocorticoid may be inadequate to restrain sympathetic nervous activity and other stressful reactions, including the action of pro-inflammatory and pro-immune cytokines.

The dynamics of the acute stress response in individuals with a history of chronic stress experience can be used as endocrine marker to monitor the allostatic load in the resistance phase. Under chronic stress the acute activation of the HPA-axis can be more profound, while it takes a longer time to shut off the HPA-axis responses to stressors. This enhanced responsiveness of the HPA axis suggests that under conditions chronic stress, the stress system has become sensitised to acute stimuli. Interestingly, this sensitization to acute stimuli also occurs in subjects that have become habituated to adversity, but is of course more pronounced under persistent conditions of adversity to which the individual did not habituate (Herman, 2013). The sensitization is caused by altered signalling pathways underlying the adaptation in structure and function of the limbic-cortical circuitry, as well as the enhanced synthesis capacity in the HPA-axis. The excessive and prolonged cortisol secretions are linked to emotional and cognitive disturbance rather than to depression per se.

The escape from suppression by the synthetic glucocorticoid dexamethasone has assisted in diagnosis of cortisol resistance at the pituitary level (Ising et al., 2005). In contrast, other adaptations after a single traumatic experience may occur that lead to low circulating cortisol levels because of hypersensitive feedback at the pituitary-hypothalamic level in the face of a very high sympathetic tone as is the case for post-traumatic stress disorder (PTSD) (Yehuda and Seckl, 2011). Hence, the feedback status can be monitored in the dexamethasone (dex) suppression test or dex-CRH test, the latter in cases that the central hyperdrive to the pituitary is mimicked by exogenous CRH.

2.2.3.3. Molecular basis. Important advances have been made in understanding the signalling pathways underlying the activating and suppressing modes of stress system operation. Thus, using advanced gene technology specific

circuits have been identified for the action of CRH, vasopressin and the steroids in the different contextual and temporal phases of the stress response (Refojo et al., 2011). An ultrashort feedback loop has been identified in fine-tuning cortisol function via FKBP5 (Menke et al., 2013). Cocktails of co-regulators are capable to modulate local cortisol actions from agonism to antagonism and novel glucocorticoid analogues are becoming available with less side effects (Zalachoras et al., 2013). Intracellular metabolism appeared an important regulator of bioavailability of cortisol (Wyrwoll et al., 2011). Genetic polymorphisms have been identified that have profound effects on emotional expressions and cognitive performance.

An important issue in understanding adaptation to stress is the possibility that sensitization to stressors actually occurs by switching to novel circuits and signalling pathways. There is indeed supporting evidence for this thesis for humans and animals where stress causes a switch between multiple memory systems, i.e. from a hippocampal spatial strategy towards a caudate-based habit learning strategy (Dias-Ferreira et al., 2009; Oitzl et al., 2012). Also gene expression profiling technology revealed that a history of chronic stress caused sensitization to acute stressors or an acute cortisol challenge by switching to alternative molecular pathways underlying the processing of stressful information (Polman et al., 2012).

Stress affects the expression of genes involved in DNA methylation and modification of chromatine structure and other aspects of epigenetic processes, particularly when experienced during early life or adolescence. These data suggest enduring changes in the transcriptome induced by stress mediators during these sensitive windows of brain development. The changes occur in the mediators and their receptors of the HPA-axis, and also in the limbic-cortical circuitry (Murgatroyd and Spengler, 2012).

2.2.4. Conclusion

Genes and neuronal circuits do not act by themselves but need to be regulated by signals from environmental changes, and the mediators of the arousal and stress systems are extremely important for this purpose. Our position is that dysregulation of the arousal and stress mediators may compromise mechanisms of resilience that can, thus, enhance the vulnerability to psychiatric disorders. The identification of biomarkers in the arousal and stress systems themselves is therefore an important objective in understanding the pathogenesis of stress-related psychiatric disorders. It is recognised that the repair and normalisation of a dysregulated arousal and stress system is the key towards causal treatment of psychiatric disorders.

2.3. Major advances

2.3.1. Technical innovation

Understanding the significance of arousal and stress systems requires approaches that link changes in molecular signalling cascades with the plasticity of neural circuitry and behaviour. New approaches using genetics or imaging or the combined methodology of imaging genetics have led to considerable advances in knowledge (Akil et al., 2011). It is now feasible to examine the whole genome for responsive genes, to identify haplotypes, copy-number variants and epigenetic profiles using the next generation sequencing technology and computational biology. Functional connectivity is examined in human and animal brains with powerful fMRI and diffusion tensor MRI. In experimental animals noninvasive optical methods are developed to turn on or off specific genes in discrete neural circuits (Deisseroth, 2012). The generation of transgenic animals or lentiviral delivery of gene constructs is a common practice. Electrophysiological approaches as well as multiphoton imaging and calcium imaging technology add to the study of circuit dynamics and synaptic plasticity.

Using these methods it becomes feasible to examine the circuits involved in the processing of arousing sensory information stemming from olfactory, auditive, gustatory, vestibular and visual inputs. Also the major ascending neurotransmitter pathways relaying and integrating sensory information into the arousal mode of the brain can be monitored. These include the (nor)adrenergic, dopaminergic, serotonergic, cholinergic and histaminergic neurons that innervate specific brain regions involved in a variety of functions involved in emotional and cognitive processes, motivational aspects, executive operations and motor outputs.

Then, neuropeptides coordinate, synchronise and activate circuits underlying e.g. adaptive and social behavioural programs. These neuropeptides include the opioids and other melanocortins, vasopressin, oxytocin, orexins and a variety of other neuropeptide families capable to modulate and direct circuits underlying stress adaptation and energy allocation. On top of this, the 'classic' hormonal systems governed by metabolic, sex and stress hormones exert an action capable to programme the brain during critical periods of development and to operate as master-switches during behavioural adaptation, reproductive behaviour and energy metabolism.

2.3.2. Conceptual advances

2.3.2.1. Stress mediator signalling and susceptibility pathways. Several hypotheses of psychiatric disorders have been developed based on dysregulation of the stress system. These hypotheses include the anxiogenic actions of excess CRH (Holsboer and Ising, 2010). Also the glucocorticoid cascade hypothesis, which states that the rising glucocorticoid concentrations due to chronic stress downregulate their GR leading to a vicious cycle that ultimately precipitates stress-related brain disorders (Sapolsky, 2000). Cortisol action is however also mediated by a second brain receptor system, the mineralocorticoid receptors (MR)

MR has an exclusive localisation in brain areas involved in processing of emotional and contextual information, while GR is found in every cell. Due to its properties MR is crucial in appraisal of novel information rapidly triggering emotions and thus the onset and progression of the stress reaction. GR controls the off-button of the stress reaction by slowly promoting cognitive functions and memory storage for coping with future events. Imbalance of MR and GR enhances vulnerability to stress-related mental disorders. Such an imbalance may occur with genetic variants of the receptors or of their co-regulators and chaperones such as operating in the ultrashort FKBP5 – GR protein feedback loop (Menke et al., 2013), or due to epigenetic modification induced by environmental inputs.

The reactive alleles associated with emotions appear crucial for vulnerability and resilience to psychopathology.

A striking example is presented by the carriers of the short allele of the 5HT transporter which are more reactive to negative life experiences, but also to positive experiences, if compared to carriers of the long-allele (Canli and Lesch, 2007). Also BDNF variants have been associated with affective states and are implicated in the plasticity hypothesis of depression (Pezawas et al., 2008). Recently, MR variants were found associated with appraisal processes, dispositional optimism and protection against depression (Klok et al., 2011). The other side of the coin are the non-reactive alleles which can be equally damaging, as for example in callous unemotional traits and psychopathy.

Unbiased genomic approaches have identified potential susceptibility pathways linked to glutamatergic transmission and glucocorticoid actions leading to rapidly acting ketamine and the antiglucocorticoid mifepristone. Gene expression profiling has provided a large number of glucocorticoid responsive genes and pathways in the hippocampus, which can be further pinpointed to neuro-anatomically defined areas by using laser capture dissection. This type of analysis revealed CREB binding protein, BDNF and the mammalian target of rapamycin (mTOR) signalling pathways, which play a central role in translational control and have long-lasting effects on the plasticity of specific brain circuits (Polman et al., 2012). These pathways may serve as biomarkers for stress-induced vulnerability.

2.3.2.2. Programming by (early) life experience and epigenetics. A major advance is that an epigenetic mechanism is evolving that underlies programming of emotional and stress reactivity during critical times of brain development with lasting consequences over the life span. Epigenetic changes may involve DNA methylation, while complementary histone acetylation, methylation and phosphorylation in response to stress presents also a novel candidate mechanism (Meaney, 2010). The studies have demonstrated that stressful experiences during early life can remodel brain circuitry underlying emotional regulation. The outcome of early life adversity can be modulated by maternal influences and frequently investigated models are animals that have experienced as pup reduced or fragmented maternal care. Such a period of early neglect enhances the pup's responsivity to adverse emotional experiences and was found to advance prematurely the development of emotional and fear circuitry involving cortisol and the locus coeruleus NE input (Sullivan and Holman, 2010).

An increasing number of studies highlight the impact of various contexts during prenatal and postnatal early life, puberty and adulthood on the mechanism of resilience and vulnerability to psychiatric disorders. Depending on these contexts as well as experience-related factors and genetic input, aggravation may occur either along the cumulative stress hypothesis of psychopathology or the predictive adaptation hypothesis. The latter hypothesis predicts that rather a mismatch between early life experiences and later life context enhances the vulnerability to a psychiatric disorder (Nederhof and Schmidt, 2012).

2.3.3. Conclusion

The adult brain shows plasticity in response to stressful experiences and we are beginning to understand its potential in vulnerability and resilience to psychiatric disorders. The mechanism underlying plasticity involves among excitatory transmission contingent on monoamine modulation also arousal and stress system mediators which power the impact of environmental influences (Joëls et al., 2012). During critical periods in development these mediators can cause lasting changes in circuitry involved in regulation of emotional expressions and the stress response. Adaptations to the programmed emotional circuitry in later life may lead to vulnerability and resilience depending on environmental context and genetic background.

2.4. Questions to be solved

2.4.1. How can early experience precipitate a resilient or vulnerable phenotype

To address this question it is crucial to understand that how early experiences can programme perinatally and during puberty emotional and stress regulations for life. This requires insight in epigenetic and epistatic mechanisms that can change brain plasticity towards a vulnerable phenotype, which may become expressed under specific circumstances in later life. Unresolved is why some individuals progressively fail to cope with stress and accumulate risks for a mental disorder, while others show adequate coping and gain strength even from seemingly abusive early life adversity as if such conditions prepare for life ahead.

For this purpose humanised models are needed that test the mismatch or the cumulative stress hypothesis. Such models depend on modulations of gene–environment interaction in a living organism which will benefit enormously from technological advances in imaging, gene modification and cell biological technology. In fact, we are witnessing a constant renewal of technology to address in these models the same questions: who is at risk, and how do we prevent and cure disorders; how can the quality of life, particularly of the elderly, be improved.

2.4.2. How can a stress response change from protective to harmful?

This question calls for research in appropriate models from gene to behaviour linking the molecular mechanism with a defined neuro-anatomical substrate. This mechanism may underly appraisal of a perceived arousing stimulus followed by processing of potential stressful information. Whatever the outcome of processing, the stress response promotes consolidation (or extinction) of the experience in the memory in preparation for the future. The question calls for research to examine the impact of chronification of the stressful experience on structure and function of the brain. Does it trigger a switch in circuitry or signalling cascades as recent research suggests? Is sensitization of the stress system a hallmark of resilience or vulnerability? The answer to these questions may give leads towards therapeutic interventions to promote a mechanism of resilience present in the disordered brain by modulating the brain's plasticity and connectivity in specific circuits.

A testable hypothesis in this reasoning is that chronic stress (high cortisol) may precipitate a depressive phenotype by inducing downregulation of 5HT function accompanied by enhanced anxiety or aggression, briefly cortisol-induced serotonin-dependent anxiety/aggression-driven depression (van Praag et al., 2004; van der Kooij and Sandi, 2012).

2.5. Gaps

2.5.1. Gap nr 1 refers to the enormous complexity and diversity in signalling mechanisms that are being identified, explored each in its own right, but all for one: the individual

The translation of the new knowledge, from signalling cascades to the functioning of the human brain in health and disease, is still poorly understood. The key towards this understanding is in the arousal and stress systems which operate in a higher order mechanism to coordinate and synchronise the functions of all cells and organs over daily activities and sleep-related events, and in coping with challenging situations. However, with a bewildering diversity in signalling mechanisms between individuals cells.

2.5.2. Gap nr 2 refers to individual differences in stress responsiveness and consequences for brain function and mental health over the lifespan, in males and females

That the arousal and stress system operate at the root of individual differences in coping abilities and life trajectories is common knowledge, but how this system is capable to mobilise psychosocial resources for better and for worse is not known. These resources include recruitment of social support, the attained social position (socio-economic status) and traits like dispositional optimism, mastery (control) and self-esteem in which the stress system mediates the effect of external demands and mobilises previously stored internal experiences and coping abilities. It is essential that gender differences and parental behaviour is included in this type of studies as well.

2.5.3. Gap nr 3 is the lack of reliable biomarkers to predict which individuals are vulnerable or resilient to psychiatric disorders

Better insight into these mechanisms of vulnerability and resilience may help to identify genes and their epigenetic modification influencing critical pathways that may on the one hand serve as biomarkers to identify individuals at risk, i. e. to monitor and calibrate allostatic load. These very same pathways may deliver clues how on the other hand individuals are capable to mobilise psychosocial resources to confer health protective benefits. It is complex because the outcome of gene × environment interactions is context-specific, and governed by predictions from either the cumulative stress or the mismatch hypothesis.

2.6. Needs

The study on causality of stress and arousal systems in the pathogenesis of psychiatric disorders requires multidisciplinary research groups capable to do studies from gene to behaviour in a translational approach. To maintain the high level of some already existing European research environments and to develop new frontline groups; standardisation of approaches and sharing of new technologies are essential. Training in concepts, theories and experimental approaches is also needed on site and in dedicated schools.

2.6.1. Integrated arousal-stress system clinical / functional phenotype – genotype profiles

Ever since Selye coined the stress concept, it is well documented that chronic unpredictable and uncontrollable stress is a risk factor for psychiatric disorders over the lifespan but how the stress-induced onset and progression of these mental disorders takes place is still not well understood. Since the arousal and stress system mediators are central to the disorder an approach is needed that integrates three levels simultaneously in the patients (de Kloet et al., 2005; Taylor, 2010b; Binder and Holsboer, 2012).

- The personality and the clinically relevant phenotype of emotional reactivity and reward mechanisms in the context of psychosocial resources and neuro-imaging data of limbic – prefrontal connectivity and plasticity.
- The functional phenotype as represented by neuro-endocrine response patterns shaped by (early) life experiences and characterised by biomarkers (Foley and Kirschbaum, 2010) and predicted by the science of allostasis and allostatic load (McEwen and Gianaros, 2011).
- The genotype of the patients based on (epi)genetic predispositions in the arousal and stress mediators themselves as represented by HPA-axis hormones and their receptors as well as the 5HT/NE/DA systems, CRH, vasopressin, oxytocin and other neuropeptides. A validated test for common stress genes would count about 200 hits and can be expanded with functional variants/haplotypes and epigenetic markers (Pfaff et al., 2007).

2.6.2. Stress and arousal mediators: action mechanism

A wealth of data is available about how stress system mediators are synthesised, released and act. One of the sobering findings is that the hormones have an enormous diversity in action on the molecular and cellular level, and yet they can act as integrators over time and coordinators of cell, tissue and organ functions as well as behavioural, autonomic and immune responses under threatening circumstances. To understand these integrative mechanisms basic science is needed with the goal:

- to identify – given the individuality and plasticity of personal genomes and environments – individually unique mechanisms converging on common susceptibility pathways leading to impairments. This would serve as an inroad to novel biomarkers of stress and arousal systems critical for assessment of vulnerability and resilience.
- To develop humanised models by modification of genes in particular environmental contexts using genetic variability to identify novel susceptibility pathways and mechanisms of brain (synaptic) plasticity. This could integrate the interaction between genetic variability and susceptibility to develop epigenetic changes in response to stress; a systems approach is needed to analyse the overall outcome of gene × environment interaction.
- To translate the outcome of these gene–environment interactions – as imposed by the action of arousal and

stress mediators – into a measurable endophenotype of a psychiatric disorder.

2.6.3. Psychiatric disorders and physical health

Brain–body interactions on the one hand reflect the impact of the environment on mental and physical health, and on the other hand the devastating influence of physical diseases on higher brain functions underlying emotion and cognition. These brain–body interactions depend on arousal and stress system mediators (Hellhammer et al., 2012). It is according to these authors therefore important:

- To understand how environmental circumstances such as socio-economic status either linked to physical or psychological deprivation or to the psychosocial impact of social hierarchy, can promote arousal and stress system dysregulations leading to disease. Likewise the beneficial effects of e.g. lifestyle, exercise and cognitive brain therapy need to be translated into *bona fide* brain mechanisms.
- To understand how stress mediators not only communicate neural information that aggravates cardio-metabolic-inflammatory disease conditions, but also how these disease conditions can affect mental health. An increasing body of evidence suggests in these interactions a crucial role of hormonal and autonomic synergis

3. Cognitive systems

A new approach to psychiatry in terms of neurocognitive systems is proposed which encompasses processes of perception, attention, working memory, long term memory, executive functioning, decision-making, metacognition and social cognition. Critical techniques and conceptual approaches include sophisticated human neurophysiology, 'brain training', functional connectivity and neural network analysis, neurocomputation, mechanisms of neural plasticity and animal models. New psychological theory will reinvigorate neuroimaging approaches in all modalities and neuropsychopharmacological investigations. These approaches will enable the identification of biomarkers (or neurocognitive endophenotypes) to provide alternative, dimensional descriptions of neuropsychiatric endophenotypes in order to reach a more accurate mapping of genetics with neuropsychiatric phenotypes, the use of 'purer' (more homogeneous) populations for clinical trials, and the identification of vulnerabilities, and hence the possibility of early detection and early interventions or treatments for disorders such as schizophrenia and depression. Following a review of the current status of research in the field ('State of the Art') and recent advances ('Major Advances'), we identify specific issues in each of the main domains surveyed, as well as gaps and needs for future advances in this research area. The main problems posed in the European context are the need for collaborative research (i) to help compensate for the withdrawal of many pharmaceutical companies from the field, and also (ii) to provide multi-disciplinary investigations of suitably large populations of patients with the major neuropsychiatric disorders, to allow definitive phenotypic descriptions and the effective application of genomics.

3.1. Definition

Psychiatric disorders implicate deficits in many cognitive systems, as well as their interface with affective, including motivational, and social processes. Cognitive systems may include processes of perception, attention, memory, learning, thinking and executive function (including decision-making, problem solving and planning).

3.2. State of the art

In the past two decades advances in cognitive neuroscience in tandem with these interfaces have promised to revolutionise our understanding, and potentially treatment, of disorders such as schizophrenia, depression, neurodevelopmental disorders such as ADHD, and addiction. Biological research into mental disorders is plagued by vague nosological definitions and boundaries which have often confounded psychiatric genetics and led to the search for 'intermediate' neurocognitive endophenotypes which may be core to particular symptom clusters (see e.g. Robbins et al., 2012). These endophenotypes may reflect basic building blocks of cognitive function which are impaired in psychiatric disorders because of malfunctioning controlling neurocircuitry. Such 'building blocks' derive from a decomponential analysis of complex cognitive processes in the healthy brain, and may include a variety of theoretical approaches, including reinforcement learning, decision theory, and cognitive constructs (many of which are listed in the new NIMH initiative R.Doc), such as working memory, and metacognition (including the 'monitoring' of cognition and thinking about the thinking of others, 'mentalising', or 'theory of mind'). These can be analysed with a variety of methods, including neurocomputation, multimodal brain imaging (including PET, fMRI, and electrophysiology) as well as neuropsychopharmacology and animal models.

A fundamental distinction for psychiatry is that between explicit and implicit cognitive processing, mainly reflecting a dissociation between conscious processing available for subjective commentary and covert, unconscious cognitive mechanisms. This may also be paralleled by the contrast between 'top-down' and 'bottom-up' processing. Many psychiatric disorders are characterised by dysfunction at both levels or by the interactions between the two. Deficits in cognition are increasingly being recognised as significant determinants of prognosis and rehabilitation, schizophrenia being a key example. However, it is important to realise that cognition comprises many components, including perception, attention, working memory, declarative and procedural memory, language, learning, decision-making and planning, social behaviour and neuroeconomics controlled by distinct, though overlapping neural systems or networks, which are also co-ordinated and optimised by sometimes poorly-characterised 'executive' functions, such as cognitive control, inhibition and effort. The precise relationship of executive functioning to metacognition (e.g. theory of mind) processes is not well understood. These cognitive components can be dissected by various laboratory cognitive tasks which are often customised for use in neuroimaging studies and for use in psychiatric patients. The expectation is that the application of these tasks in a

theoretical context in combination with neuroscientific methods will provide new, refined measures of dysfunction which will (i) improve the definitions of psychiatric phenotypes (ii) better explain psychiatric symptoms (iii) enable more homogeneous samples for treatment trials and (iv) better predict vulnerability, risk and functional outcome, including quality of life. We now describe some specific examples and applications which illustrate the potential of this exciting new approach.

3.3. Major advances

3.3.1. Perceptual dysfunction and electrophysiological biomarkers

Subtle perceptual deficits are present in many psychiatric disorders, notably including schizophrenia and autism, that may impinge on highly relevant capacities such as the perception (and eventually the production) of emotional pitch in spoken language. These dysfunctions are paralleled by specific abnormal patterns of electrical brain activity, namely attenuated or absent mismatch negative (MMN) potentials to auditory, and even visual, stimuli. The MMN is an auditory evoked potential measured by EEG, which is generated by a bilateral superotemporal-frontal network involved in auditory change detection. A common finding is that schizophrenic patients have reduced MMNs elicited by surprising stimuli that violate predictions established by previous input history, e.g., with regard to expected duration or amplitude (Umbricht and Krljes, 2005). Abnormal MMNs have been observed for mood disorders, ADHD, post-stress traumatic disorders, chronic alcoholism, and a range of neurological disorders, such as Alzheimer's disease, Parkinson's disease, and stroke. Moreover, the abnormal MMN found in this broad range of disorders points to a common dysfunction in NMDA-mediated neurotransmission (Näätänen et al., 2011). A major advantage of the MMN is that it can be obtained even the absence of patient collaboration, being elicited automatically in the absence of direct attention. As well as MMN, studies on brain connectivity (see below) can be implemented via neurophysiological techniques.

3.3.2. Attention and neural networks of cognition

Attentional deficits are often among the most obvious behavioural symptoms of psychiatric patients, but attentional processes are diverse and one product of cognitive neuroscience has been the recognition of a variety of neuronal mechanisms and neural networks mediating different aspects, including selective, divided and sustained attention. A recent major discovery of cognitive neuroscience has been that of the so-called 'default system' (comprising several midline structures such as the medial prefrontal, and portions of the anterior and posterior cingulate cortex and the pre-cuneus) which is deactivated during most cognitive tasks requiring external orientation to the world and generally activated during a wakeful resting state in fMRI tasks or during periods of passive reflection (Fair et al., 2008).

The study of 'neural networks' has expanded across many scientific disciplines from social sciences to neuroscience due to the discovery that complex interconnected and dynamic systems can be described and analysed using a set of mathematical techniques termed 'graph theory' (Sporns et al., 2004). Brain graphs provide a relatively simple way of representing the human brain as a comprehensive map of neural connections, (the 'connectome'). Using graph theory the CNS can be represented as a set of nodes (denoting anatomical regions or functional neuronal aggregates) and interconnecting edges (denoting structural or functional connections). Network analysis is being used to identify neural changes in human neurological or psychiatric disorders which may provide novel endophenotypes (or 'biomarkers') for the purposes described above (Fornito and Bullmore, 2012). Additionally, during the periods of early brain development and maturation, when it is clear many neuropsychiatric disorders originate, this method could be used to define important dynamic changes of anatomical, functional and effective connectivity [Functional connectivity is defined as the "temporal correlations between spatially remote neurophysiological events" (Friston et al., 2003), whereas effective connectivity is defined as "the influence that one neural system exerts over another either directly or indirectly" (Friston et al., 2003)]. These network properties are being studied with a mixture of electrophysiological (EEG, MEG and transcranial magnetic stimulation) and functional imaging methods, thus setting the foundations for novel approaches to understand the brain 'at work' in health and disease. Applications so far have ranged from Alzheimer's disease and stroke to obsessive-compulsive disorder and schizophrenia, re-conceptualising some of these disorders as complex examples of 'disconnection syndromes'.

3.3.3. Working memory and cognitive training

The definition of working memory differs widely between research areas. Important knowledge about neural mechanisms has come from electrophysiological and neuropharmacological studies of nonhuman primates, specifying delay specific activity in prefrontal and parietal areas. Neural network models have successfully made biologically realistic models of reverberatory, re-entrant circuitry that maintains the activity of cue-specific neurons. The neurophysiological data are largely consistent with neuroimaging studies of sustained activity in humans. There is an overlap between 'top-down attention' and 'working memory' regarding both behavioural and neuroimaging findings and the relationships between certain aspects of attention and working memory need to be resolved. One promising facet of working memory are the translational findings from animal and human volunteer research that it is possible to enhance working memory function acutely using pharmacological treatments such as D1 dopamine receptor agonists.

Training can lead to sustained improvement of working memory capacity, which also translates to improvements of other executive functions relying on working memory and top-down attention (Jaeggi et al., 2008), as well as increased attentiveness in everyday life. This has implications for use as a remediating intervention for individual where low working memory capacity is a limiting factor for academic performance or everyday life. Working memory training is the beginning of a new research field exploring the possibilities of enhancing other executive functions such as self-control with help of computerised training methods,

possibly combined with neuroimaging and pharmacological treatment (Klingberg, 2010).

3.3.4. Long term memory and plasticity

Profound deficits in declarative memory are not only present in early Alzheimer's disease but also in schizophrenia, probably as a result of overlapping pathology within the medial temporal lobe, including the hippocampus. Moreover, stress can profoundly impact neuronal plasticity and neurogenesis within the hippocampus relevant to a range of affective disorders (Lupien et al., 2009). Considerable neuroscientific advances have characterised molecular mechanisms of plasticity relevant to memory consolidation and extinction that may be related to such disorders as pathological anxiety, post-traumatic stress disorder and addiction. In particular, the phenomenon of memory reconsolidation provides a basis for eliminating maladaptive plasticity of memory circuits (Milton and Everitt, 2010). These advances have also motivated the development of a range of 'cognitive enhancing' drugs, often based on potentiating glutamate neurotransmission through the NMDA receptor.

3.3.5. Decision-making, learning and neurocomputation

Reinforcement-related decision-making cognition broadly encompasses: how individuals learn the value of stimuli (e.g. associations with reward or punishment); how those stimulus values can influence choices and actions (both explicitly and implicitly); and how conflicts between different possible choices are resolved. In the human decision-making literature, paradigms have often been developed such that behaviours can be compared directly with those seen in experimental animal models of psychiatric disorders. The study of reinforcement-related decision-making has important implications for understanding cognitive performance in other domains, since tasks often feature elements that are intrinsically reinforcing (for example, performance feedback). Decision-making deficits in various forms have been found in virtually all psychiatric disorders, including depression and bipolar illness, addiction, attention deficit/hyperactivity disorder, obsessive-compulsive disorder and antisocial behaviour.

Advances within the past decade include: the use of formal computational approaches to analyse decision-making; and the study of human behavioural phenomena identified in the field of economics ('neuroeconomics'; Glimcher et al., 2008). The neuroeconomics literature has focused on understanding why humans depart from rational, normative accounts of decision-making (such as expected utility theory) when performing value-based choice tasks. Examples include: loss aversion (the tendency for losses to appear proportionately worse than gains); risk aversion (the tendency to prefer certain outcomes to risky outcomes); framing (the influence of the way that a decision is presented on choice); and temporal discounting (the preference for smaller, sooner outcomes than larger more temporally distant ones). More generally, there has been considerable expansion in the use of fMRI to understand the brain bases of decision-making in (mainly healthy) volunteers, largely replicating an earlier animal literature, and also a great focus on investigating the role of chemical neurotransmitters in decision-making through both experimental psychopharmacology and naturally-occurring (e.g. genetic) variation. These investigations have confirmed important roles for the following brain regions (among others) in decision-making: striatum; orbitofrontal cortex; anterior cingulate; amygdala; pallidum; thalamus; the midbrain dopaminergic and serotoninergic nuclei.

Computational modelling approaches are attractive as they appeal more directly to mechanistic hypotheses and can sometimes be directly linked to putative neurophysiological processes. For example, reinforcement learning theory has highlighted the importance of prediction errors as teaching signals for learning and has related these to phasic firing of midbrain dopamine neurons (Schultz, 1997). This has triggered a wide range of investigations into psychiatric diseases, trying to understand maladaptive behaviour as a consequence of aberrant prediction error processing and learning (e.g. Murray et al., 2007).

These approaches differ from previous attempts to correlate brain signal with clinical data in some important ways: first, explaining behavioural observations in terms of mathematical models of the underlying computations (e.g. by assessing learning rates and prediction error signals in different disorders, see Park et al., 2010), can dissect out a number of influences on behaviour that may be conflated together using traditional measures (e.g. the number of errors made on a probabilistic learning task might be influenced by both the learning rate and the deterministic nature of responding). Second, the systematic use of statistical model selection, which enables one to disambiguate between competing models (hypotheses) and select the model that generalises best (i.e., has the best trade-off between accuracy and complexity) allows inference on 'hidden' quantities that are otherwise very difficult to measure (e.g. neuronal processes that underlie measured EEG, fMRI or behaviour). This particularly benefits from combining computational models with physiological models (e.g., how prediction errors drive short-term synaptic plasticity of task-relevant circuitry denOuden et al., 2010). These model-based estimates of hidden physiological quantities can dramatically increase both sensitivity and interpretability of diagnostic classification based on imaging (Brodersen et al., 2011). Third, recently developed Bayesian model selection procedures account for population heterogeneity, specifically the possibility that patients may solve problems differently and hence display alterations in brain signals that simply reflect alternative cognitive strategies and not biological differences (Stephan et al., 2009). The use of computational modelling will thus enable us to look at cognitive mechanisms and their behavioural and biological correlates in a manner that cuts across traditional disease entities (Heinz, 2002; Robbins et al., 2012).

Recent computational approaches to decision-making often take a Bayesian perspective (Behrens et al., 2007; Mathys, 2011; Frank and Badre, 2011) which is beginning to be applied routinely in pharmacological (e.g., Passamonti et al., 2012) and clinical studies (Averbeck et al., 2011). Moreover, the Bayesian model comparison is becoming a

standard approach for computational analyses of decision-making, including reinforcement learning models (Shiner et al., 2012). Notably, the Bayesian model selection can also be applied to assess which model (e.g. single SNP vs. haplotype analysis) is most appropriate for explaining genotype x phenotype interactions (Puls et al., 2009).

3.3.6. Metacognition, executive function and social cognition

Metacognition includes thinking about the thinking of others, where it is usually called mentalising or theory of mind (ToM). There is ample evidence that both these aspects of metacognition are impaired in psychiatric disorders, in particular schizophrenia and autism. A particular aspect of metacognition of great relevance to psychosis is insight. Lack of insight is one of the defining features of psychosis.

The monitoring and control of cognition is also referred to as 'executive function' (EF). Several studies suggest that EF and ToM can be impaired independently of one another, but this is not always found, one problem being that EF is not a single entity. Recent developments in the study of ToM have revealed the existence of an implicit form (Senju et al., 2009). In autism there is evidence that implicit ToM is impaired, while the explicit form is intact, or at least can be acquired. Implicit ToM is closely linked to the other major theme in social cognition. This theme involves such phenomena as emotional contagion, mirroring of action and learning through observation/imitation of others (Rizzolatti et al., 1996). These phenomena underlie implicit ToM. Many tasks have been developed for the study these aspects of social cognition and are being applied to the study of autism.

Considerable advances have been made in computational modelling of mechanisms of top-down control. These are often described in terms of a Bayesian algorithm that optimally combines prior expectations (the top-down component) with new sensory evidence in order to determine perception and behaviour (Fletcher and Frith, 2008). This approach has been most successful in relation to understanding the experience of action and delusions of control (Frith, 2012). There is now much evidence for failure in the adaptation or updating of predictions (i.e. prior expectations), based on prediction errors, in schizophrenia.

Theory in social cognition has been enriched by the cognitive neuroscience of social decision-making that has derived from the study of economic games (such as 'the ultimatum game' (e.g. Sanfey, 2003) or "the prisoner's dilemma").

3.3.7. Conclusion

We have summarised some of the main themes for psychiatry arising from a cognitive neuroscience approach. This new approach evidently embraces advances in both methodology and theory: virtually all of the conceptual themes outlined above can be associated with such developments. As noted in the Introduction, one product of the approach will be the definition of more accurate psychiatric phenotypes. Another will be in the development of new treatments, whether cognitive, electrophysiological or pharmacological. An example of the general process would be initially establishing relationships between neural processing, behavioural performance and decision-making models. The fitting of a model would then allow identification of dysfunctional processes and potentially a suitable target for therapeutics. The application of the cognitive systems perspective will necessarily involve interfaces with other approaches, e.g. with respect to affective systems, comorbidity and psychiatric genetics. We have not attempted in this brief review to relate dysfunctions of specific neural systems to underlying molecular pathology and neurogenetics, but these will also be important goals.

3.4. Questions and problems to be solved

3.4.1. Perceptual dysfunction and electrophysiological biomarkers

Future research should focus on establishing animal, human electrophysiological and neurocomputational models of short-term plasticity subserving regularity encoding, and mechanisms of deviance detection, as to provide a solid basis for the use of the MMN, and related human electrophysiological responses as markers of cognitive dysfunction in psychiatric disorders.

3.4.2. Attention and neural networks of cognition

A detailed understanding of network properties of cognitive systems will enable the rational development of emergent procedures of deep brain stimulation and transcranial magnetic stimulation (Rossini and Rossi, 2007), as therapeutic interventions for disorders such as obsessive-compulsive disorder and depression, and potentially other indications.

3.4.3. Working memory and cognitive training

There are many questions yet to be answered regarding cognitive training, including: what are the optimal tasks to use for training; what is the optimal training regime in terms of amount, length and spacing of training; how can training be tailored individually; what are the neural and biochemical correlates of training-enhanced capacity; and can the training effect be enhanced by a combination with other interventions, such as other types of cognitive training, medication or cardiovascular training?

3.4.4. Long term memory and plasticity

A notable challenge for the next period is whether the preclinical development of compounds with relatively new modes of action, including various ways of boosting glutamatergic transmission, can be translated to the clinic, possibly via experimental medicine and back-translation studies.

3.4.5. Decision-making, learning and neurocomputation

Future research will need to focus on parsing the contribution of different aspects of learning to decision-making relevant to neuropsychiatric disorders; for example, the distinction between Pavlovian, instrumental (goal-directed) and habit-based learning systems, which have been shown to have different neural substrates, and their relationships to valuation, including the subjective hedonic response to receiving a reward. Again, such effects can be assessed using the same computationalized approach in animal

experiments and human studies across traditional disease entities (Robbins et al., 2012; Huys et al., 2011). These will benefit from further development of 'hybrid' models that allow for inference on disturbances of synaptic plasticity in individual patients by combining physiological models of neuronal dynamics with computational models of trial-wise prediction errors (c.f. denOuden et al., 2010). Finally, the existence and workings of opponent motivational systems, as has been posited for example in addiction, also remains to be characterised.

Knowledge generated by better understanding decision-making may be critical in improving the diagnosis, treatment and nosology of mental health problems. The most straightforward translational targets would include: depression (where anhedonia and difficulty in decision-making are diagnostic features); schizophrenia (where motivational impairments [apathy] and anhedonia are key negative symptoms that pose a barrier to rehabilitation); and substance dependence (where addictive drugs effectively hijack the brain's reinforcement-based decision-making circuitry). Better understanding of the different reinforcement-based decision-making deficits in these conditions, and their neural bases, will additionally be of importance in the development of novel and more valid, animal models of psychiatric disorder.

3.4.6. Metacognition, executive function and social cognition

We need to specify which components of EF are relevant to ToM. Part of this new research will involve the development of new and better tasks for measuring ToM abilities. More studies of metacognition in psychosis are also required; for example, new tasks are needed for contrasting implicit and explicit metacognition, especially in relation to ToM. Following the achievements of applications of studies of social cognition studies to autism, similar studies are needed for psychosis. Moreover, we will need to consider whether a computational account of delusions is feasible based on work on expectancies and prediction errors. Deviations from the 'rational' concept of human decision-making approach assumed by economic theory are highly relevant to psychiatry and may provide a rich new source of measures and concepts.

3.5. Gaps

Given the considerable advances in other aspects of neuroscience, including molecular genetics and new ways of imaging the CNS at all levels, there needs to be a greater interdisciplinary integration of these advances with the new concepts of neuropsychiatric disorder emerging from the theoretical opportunities afforded by cognitive neuroscience. At present the best routes to achieve this may stem from (i) the development of more realistic animal models to bridge the gap in genetics, improving the availability of new sensitive PET ligands to measure molecular changes in the disordered brain; and (ii) defining more detailed connectomics through cellular and systems imaging in various modalities and application of electrophysiological methods, in order to facilitate the more sophisticated application of therapeutic methods such as deep and non-invasive brain stimulation.

3.6. Needs

There is an urgent need to provide new research groups or networks to help compensate for the void left by big Pharma into research into therapeutics in this area. Such groups would combine expertise in relevant areas from molecular and genetic to the methodology of cognitive neuroscience for improved definitions of disease endophenotypes and assessment of new therapeutics. These groups would also combine clinical neuroscientists to enable experimental medicine studies, with basic neuroscientists, including those working with experimental models and cognitive neuroscience. Collaborative networks will increasingly be needed for investigating the large populations needed to investigate psychiatric disorders, in order to resolve the difficulties posed by their heterogeneity.

4. Positive and negative valence

Positive and negative valence are evolutionarily essential states underlying two opposite behavioural tendencies: reward and punishment. Given the fundamental importance of reward and punishment-related behaviour it is unsurprising that maladaptive forms of these traits are a pervasive component of psychopathology, most often associated with anxiety and mood disorders as well as substance and behavioural addictions. Here, we provide an overview of the state of the art of biomedical research on positive and negative valence, describing findings at the following levels: (1) genetic, molecular and cellular level, including molecular mechanisms of environmental influences and systems approaches. (2) Circuit and physiological levels where we review brain structures and neural circuits associated with different behavioural manifestations of positive and negative valence, including reward, reward learning, habit, fear, anxiety and sustained threat. (3) Clinical and behavioural level, including studies in humans on addiction and affective disorders, anxiety and schizophrenia. We describe major advances in the respective research areas and identify key challenges for future research, necessary to characterise and develop specific treatments that target pathological processes involving positive and negative valence rather than heterogeneous categories of mental illness.

4.1. Definition

Positive and negative valence are evolutionarily essential states underlying two opposite behavioural tendencies: approach and withdrawal also referred to as reward and punishment. These two opposite ancestral behaviours guide an organism to generate the necessary responses to search for life-supporting events and to avoid harms. Thus they warrant survival and evolution and are highly conserved states common to vertebrates, reptile birds, amphibians and probably to other simpler species like invertebrates (Alcaro and Panksepp, 2011; Huber et al., 2011; O'Connell and Hofmann, 2011). Given the fundamental importance these behaviours it is unsurprising that maladaptive forms of

these traits are a pervasive component of psychopathology, most often associated with anxiety and mood disorders as well as substance and behavioural addictions.

In the Research Domain Criteria (RDoC) approach motivation, initial responsiveness to reward, sustained responsiveness to reward, reward learning and habit have been proposed as constructs related to positive valence. For negative valence, the proposed constructs are: active threat ("fear"), potential threat ("anxiety"), sustained threat, loss and frustrative nonreward. The use of these constructs may allow a more translational approach that will permit researchers to understand positive and negative valence on a genetic, molecular, cellular, systems and behavioural level and from that may allow inference of important concepts for the neurobiology of psychiatric pathologies.

4.2. State of the art

4.2.1. Genes, molecules and cells

Human genetic studies thus far have not usually investigated positive and negative valence as such but have mainly analysed the genetic contributions to maladaptive reward and punishment-related behaviour in clinical samples. These include genome-wide association studies (GWAS) on tobacco smoking (Thorgeirsson et al., 2008; The Tobacco and Genetics Consortium, 2010; Liu et al., 2010), alcohol drinking behaviour (Schumann et al., 2011) and other addiction phenotypes. Similarly, GWAS studies analysing both common variants, as well as rare variants and copy number variations have been carried out in mood disorders, including bipolar disorders (Ye et al., 2012), and major depression (Ripke et al., 2013), often finding common polygenic variation contributing to more than one disorder (Smoller et al., 2013).

These, non-hypothesis driven, human genomic investigations as well as studies in animals have identified diverse classes of genes and molecules associated with positive and negative valence. It thus became increasingly evident that in addition to neurotransmitter systems, other types of molecules are equally important including cell-cell adhesion molecules, cytoskeleton and synaptic molecules, transporters not only of neurotransmitters but also amino acids, neurosteroids, second messenger systems, transcription factors and others. Consequently, this highlighted the importance of brain cells other than neurons for the neurobiological regulation of behaviour. These include astrocytes and microglia as well as modulatory influences of peripheral cells such as immune cells (Eroglu and Barres, 2010; Graeber, 2010; Miller et al., 2009). Understanding the neurobiological functions of the genes and genetic variations thus identified and assessing their relevance for positive and negative valence is a critical challenge to better understand the neurobiological basis of reward and punishment in psychopathology and normal behaviour.

Positive and negative valences are constructs which are captured rather well in behavioural animal models. In fact, animal studies have been crucial in elucidating neurobiological circuitry of reward and punishment-related behaviours and have thus helped identify candidate genes for further studies. Conversely, animal studies are invaluable tools to functionally characterise those GWAS hits, which do not easily fit into existing neurobehavioural concepts. An example is the demonstration in mice of dramatically increased nicotine intake associated with polymorphisms of the CHRNA5 gene, encoding the $\alpha 5$ subunit of the nicotinic acetylcholine receptor (Fowler et al., 2011). Good animal models exist for constructs related to threat and reward, whereas constructs such as loss are beginning to emerge (Huston et al., 2013). Important advances in our understanding of the genetic underpinning of positive and negative valence have been made possible by an increasing number of molecular tools, allowing site- and timing specific manipulations of specific genes as well as the study of human genetic polymorphisms in laboratory animals (Barr et al., 2003; Carola and Gross, 2012; Chen et al., 2006; Kaun et al., 2011; Müller and Holsboer, 2006; Soliman et al., 2010; Stewart et al., 2012).

Increasingly studies have shown significant interactions and correlations of environmental factors with genetic factors influencing phenotypes related to both positive and negative valence. Environmental factors relevant for both positive and negative valence, such as stressful life events, parental attachment have been shown to have effects not only on specific genes, but on a large number of loci, to possibly allow orchestrated changes across several systems. For example, McGowan et al. (2011) have reported that the epigenetic response to maternal care is coordinated in clusters across broad genomic areas and not restricted to single candidate genes. In addition, data emerge that miRNA can be stress sensitive and orchestrate gene expression changes in a number of important target (Haramati et al., 2011). An important emerging concept, related to the molecular mechanisms of positive and negative valence is that inherited genetic variation in sites determining miRNA transcription, environment induced epigenetic changes or the effects of transcription factors could have broad effects on a number of downstream systems and targeting such master regulators may be promising preventive or therapeutic approaches.

4.2.2. Circuits and physiology

As stated above, positive and negative valence are highly conserved states. Hence, it is not surprising that the neuroanatomical correlates of these responses consists of ancient neuronal structures, which include the basal ganglia, the amygdaloid complex, the hypothalamus and other conserved areas of the brain. Of note, however, research has also shown that in evolved species such as human and nonhuman primates evolutionarily recent neuronal structures including the neocortex also play a role in shaping these responses thus suggesting that unique features may distinguish these species from others (Noonan et al., 2012).

A common feature of positive and negative valence states is that they both guide a live organism to emission of goal oriented responses, in the first case to approach the reward in the second to avoid the threat (Everitt and Robbins, 2005). Accordingly, these two opposite emotional states are regulated largely by the same neurotransmitter systems, and their fine tuning is responsible for approach and reward or withdrawal and aversion. This has been described for dopamine (DA) serotonin (5-HT), noradrenalin (NE), opioids, corticotropin releasing factor (CRF), orexin and others.

4.2.2.1. Positive valence – reward. The first evidence unravelling neuroanatomical and functional correlates of reward and appetitive responses originates from the seminal work of Olds and Milner (1954) showing that rats learn electrical self-stimulation when an electrode is placed in the lateral hypothalamus-medial forebrain bundle. Subsequent studies demonstrated that activation of the mesolimbic DAergic A10 pathway originating from the ventral tegmental area (VTA) and projecting to the nucleus accumbens (Nac) is a key neurocircuitry in reward processing and positive salience attribution (Volkow et al., 2009). The opioid system has been also implicated in the regulation of reward mechanisms and positive valence attribution. The major role appears to be played by the μ-opioid receptor system which acts through at least two neuroanatomically distinct mechanisms (Johnson and North, 1992). Brain imaging studies using PET ligands to monitor DAergic as well as μ-opioidergic activity in response to drugs of abuse have confirmed these preclinical findings (Heinz et al., 2005; Volkow et al., 1997).

4.2.2.2. Positive valence: reward learning. A positive valence of a stimulus may trigger 'wanting' and 'liking' in an organism (Robinson and Berridge, 1993). Thereby the 'wanting' predominantly determines approximatory and consummatory behaviour while 'liking' describes subjective pleasure and estimation of a stimulus. 'Wanting' determines behavioural plasticity and is a key to psychopathologies like obsessive compulsive disorders and addiction (Robinson and Berridge, 2001, 2003). It is assumed that 'wanting' is particularly driven by DA activation in the mesolimbic system (Wise, 2004; Berridge, 2007). DA neurons in the VTA increase firing rate after presentation of an unconditioned stimulus (UCS) with positive valence (Hollerman and Schultz, 1998). In natural habitats, certain stimuli may predict the availability of the UCS with positive valence. This natural contingency can be learned and a formerly neutral stimulus may become a conditioned stimulus (CS), which can by itself trigger conditioned responses. This learning process is supported by a transfer of the DA activation from the UCS to the CS (Hollerman and Schultz, 1998; Roitman et al., 2004).

It should be noted that mesolimbic DA activity is not only important for behavioural adaptations towards stimuli with a positive valence. DA appears equally important for adaptations to stimuli with negative valence. Those may require active avoidance responses, which may also get more efficient once guided by predictive cues (Ikemoto and Panksepp, 1999). Extracellular DA levels in the Nac increase not only after positive stimuli but also after negative ones (Young et al., 1993). Likewise, there are DA neurons in the dorsal VTA which increase phasic firing predominantly after negative stimuli (Brischoux et al., 2009). Current evidence suggests that there are at least two different populations of VTA DA neurons projecting to the Nac or prefrontal cortex (PFC), one type coding for positive and one for negative events (Hollerman and Schultz, 1998; Brischoux et al., 2009; Lammel et al., 2011, 2012).

4.2.2.3. Positive valence: habit. Stimuli with a positive valence may trigger approach and consummatory behaviours. During an early phase of instrumental conditioning, behavioural plasticity is outcome controlled and relies on Nac DA activation (Ikemoto and Panksepp, 1999). With increasing experience a behavioural response may become a habit. The behaviour is no longer dependent on its outcome, but only on predictive cues (Everitt and Robbins, 2005). Habits are mediated by the dorsolateral striatum (DS) and its dopaminergic innervation (Yin et al., 2004; Faure et al., 2005). There is a spiralling loop projection which links the VTA-Nac dopaminergic projection to the substantia nigra-DS projection (Haber et al., 2000). Via this loop behavioural control can be shifted from outcome-controlled to stimulus-controlled. During early learning of e.g. cocaine self-administration behaviour, predominantly the ventral striatum is recruited. With increasing learning trials also the DS becomes involved (Porrino et al., 2004). Functional studies have shown that activation of these loop projections are crucial for the transfer of outcome- to stimulus-controlled behaviour (Belin and Everitt, 2008).

4.2.2.4. Negative valence: responses to acute threat (fear). Activation of the brain's defensive motivational system promote behaviours that protect the organism from perceived danger. Normal fear involves a pattern of adaptive responses to conditioned or unconditioned threat stimuli (exteroceptive or interoceptive). Fear can involve internal representations and cognitive processing, and can be modulated by a variety of factors.

The neurocircuitry and physiology involved in response to acute threat (fear) has been extensively studied in non-primate animals, especially rodents, and in non-human primates and in healthy humans. Experiments typically involve classic condition and extinction learning or use unconditioned threat stimuli using molecular and electrophysiological studies as well neuroimaging methods. The 'fear' circuitry consists of the amygdala, the hippocampus, the dorsomedial and ventromedial prefrontal cortex, the anterior cingulate cortex, the orbitofrontal cortex, the insular cortex, and a number of brain areas involved in initiating physiological and behavioural responses (Shin and Liberzon, 2010). These latter areas are the periaquaductal grey, ventral striatum, brainstem nuclei (autonomic nervous system) and hypothalamus (HPA-axis). A distinction can be made between the 'fast' or quick and dirty route and the slower, indirect one that allows regulation of the initial response by higher cortical areas.

4.2.2.5. Negative valence: responses to potential harm (anxiety). Activation of a brain system in cases in which harm may potentially occur, but is distant, ambiguous, or low/uncertain in probability, characterised by a pattern of responses such as enhanced risk assessment (vigilance). These responses to low imminence threats are qualitatively different than the high imminence threat behaviours that characterise fear.

The anxiety circuitry has been less studied and characterised as compared to fear circuitry, especially in humans. Typically used paradigms are darkness in humans or light in rodents or slowly fluctuating indicators of potential risk, typically leading to an enhanced specific environmental threat monitoring. Work in rodents and non-human primates has shown this type of hypervigilant monitoring to be more dependent on involvement of the bed nucleus of the stria terminalis (BNST) and its reciprocal connections with the central nucleus of the amygdala. Recent neuroimaging studies have implicated the BNST, the insular cortex and lateral prefrontal cortex in anxiety in healthy humans

(Somerville et al., 2010). Exaggerated responses in this circuitry correspond with higher trait anxiety.

4.2.2.6. Negative valence: sustained threat circuitry. This construct refers to an aversive emotional state caused by prolonged (i.e., weeks to months) exposure to internal and/or external condition(s), state(s), or stimuli that are adaptive to escape or avoid. The exposure may be actual or anticipated; the changes in affect, cognition, physiology, and behaviour caused by sustained threat persist in the absence of the threat, and can be differentiated from those changes evoked by acute threat.

The concept of sustained threat is applicable to subclinical and clinical forms of anxiety, but also to other stress-related states, probably including some depressive symptomatology. It is a more complex construct than the previous two, because of its broad definition (internal/external, weeks to months, actual or anticipated exposure etc.). The sustained threat circuitry and physiology overlap with those of fear and anxiety, but also include frontostriatal circuitry and probably circuitry involved in for instance self-processing in humans (Shin and Liberzon, 2010).

4.2.3. Behaviour and clinical

4.2.3.1. Positive valence. Alterations in reward processing are a component of psychiatric disorders, including substance use disorders, eating disorders and behavioural addictions as well as affective disorders and schizophrenia (namely negative symptoms). Each reward-related illness is characterised by its own collection of aetiological predisposing factors, psychopathological dysregulations and symptoms. Identification of specific mechanisms and risk factors underlying the different clinical presentations will enable the development of individualised diagnostics and targeted prevention and therapeutic strategies. However, clinical presentations of maladaptive reward processing also share important common features.

In the case of addictive behaviours, dopaminergic activation of the reward circuitry through substances as well as natural reinforcers appears to be crucial for development and early stages of addictive behaviour (Bassareo and Di Chiara, 1997, 1999; Lutter and Nestler, 2009; Volkow et al., 2012). A better understanding of similar and distinct mechanisms underlying the development of addictive behaviours is one important challenge of the field.

The later stages of addictive behaviours involve allostatic changes of the brain reward system that is shifted towards a hypohedonic state (Eshel and Roiser, 2010; Le Moal and Koob, 2007) and contribute to the compulsive character of habit formation. This may involve a switch from positive valences to negative valences as the motivational driver maintaining addictions.

High comorbidity between addiction and depression or psychosis has been also well documented (Nunes and Rounsaville, 2006; Schuckit, 2006). Notably, both depressed and psychotic patients appear to be more prone to abuse addictive substances that, at least in part, are used to self-medicate from the negative affect associated with the primary disease. On the other hand, addiction is known to trigger psychotic episodes and exacerbate depression in some individuals, and is probably a cause of depression as well (Munafò and Araya, 2010). The intimate nature of these intricate disease interactions is unknown at present but alteration of brain reward processing seems to play a pivotal role. A transdiagnostic approach to disorders has already been used during the 1990s with positron emission tomography investigations of the relationships between clinical dimensions in affective or psychotic disorders and measures of the dopamine system (e.g. Martinot et al., 2001). These brain imaging studies were associated with controlled trials aiming at improving the targeted clinical dimension.

4.2.3.2. Negative valence. Changes in fear/anxiety circuitry, frontostriatal circuitry, and physiology (i.e. HPA axis and autonomic nerve system) related to sustained threat have been typically studied in animal models and in anxious and depressive patients. The neurocircuitry of some clinical anxiety states has been relatively well studied including post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD), but the 'common' anxiety disorders, i.e. panic disorder, social anxiety disorder and generalised anxiety disorder, in which the fear/anxiety circuitry is believed to be the key circuitry involved, are understudied. In PTSD and OCD the fear/anxiety circuitry is involved, but other circuits are also clearly involved, especially in OCD where frontostriatal circuitry is probably even more relevant for the phenomenology (van den Heuvel et al., 2011).

Meta-analyses and reviews of functional neuroimaging studies show the presence of a hyper-responsive amygdala (and insula) across the different anxiety disorders, but findings in the other elements of the circuits vary with disorder and scan paradigm (Etkin and Wager, 2007). A meta-analysis of more than 250 brain-imaging publications on mental disorders in children and adolescents (Mana et al., 2010) suggested that when various types of brain imaging techniques are collapsed (i.e. brain coordinates of functional or structural imaging deviations) the disorders involving negative affects are characterised by reports of abnormalities in amygdala, bilateral cingulate cortex, bilateral middle (vmPFC) and inferior frontal gyri, caudate nuclei and hypothalamus. In children and adolescents, the group of affective disorders encompassed MDD, bipolar, and anxiety disorders (except OCD). On the physiological level, abnormalities in HPA axis regulation have been demonstrated in anxiety disorders, most consistently for PTSD.

4.3. Major advances

1. Novel *in-vivo* neurobiological techniques involving genomics, stem cell-biology, multimodal neuroimaging and neuropsychology have facilitated characterizations of cognitive functions at multiple biological levels, thus crucially advancing our understanding of the human brain. Increasing sample size in neuropsychiatric genome-wide association studies have yielded multiple new genetic associations and annotation of the function of these variants will be a potential window into new biology.
2. Progress in genomic and molecular techniques has resulted in advances in our knowledge of processing of reward and punishment. On a genetic level this includes an appreciation of the limited contribution of single genes even to behaviourally and neurophysiologically circumscript phenotypes and the fact that genes and gene products not immediately involved in

neurotransmitter signalling can be important for reward or punishment associated neurobiological mechanisms and behaviours.
3. On a systemic level we have learned much about the interdependency of different neurobiological systems, for example stress and reward system, circadian system and reward system etc. There is a substantial body of knowledge available for especially the fear and reward circuitry, linking the circuitry to specific physiological reactions, behaviour, genes, and neurotransmitters and other psychotropic molecules.
4. Neuroimaging analyses in humans, using both MRI and PET have validated and extended neurobiological information acquired from animal models. They have aided in describing specific neurobiological circuits involving reward and punishment and are indispensible to investigate the relation of such circuits to observable behaviour, including psychopathology.
5. Findings from transdiagnostic approaches in neuroimaging studies suggest that to investigate the neurobiological basis of psychiatric disorders, biological, biomarker and human genetic studies need to move away from diagnosis and symptom-based associations towards intermediate phenotypes that might better reflect these domains (Loth et al., 2011). For example, we hypothesise that distinct neurobehavioural mechanisms such as reward processing and impulsivity lead to adolescent substance use. It was recently shown that specific brain networks contributing to impulsivity are associated with adolescent drug use behaviour, and a genetic variation in the norepinephrine transporter gene (Whelan et al., 2012).

4.4. Questions and problems to be solved

However, to fulfil the promise of stratified psychiatric diagnosis and treatment it is necessary to generate more knowledge on reinforcement-related mechanisms, including a better understanding of how valence contructs map to clinical measures, a particular emphasis on normal and abnormal development across the life span, as well as the influence of environmental factors in humans. To achieve this we need to further characterise at risk individuals at the circuitry and molecular level and translate our findings into clinical applications. This includes:

1. Functional characterisation of neurobehavioural mechanisms across the life span. While the mechanism of action of single molecules or some specific chain of molecular events important for positive and negative valences have been elucidated – (see Attwood et al., 2011; Spanagel et al., 2005 as selected examples), our understanding of how the many different types of molecules act in a concerted way is insufficient. One of the challenges in the coming years will be to explore the systemic context of such molecules on different cell types, investigate their relation to our current molecular understanding of the neural underpinnings of positive and negative valence (Geschwind and Konopka, 2009) and assess their function across the life span.
2. In order to better understand the relation of individual vulnerability/resilience in adverse conditions as well as the consequences of a nurturing environment on reward and punishment-related behaviour and mental health in general we require better understanding of gene × environment interactions as well as gene × environment correlations (the genetic influences on environmental exposure) and their mediation through epigenetic and transcriptional mechanisms. Such studies will require novel animal models as well as massive data sets if current crude environmental measures are used due to the modest effect sizes associated with single genes; development of more relevant environmental measures are sorely needed. On the other hand, as more and more genes are identified to be associated, use of genetic risk scores and genome-wide scores will bring much more power to such studies, permitting analyses in sample of reasonable size.
3. Neurobiological pathways of progression from subclinical/subthreshold state to clinical state which in the case of addictions may reflect a change in valences driving motivations for addictive behaviour, from positive valence at the subclinical state to negative valence (dark side) during chronic disease. For affective disorders this is probably a more gradual progression in which adequate processing of negative valences shift temporarily towards sustained threat.
4. Characterisation of underlying mechanisms for shared and distinct symptoms of reward and punishment processing within and across disorders. Identification of predictors and prognostic markers for risk, disease progression and therapy response.
5. Identification of treatment targets, both pharmacologic and psychotherapeutic, and delivery of prophylactic, or early intervention using therapies that target causal mechanisms of disease.

5. Systems for social processes

Social interactions represent a core feature of the human species. The interpretation of social cues, facial expressions, human actions and goal-directedness, allows the "social brain" to produce constructs as complex as theory of mind and empathy, resulting in amazingly multifaceted responses such as altruism, sense of equity, love, and trust. Systems for Social Processes (SSP) include neurobiological systems and psychological functions that prepare individuals for social interaction, while supporting the development of mental health and well-being throughout the life of an individual. The present contribution briefly summarises social brain functions, spanning from socially relevant sensory input processing to information processing yielding socially adaptive responses. Questions and problems in different domain are identified, as well as three overarching gaps present in current classification systems, affecting "validity", "translation", and "continuum-category", and two SSP-specific "developmental" and "environmental" gaps currently hampering appropriate recognition and use of SSP deficits in psychiatry. We finally identify an urgent need to chart developmental and normative variation in each social domain, to design reliable tools able to "weigh" environmental contributions to SSP, and multidisciplinary approaches aimed at integrating information from multiple levels of analysis.

5.1. Definition

Systems for Social Processes (SSP) refer to the intraindividual neurobiological and psychological systems and functions that (1) develop both prenatally and postnatally throughout the life of an individual, (2) prepare and set up individuals for social interaction, and (3) are directly relevant to support and promote development of mental health and well-being and causal understanding, clinical assessment, treatment and prevention of mental impairment. A clear theoretical delineation of SSP from systems of emotion, cognition and language is hardly possible and has to be done pragmatically. The social brain is the cortical and subcortical network of regions that underlies SSP. Its regions include ventral and medial prefrontal cortex, superior temporal gyrus, fusiform gyrus (FG), cingulate gyrus and amygdala, which are specialized to process social information such as the face, gaze, biological motion, human action, goal-directedness, theory of mind and empathy. Deficits in SSP, either alone or in interaction with cognitive, affective, and motor systems, are implicated in many psychiatric disorders.

SSP build upon sensory systems including hearing, touch and vision, extend into multifaceted socially-relevant processes like empathy, recognition of emotional expression, imitation and simulation involving mirror neuron systems, to yield constructs as complex as theory of mind (social cognition), social approach-avoidance, attachment, and self-representation.

5.2. State of the art

5.2.1. Hearing

Sounds produced by emotionally relevant figures accompany humans throughout life ever since prenatal development. Astonishingly, humans develop maternal voice recognition in utero as early as at 33–34 weeks of gestation (Jardri et al., 2012); mothers are able to discriminate the cries of their own child from another's within 48 h of birth: this is a feature shared with many gregarious mammalian species (Pitcher et al., 2010) and thus it is genetically encoded, neurobiologically hardwired, and evolutionarily conserved. As all other senses, hearing does not analyse only the physical properties of sounds but also their emotional content, so much so that facial expression recognition is significantly delayed in preschoolers with congenital deafness or cochlear implants, as compared to normal hearing children (Wang et al., 2011).

5.2.2. Touch

Touch plays an important role in our everyday social interactions from birth through to adulthood and old age. However, little scientific research has been conducted on the topic of interpersonal touch. Tactile sensations elicited under ecologically-valid conditions that involve interpersonal interaction can have powerful effects on people's behaviours and emotions. Interpersonal touch appears to be capable of modulating people's compliance with a variety of different requests. Interpersonal touch can affect people's attitudes toward particular services, facilitate bonding between pairs in a couple or groups in both animals and human, and it plays an even more important role in people's romantic and sexual relationships, regardless of whether or not the tactile contact itself can be remembered explicitly. The emotional somatic system, similarly to pain sensation, is temporally delayed as compared to discriminative touch (McGlone et al., 2007).

The use of touch therapy, when properly trained, can be very helpful when the child's development is in its very critical stages early in life. By spending as little as thirty minutes per day giving a child tactile stimulation increases weight gain and cognitive reflexes, as well as the release of hormones and neurotrophic factors, including IGF1, which plays a trophic role in synaptogenesis (Field et al., 2008). This has been shown in humans as well as animal models. Children who have received regular tactile stimulation show more cognitive stability as well as more social stability (Bell, 2011).

5.2.3. Eye contact

Human infants already shortly after birth have innate tendency to preferentially orient to social stimuli and look at and process the face of other persons. Direct gaze signals that the gazer is looking at the perceiver. In many species, the perception of direct gaze elicits an aversive response, probably because it is a salient signal for potential threat. This response may be maintained in autistic individuals, leading to reduced direct gaze at the eye-and-mouth facial area, accompanied by reduced activation of the fusiform gyrus and the amygdale (Corbett et al., 2009). In typically developing children, by contrast, eye contact provides a foundation of communication and social interaction. In the first months of life, eye contact develops into gaze following, i.e. following the gaze movements of other person towards salient stimuli. Next, in typical development, joint attention behaviours emerge between 6 and 12 months and involve the triadic coordination or sharing ('*joint*ness') of *attention* between the infant, another person, and an object or event (Bakeman and Adamson, 1984). The term encompasses a complex of behavioural forms including gaze and point following, showing and pointing. Deficits in joint attention skills play an important role in the development of autism spectrum disorders (Bakeman and Adamson, 1984).

5.2.4. Imitation

One may discern imitation of emotional and non-emotional behaviours, and differentiate between automatic and voluntary imitation. In particular the mirror neuron system provides an important neural substrate for humans' ability to imitate (Gallese et al., 1996). Meta-analyses using activation likelihood estimation (ALE) seem to reveal that the superior parietal lobule, inferior parietal lobule, and the dorsal premotor cortex but not the inferior frontal gyrus, are all commonly activated in fMRI studies of imitation. This questions the crucial role of the frontal mirror neuron area, the pars opercularis of the IFG, during imitation and suggests that parietal and frontal regions which extend beyond the classical mirror neuron network are crucial for imitation (Molenberghs et al., 2009).

5.2.5. Empathy

Empathy is the capacity to recognise, understand and share the emotional states of others (Decety and Jackson, 2004;

Decety and Moriguchi, 2007), and is considered to be the cornerstone of genuine and reciprocal human relationships. Lack of empathy has been invoked as an explanatory mechanism in various forms of psychopathology, but foremost in autism spectrum disorders and conduct disorder. Empathy is assumed to consist of three components: motor, emotional, and cognitive empathy (Blair, 2005). Motor empathy refers to automatically and unconsciously mirroring the facial expressions of another person, known as facial mimicry. Emotional empathy refers to the experience of emotions consistent with and in response to those of others. Cognitive empathy is the ability to rationally understand and recognise the emotional state, and take the perspective of other persons; so called Theory of Mind (ToM). The key brain areas involved in empathy are the sensorimotor mirror neuron system for motor empathy, the inferior frontal gyrus for emotional empathy, and the ventromedial prefrontal cortex for cognitive empathy (Baird et al., 2011). Naturally, motor, emotional, and cognitive empathy are interdependent. The perception-action model posits that observation of emotions activates neural circuits responsible for generating the same emotion and thus activating the motor representation, i.e. motor empathy, and associated emotional autonomic responses. This is suggested to result in resonance with the emotional state of another person, i.e. emotional empathy, and facilitating emotion recognition, i.e. cognitive empathy. Automatically mimicking and synchronizing emotions with other people facilitates emotion recognition, social interaction, as well as empathic functioning (Singer, 2006; Sonnby-Borgström, 2002; Stel and van Knippenberg, 2008; Stel and Vonk, 2010).

Theory of mind (ToM) is a broader concept than empathy and refers to the ability to understand mental states, intentions, goals and beliefs, irrespective of the emotional state and relies on structures of the temporal lobe and the pre-frontal cortex (Singer, 2006). ToM has both cognitive and emotional underpinnings, processed by two distinct, yet highly interactive networks, the cognitive ToM network, primarily engaging the dorsomedial prefrontal cortex, the dorsal anterior cingulate cortex and the dorsal striatum; and the affective ToM network involving the ventromedial and orbitofrontal cortices, the ventral anterior cingulate cortex, the amygdala and the ventral striatum (Abu-Akel and Shamay-Tsoory, 2011). Although empathy and ToM are often used as synonyms in the literature, these capacities represent different abilities that rely on different neuronal circuitry. Finally, the abilities to understand other people's thoughts and to share their affects display different ontogenetic trajectories reflecting the different developmental paths of their underlying neural structures. In particular, empathy develops much earlier than mentalizing abilities, because the former relies on limbic structures which develop early in ontogeny, whereas the latter rely on lateral temporal lobe and pre-frontal structures which are among the last to fully mature.

5.2.6. Attachment

The neural basis of human attachment security is poorly understood. Performance during a stress but not a neutral prime condition was associated with response in bilateral amygdalae in an fMRI paradigm. Furthermore, levels of activity within bilateral amygdalae were highly positively correlated with attachment insecurity and autonomic response during the stress prime condition. This suggests a key role of the amygdala in mediating autonomic activity associated with human attachment insecurity (Lemche et al., 2006). On the other hand, the pleasure intrinsic to secure human attachment and interpersonal relationship is mediated by activation of reward circuits. In fact, synchronous mothers, whose maternal behaviour is coordinated with infant signals, display greater activations in the left nucleus accumbens tightly coordinated with oxytocin release, while intrusive mothers exhibit higher activations in the right amygdala (Atzil et al., 2011). Adult attachment representations are associated with neural, emotional and behavioural responses to infant crying. Individuals with insecure attachment representations showed heightened amygdala activation when exposed to infant crying compared to individuals with secure attachment representations (Riem et al., 2012). Amygdala hyperactivity might be one of the mechanisms underlying the experience of negative emotions during exposure to infant crying in insecure individuals and might explain why insecure parents respond inconsistently to infant signals and might even become abusive. Intranasal administration of oxytocin, a hormone that enhances parental sensitivity and parent-infant bonding (Naber et al., 2012), decreases amygdala responses and increases insula and IFG responses to infant crying (Riem et al., 2011). These findings point to a role of empathy-related brain regions in sensitive parenting and adult attachment representations, and to the possibility of psychopharmacological interventions.

5.2.7. Recognition of emotional expression

Human social skills require the ability to adapt and regulate instinctive reactions to emotional signals, in particular the communicative signals of threat or appeasement conveyed by emotional facial expressions (ÖHman, 1986; Blair, 2003). In particular, the lateral OFC and the adjacent ventrolateral prefrontal cortex are involved in the selection of actions that override automatic and motivationally (reward) driven response tendencies (Elliott et al., 2000; Passingham et al., 2000; Rushworth et al., 2007). Numerous studies have addressed the neural bases of perception of social emotional signals, in particular facial expression (Adolphs, 2003), detailing the crucial role of the amygdala and other limbic structures in the automatic processing of (negative) facial expressions (Adolphs, 2002; McClure et al., 2004; Strauss et al., 2005). The cerebral and cognitive mechanisms controlling the behaviour evoked by these perceptual processes, i.e. approach-avoidance tendencies, appear to be controlled by the lateral OFC (Roelofs et al., 2009).

5.2.8. Self

The '*self*' is a complex multidimensional construct deeply embedded and in many ways defined by our relations with the social world. Normal individuals preferentially recruit the middle cingulate cortex and ventromedial prefrontal cortex in response to self compared with other-referential processing. In particular, the self construct is hypothesised to be embedded in the "default mode network" (DMN), encompassing the middle frontal gyrus, frontal medial area,

middle temporal and occipital gyrus, as well as left and right pre-cuneus, bilaterally. Recent studies on several pathological conditions suggest that the strength of DMN functional connectivity could mediate the strength of self-consciousness expression (Fingelkurts et al., 2012).

5.2.9. Behavioural systems

Psychology and human communication research has identified a number of behavioural systems that tend to be organised rhythmically and to synchronise with other individuals during face to face interaction. These include autonomous motivation for prosocial behaviour, mechanisms of interpersonal attraction, gestures and mimicry. Impairment of these systems is found across diagnostic categories (Littlejohn and Foss, 2011).

5.2.10. Language

Language, a central expression of human cognitive ability, is the most powerful communication system that evolution has produced. In addition to its strictly communicative uses, language also has many social and cultural uses, such as signifying group identity, social stratification, as well as for social grooming and entertainment. We all share the capacity to acquire language within the first few years of life, without any formalized teaching programme. Language is processed in many different locations in the human brain, but especially in Broca's and Wernicke's areas. Language has many different aspects, such as phonology, semantics and syntax. Particularly relevant is here pragmatics, that is the use of language in context. Linguistic pragmatics implies difficulties in the ability to disambiguate meaning, the ability to structure coherent discourse and to understand irony and implied meaning. The ability to understand other people's intentions, social rules of conduct and non-verbal communication gestures are regarded as non-linguistic pragmatics. Deficits in pragmatic functioning may be evident at all developmental stages. There is hardly any research on the relationship between pragmatic language competence and the risk for psychiatric disorders and behavioural problems (Adams, 2002).

5.3. Questions and problems to be solved

5.3.1. Touch

Research has not yet uncovered why interpersonal touch has such dramatic effects on people. Nor do we know all that much about the cognitive, neural, and physiological mechanisms underlying the effects of touch on social interactions. Researchers have only just started to address the neural aspects of interpersonal touch by showing that different patterns of brain activation can differentiate between the more perceptual and the more social aspects of tactile sensation (Gallace and Spence, 2010; Gazzola et al., 2012). Oxytocin (OT), a brain peptide, has been implicated in maternal bonding, sexual behaviour and social affiliation behaviours. OT is of potential use in enhancing interpersonal and individual well-being, and might have more applications in mental disorders especially those characterised by persistent fear, repetitive behaviour, reduced trust and avoidance of social interactions (Ishak et al., 2011; Dunbar, 2010), or abnormal attachment (perversion).

The significance of mediated social touch needs to be empirically established, and grounded within a multidisciplinary theoretical framework that encompasses multisensory perception, social psychology, and communication theory (Haans and IJsselsteijn, 2005).

5.3.2. Hearing

The study of children with cochlear implants has thus far mainly focused on the consequences of auditory deprivation on hearing, speech perception, word learning and phonological development. In this regard, novel areas of mounting interest include social development and neurocognitive processes. Different ages at onset of hearing impairment also offer great opportunities to study the critical periods for hearing contributions to social cognition, which seemingly do not overlap with those for language development. This area of investigation is especially relevant to the design of therapeutic interventions aimed at promoting interpersonal synchrony in children with hearing loss receiving cochlear implants (Mellon et al., 2009). Also the role of hearing in socially-relevant multisensory perception and exploration still remains to be fully appreciated and characterised.

5.3.3. Eye contact

Although it is commonly agreed that eye contact modulates the development and activation of the social brain network, the precise mechanisms and developmental processes involved remain unclear. Two general accounts have often been invoked to explain the mechanisms underlying the eye contact effect. The affective arousal model argues that eye contact directly activates brain arousal systems and/or elicits a strong emotional response. This raised arousal or emotional level then influences subsequent perceptual and cognitive processing. Other researchers have argued that eye contact directly activates theory-of-mind computations or a pedagogy brain system because it signals the intent to communicate with the perceiver. A more recent account, the fast-track modulator model, presumes that the eye contact effect is mediated by the subcortical face detection pathway hypothesised to include the superior colliculus, pulvinar and amygdala. This route is fast, operates on low spatial frequency visual information and modulates cortical face processing (Senju and Johnson, 2009).

5.3.4. Imitation

Imitation is a primary means through which children learn new skills. Most children learn to imitate without being taught but some children with disabilities fail to develop or use imitation in the absence of direct instruction. Whether this is due to an abnormal mirror neuron system, or whether the mirror neuron system in these individuals is not fed the necessary information due to direct gaze deficits remains to be conclusively established. More intervention studies are needed to improve imitation skills in children with disabilities, and to examine which strategies to improve imitation are most effective. These strategies should include the implementation of specific prompting cues; embedding instructions across activities; teaching imitation of

multiple, salient models; and using reinforcing behaviours and materials. Future research is needed on questions regarding instructional sequence, effective instructional practices, and measurement and promotion of generalised imitation (Ledford and Wolery, 2010).

5.3.5. Empathy

There are two, typically distinctive views on how emotions and action intentions are perceived by an observer. The first view stresses the importance of simulation, whereas the second notion stresses the importance of mentalizing. At the level of the brain, likewise a distinction is made between simulation mechanisms linked with the fronto-parietal network referred to as the Mirror Neuron System, and mental inference processes, linked with the mentalizing network, Theory of Mind. What is poorly understood is whether simulation and mentalizing are completely independent processes, reflect different styles of processing emotional and social information at the levels of individual subjects, have different developmental trajectories, and interact with each other during development.

5.3.6. Language

There are many unanswered questions about "language in action", i.e. the relationship between linguistic and in particular pragmatic competence and social and communicative ability: (1) How is multi-sensory information (e.g. eye gaze, hand gestures such as in pointing) integrated with linguistic information during social interactions? (2) What is the role of action simulation or predicting other's goals (i.e., conceptual simulation) in language comprehension and production? If one is able to predict the communicative goals of a speaker, one might also be able to predict the content and perhaps the form of their utterances. (3) What is the contribution of cognitive control to language planning and processing? Accumulating evidence suggests that cognitive control over language processes is achieved by goals and rule systems that interact with basic language functions, including lexical memory. (4) How does pragmatic language competence interacts with social processes in modulating risks for the onset and course of psychiatric disorders (Mahon and Caramazza, 2008; Hagoort, 2005)?

5.4. Gaps

At least three overarching gaps, shared with other areas in Mental Health, and several SSP-specific gaps can be identified at this time. The general gaps include:

5.4.1. The validity gap

The current classification systems (ICD/DSM) are not very suitable to handle failures in SSP.

1. Although failures in SSP are among the most socially impairing handicaps in human life, there is no single diagnosis for SSP-failure. Most frequently SSP-failure is only one of several interchangeable criteria underpinning a diagnosis (e.g. social anxiety, autism, several personality disorders).
2. Several obvious clinical phenomena where SSP failure is a core problem, are not covered by the current diagnostic system (e.g. shyness vs. unsocial personality traits; callous/unemotional vs. reactive/impulsive aggressive behaviour; lonely mass murderers).
3. Because failure in SSP is a core problem across a large number of both mental developmental, personality and symptom disorders and only to a modest degree contribute to differentiation between diagnostic categories, failures in SSP often go undiagnosed. Psychiatric disorders also encompassing SSP failure or SSP distortions among several clinical features are typically diagnosed neglecting SSP whereas symptoms pertaining to the behavioural or cognitive domains are much more frequently set as diagnostic criteria (schizophrenia, affective disorders, etc).

5.4.2. The translation gap

The current classification systems (ICD/DSM) are largely based on clinical opinions, often weakly related to current knowledge in SSP neurobiology and neurochemistry. This dissociation between basic science and clinical experience is a major barrier for translation of findings from basic to applied research, assessment and intervention.

5.4.3. The continuum-category gap

As long as we try to force continuous/dimensional phenomena into discrete categories, patients with impaired SSP will by necessity frequently end up with several co-morbid diagnoses and the explanatory power/explanation of variance in these categorically defined "diseases" will continue to be modest.

Until these three overarching gaps have been closed, scientific achievements in the field of mental disorders will by definition continue to be modest.

Additional SSP-specific gaps include:

5.4.4. The developmental gap

Normative data describing the developmental trajectory of different key components of SSP in typically developing paediatric populations are largely not available. This lack of European- and nation-based reference data hampers both scientific research and a clinically-usable definition of SSP failure, currently available only for major global SSP deficits.

5.4.5. The environmental gap

While genetic, neurochemical and neuroimaging approaches usually provide reliable quantitative data, environmental factors are often overlooked in biomedical research or lack appropriate tools to approach their complexity and provide some measure of their relative "weight". This dramatically reduces the reliability of gene x environment interaction models and their explanatory potential, when considering the amount and complexity of the variance involved in human social processes.

5.5. Needs

5.5.1. Developmental studies

There is a critical need for developmental behavioural and neuroscience studies in all these different components of

SSP. These should chart developmental and normative variations, obtain reference values for key components as eye-contact, face scanning, and emotional responsivity, and describe the neurobiological bases of behavioural phenomena observed by developmental psychologists many decades ago.

5.5.2. Environmental studies

Practical and reliable tools to measure SSP-related phenomena known to bear a major impact on the later development of mental disorders, on their onset or their clinical course, as well as on stable personality structures associated with social malfunctioning are urgently needed. Examples include measures of intrafamilial interactions and family structure, mother–child synchronicity during neonatal life, and peer interactions in social networks or work environments (or, more in general, social structure).

5.5.3. Integrative approaches

Experimental and statistical paradigms, able to integrate information obtained through multiple different approaches into unitary paradigms by employing artificial adaptive systems for data mining in hypothesis-driven and hypothesis-free experimental designs. Areas which could especially benefit from objective and measureable multidisciplinary approaches include the study of parent-child interactions, as well as SSP-related multisensory perception and exploration.

These needs essentially refer to the SSP-specific gaps summarised above. Their satisfaction represents a prerequisite to then confront the three general gaps, having developed solid and broad-based normative data, appropriate measures, reliable and consistent bioinformatic/biostatistical tools and procedures.

6. Pharmacological treatments

Since the development of effective treatments for mental disorders 60 years ago, further drug development has concentrated on animal models validated using drugs of known efficacy or relying on resemblance between animal behaviours and human psychiatric symptoms. These approaches have succeeded in improving the tolerability of the prototypical psychiatric drugs. However recent years have been characterised by a paucity of novel drug treatments and reduced investment in their development, in spite of manifest unmet clinical needs. As we will point out, another promising approach is to consider compounds as treatments for specific symptoms or groups of symptoms (‘symptom clusters’). When coupled with translational neuroscience (based on endophenotypes and intermediate phenotypes) such an approach has the potential to improve the discovery and validation of novel drug targets as well as provide biomarkers to stratify patients and realise personalised psychiatry. The effective use of such strategies will require increased private-public collaboration and new regulatory frameworks. Here we summarise some of these issues, point out gaps in current approaches and strategies required to address these. The issues are illustrated using the treatment of schizophrenia and depression as examples.

6.1. Definition

Psychopharmacology studies compounds that affect mental functions (such as mood and cognition) and behaviour. Clinical psychopharmacology examines those compounds that show efficacy in treating mental disorders. As we will point out, another promising approach is to consider compounds as treatments for specific symptoms or groups of symptoms (‘symptom clusters’). Such an approach has important implications for both clinical practice and drug development and regulation.

6.2. Major advances

One of the great advances in psychiatry over the last 60 years has been the establishment of safe and effective pharmacological treatments for mental disorders. In the absence of knowledge about underlying neurobiology to guide rational drug development, treatments for depression, mania and psychosis were discovered by a combination of careful clinical observation and serendipity (Lopez-Munoz et al., 2012). Such treatments are classified into broad categories based on their indication such as antidepressants, mood-stabilisers and antipsychotics. The tolerability, pharmacokinetics and toxicology of the drugs in each class have been greatly improved by the development of successive generations of drugs, a process largely based around the screening of candidate compounds in animal models of the relevant disorder.

6.3. State of the art

6.3.1. Clinical psychopharmacology

Typically pharmaceutical companies release medications for diagnoses that are based on observed behaviour and described symptoms. Psychiatrists deliver pharmacological treatments according to evidence base and clinical experience, while tailoring the most probable side-effects to a patient's presentation (e.g. selecting a more sedating drug for a more agitated and anxious patient). Certain compounds are indicated for particular symptoms rather than diagnoses, for example benzodiazepines for (short-term) treatment of anxiety and insomnia in the context of many different diagnoses. Others are indicated for particular disorders, though frequently there is not a one-to-one correspondence between disorder and drug response (e.g. the selective serotonin reuptake inhibitor (SSRI) antidepressants are effective in OCD as well as depression). Although developments in molecular biology and neuroimaging provide many candidate biomarkers which may be relevant to selecting treatment and predicting response, so far there are only a few circumstances in which biomarkers are clinically useful to the psychiatrist.

6.3.2. Psychopharmacological drug development

Our initial antipsychotics and antidepressants were developed without any knowledge of possible targets, based on interesting behavioural effects in normal rodents (not even animal models of disease) and excellent clinical observation of their effects in psychiatric patients by experienced psychiatrists, a type of phase II study which is largely missing today. Thus, extensive behavioural pharmacology (preclinical and clinical) was crucial

for the impressive success of the early years of psychotropic drug development. More recently drug development has been based on neurotransmitter hypotheses of psychological diseases. The development of a new psychiatric drug typically starts with the identification of ligands with a high affinity and selectivity for a molecular target associated with the mechanism of action of the original compounds. Candidate compounds are then screened in rodent behavioural assays. These assays were developed and validated using the effects of psychiatric drugs already known to exert benefit in humans. A compound demonstrating similar effects to a previously proven one may then be further developed as a drug of the same class. This approach has succeeded in improving the tolerability, pharmacokinetics and toxicology of the prototypical psychiatric drugs but has not led to new mechanistic approaches. The most recent approaches use the development of new targets independent of the mechanisms of action of previous compounds. Examples include antiglutamatergic drugs for schizophrenia and neurokinin-1 (NK1) antagonists or corticotropin-releasing hormone 1 (CRH1) antagonists for depression and anxiety. In many cases however, this approach has led to compounds with inferior efficacy, reducing our hope for new and better psychotropic drugs arising from our much improved understanding of the neurobiology of schizophrenia and depression. Nevertheless conceptually this approach seems to be most promising especially when combined with extensive behavioural observation in animals and patients, a field of psychopharmacology which has been neglected too much.

6.3.3. Neurobiology

In recent years functional neuroimaging has elucidated cerebral circuits underpinning mental processes disrupted in psychiatric disorders. At the same time the application of high-throughput genetic techniques has allowed genome-wide approaches to examine polymorphisms associated with psychopathology. The application of such techniques to traditional nosological entities such as schizophrenia has led to the discovery of many associated genes of small effect. It is likely that such entities involve complex gene-gene and gene–environment interactions and moreover involve not a single but a variety neurobiological processes and hence underlying genetics. The current state of the art is therefore exemplified by convergent approaches combining neuroimaging with genomics, clinical and neuropsychological testing and validation in relevant animal models. In the terms of the NIMH Research Domain Criteria (RDoC) (Insel et al., 2010), such approaches can be thought of as probing multiple 'units of analysis' for each behaviour or psychopathology. Such a convergent approach harnesses the closer correspondence from genotype to brain function than to clinical diagnosis. It allows the investigation of the genetic vulnerability and neurobiological underpinning of psychological traits and their value for predicting the development of mental disorders. Moreover it has the potential to provide novel drug targets, particularly when coupled with a symptom cluster approach to psychopathology.

6.3.4. A translational approach based on symptom clusters

The symptom cluster approach has the potential to inform more effective drug development as well as more personalised, effective treatment (Tricklebank and Garner, 2012). Common factors, symptom clusters or endophenotypes can be discerned that are dysfunctional across different diagnostic categories. An alternative approach to drug discovery would therefore be to examine the neurobiology and pharmacology of the endophenotypes within these broad functional domains via translational neuroscience and experimental medicine: the biology of affect (negative and positive valence), arousal and regulatory systems, social processes and cognition. In essence, treatments might be developed for specific aspects of several diseases, rather than the unrealistic aim of finding a single treatment for complex multifactorial conditions. This also removes the equally unrealistic requirement for animal models to exhibit the full range of symptoms encompassed by ICD-10 diagnoses.

This approach is different from disorder-guided treatments as well as from syndrome-based procedures which is the historical starting point of psychopharmacology: those were not founded on biologically validated symptom patterns but on clinical patterns defined by concurrence of symptoms.

Integrative approaches are therefore needed combining the assessment of different neurobiological levels underlying human behaviour. One example is the Imagen project, which uses neuropsychological testing, brain imaging and genetic analysis coupled with pertinent animal models to examine the constructs of impulsivity, inhibition, attention, reinforcement sensitivity and novelty seeking (Schumann et al., 2010b). Identification of genetic traits in humans that influence the animal phenotype following targeted genetic mutation would allow investigation of the underlying biology and the possible identification of new drug targets.

Research that focuses on symptom clusters paves the way for personalised psychiatry. In this context specific symptoms and symptom clusters can be considered as 'final common pathways' emerging from a variety of interindividual different aetiological and pathogenic pathways: the goal is to treat a patient's unique symptoms on the basis of their underlying biology. Genetic variants coding for a specific mental disorder are not necessarily more specific. Thus, the predisposing genetic pattern of a specific patient is likely to be different from the pattern of another patient with the same ICD-10 diagnosis. Furthermore many genetic risk factors are found to be common between traditionally separate disorders, for example the risk variants in the genes for TCF4, CACNA1c or ANK3 in both schizophrenia and bipolar disorder (Schizophrenia Psychiatric Genome-Wide Association Study Consortium, 2011). Coupled with the familial comorbidity observed for these disorders, this implies biological commonality between them, or at least certain symptoms within them. Investigating the biological dysfunctions responsible for common symptoms may provide novel pharmacological targets, and facilitate the development of compounds indicated for a particular symptom-biomarker profile.

6.3.5. Animal models

Animal models, typically in mice, are traditionally tailored to specific disorders. Yet, the face validity of these is often limited. An example is the forced swim test (FST), used as an indication of antidepressant potential. Rats are placed in water where they initially demonstrate escape-related behaviour followed by passive immobile behaviour,

considered to reflect behavioural despair or disengagement from active forms of stress coping. In practice many antidepressant compounds consistently reduce the immobility time (by increasing escape behaviour) whereas a wide range of non-antidepressant compounds do not. While abnormal stress coping is one of the hallmarks of depression, it is not its defining characteristic. This emphasises the need to consider discrete aspects of a disorder's symptoms and aetiology: the FST appears appropriate to investigate some such aspects of depression while lacking validity for other core endophenotypes of the syndrome.

6.3.6. Biomarkers

A biomarker is an objectively measurable biological variable used as an indicator of a normal or abnormal biological process. It is typically a necessary step in a cascade of changes which produce the symptoms of a disease. It may indicate vulnerability to a disease, an incipient disease process, active disease or recovery from a disease. It may also predict a future disease state or the success or side effects of treatment. Biomarkers may be useful for monitoring the disease course and treatment. Many biomarkers have the potential to be reverse translated, i.e. adapted from humans to animals. This allows more precise validation of animal models by ensuring they encompass precisely homologous aspects of disease aetiology, rather than simply an approximation of symptoms. Furthermore, forward validation of novel biomarkers discovered in animals may lead to the discovery of entirely novel disease mechanisms. Despite these opportunities, biomarker and test-based definitions of most psychiatric disorders suffer from the lack of a 'biological gold standard' (Kapur et al., 2012), such as amyloid plaques and tau tangles for Alzheimer's disease.

6.3.7. Examples of the symptom cluster – biomarker approach

There is preliminary evidence that tailoring antidepressant treatment to predominant symptoms may improve response rates and remission. Nutt et al. (2007) note that symptoms of 'decreased positive affect' (including loss of pleasure, interest and energy) may be better treated by drugs that enhance noradrenergic and dopaminergic function, whereas symptoms of 'increased negative affect' (including anxiety, fear and guilt) may respond better to agents that have noradrenergic and serotonergic activity. While antidepressants show similar efficacy when measured in relation to the overall syndrome of depression, different drugs show greater efficacy for the different symptom clusters. Hence personalising a patient's treatment based on predominant symptoms could yield increased response and remission rates. Nutt et al. (2007) further reviewed particular neurotransmitters and circuits which may account for these differences, thus illustrating the general approach of breaking down a traditional syndromic diagnosis into symptom clusters which are individually more neurobiologically tractable than the diagnosis as a whole, enabling more targeted and rational treatment.

Schizophrenia is another example of a traditional nosological entity that is made up of several symptom clusters, including positive symptoms (psychosis), negative symptoms (including lack of motivation, poverty of speech and action) and cognitive impairment. Current antipsychotics are mainly effective in the positive symptom domain but relatively ineffective for treating cognitive deficits and negative symptoms (Carpenter and Davis, 2012). Cognitive deficits are particularly impeding as they compromise rehabilitation efforts and create barriers to resume employment. Intense efforts are underway to develop new medications to address cognitive impairment, making use of new understanding at the molecular, cellular and circuit level. The cerebral circuits underlying cognitive function include loops between frontal lobes, basal ganglia and thalamus as well as structures underlying contextual memory and fear conditioning (hippocampal formation and amygdala) (Millan et al., 2012). Understanding these circuits allows the use of fMRI of defined brain regions to explore the actions of putative pro-cognitive agents and validate models.

6.4. Questions and problems to be solved

6.4.1. What are benefits, challenges and unmet needs of currently available psychopharmacological treatments?

A psychiatrist is unable to predict confidently response to a medication in an individual patient. For example in schizophrenia or affective disorders 25–40% of patients do not respond to their first prescribed treatment and 10–20% show clinically significant adverse effects (Broich and Möller, 2008). Up to 50–60% of patients fail to respond adequately to antidepressant therapy (Fava, 2003). In the informative Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial only 47% responded to the representative SSRI citalopram and only 37% achieved a final full remission (Rush et al., 2006). Even after subsequent steps with alternative and augmentation treatments remission rates in initial non-remitters remained insufficient (29% in the second and 16–17% in the third and fourth turns). Thus in patients with recurrent depression a substantial number do not achieve remission, even after a sequence of medication switches and augmentations. These problems may in part be due to the heterogeneous syndromic nature of depression coupled with the lack of symptom-specific indications for different drugs. Currently there is no way to accurately predict response to antidepressants. The evidence for the relative advantages of switching an antidepressant to one of the same or different class is limited (National Institute for Health and Clinical Excellence, 2009). Though the SSRIs represent improved tolerability, side-effects are nevertheless a cause of noncompliance with antidepressant therapy (Papakostas, 2008). Moreover even when treatment is successful full response does not occur for several weeks (Gelenberg and Chesen, 2000), lengthening the process of trialling different treatments and hence lengthening the time for which a patient is vulnerable to decreased functioning, morbidity and mortality. Current antidepressants may not be more effective than placebo for patients with mild depression (Vöhringer and Ghaemi, 2011). While generally reducing suicide-related behaviour, antidepressants may cause an increase when used in children and adolescents, leading to warnings issued by the European Medicines Agency and other regulatory agencies. While there is growing recognition of a prodrome to depressive episodes

(Iacoviello et al., 2010) the effects of commencing antidepressant treatment at this point are unknown. Thus, taken together, the effectiveness of current antidepressant therapy is seriously limited.

Similarly low response rates have been reported for antipsychotic drugs in treating schizophrenia, for example a meta-analysis by Leucht et al. (2009) found a response rate to second generation drugs of 41%. Even given three periods of treatment with antipsychotics from two or more different chemical classes, up to 20% fail to respond, for whom the treatment of choice is clozapine (Kane et al., 1988). However 30% of patients started on clozapine will not respond (Kerwin, 2005). Antipsychotic polypharmacy is often resorted to in such clozapine-resistant patients, a practice with little evidence base and increased risk of side-effects (Taylor, 2010a). These problems are compounded by the current impossibility of predicting which patients will respond to antipsychotic treatment. For patients who do respond full remission is unusual. Taking remission as the ultimate aim of treatment, the majority of schizophrenia cases are 'treatment-resistant'. Furthermore current antipsychotic drugs are ineffective in addressing negative symptoms (blunted affect, alogia, lack of motivation and social interaction) and cognitive impairment. This highlights the fact that schizophrenia is a syndrome made up of several symptom clusters, for which we lack symptom-specific drugs.

Retrospective studies clearly demonstrate a reverse relationship between length of untreated psychosis and degree of treatment success suggesting early recognition and treatment (Marshall et al., 2005). Beyond effectively treating schizophrenia, a more desirable goal would be to achieve prevention by starting treatment during the prodromal phase, seeking to prevent conversion to full psychosis. Early detection and treatment appears in the long term (15 years) to augment functioning, to increase recovery rates and to reduce the remaining deficits (ten Velden Hegelstad et al., 2012). However current antipsychotic drugs have not convincingly been shown to reduce conversion rates (McGlashan et al., 2006).

The urgent need for novel antidepressants and antipsychotics is widely recognised (e.g. Murrough and Charney, 2012). Although optimising currently used paradigms for drug development is one approach (e.g. triple reuptake inhibitors as antidepressants) only new mechanisms of action have the potential to overcome the actual barriers of effectiveness. In this vein preferentially glutamatergic substances are being explored for efficacy in affective as well as psychotic disorders. The driving forces of this innovative development have been model systems revealing the crucial role of the glutamatergic system.

6.4.2. What are the most important patient related outcomes?

Two components of treatment outcome are currently used: (a) symptom patterns and their severity, defining the global concepts of remission and recovery; (b) everyday functioning as well as participation in social activities and professional employment. Both aspects (a) and (b) are only partly correlated. Employment status is particularly relevant in the long term, whereas symptom remission is the main focus of RCTs designed for acute treatments. There is a growing trend towards including long term functional outcome in the assessment of treatments (e.g. NICE estimating benefit-risk ratios). Major international efforts are currently establishing new comprehensive tools to measure Personal and Social Performance and Skills (Figueira and Brissos, 2011).

Both aspects (a) and (b) can be measured either by observer as well as by patients themselves (self-assessment). Outcomes of treatment as judged by patients themselves have acquired increasing importance in psychiatry. The use of such measures rightly places patients at the centre of their care as consumers rather than passive subjects of mental health services. Moreover they capture aspects of mental wellbeing that may not be evident in objective assessment.

Recovery and quality of life have been identified as important patient related outcomes, beyond symptom remission. Improvements in such outcomes related to everyday functioning and wellbeing rated by patients may not correlate with psychiatric symptoms as rated by clinicians (Fleischhacker et al., 2005). Oorschot et al. (2012) found that symptom remission status was not related to functional recovery in schizophrenia. Yet the application of such concepts to assessing treatments for mental disorders is complicated by the lack of consistent definitions (Leucht and Lasser, 2006; Katschnig, 2006).

6.4.3. How can advances in understanding the functional circuitry supporting cognition, mentalizing, perception, behaviour and emotions inform the search for new therapeutic targets?

Alterations in such functional circuitry underlie mental disorders (Insel, 2010). Coupled with the symptom cluster approach described above, understanding these alterations will allow selection of more informative animal models based on their showing similar altered functional circuitry. This avoids the circularity of models based on response to agents of known efficacy, which are less likely to provide truly new therapeutic targets. Furthermore models based on functional circuitry have higher construct validity than those based on comparing rodent and human behaviour, which rely on face validity. Such face validity is sometimes questionable or impossible. For example while rodents certainly display social cognition, some aspects which are highly developed in humans such as theory of mind and language do not have sufficient correspondence to allow easy development of valid models.

Conversely other cognitive domains such as working memory and episodic memory are based on functional circuitry that appears to be relatively conserved between different mammals. Such circuitry includes loops between frontal lobe, basal ganglia and thalamus as well as hippocampal and other territories (Millan et al., 2012). Notably working and episodic memory are impaired in schizophrenia and may constitute endophenotypes marking increased risk of developing the disorder. Hence they are examples of cognitive domains where valid translational models are possible and important. Such models are instrumental to initiatives seeking to improve the search for new therapeutic targets, for example CNTRICS (Cognitive Neuroscience-Based

Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia) (Carter and Barch, 2007).

Anhedonia is another example of a psychiatric symptom that is core to mental disorders including schizophrenia and depression where advances in understanding functional circuitry will provide models with better construct and predictive validity. Traditional models relying on face validity involve anhedonia-like rodent behaviour such as reduced sweet solution preference. However findings correlating anhedonia with decreased nucleus accumbens (Nac) activation in response to reward, decreased Nac volume and decreased rostral anterior cingulate cortex resting activity point to underlying functional circuitry that can be assessed by such translational measures (Wacker et al., 2009). These measures can be used to assess models based on construct rather than face validity, similarly enhancing the search for new therapeutic targets.

6.4.4. What is the relationship to neurotransmitter based pharmacology?

Mental disorders emerge from altered functional brain circuits. Yet currently available drugs do not directly target functional circuitry per se. They are designed as ligands to neurotransmitter transporters and/or receptors involved in neuronal signalling, the functional basis of all circuit loops. However as a specific receptor or transporter for a specific neurotransmitter is likely to be involved in a very large number of brain circuits widely distributed in the brain those treatment approaches are insufficiently focussed. Furthermore multiple neurotransmitter systems modulate a specific circuitry. For example the circuitry underling working memory involves many different interacting neurotransmitters whose roles are increasingly understood. These include interaction between glutamate NMDA and dopamine D1 receptors in circuitry linking prefrontal and other cortical areas implicated in the maintenance of sensory information crucial for working memory (Castner and Williams, 2007). Knowing which receptors are involved implicates drug classes acting on those receptors, however the relationship between a receptor effect and efficacy may not be simple. In the case of D1 receptor function there is evidence of an 'inverted-U' response curve (Williams and Castner, 2006). Knowledge of such a relationship in a specific circuit suggests prototypes for pharmacological modulators of that circuit; it further allows the prediction that careful titration of a putative drug may be required to achieve therapeutic response.

In the case of anhedonia, the Nac and prefrontal cortex are linked by the mesocorticolimbic dopaminergic pathway. It is therefore rational to use antidepressants that enhance dopamine release to treat cases of depression where diminished pleasure is predominant. This is an example of the clinical relevance of combining a symptom cluster approach with understanding of the neurotransmitters involved in relevant functional circuitry, and forms part of the rationale behind delineating a subtype of depression dominated by reduced positive affect that is inadequately addressed by serotonergic antidepressants (Nutt et al., 2007).

The most recent advances in preclinical depression research involve the characterisation of multiple circuit-related symptom clusters using emergent techniques including optogenetics as well as functional imaging, neurophysiology and genomics (Berton et al., 2012). These promise the possibility of more valid models for drug discovery and novel therapeutic targets.

6.4.5. How can molecular genetic and epigenetic discoveries inform drug and biomarker development?

The high heritability of psychiatric disorders suggests that certain genetic variants convey increased risk. Such variants might be used as biomarkers to stratify patients. It is also evident that genetic variants have a bearing on pharmacokinetics, due to their effect on metabolising enzymes, as well as pharmacodynamics by affecting targeted receptor systems. Hence it is reasonable to expect that genetic biomarkers should predict treatment response. Moreover studying the functional significance of such variants should shed light on the pathophysiology of mental disorders and lead to new therapeutic targets. This line of development has already turned out to be very successful in monogenic mental disorders. For example Fragile X syndrome is caused by mutations in the FRM-1-gene on the X chromosome. This most commonly occurring X chromosome related mental retardation was until recently considered to be untreatable. The functional consequence of the underlying FRM-1 gene mutation is a reduced repression of metabotropic glutamate receptor expression during development resulting in mental retardation, autistic behaviour and somatic malformations. Based on these insights which emerged from 20 years of intensive research (particularly in animal model systems) a metabotropic glutamate-receptor-antagonist currently demonstrates cognitive enhancing effects in clinical trials in Fragile X boys (Hovelsø et al., 2012).

Genetic discoveries have the potential to inform the development of more valid animal models. These include mouse models carrying humanised mutations or engineered deletions or insertions. One example is the 22q11.2 deletion syndrome (which confers a 20% risk of schizophrenia) and the corresponding model of Df(16)A$^{+/-}$ mice. The Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS, 2013) project has made use of this model to understand the pathophysiology of schizophrenia. Genetic, anatomical and behavioural measures are taken in schizophrenic and non-schizophrenic individuals with 22q11.2 deletion as well as translational measures in the Df(16)A$^{+/-}$ mice. Preliminary results suggest that the animals have deficits in spatial memory and a loss of hippocampal-frontal synchrony. By administrating tests that are known to engage these regions in both mice and individuals with the deletion the human to mouse genetic translation is tested. Similarities will provide a framework for investigating the pathophysiology and symptoms induced by the manipulation. Where the symptoms are relevant to schizophrenia (or other neurodevelopment disorders), the animals and human carriers will provide the means to investigate the biology underlying these symptoms and search for new pharmacological targets.

Epigenetic factors including DNA methylation and histone modification influence psychiatric disease phenotypes. They are likely to be among the mechanisms by which early life adversity increases disease risk in adulthood and they offer novel drug targets and additional ways of validating models. For example Covington et al. (2009) found changes in

histone acetylation within the nucleus accumbens, in both depressed humans and mice exposed to chronic social defeat stress. They demonstrated that a histone deacetylase inhibitor exerted antidepressant effects and reversed the effects of social defeat stress on gene expression in the nucleus accumbens, pointing to the potential of such compounds as novel antidepressant agents.

6.4.6. Which measures of specific phenotypes and/or associated functions can serve as outcome measures or biomarkers?

Biomarkers may be used as measures of treatment response and outcome. Where a biomarker is correlated with a relevant clinical endpoint it may be used as a surrogate endpoint. A clinical endpoint measures how a patient feels, functions or survives and a surrogate endpoint is a biomarker that can substitute for this (Biomarkers Definition Working Group, 2001). Surrogate endpoints for psychiatric drug development will become more evident with increasing understanding of pathophysiology. Examples include functional brain imaging of relevant regions, such as prefrontal cortex and hippocampus in the case of cognitive impairment in schizophrenia.

6.4.7. What is the role of the environment?

Mental disorders represent the final common pathway of diverse pathophysiologies involving environmental as well as genetic contributions. For example schizophrenia is associated with environmental insults during late embryonic gestation. Knowledge of such environmental factors informs the development of valid animal models. These include the MAM E17 rat model of schizophrenia which involves the administration of the DNA-alkylating agent methylazoxymethanol acetate (MAM) on embryonic day 17, producing a pattern of neurodevelopmental and behavioural effects that bear similarity to some aspects of schizophrenia (Moore et al., 2006). However ascribing construct validity to such a model must be tempered by the knowledge that schizophrenia does not arise from a sudden transient inhibition of embryonic mitosis, such as that induced by MAM. A closer fit to the aetiology of schizophrenia might be provided by my a model that involves a genetic predisposition coupled with an environmental insult, such as the complexin2 knockout mouse in which schizophrenia-like behaviour manifests following a mild parietal lesion during puberty (Radyushkin et al., 2010). However neither of these models accurately mirrors the complex and subtle gene–environment interactions of schizophrenia, which remains a challenge for future model development.

6.4.8. What are the consequences for drug trials, industry–academia interaction and regulatory activities?

Pharmaceutical companies that formerly developed new treatments have cut resources devoted to neuroscience research. Reasons cited include the subjective nature of endpoints in psychiatry making it difficult to demonstrate efficacy even after large scale trials. In addition psychopharmaceutical development cycles are relatively costly and often fail at a late stage. This 'attrition' results in a situation where each psychiatric drug marketed must provide enough profit to recoup the losses incurred by ten other failed compounds, a situation many companies find unsupportable. The rational use of more valid animal models based on translational neuroscience will allow earlier 'go/no go' decisions to be made about candidate compounds leading to more economical and successful drug development. Industry-academia collaboration will be crucial as the variety of techniques and resources required is beyond the capabilities of any one organisation.

6.5. Gaps and needs

6.5.1. More valid animal models

These may be based on translated biomarkers of disease processes reverse translated from humans. Increased knowledge of the underlying biology of mental disorders will allow models based on endophenotypes and intermediate phenotypes, having greater construct validity than previous models based on superficial resemblance to human psychopathology (face validity). While rodent models have dominated drug development, there is need for a cross-species approach including non-mammalian models as appropriate for each unit of analysis. It would be desirable to have models that recapitulate gene–environment interactions and model disease development rather than approximating ultimate symptoms in affected humans in order to develop treatments effective for early intervention.

6.5.2. Predictive clinical biomarkers

There is a need for biomarkers that can be used to stratify patients based on risk, prognosis and predicted treatment response. These will be based on increased knowledge of the biology of mental disorders and may arise from forward translations of biomarkers from animal models.

6.5.3. Convergence of methods

Different translational tools are complementary and must be integrated across units of analysis to provide novel biomarkers, endophenotypes and intermediate phenotypes. Examples include relating altered functional connectivity as measured using fMRI with genetic findings to yield a systems view of genetic risk architecture. Within neuroimaging, efforts to integrate EEG/MEG (high temporal resolution) with fMRI (high spatial resolution) are expected to be increasing applied to psychiatric disorders. Another example is the development of a prototype MRI/PET scanner for human and rodent brains to acquire structural and molecular functional data simultaneously.

6.5.4. Collaboration between organisations

The convergent translational approach described here requires a range of expertise and capabilities that lies beyond any single commercial or academic organisation. It requires cooperation that is incompatible with the traditional closed and secretive approach to drug development. Thus there is a need for further public–private projects such as the European Innovative Medicines Initiative (IMI), as well as further cooperation between laboratories specialising in different methods.

6.5.5. New regulatory frameworks

The European Medicines Agency has constructed a qualification procedure for biomarkers in drug development. There

is a need to further extend clinical trial methodology to include, for example, the targeting of symptom clusters such as impulsivity in substance misuse and attention deficit hyperactivity disorder.

6.5.6. New genetic tools to shed light on the 'dark matter' of psychiatric genetics

The unaccounted heritability of psychiatric disorders likely includes rare copy number variations or point mutations, or single nucleotide polymorphisms in exons. Exome and whole genome sequencing techniques are predicted to lead to the discovery of further moderate and high risk mutations, increasing understanding of underlying neurobiology and providing novel drug targets.

6.5.7. The application of novel basic cellular and molecular techniques to drug target discovery and drug development

These include optogenetic methods which allow the measurement of activations in different neural cell types with high temporal resolution in transgenic animals carrying psychiatric risk genes, which may provide novel means for target validation. Another promising field is induced pluripotent stem (iPS) cell technology, potentially allowing the modelling of psychiatric disorders in cultured neurons.

7. Psychiatric somatic comorbidity

Comorbidity between psychiatric and somatic disorders is more a rule than an exception, and patients with severe mental disorders have a 2–3 fold excess mortality compared to the general population, half of this excess being caused by physical disorders. Comorbidity may be explained by many psycho-social and environmental factors, but can also be related to a common biological disease pathology or aetiology. In this paper we have described some major psychiatric disorders in relation to comorbid somatic disorders. We propose allostatic load as an overarching theory to explain causal relations for comorbidities, and that systematically related research questions should focus on epigenetic, inflammatory or neuroendocrine pathways as possible mediators of shared/joint aetiology. In addition, studies aiming at entangling the pharmacogenetics of efficacy and safety need to focus on comorbidity profiles in order to develop new insights into disease pathophysiology and to reduce the risk of pharmacogenically induced somatic diseases. We also point to negative comorbidity as an understudied, potentially valuable model, for investigating biological relations between psychiatric and somatic disorders. A greater understanding of the associations between clinical constellations of symptoms from both psychiatric and somatic disorders as they develop over time and relate to genetic, epigenetic, biochemical, cellular, neurophysiological, morphological or other biological markers is needed. From a biomedical perspective there is a need to establish a collaborative network of scientists to combine expertise in clinical, pharmacological, molecular and genetic methodology, and to set up a large clinical cohort that can be prospectively followed with a series of emerging biological markers as the clinical picture of psychiatric and somatic symptom manifestations develops over time.

7.1. Definition

The term 'comorbidity' was established in medicine by Feinstein (1970) to designate those cases in which a 'distinct additional clinical entity' occurred during the clinical course of a patient having an index disease. The concurrent presence of several pathological conditions in the form of comorbidity and multimorbidity is more a rule than an exception in all populations of patients. Comorbidity can be explained by many factors, such as modifiable lifestyle issues, side effects from medications, insufficient health care, but may also be related to a common disease pathogenesis or aetiology. The well described comorbidity of psychiatric disorders and somatic diseases may be used to identify existing gaps in our knowledge to define targets for future research.

7.2. State of the art

A recent review conducted as part of the World Psychiatric Association Action Plan 2008–2011 demonstrated a 2–3 fold excess mortality in patients with severe mental disorders, compared to the general population. They found that the mortality gap was mainly due to physical illness and, that this gap seems to have increased in recent decades, even in countries where the quality of the health care system is commonly recognised to be good (De Hert et al., 2011).

Several factors and theories are used to explain comorbidity of mental disorders and somatic diseases including shared predispositions (genetic, temperamental and personality traits), shared risk factors (stress, trauma, food intolerance, life styles, social support, negative emotions) or, shared mechanisms (coping, resilience or defence mechanisms, endocrine and immune disruption) (Jakovljević et al., 2010).

The anticipation is that a better understanding of psychiatric-somatic comorbidity in combination with increasingly advanced methods of neurobiological research will contribute to provide (1) descriptions of systemic clinical manifestations of psychiatric phenotypes, (2) sub- (or even) endophenotypes for genetic research based on co-occurring somatic and psychiatric symptoms, (3) a better understanding of the biological pathomechanisms of psychiatric disorders and somatic diseases, and (4) improved understanding of biological treatment mechanisms, including its potential for harmful side effects, and the detection of new targets for psychopharmacological treatment interventions.

7.3. Major advances

7.3.1. The somatic comorbidity of schizophrenia and bipolar disorder

It is commonly accepted that both schizophrenia and bipolar disorder have an increased risk of developing somatic diseases, and higher mortality rates in comparison with the general population (De Hert et al., 2011). A review including 15 original research articles on somatic comorbidity in patients suffering from psychotic disorders concluded that these patients run a substantial risk of developing diabetes mellitus, metabolic syndrome, hypertension, cardiovascular diseases, lung diseases such as COPD, hypothyroidism and visual problems (Oud and Meyboom-de Jong, 2009). A recent population-based cohort

study from Denmark investigating the impact of 19 severe chronic diseases on excess mortality due to diseases and medical conditions (natural death) in individuals with schizophrenia and bipolar disorder found that somatic diseases accounted for half of the excess mortality (Laursen et al., 2011). Furthermore, almost all somatic chronic disorders investigated in this study were more frequent in schizophrenia and bipolar disorder than in the general population. The only somatic disorder with a lower prevalence in psychotic patients was connective tissue disease, mainly rheumatoid arthritis (with symptoms of musculoskeletal pain). According to a recent study comparing the prevalence of somatic comorbidity in a clinical sample of patients with bipolar disorder and schizophrenia, somatic comorbidity appears to be more frequent in bipolar patients than in schizophrenia (67.1% vs. 50.6%). (Oreški et al., 2012). Whereas rheumatoid arthritis is less prevalent in schizophrenia compared to the general population this is not the case in bipolar disorder (Mors et al., 1999). Conversely, fibromyalgia is more prevalent in bipolar disorder but not in schizophrenia (Wilke et al., 2010). Interestingly, several studies have also found a significantly lower risk of respiratory and prostate cancer in people with schizophrenia (Tabarés-Seisdedos et al., 2009). Some studies indicate cardiovascular disease is "truly" more prevalent in bipolar disorder, whereas it in schizophrenia most likely is secondary to atypical antipsychotic medications and smoking (Osby et al., 2001). There is however also emerging evidence of a shared genetic basis for schizophrenia and at least some cardiovascular disease risk factors (Andreassen et al., 2013).

7.3.2. Physical health in patients with depressive disorders

There is evidence that patients with affective disorders suffer from greater physical morbidity and mortality than the general population (Vieta and Colom, 2011). Mortality rate is approximately twice that of the general population with suicide mortality being up to 20 times higher (Osby et al., 2001). The relationship between affective disorders and physical illness is reciprocal: many chronic illnesses cause higher rates of depression and affective symptoms have been shown to forerun many chronic diseases and worsen their outcomes (Kupfer et al., 2012). People suffering from chronic illnesses are almost three times more likely to be depressed (Egede, 2007), and having two or more chronic illnesses increases the risk of being depressed to up to seven times that of healthy subjects (3.2% vs 23%) (Moussavi et al., 2007). Moreover, depression is associated with a decrement in health significantly higher than those associated with other chronic diseases (Moussavi et al., 2007). This includes increasing illness-related morbidity and mortality and decrement in functional outcomes, such as disability and decline in health-related quality of life (Kupfer et al., 2012).

Depression can also precede physical disease and act as a risk factor. It has been shown to act as a predictor to coronary heart disease (Kendler et al., 2009), stroke (Everson et al., 1998), obesity and metabolic syndrome (Luppino et al., 2010), diabetes (Campayo et al., 2010a, 2010b) colorectal cancer, back pain, irritable bowel syndrome, multiple sclerosis and infant stunting and death if depression occurs during pregnancy (Goldberg, 2010).

The association between affective disorders and a higher prevalence of physical morbidity and mortality can be partially explained by considering health behaviours (e.g. smoking, physical inactivity, poor diet), psychosocial functioning and chronic medication exposure (Leboyer et al., 2012). However, this association remains significant after controlling for these confounding factors, which suggests additional and specific mechanisms (Leboyer et al., 2012) (Krishnadas and Cavanagh, 2012).

7.3.3. Anxiety disorders and physical illness

Comorbidity between anxiety disorders and physical illness is a limited but expanding area of the scientific literature. Several studies relying on clinical or epidemiologic samples have shown higher rates of medical illnesses among patients with anxiety disorders compared to controls (Rogers et al., 1994). Clinical and community studies have also reported an association of physical illness with anxiety disorders as strong as or stronger than that with mood disorders (McWilliams et al., 2004).

Studies examining associations with specific illnesses, such as thyroid disease, cancer, diabetes, cardiac disease, gastrointestinal disease, respiratory disease, and chronic pain, have found levels of anxiety disorders among patients seeking treatment for medical conditions to be higher than expected compared to the general population (Härter et al., 2003).

Data on comorbidity according to specific subtypes of anxiety and medical illness reveal that the association is greater for panic disorder and generalised anxiety states than for phobias. Patients with panic disorder are more likely to have specific comorbid medical disorders such as angina, mitral valve prolapse, idiopathic cardiomyopathy, labile hypertension, respiratory illnesses, migraine headaches, peptic ulcer disease, diabetes mellitus, or thyroid disease (Rogers et al., 1994). With the publication of DSM-IV, individuals could receive a diagnosis of PTSD as a direct result of being traumatised by the experience of a life-threatening illness. This development has contributed to an interest in the association between PTSD and physical illness. Among DSM-IV anxiety disorders, PTSD had the greatest number of significant associations with chronic physical disorders, including neurological, cardiovascular, gastrointestinal, metabolic/autoimmune, and bone or joint conditions (Sareen et al., 2005).

7.3.4. Alcohol use disorders and comorbid somatic disorders

Clinical experience supports the evidence that somatic disorders are frequent in subjects with alcohol use disorders. An important proportion of cases of cancer can be attributed to alcohol consumption and in a recent study from Western Europe one in 10 of all cancers in men and one in 33 in women were caused by past or current alcohol intake (Schütze et al., 2011). Depending on the sample investigated, the rates of somatic disorders as a consequence of chronic and pathological alcohol use vary. Further, since alcohol is widely distributed in the human body, several tissues and organ systems can be affected by the toxicity of alcohol. Most frequently investigated are alcohol-associated liver and pancreatic diseases, followed by malignant tumours and disorders of the central and peripheral nervous system.

Earlier epidemiological data of more than 10,000 inpatients from the U.S. demonstrated that more than 70% of the alcohol-dependent men and 73% of the women had a

significant comorbid medical problem (Mendelson et al., 1986). The most prevalent disorders among them were diseases of the liver, gallbladder and pancreas; bronchitis; emphysema; and asthma. Hypertensive disease was found in 15% of the men and 7% of the women.

Significant comorbidity was also detected in European samples. In alcohol-dependent subjects in inpatient detoxification treatment, a Polish study reported a rate of almost 44% of alcohol-related liver disease (Kroch et al., 2004). 5.2% of the patients had pancreatitis and suffered from hepatitis B. Approximately 1/3 of the sample had diabetes and cardiovascular diseases. 55 patients (12.4%) had a history of severe head trauma, and 51 (11.3%) were treated for "multiorgan trauma". In addition, comorbidity with other mental disorders was high. 102 patients (23%) reported affective disorders, and in 92 (20.7%) personality disorders were diagnosed.

7.3.5. Medication related somatic disorders

Psychotropic drugs have proven to compare favourably with medications used in other fields of medicine with regards to effective clinical disease control (Leucht et al., 2012). However, the optimal use of the psychotropics is often hampered by adverse effects, some of which can develop into treatment-emergent comorbid medical conditions. As opposed to psychopharmacology-associated acute medical reactions such as sudden cardiac death or malignant neuroleptic syndrome that are dramatic but rare, there are several delayed or chronic somatic disorders that are rather frequent. Examples include lithium-induced thyroid dysfunctions (Lazarus, 2009); valproate-associated hormonal dysregulations and the polycystic ovary syndrome (Hu et al., 2011); antipsychotic-induced weight gain and adverse metabolic influences (De Hert et al., 2009), hyperprolactinemia (Cookson et al., 2012) and movement disorders (Dayalu and Chou, 2008). The different somatic disorders are generally not restricted to one particular group of psychotropics. For example mood-stabilizers, antidepressants and antipsychotics all share propensities for inducing weight gain. This point is important as the concomitant use of several drugs is common in clinical practice, which increases the risk of additive or even potentiated adverse somatic effects (Fleischhacker and Uchida, 2012).

Metabolic drug effects have received particular attention in recent years as patients with severe mental disorders have a high degree of glucose and lipid regulation disturbances (Fleischhacker et al., 2008) believed to contribute significantly to a reduced life-expectancy of about 25 years compared to the general population (Tiihonen et al., 2009), and cardiovascular diseases account for the majority of these premature deaths (De Hert et al., 2009). Psychotropics, and antipsychotics in particular, are prone to adversely influence several of the components of metabolic health although the mechanisms are only fragmentarily known. Differential propensities among antipsychotic drugs for inducing weight gain and other metabolic disturbances have been found in recent meta-analyses of clinical trials (Rummel-Kluge et al., 2010), with clozapine and olanzapine being the most prominent offenders.

Although movement disorders have become much less of a clinical problem since the introduction of new generation antipsychotics, a certain risk of acute and tardive motor adverse effects remains. Of these, tardive dyskinesia is by far the most worrisome, as in contrast to acute dystonia, parkinsonism or akathisia, an appreciable percentage of tardive dyskinesia does not respond to treatment and may turn into a chronic comorbidity (Dayalu and Chou, 2008).

Most of the adverse events exemplified above are relatively easy to either prevent or manage. A pre-requisite to reduce the risk of psychotropic induced comorbidity therefore lies in the awareness of such side effects and the regular monitoring of a respective drug's safety and tolerability.

7.3.6. Conclusion

In summary, many physical disorders have been identified that are associated with severe mental health disorders and alcohol abuse, and medical disorders account for more than half of the excess mortality found in these patients. The increased somatic comorbidity is due to many factors such as side-effects of pharmacological treatment, unhealthy diet, and high levels of cigarette smoking, as well as inadequate medical treatment or provision of health care. However, a better understanding of comorbidity and multimorbidity also carries the potential of developing new insights into the biological underpinnings of both psychiatric disorders and somatic diseases, and improving the treatment in these patients.

7.4. Questions and problems to be solved

7.4.1. Allostatic load in relation to comorbidity

There is an overarching need to better understand the causal relation between comorbid diseases. Allostatic load refers to the "cost of chronic exposure to fluctuating or heightened neural or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to as being particularly stressful" (McEwen and Stellar, 1993). Allostatic load is highly relevant in comorbidity studies as it is associated with oxidative and nitrosative stress, mitochondrial dysfunction, inflammation and lowering of neuroprotective factors, which relate to impaired immunity, atherosclerosis, apoptosis and atrophy of nerve cells in the brain. We propose allostatic load as an overarching theory of shared/joint aetiology and a model to explain causal relations between comorbidities. The conduits for allostatic load may be epigenetic, inflammatory or neuroendocrine, and the different pathways mediating this relation should be targets for a large number of systematically related research questions

7.4.2. Epigenetics of multimorbidity and comorbidity

Several common somatic and psychiatric diseases may be caused by epigenetic dysregulation, and this has been emphasised for schizophrenia, bipolar disorder, depression, post-traumatic stress disorder, diabetes, cancer, coronary heart disease, etc., and epigenetic influences from present or previous life events or exposures may be responsible for the vast variation in the presentation and clinical outcome of disease and disease comorbidity. Future studies on epigenetic changes open new opportunities in understanding the pathophysiology of the comorbidity between mental and somatic disorders.

7.4.3. Inflammation as a frequent mechanism in disease comorbidity

Inflammation seems to be an omnipresent pathomechanism in many diseases including cardiovascular disease, diabetes, cancer, bipolar disorder and schizophrenia, and over the last decades, there has been increasing evidence that inflammation may be implicated in the pathophysiology of affective disorders, sharing common pathways with physical illness. Studies of epigenetic regulation of the inflammatory response systems may reveal a molecular basis for the frequently occurring phenomenon of comorbidity and multimorbidity.

7.4.4. Stress and the HPA axis and comorbidity

The HPA axis is involved in the neurobiology of mood disorders and functional illnesses, including anxiety disorder, bipolar disorder, insomnia, post-traumatic stress disorder, borderline personality disorder, ADHD, major depressive disorder, burnout, chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and alcoholism. The HPA axis can be activated both through social as well as physical stressors, and the different pathways involve the monoamines dopamine, noradrenaline and serotonin, and could explain how mental and physical disorders interact in a comorbid manner.

7.4.5. Pharmacogenetics and comorbidity

Large inter-individual differences exist with respect to safety of psychotropics. The major inter-individual variability in susceptibility to adverse effects points to genetic mediators and modifiers of a drug's effects. Pharmacogenetic approaches have thus far not provided a breakthrough of relevance to clinical psychopharmacology although promising results have been reported. Studies aiming at entangling the pharmacogenetics of the adverse drug effects, as well as the complex gene–environment interactions are needed using the steadily evolving new techniques, thus providing a basis for personalised medicine with individually tailored drug regimens based on personal comorbidity profiles.

7.4.6. Negative comorbidity

In contrast to co-occurrence, few population based studies have explored in detail the “negative” or “inverse” comorbidity in psychiatric and somatic disorders (Tabarés-Seisdedos et al., 2009). It is interesting that two population based studies and a metaanalysis of cancer incidence rates found a significantly lower risk of respiratory and prostate cancer in people with schizophrenia after adjusting for confounding variables, as this is the opposite of what would be expected from what is known about general risk factors in these patients. Furthermore, it is intriguing that a reduced occurrence of rheumatoid arthritis has been found in patients with schizophrenia. Negative comorbidity may be a valuable model for investigating common or related pathways in the effort of understanding the biological relations between psychiatric and somatic disorders.

7.5. Gaps

Despite existing knowledge about the high frequency and severe consequences of somatic comorbidity in patients with mental disorders, the mortality gap between psychiatric patients and the population seems to be increasing. Although it is well known that many psychosocial factors like lack of social support, negative lifestyle habits, inadequate health care and awareness, the potential biological mechanisms (including psychopharmacologically induced somatic disorders) underpinnings of those comorbidities are far from well understood. A greater understanding of the associations between clinical constellations of symptoms of both psychiatric and somatic disorders as they develop over time and relate to genetic, epigenetic, biochemical, cellular, neurophysiological, morphological or other biological markers is needed. At present, much of the existing information stems from cross-sectional studies, epidemiological studies with inaccurate clinical diagnosis or from clinical studies of patient cohorts afflicted by Berkson's bias or with insufficient clinical or biological information.

7.6. Needs

There is an immediate need to establish new research that can contribute to diminishing the mortality gap and negative health impact, caused by physical disease in patients with mental health disorders. From a biomedical perspective there is need to establish a collaborative network of scientists to combine expertise in clinical, pharmacological, molecular and genetic methodology, and to set up a large clinical cohort that can be prospectively followed with a series of emerging biological markers as the clinical picture of psychiatric and somatic symptom manifestations develops over time, in order to determine the biological underpinning of the important phenomenon of psychiatric-somatic comorbidity.

8. Consensus discussion

In the preceding statements the experts identified more than 50 gaps and advances needed, which are of significant effectiveness, impact and feasibility to add to European research strength. However, in order to appropriately rank the suggestions from various research domains, relevant overarching criteria, which are intrinsic to mental health research, and in particular biomedical research, are essential. Among the members and experts of the Workpackage on Biomedical Research (WP4) of ROAMER the overarching criterion was identified as being the effort to strive to reduce illness and improve mental health, reduce suffering and increase well being, and decrease the economical burden of mental disorders.

The expert recommendations proposed by this workpackage will now be considered and ranked by members of the ROAMER consortium, by the scientific community as well as by stakeholder groups. Their likely costs and chances of impact on mental health burdens and the European agenda of competitiveness, growth and jobs will be assessed. The final recommendations made by ROAMER will balance the priority levels of each of the potential gaps in research identified across all work packages. Thus the

recommendations made in this article do not represent official ROAMER consortium statements but contribute to its comprehensive and participatory approach.

While it is necessary to identify gaps and advances, which characterise (1) areas of discovery, it is equally important to establish (2) the structural (and infrastructural) gaps and advances needed to achieve the discovery goals.

(1) To determine the areas most relevant for discovery, assessment of psychopathological burden across the lifespan, as well as in various environmental conditions is a useful indicator. Here it is important to note that the main psychopathological burden across the lifespan occurs in transitional periods, namely during transition from childhood to adulthood. In fact, half of the lifetime psychopathological burden can be detected by the mid-teens and 75% by the mid-20s (Kessler et al., 2007). Therefore, biomedical research focussing on transitional periods should have high priority. In addition, most mental disorders are the result of an interaction of individual biology and environmental factors. Identification and characterisation of environmental factors conferring risk and resilience for mental disorders and their interaction/correlation with biological mechanisms is thus also of high priority.
While it is crucial to take into consideration the amount of psychopathological burden to prioritise gaps and advances needed it is of equal importance to identify areas where scientific progress is most likely to occur in the future. In recent years there has been a tremendous advance in basic neuroscience, which took advantage of new technologies, as well as emerging disciplines, such as systems biology. This progress has allowed the identification of brain mechanisms, including an increasingly evolved characterisation of individual differences. However, these advances did not yet induce a comparable progress in diagnosis and treatment of mental disorders. Thus a "translational gap" has emerged which calls for the application of scientific and methodical advances in basic neurosciences to better understand human diversity and develop diagnostics and interventions that target specific pathological processes across mental disorders. Research aiming at decreasing this "translational gap" should be prioritised.

(2) The structural and infrastructural advances needed to achieve the discovery goals on a European scale include the creation of sustained transnational collaborative structures and infrastructures which take into account the competitive advantages of different European regions, collaboration with existing institutions, European research infrastructure projects, national cohorts etc., as well as capacity building across Europe. The scope of the effort to establish structural and infrastructural advances is considerable and includes the establishment of dedicated centres for data acquisition and data analysis, as well as research networks.
Together dedicated centres and networks may contribute to developing and support a sustained research infrastructure to maximally benefit from Europe's unique universal access to healthcare and its cultural diversity, which allows differentiated analysis of environmental and cultural influences. This infrastructure should lead to the creation of a "European Institute of Mental Health" as a counterpart to the American National Institute of Mental Health, which in addition to reducing the personal and public burden of mental disorders, might be an important partner for pharmaceutical industry and strengthen European competiveness and advantage of location.

The proposed research infrastructure should be adapted to the regional strengths and needs in the different countries of the European Community thus benefiting from the competitive advantages of different regions. While the integration of research groups from the new member states into European research structures is in progress, their research potential has not been fully understood and properly utilised. Whereas there is an educated workforce and a strong tradition of psychiatric and neuroscience research in most Eastern European countries, there remains stigma associated with psychiatric disorders resulting in disinvestment and regulatory instability in some regions. This is further complicated by brain drain into Western European or non-European countries and – with notable exceptions – limited access to European funds. A successful integrative strategy will respond to regional needs, for example by creating and/or improving a basic clinical research infrastructure and providing measures to counteract brain drain in these regions. Conversely, highly developed regions within the European Community might have access to worldwide leading academic centres and facilities. Here providing for sustained collaborative ties and targeted research programmes may improve synergy and further increase competitiveness. Despite regional differences, the united Europe should be considered as a "single space" competing at a global level. Development of a regionally adapted research infrastructure, including investment in electronic communication and research technologies will contribute to preserving Europe's competitiveness at "big science projects", for example in genetics, epidemiology and non-industry funded clinical trials. Furthermore, certain overarching public health issues in Europe (e.g., alcohol and substance abuse, cognitive and psychiatric effects of aging) require the old and the new member states to reach out to one another. Therefore, clear incentives are needed to promote and strengthen processes and structures to break down traditional European barriers, and encourage collaborative research in order to capture local expertise in the most efficient way.

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Conflict of interest statement

E Binder is co-inventor on the following patents and patent applications: (1) means and methods for diagnosing predisposition for treatment emergent suicidal ideation (TESI). European application no.: 08016477.5 International application number: PCT/EP2009/061575. (2) FKBP5: a novel target for antidepressant therapy. International publication number: WO 2005/054500 and (3) polymorphisms in ABCB1 associated with a lack of clinical response to medicaments. International application no.: PCT/EP2005/005194. Dr. Binder has received grant support from PharmaNeuroBoost.

E Johnsen has received lecture honoraria from Bristol-Myers Squibb, Eli Lilly, and AstraZeneca. He has also been reimbursed by Eli Lilly and Janssen-Cilag for attending conferences.

E Ron de Kloet is a scientific advisor (and stock owner) to Corcept Therapeutics Inc, Pharmaseed Ltd & Dynacorts Therapeutics, and recipient of a grant of Top-Institute Pharma with Lundbeck T5-209.

K Mann is a part of the international advisory board and receives honoraria from Lundbeck and is a paid member of the German advisory board for Pfizer.

CP Müller has received honoraria from Lundbeck.

D Nutt is a consultant to Lundbeck , Servier, GSK, Reckitt Benkiser, Shire, Novartis and has grants from Lundbeck, GSK and Gilead. He also receives lecture honoraria from Lundbeck, GSK, Pfizer, BMS, Otsuka, D&A Pharmaceuticals and Eli Lilly.

JK Rybakowski has acted as a consultant or speaker for Adamed-Poland, AstraZeneca, Bristol-MyersSquibb, Eli Lilly, Janssen-Cilag, Lundbeck, Sanofi-Aventis and Servier.

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