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Neurobiological research in psychiatry—classification of dimensions of learning mechanisms instead of reification of categories?

The current revisions of the international classification systems—the Diagnostic and Statistical Manuals (DSM) of the American Psychiatric Association and the Classification of Diseases (ICD) of the WHO—bring an important dilemma of psychiatric imaging research into focus: is it really plausible that there is a reliable neurobiological correlate for each of the 300 described disorders?

While it seems rational that severe (major) depression can be distinguished from mild (minor) depression on the basis of the degree of neurobiological changes, is it really plausible to assume that long-term dysthymia, depressive adjustment disorder, or depressive symptoms in the course of an addictive disorder have a specific and reliably definable neurobiological correlate? At present, an almost unmanageable number of neuroimaging studies with different single findings, showing differences in brain responses in patients with or without medications compared to healthy controls, have been published in the field of psychiatry. On the other hand, little or no efforts have been made to systematically compare these results beyond the borders of specific disorders. Attempts to do so are mostly discouraging—dysfunctions in working memory are not only found in patients with schizophrenic psychoses, but also in numerous affective and addictive disorders (e.g. [5, 11, 22, 33, 35]). Even within one category of disease, evidence of neurobiological correlates is heterogeneous: high intra- and inter-individual variability within neuronal activation patterns even in highly standardized experiments (e.g. presentation of alcohol-associated versus neutral pictures, which are matched for valence and arousal) lead to similar results, but not at all to identical findings that could be used diagnostically. Thus, in one study, activation maxima evoked by the processing of addiction-specific versus neutral stimuli were found in the central striatum and dorsal parts of the medial prefrontal cortex, while in other studies such stimuli elicited activation in the anterior cingulate cortex and more ventral parts of the medial prefrontal cortex, as well as in the ventral rather than the central or dorsal striatum [4, 14, 46]. Such results are useful to delineate a general pattern of neuronal activation and connectivity for one disorder, which can be validated by animal models; for example, in addiction, there seem to be characteristic abnormalities in fronto-striatal circuits associated with behavioral control. Moreover, these studies are of clinical relevance, since they can help to identify individuals who have an especially high risk for relapse and therefore would benefit from specific therapeutic approaches [4, 14]. However, due to large variability as well as a high overlap with healthy controls, such evidence is not suitable for the validation of disorder categories.

A similar picture arises in the field of genetic research and so-called imaging genetics. On the one hand, the number of non-replicable results is similarly high, while on the other, different candidate genes identified with respect to a specific disorder increase the risk for multiple, clinically differently categorized disorders, such as schizophrenia and bipolar psychosis, as well as unipolar depression [7, 38]. An approach to solve this problem is the investigation of so-called endophenotypes, i.e., neurobiological mechanisms that can be linked to the gene effect more closely than observable behavior. It was for example shown that the genetic constitution of the promoter region of the serotonin transporter (5-HTTPR) significantly influences the function and density of the transporter in vitro [32] and likewise affects serotonin transporter availability in the brainstem in vivo [19, 37, 40]. It was also shown that the genetic constitution of the serotonin transporter modulates amygdala response during the presentation of aversive versus neutral pictures [15, 24]. Thus, it was assumed that genetic variation within the promoter region of the serotonin transporter directly affects serotonin transporter availability in vivo, which then influences the activation of central nervous structures during the processing of threatening stimuli (e.g., the amygdala) and thus (weakly) modifies levels of subjective anxiety: while 0%–3% of anxious behavior in humans can be explained by the described serotonin transporter polymorphism [32], 5%–20% of functional amygdala activation in healthy subjects is modulated by serotonin transporter genotype [16, 45], whereas function and availability of serotonin transporters varies two-fold as a function of this polymorphism (◘ **Fig. 1**). However, other studies observed that further genetic variations within the region of the serotonin transporter polymorphism, as well as within other neurotransmitter systems (such as the dopaminergic system), interact with the effect of the described genetic variation of the promoter region of the serotonin transporter [45]. In addition, activation of a limbic brain area such as the amygdala—which is clearly relevant for the processing of aversive stimuli—does not explain the degree of anxiety of a human individual per se, but only in functional interaction with brain regions like the anterior cingulate and medial prefrontal cortex, which account for emotion regulation [24, 28]. Thus, conscious control and reduction of emotional responsiveness can compensate genetic differences in amygdala responsiveness, which thus contribute to the high intra-individual variability of results [41].

Finally, it has been shown that environmental factors like nicotine consumption interfere with the influence of the genetic constitution of the serotonin transporter promoter region on in vivo transporter availability in the brainstem [30]. In addition, as described above, serotonin transporter availability per se has only a moderate influence on amygdala response during the presentation of aversive versus neutral pictures (◘ **Fig. 1**). Independent of the actual serotonin transporter availability in the brainstem, the genetic constitution of the transporter affects amygdala responsiveness via a second modality: it influences the size or the volume of the amygdala, most likely by affecting the central nervous system during ontogenesis [30].

These interactions are described in detail here to illustrate that the hope of closing the gap between the complexity of human behavior on the one hand and genetic effects on the central nervous system on the other by using imaging techniques appears to have reached its limits, since functional activation patterns and alterations within neurotransmitter transporters or receptors are influenced by a multitude of factors such as smoking, as well as by interactions with other neurotransmitter systems and functional interactions between different brain areas. In this context, the application of innovative mathematical approaches such as support vector machines could help to analyze these complex interactions of geno- and phenotypes. However, the simple addition of more and more variables with genetic and phenotypic information is not an adequate solution and equals the attempt to increase explained variance within a multiple regression analysis by taking more and more independent factors into account. To decide whether such an approach indeed elucidates interactions, or rather leads to individually very precise but poorly reproducible solutions, application of information criteria like the Bayesian information criterion (BIC) or the Akaike information criterion (AIC) can be useful. Initial investigations using this approach showed that haplotype analyses or the introduction of complex genetic interactions to explain brain volume or functional activation patterns might be inferior to simple associations of single genetic polymorphisms with these phenotypic variables ([39], ◘ **Fig. 2**).

These considerations show that the complexity of human behavior, which is diagnostically categorized within a multitude of behavioral patterns and disorders, cannot be reduced to reliably observable correlates using current neurobiological methods. So what approaches could be relevant for future research?

Dimensional instead of categorical approaches in psychiatry and psychotherapy

The conceptualization of the recent DSM 5, the new classification of disorders of the American Psychiatric Association, will explicitly integrate dimensional approaches in the classification of diseases. Early stages of schizophrenic psychoses, for example, are assumed to resemble the manifest disorder and therefore be reliably identifiable. Thus, such an early stage could be diagnosed and form a separate disorder entity. Moreover, it is assumed that certain personality traits or "abnormalities," which are common among relatives of individuals with schizophrenic psychoses, are disorders associated with schizophrenic psychosis. Thus, in the clas-

Abstract

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Abstract

Neuroscientific research in mental disorders is plagued by unclear nosological boundaries, phenotypic diversity, and high intra- and interindividual variability of identified neurobiological correlates. Likewise, genotypes associated with an increased risk for, e.g., schizophrenia are regularly found to also increase the risk for uni- and/or bipolar affective disorders. Therefore, one major research strategy of the last decade was to avoid correlation of genetic variation with complex clinical disorders and instead to focus on so-called intermediate or endophenotypes, i.e., neurobiological variables such as in vivo receptor expression or neuronal activation patterns, which are hypothetically more closely related to direct gene effects. We describe one such attempt and show that intermediate phenotypes such as brain activation patterns elicited by more or less complex cognitive tasks underlie complex regulations and influences and may thus not be the best target for neurobiological research. We suggest that instead of reifying brain activation as correlates of mental disorders, such disorders may best be conceptualized as results of alterations/biases in basic learning mechanisms (e.g., Pavlovian and operant conditioning) interacting with individual and social environments and that neuroscientific research can rely on animal models and computationalized modeling to reveal their neurobiological correlates.

Keywords

Research strategy · Mental disorders · Learning mechanisms · Conditioning · Computational modeling

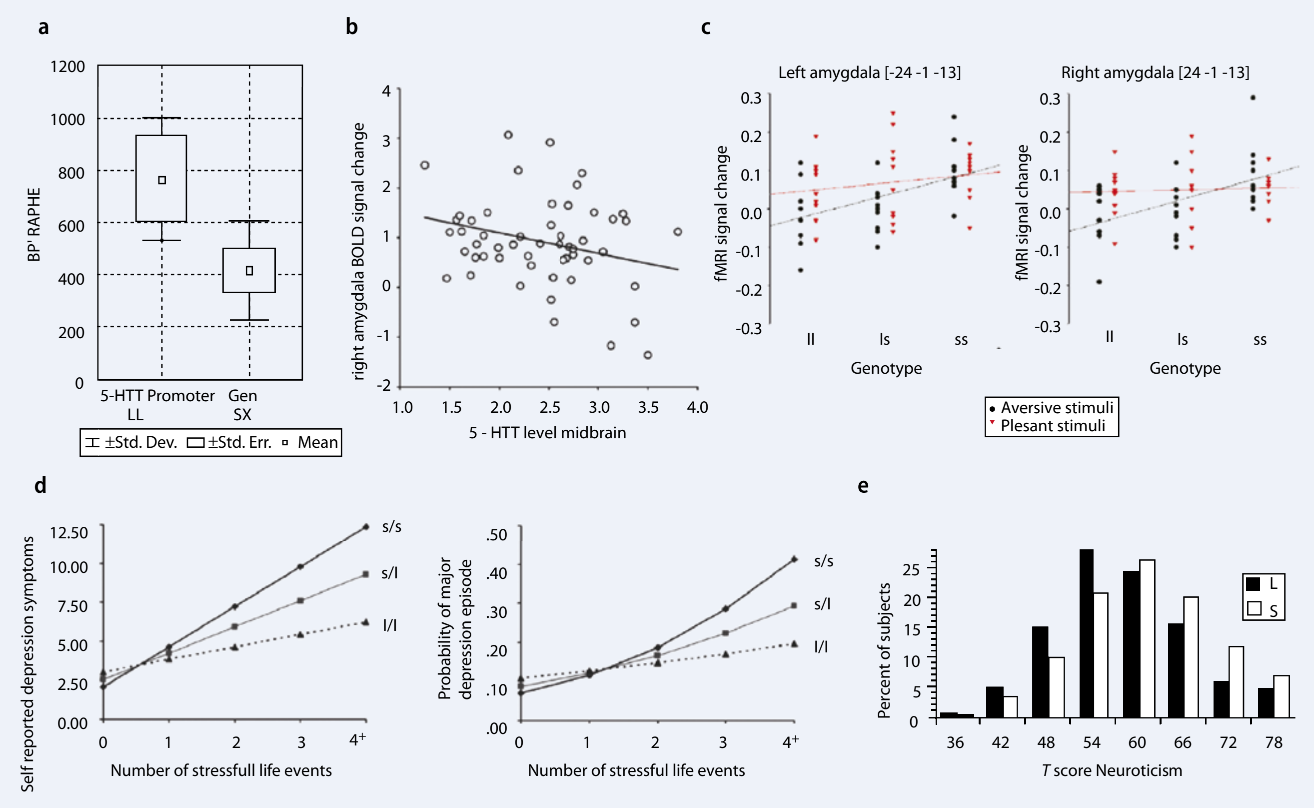

Fig. 1 ▲ Effect of a functional genetic polymorphism [here within the regulatory region of the serotonin transporter gene (5-HTTLPR)] with respect to its influence on a direct biological and behavioral correlate: serotonin transporter availability in brain stem (**a**) [19] versus anxiety (**e**) [32]. The effect of 5-HTTLPR on mood states is partly mediated by the interaction between the serotonin transporter availability and activation of the amygdala during the presentation of aversive versus neutral stimuli (**b**) [30]: the 5-HTTLPR has a moderate yet still statistically significant influence on the amygdala response during the presentation of aversive versus neutral, but not positive versus neutral stimuli (left and right amygdala; *circle* = aversive vs. neutral; *triangle* = positive vs. neutral) (**c**) [24]. While 5-HTTLPR still has a weak but verifiable influence on the occurrence of depression following stressful life events (**d**) [6], its relation to anxiety is rather weak (**e**) and often not even significant [13]

sification system, these disorders will be separated from the domain of personality disorders and positioned directly next to schizophrenic psychoses. These approaches, however, bring with them the difficulty that unreliably diagnosable personality disorders—which are ultimately variations of human existence without cross-cultural valid diagnostics criteria—will be reified as mild forms of schizophrenic psychoses. One example is the diagnosis of schizotypical personality disorder, a disorder with classification criteria like an unusual (e.g., vague or cumbersome) way of thinking and speaking, as well as a mistrust or lack of close friends. In contrast, the cardinal symptoms of schizophrenic psychoses are self-reported, relatively reliable, and distinctly classifiable symptoms such as the belief that one's own thoughts are controlled or inserted from the outside or that voices (in the sense of acoustic hallucinations) are commenting on one's own behavior. The cardinal symptoms of personality disorders, on the other hand, are rather ubiquitous phenomena, the appraisal of which as a mental disorder clearly underlies cultural influences. For example, how much social reclusiveness is expected within one culture and what degree of eccentricity is deemed conspicuous?

Altogether, a simple dimensional lineup of mild versus severe disorders or impairments may not help to identify biological correlates of mental disorders due to the vague boundaries of some syndromes. Therefore, the question arises as to whether biological correlates of psychiatric disorders should be interpreted in a completely different way, namely as relatively basic alterations in learning mechanisms, which only in interaction with personality and environmental factors lead to complex forms or patterns of impairments. The marked advantage of this approach, which focuses on learning dysfunctions and its neurobiological correlates, is the opportunity to directly measure the influence of neurochemical and neurobiological factors on neurotransmitter systems involved in learning processes. In addition, such an approach would explicitly take the impact of social and autobiographical influences on human development into account without attempting to reify each individual pattern of suffering and impairment on a neurobiological level.

Dysfunctions in negative and positive reinforcement learning: neurobiological correlates and clinical relevance

The most sophisticated attempt at present to explain mental disorders as manifestations of clearly definable alterations in reward- and punishment-associated learn-

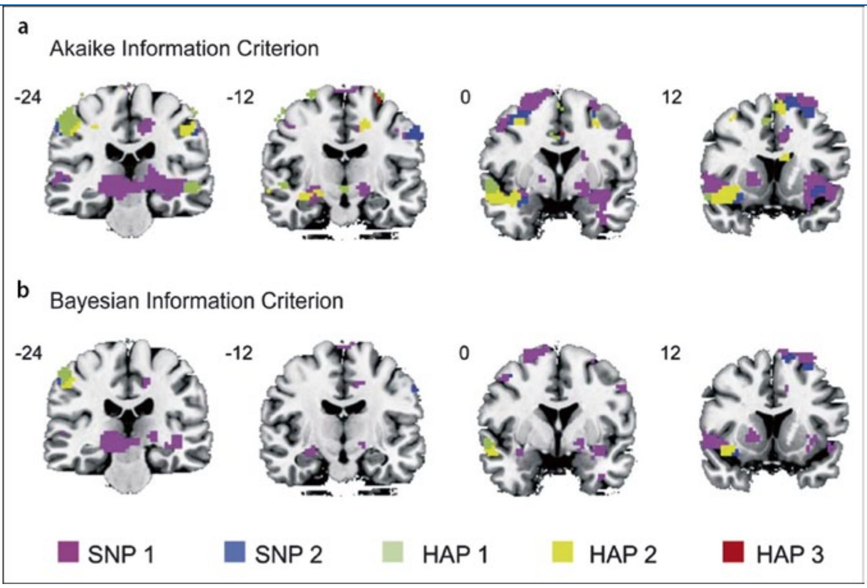

Fig. 2 ▲ Brain regions in which the processing of emotionally aversive pictures is associated with the genetic constitution of the COMT. Puls et al. [39] compared the influence of individual single nucleotide polymorphisms (SNPs) with haplotypes regarding the influence of variation in the catechol-O-methyltransferase (COMT) gene on neuronal processing of affectively negative vs. neutral stimuli using information criteria (Akaike information criterion and Bayesian information criterion). Similar to multiple regression analyses, introducing more independent variables (i.e., more SNPs or haplotype constructs) resulted in a slight increase in explained variance (in the figure: more voxels, whose activation is explained by genetic information); however, solutions become overfitted and thus may lack replicability. The single SNP (SNP 1) was identified by both information criteria to best explain variance within imaging data

ing is occurring in the field of addictive disorders. It is well-known that all drugs of abuse elicit dopamine release and that this dopaminergic neurotransmission is associated with increased drug-seeking and consumption [4, 9, 21]. Further studies showed that chronic drug intake leads to neuroadaptive changes in dopaminergic neurotransmission, e.g., a down-regulation of striatal dopamine-D2 receptors, which is clinically associated with the risk to relapse and neurobiologically related to a modified reagibility towards alcohol-associated versus other reward-indicating stimuli. Imaging studies, for example, showed that the degree of down-regulation of dopamine-D2 receptors in the ventral striatum in alcohol-dependent patients was directly correlated with an increased neuronal response in the medial prefrontal and anterior cingulate cortex during the presentation of alcohol-associated pictures [23]. Such an increased responsiveness of the medial prefrontal cortex during the processing of alcohol-associated cues as well as a reduced sensitivity of dopamine-D2 receptors are predictive for relapse [4, 14, 17]. Dopaminergic dysfunction thus contributes to increased processing of addiction-specific (here: alcohol-related) stimuli. Moreover, it induces diminished activation during the processing of non drug-associated yet reward-indicating cues in the ventral striatum, the core region of the so-called reward system [2, 46]. Recent studies suggest that, beyond this reduced reagibility towards reward-indicating cues, there is a quantifiable decrease in reward-dependent learning speed and efficiency in alcohol-dependent patients ([34], ◘ **Fig. 3**). This dysfunction seems to be caused by a disrupted functional interaction between the encoding of so-called prediction errors (i.e., the difference between received and expected rewards) within the ventral striatum and the prefrontal cortex, a key factor for behavioral planning and control. Based on animal models [10, 43], the impact of changes in phasic and tonic dopamine release can be related to computable changes in reward- and punishment-associated learning (the above-mentioned prediction error) and simulated in models of neuronal circuits [12, 44]. This line of research reveals a direct pathway leading from an animal model and systematic evaluation of neurobiological observable changes within circuit models to the formulation of hypotheses that can be falsified in humans.

Similarly, it has been shown that chaotic or stress-dependent activity of dopaminergic neurotransmission, as indirectly measured in studies with schizophrenia patients using positron emission tomography [1, 31], can lead to changes in neuronal responsiveness during the anticipation of gain and loss and impairments in reward-dependent learning in patients with schizophrenia [25, 27, 42]. Combining genetic and neurochemical investigations as well as functional imaging (i.e., spectroscopy, positron emission tomography, and functional magnetic resonance tomography) with computational modeling of behavior can thus answer two questions: First, which genetic and/or neurochemical factors influence neurotransmitter systems that play a central role in Pavlovian and instrumental learning; and second, are those factors indeed associated which observable and computable changes in human learning and goal-directed behavior.

Similarly, in affective disorders, punishment-associated learning and dysfunctions in the domain of negative affects have been examined. Peter Dayan and Quentin Huys, for example, postulated that the serotonergic system plays a central role in learning from aversive states [8]. Indeed, the studies on serotonin transporter genotype and availability mentioned earlier showed that genetic variations with a functional effect on serotonin re-uptake have an impact on the response of central nervous structures towards aversive, environmental stimuli. Stress-associated long-term changes within serotonergic neurotransmission, as found in socially isolated primates [18, 20], can systematically influence central processing of threatening environmental stimuli and thus influence learning from aversive situations (“punishment”) [30]. While imaging studies focusing on learning mechanisms in affective disorders are very sparse, it would be reasonable to search for relatively basic changes in computable/quantifiable learning mechanisms such as Pavlovian or instrumental learning in disorders with negative affects (e.g., anxiety or depressive disorders).

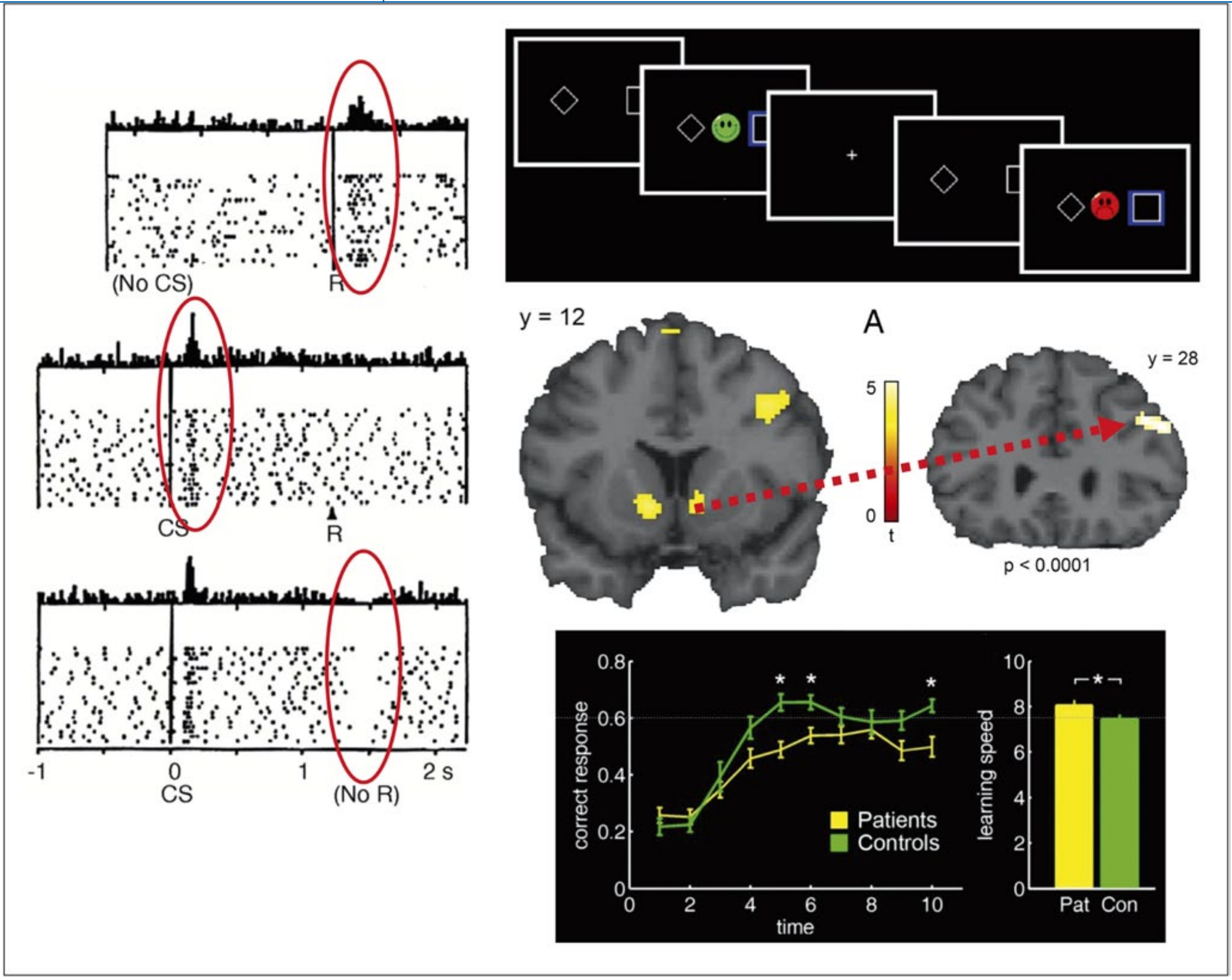

Fig. 3 ▲ Dysfunctions in reward-associated learning in alcohol-dependent patients. *Left*: In a primate study, Schultz and colleagues [44] analyzed the relationship between dopamine function, reward, and learning. They showed that an unexpected reward elicited a phasic dopamine release (*top left*). They then associated this reward with a conditioned, reward-predicting cue. The monkeys now only showed an increase in dopamine release during the presentation of this reward-predicting cue, not during the delivery of the reward itself, which was fully predicted by the cue and therefore was not surprising (*centre left*). When the reward was expected but did not appear, there was a phasic decrease in dopamine release. This observation led to the hypothesis that this dopaminergic neuronal "firing," which projects to the ventral striatum, is associated with a so-called prediction error, an error that can be computed whenever something is better or worse than expected. This error signal seems to be crucial for updating reward contingencies and adapting goal-directed behavior accordingly—processes that we summarize as learning. Park et al. [34] investigated such learning processes with respect to behavioral adaptation during switching of stimulus-reward contingencies in a group of alcohol-dependent patients compared to healthy controls with a so-called "reversal learning" paradigm (*topright*): In this task, participants had to choose between two geometric figures via button press and were asked to find the "better" (more rewarding) stimulus by trial and error. On a behavioral level, it was shown that alcohol-dependent patients made significantly more mistakes and learned slower. On a neurobiological level, there was significantly reduced functional connectivity between the ventral striatum, a core-region of the reward system where the prediction error is encoded, and the dorsolateral prefrontal cortex, a brain area associated with executive behavior control. Impaired connectivity in alcohol-dependent patients was correlated with reduced learning speed

The approach proposed here thus comprises close cooperation and exchange of information between basic research, especially for quantifying neurochemical as well as genetic effects on basic learning mechanisms in animal models and both computational modeling of individual learning strategies and identification of their neurochemical and functional correlates via imaging techniques. Such a central cross-nosological research strategy will focus on basic learning mechanisms involving environmental stimuli (as in Pavlovian conditioning) or positive and negative feedback (as in instrumental conditioning), since it is hypothesized that neurobiological factors directly affect these basic mechanisms. For example, it can be assessed how a change in the serotonergic system caused by stress due to social isolation systematically affects learning from aversive situations as well as reactions towards threatening environmental stimuli. Whether such alterations ultimately lead to anxious, depressive, or aggressive behavior depends on multiple interactions with individual genetic and environmental factors including individual experiences. These experiences can only in part be objectified neurobiologically [26]. They are related to social and cultural factors, which influence the individual manifestation of mental conditions [29, 36].

Neurobiological research strategies and results do not preclude the necessity to define reliable diagnostic criteria in daily clinical routine as well as clear and clinically relevant disorder categories. In contrast to the current diversification of mental disorders, it may help to focus on universally applicable, cross-culturally valid descriptions of disorders (which is feasible for dementia and deliria and which appears to be possible for schizophrenic psychoses and severe affective disorders). On the other hand, a neurobiological reification of every clinically definable mental condition, which can manifest in different socially alienating situations, does not appear to be expedient. However, such clinical conditions can be serious expressions of human suffering, which require neither justification nor reification by neurobiological research.

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