Between Temperament and Psychopathology: Examples from Neuropharmacological Challenge Tests in Healthy Humans

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Keywords

Neurotransmitter challenge tests · Temperament · Adaptability · Depressiveness · Impulsivity

Abstract

Background: This paper tries to demonstrate that the questionnaire-based continuum between temperament traits and psychopathology can also be shown on the biochemical level. A common feature is the incapacity to adapt to external demands, as demonstrated by examples of disturbed hormone cycles as well as neurotransmitter (TM) responses related to affective and impulse control disorders. **Methods:** Pharmacological challenge tests performed in placebo-controlled balanced crossover experiments with consecutive challenges by serotonin (5-HT), noradrenaline (NA), and dopamine (DA) agonistic drugs were applied to healthy subjects, and individual responsivities of each TM system assessed by respective cortisol and prolactin responses were related to questionnaire-based facets of depressiveness and impulsivity, respectively. **Results:** The depression-related traits “Fatigue” and “Physical Anhedonia” were characterized by low and late responses to DA stimulation as opposed to “Social Anhedonia,” which rather mirrored the pattern of schizophrenia. Reward-related and premature responding-related impulsivity represented by high scores on “Disinhibition” and “Motor Impulsivity,” respectively, as well as the questionnaire-based components of attention deficit hyper-

activity disorder, “Cognitive” and “Motor Impulsivity,” could be discriminated by their patterns of DA/NA responses. 5-HT responses suggested that instead of the expected low availability of 5-HT claimed to be associated with impulse control disorders, low NA responses indicated lack of inhibition in impulsivity and high NA responses in depression-related “Anhedonia” indicated suppression of approach motivation. **Conclusions:** In spite of the flaws of pharmacological challenge tests, they may be suitable for demonstrating similarities in TM affinities between psychopathological disturbances and respective temperament traits and for separating sub-entities of larger disease spectra.

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Introduction

Since this special issue deals with the continuum between temperament dimensions of healthy persons and psychiatric diseases, one of the aims of this contribution is to show that this continuum can be demonstrated on the basis of neurochemical similarities. People scoring high versus low on a temperament trait may show similar neurochemical differences to the ones observed between patients with the respective psychopathological disturbance and healthy controls.

Dimensionality between personality traits in healthy people and related psychopathological disturbances (like

depression and impulse control disorders) has already been described in the theory of “physique and character” by Kretschmer [1], which was corroborated on the questionnaire level by Eysenck [2] and subsequent researchers on individual differences. There is also a tradition in demonstrating similarities between biological markers, in particular, neurotransmitter (TM) activity in psychopathological symptoms and temperament traits in the normal range [2–7], but this major question has not been much attacked experimentally with respect to TM responses to respective pharmacological substances in healthy humans.

Furthermore, in psychiatry, symptoms as sub-entities of psychiatric diseases are nowadays more often defined and emphasized for classification [8]. The large variances encountered, when trying to relate symptoms or traits to certain biomarkers, often result from lack of specificity, that is, the observation that different subtypes of a disease or symptom or of a psychological trait show different affinities to certain biomarkers. Therefore, a second aim of this contribution is the discrimination between subtypes of psychopathological disturbances and their corresponding temperament dimensions in healthy persons on the basis of TM activities. These goals will be pursued in 3 sections devoted to a general trait of adaptability, depression-related traits, and impulsivity-related traits.

Adaptability

The Concept

Adaptability refers to the ability of an organism to adjust to demands of the environment like day/night or work/rest activities and to numerous types of stressor stimuli as well as to internal stimuli, like rhythms of physiological, endocrine, and metabolic functions, and it involves neurochemical responses required for mastering the situation adequately (increase of energy supply for action-related activities, reduction of energy in conditions of relaxation, recreation, non-threat conditions, and sleep, which requires the capacity to discriminate between the conditions). According to this definition, adaptation implies a change from one state of the organism to another. It also, however, implies the decrease of the response signals upon continuous exposure to a stimulus as in the case of sensory organs exposed to a continuous stimulus (light, sound, smell, and temperature), as well as gradual non-response to repeated stimuli of the same quality as in the paradigm of habituation and extinction in learning paradigms.

In psychopathology, the deficits in adaptability may be observed in several disease entities:

- the incapacity to initiate required behavioural, affective responses or cognitive effort as in major depression-associated disorders manifested by lack of motivation and initiative and anhedonia;
- the inability to switch from one activity or state of mind to another as in obsessive-compulsive disorders and as represented in rumination on the cognitive/affective level;
- the inability to remain with a certain exhausting activity or unpleasant state of mind as in impulse control disorders like addictive or attention deficit disorder;
- lack of inhibition of unintended, inappropriate, or socially unacceptable impulses as in impulse-control disorders like attention deficit hyperactivity disorder (ADHD) or in manic phases of bipolar depression.

These incapacities represent partly overlapping temperament traits, governed by different neurochemical systems [5]. All of them, nevertheless, represent elements of the major construct of neuroticism as originally defined by Eysenck [2]. Neuroticism in this broad sense comprises irritability, lack of drive, energy and speed, lack of perseverance and flexibility, negative affect, low self-confidence, timidity, and rumination. It is inherent in many psychopathological disorders, as evidenced by correlations between questionnaire scores on this personality trait and psychopathology [9]. Therefore, research on adaptability in the broad sense used in this section will partly cover the construct of neuroticism.

Adaptability as defined in temperament theories is used in a narrower definition as mobility [10], plasticity, and flexibility [11, 12]. Major sources of research on adaptability in the broad sense are studies in the context of *stress research*, studies performed in the field of *chronobiology*, and, in more recent times, studies on *neurochemistry* in psychopathology and temperament research. While stress research uses peripheral measures of catecholamines in plasma indicating the activity of the sympatho-medullary axis and cortisol as indicators of stress responses, brain noradrenaline (NA) is not reflected by plasma levels but is assessed indirectly by hormone responses like cortisol for assessing brain TM responsivity in TM research.

Adaptability and Reactions to Stressors

The most relevant model of adaptation coming from stress research is Selye’s general adaptation syndrome [13], which founded biological stress research and is defined as changing from the alarm phase across the stage

of resistance and in the case of unsuccessful counter-responses, into the phase of exhaustion, the phase of constant non-response to enduring or repeated stimulation. These phases may also be represented as enduring traits, representing persons permanently in states of anxiety and hyper-responsiveness (equivalent to the temperament trait of emotional reactivity [10, 11]), those rather representing resilience and good coping (equivalent to the temperament trait of satisfaction, or confidence [12, 14]), and those in the stage of defeat and giving up as in depression (equivalent to low ergonicity, endurance, or low “activity” level [10, 12, 15]). The obvious question therefore is if persons who differ with respect to trait-like indicators of bad adaptability also exhibit equivalent responses to acute stressors in peripheral physiological systems.

As outlined above, bad adaptability would result from

- a. the mismatch between energy needed according to the environmental conditions and energy mobilized by the organism at that particular moment;
- b. the inability to activate counter-regulating processes in case of exaggerated biological response;
- c. a deficit in the learning process implied in not responding to a continuous stimulus (= adaptation in the physiological sense) as well as to repeated identical stimuli (habituation). This means that biological responses indicating lack of adaptation may turn out as too high, too low, too late, or too long, resulting in inadequate responses, which may be observed on the behavioural, affective, mental, and biological levels.

Evidence for these representations of bad adaptability on the level of peripheral physiological measures has predominantly been reported for measures of the sympathomedullary axis as well as of the hypothalamo-pituitary-adrenal axis (HPA). Increased or prolonged cardiovascular responses to acute stressors [16, 17] seem to mirror some of the criteria for lack of adaptability outlined above. Similarly, abnormal stress-induced catecholamine responses in plasma may serve as indicators of inadequate stress responses, for example, extended duration of NA responses to mental stressors in neurotic participants (e.g., [18]), particularly high NA responses in high anxiety as opposed to low anxiety type males upon pain of venipuncture [19] or inadequately lower catecholamine response to a more intensive than to a less intensive stressor [20].

In particular, it is the slow return to baseline of catecholamine stress responses which reflect depressive behaviour [21]. Similarly, high and extended cortisol responses to acute stressors observed in vulnerable individuals are examples of inability of the HPA axis to adapt

(e.g., high-anxiety participants exposed to a mental discrimination task [22]). However, repeated continuous high responses are supposed to develop into blunted or non-response to stressors due to the development of insensitivity of the corticotropin-releasing hormone (CRH) receptors in the hypothalamus. Blunted or non-response of cortisol has not only been observed in depressed patients exposed to mental stressors (e.g., [23]) but also in healthy persons scoring high on anxiety [24] or high on depressiveness [25], or even when neurotic behaviours like rumination are experimentally induced [26]. Moreover, lack of habituation of cortisol responses to repeated stress exposure can be observed to indicate inability to adapt [27]. Since these peripheral indicators of bad adaptability are too highly dependent on quality and intensity of stressors [19] and environmental factors and are usually rapidly fluctuating, they are less reliable and will not be discussed in detail.

Adaptability as Related to Endogenous Hormone Cycles

A major source of research on adaptability is found in chronobiology. Psychiatry is well aware of the relevance of phases and cycles in bipolar disorder and seasonal depression (see special issue *Neuropsychobiology*; and [28, 29]). The importance of disrupted circadian cycles has been emphasized as a major symptom in pathophysiology (e.g., [30, 31]). An important manifestation of the inability to adjust to external demands is expressed by disturbances of the sleep-wake cycle, as particularly pronounced in major depression [28–32]. This has often been shown to be associated with disturbances of endocrine circadian (cortisol) and lunar (reproductive) cycles [33, 34]. Therefore, in the present section, we wish to present 2 examples regarding the relationship between lack of adaptability as a trait and the endogenous gonadal and cortisol rhythms, respectively.

In order to more specifically characterize the inability to adjust to external demands also on the behavioural level in the range of healthy persons, a questionnaire had been developed specifically for testing this inability to shift from one stage to the other, that is, to adapt working, resting, sleeping, and eating behaviour to requirements of environmental schedules [35]. Typical items are “I am tired during day time, but I cannot fall asleep, when in bed” or “I work without interruptions, stop, when work is done and enjoy leisure time without worrying about work anymore” (inverse scoring). This 10-item Behavioural Adaptability Questionnaire with a Cronbach’s alpha reliability of 0.82 showed convergent validity by high

Fig. 1. Levels of E2 and P at respective peak phases of the menstrual cycle and cortisol levels on day 5 of the cycle in 40 females divided according to the median of the Behavioural Adaptability Questionnaire score into good and bad adaptors, $n = 20$ each (** $p < 0.01$) (modified from Netter et al. [35]). E2, oestrogen; P, progesterone.

correlations with the trait of neuroticism as well as with scales of depression, irritability, and lack of activity and assertiveness (FPI, [36]), all $p < 0.001$ [35]. So it could be identified as representing a major feature of neuroticism, which, as described above, is manifested in different symptoms of inability to adapt as well as in different psychopathological disorders.

In an experiment on 40 healthy females (aged 21–30 years) reporting regular menstrual cycles and not using oral contraceptives, the Behavioural Adaptability Questionnaire scores [35] were median dichotomized into good and bad adaptors, and their gonadal hormones (oestrogen [E2], progesterone [P], and cortisol) were measured in plasma at relevant time points of the menstrual cycle, defined by core temperature. Results revealed that bad adaptors showed reduced levels of E2, in particular in the follicular phase and at ovulation, reduced levels for P in the luteal phase and at the time of the peak level of P, as well as increased levels of cortisol on day 5 of the cycle (see Fig. 1).

Furthermore, the number of cases with corpus luteum deficiency (defined as low levels of $P < 10$ ng/mL) and/or abridged luteal phase (< 10 days) were significantly increased in bad adaptors ($\chi^2 = 7.74$, $p < 0.01$). Both levels of E2 and P and corpus luteum deficiency are essential clinical parameters of fertility.

On the other hand, morning levels of cortisol which had been assessed on day 5 were increased as observed in people scoring high on questionnaires of neuroticism [37]. While the above example refers to altered endogenous cycles of the gonadal and cortisol rhythm, the inability to adapt biological cycles to external conditions of day/night shift induced by trans-meridian flights or by shift work may be an even better indicator of biological adaptability [38–40]. Only a few of the studies have investigated this with respect to temperament or personality traits.

A study on 24-h-shift working nurses on a 7-day-shift schedule of night work (9 p.m. to 6 a.m. [41]) may serve as an example: the diurnal cortisol levels (high after waking up and continuously declining during the day) gradually switches to the opposite pattern (higher values in the evening than in the morning after a continuous period of night work). This was gradually achieved from day 5 onward in the total group. Some participants, however, never reached higher evening than morning levels up to day 7, that is, they were unable to adjust their cortisol profile to the new condition. In spite of the very small sample, a tendency became manifest that these persons showed higher neuroticism-related questionnaire scores (irritability, low satisfaction with life, and feeling

Fig. 2. Interaction between the HPA (left) and gonadal axis (right) and with catecholamines and opiates. ↓, inhibition; ↑, stimulation; HPA, hypothalamo-pituitary-adrenal axis; NE, norepinephrine; 5-HT, serotonin; DA, dopamine; CRH, corticotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Catech, plasma catecholamines; epi, epinephrine; Cort, cortisol; E2, oestrogen; P, progesterone; Te, testosterone; –, decrease; +, increase (figure modified from Netter [42]).

stressed) and in particular reported higher irregularity of working and sleeping habits as assessed by questionnaire items [41].

From the above results, it is obvious that disturbances of the HPA and the gonadal axis are both affected by disturbances of behavioural adaptation. The 2 axes are linked to each other and are both governed by TMs in the brain, as demonstrated in Figure 2. Therefore, analysis regarding relationships between TMs and adaptability has gained interest, in particular in neuroscience related to temperament traits [5, 12] which, however, have a more specific meaning than the general concept of adaptability outlined above.

Adaptability and TM Activity

Due to lack of accessibility of brain TM measures in humans, most of the results related to DA activity in this context have been derived from DA-related experimental basic and animal research. Symptoms related to lack of flexibility in psychopathology, like the inability to change motor and cognitive behaviour as in Parkinson's disease (e.g., [43, 44]) or in obsessive-compulsive disorder [45] as well as tasks requiring a switch from one behavioural strategy to another in animal experiments [46–48], have been found to depend on an intact dopaminergic system. Also the temperament trait of flexibility/plasticity has been demonstrated to be related to dopaminergic function [5, 12].

As stated by Beeler [49], “instead of thinking of dopamine (DA) as a ‘reward TM,’ we might as well consider

it a “flexibility TM.” Experiments on humans have primarily focused on reversal learning and set shifting indicating cognitive flexibility [50]. Basic research on the molecular nature of adaptability and flexibility demonstrates that it is not merely the overall activity of the dopaminergic system but that different functions of the transmitter depend on:

- The location in the brain: prefrontal DA is more relevant for cognitive flexibility, related to learning and memory; mesolimbic DA is involved in appetitive and reward-related behaviour; ventral tegmental neurons act as a source for influencing goal-directed behaviour in several regions of DA activity; and striatal DA is responsible for motor activity [46, 51, 52].
- The state of activity of dopaminergic neurons: phasic and tonic firing of DA neurons are responsible for the possibility to shift and change or to remain in a constant state, respectively [51–53].
- The activation of either D1 or D2 receptors in the nucleus accumbens, which determine if individuals can switch between experimental tasks or merely discriminate between tasks [51].
- The balance between limbic and prefrontal DA activity which is important for the function of goal-directed behaviour [51].
- The initial level of DA available since the relationship between flexibility and DA activity follows an inverted u-shape function, depending on initial levels of DA production [46, 54, 55]. For example, individuals exhibiting

low levels of prefrontal DA activity as genetically represented by the Val Val genotype of the catecholamine-O-methyl-transferase gene (responsible for high enzyme activity) have been shown to exhibit better flexibility on a cognitive task of switching than carriers of the Met allele [56]. On the other hand, dopaminergic stimulation of cognitive flexibility by methamphetamine may impair reversal learning [57], that is, improvement of flexibility by increasing DA in the brain is only achieved in individuals suffering from low basic DA activity and may even be impaired in individuals starting from normal or high DA activity levels, as shown experimentally by several authors [54, 55, 58].

- Finally, the significance of influences from the noradrenergic, glutamatergic, and GABAergic systems required for behavioural switching has to be considered [51].

These molecular processes can hardly ever be identified in experiments investigating “responsivity” to certain TMs in healthy humans, as intended in the following sections but may help to direct attention to the significance of individual differences in basic TM affinity when investigating drug responses.

Problems in Assessing TM Responsiveness

Due to lack of direct accessibility of neurochemical processes in the brains of healthy humans and because of low validity and reliability of methods trying to assess TMs in body fluids, much of our knowledge on neurochemical biomarkers of psychological abnormalities in healthy humans has to rely on pharmacological challenge tests which bridge the gap between biochemical analyses in animal brains and results from pharmacotherapy in psychiatric patients. Application of TM-related drugs which hit specific TM receptors or the TM transporter usually leads to a co-release of neuropeptides in the hypothalamus, some of which can induce or inhibit release of pituitary or peripheral glandular hormones. These hormone responses can be used as indirect indicators of specific TM activities. However, this approach bears a number of difficulties:

1. Disturbances of TM functions may be caused at different steps of TM action within the same system (synthesis, release, different receptors and their sensitivities, reuptake by transporter, metabolizing enzymes, sensitivity of the related hormone system).
2. Each TM influences several psychobiological functions (e.g., serotonin [5-HT] affects sleeping, feeding, impulsivity, aggression, depression) and therefore lacks specificity.

3. Every single behaviour or personality trait is influenced by a synergy and interaction of several TMs (e.g., by a combined action of 5-HT, DA, and NA).
4. Hormone responses may also vary with respect to their time of onset of responses which may derive from slow transmitter release or low sensitivity of receptors as well as from insensitivity of the target hormone system.
5. Since most specific TM-related drugs elicit different types of hormone responses (e.g., cortisol, prolactin [PRL], growth hormone), it is often hard to tell which of them is most specific for the TM/behaviour or TM/temperament relationship.
6. Frequently immediate counter-regulators of TM release or of the target hormone system disguise the actual drug-induced change of the TM.

Considering these difficulties, a modest step to partially improve specificity of neurochemical responses in different temperament traits could be achieved by addressing points 1–4 above:

1. Using different drugs targeting the same system by different mechanisms (releasers, different receptor agonists/antagonists, and reuptake inhibitors), in the same persons. However, the discrimination between availability and responsivity of a TM by using releasers and receptor-related drugs, respectively, yet remains inconclusive. Therefore, the gold standard for solving this question would be assessment of TM release by positron emission tomography which, however, requires highly expensive technology and implies restricted numbers of participants. It would be desirable that future drug challenge experiments could be complemented by positron emission tomography measurements.
2. Testing different behaviours or personality aspects in relation to the same drug challenges on the same individuals.
3. Applying different drugs targeting different TMs (5-HT, NE, and DA) with respect to the same personality aspect in the same individuals.
4. Trying to address the temporal aspect (delayed responses), that is, the time of onset of hormone responses.

Therefore, when analysing TM responsivity, one has to be aware of interactions between different transmitters, between time and size of responses, and between different mechanisms of action of a drug. These principles were applied in selected experiments used for demonstrating individual differences in drug-induced TM responsiveness in healthy humans.

Depression-Related Traits and TM Responses

Selection of Facets

Only a few of the large set of depression-related symptoms represented in respective personality scales will be selected for demonstrating TM responsiveness by drug challenge experiments. These partly cover aspects of traits in temperament theories [12], which are added in italics in brackets.

- General depressiveness assessed by a depression scale [59] or by one of the major correlates of depressiveness, Satisfaction with Life from FPI [36] (*negative mood, low self-esteem, low activity, low endurance, low tempo, and low flexibility*);
- Anhedonia represented by the anhedonia scales [60];
 - Physical Anhedonia (PA) representing low enjoyment of rewarding sensory stimuli and motor activities (*low dispositional satisfaction*);
 - Social Anhedonia (SA) representing social withdrawal and lack of enjoyment of social company (*low social endurance*);
- Retarded depression represented by the scale Fatigue (FA), subscale of the Harm Avoidance (HA) Scale of the TPQ [61], which covers slow physical recovery from stress and disease and lack of drive (*low physical endurance, low tempo*);
- Agitated depression represented by the scale Stress Reactivity (SR) subscale of the MPQ [62], indicating high emotional reactivity and emotional arousal in stress conditions (*impulsivity and neuroticism; low physical and social endurance*).

All scales selected share the inability to properly adapt to the demands of the situation or environment as described in the broad concept of adaptability.

The Noradrenergic System: The Role of Dose and Time of Onset of Responses

Examples of noradrenergic disturbances in depressive disorders are numerous (e.g., [63]) and are primarily based on the original “catecholamine hypothesis” of affective disorders [64] relating catecholamines of the brain to depression and to associated traits in the normal range. Corresponding relationships could for instance be demonstrated in a placebo-controlled balanced crossover experiment on 24 healthy males divided into high and low scorers on the depressiveness scale of the FPI questionnaire [36], in which a challenge test with 2 and 4 mg of the specific NA reuptake inhibitor reboxetine was applied [65].

Results obtained by cortisol responses (the most reliable indicator hormone of the reuptake inhibitor compared to PRL and growth hormone) revealed that depressives showed higher cortisol responses already with the lower dose of the drug. This confirms responses obtained with reboxetine in depressed patients [66] and indicates that high depressives have a very sensitive noradrenergic system (alpha 1 or alpha 2 receptors or NA transporter) as demonstrated in several reviews and single experiments on patients [67, 68].

Similar results were obtained in a 4-fold placebo-controlled crossover study on 36 healthy males with the NA reuptake inhibitor reboxetine (2 mg), the 5-HT reuptake inhibitor citalopram (30 mg), and the D2 agonist bromocriptine (1.25 mg) [69, 70]. Participants were divided according to high and low responders to each drug (above and below 0.60 standard deviations from the maximal amplitudes of hormone responses). In addition (following point 4 of the strategies mentioned above), early and late responders were defined by the time of onset of hormone responses for each of the 3 drugs before and after 90-min post-drug application (a critical latency of response for all 3 drugs).

Participants were tested on the questionnaires listed in section “Selection of Facets” (General Depression, PA and SA, FA, and SR) [59–62]. All scales represent the shared inability to adequately adapt to demands of the situation and are significantly correlated with the scale of General Depressiveness [59] (FA $r = 0.588$; SR $r = 0.736$; PA $r = 0.381$; and SA $r = 0.130$).

Separation of these different questionnaire-based components of depressiveness was tested by measures of dichotomized size and time of responses to the NA, DA, and 5-HT challenges and questionnaire scores as dependent variables [69, 70]. The results of TM responses and their interactions in each facet are summarized in Figure 3.

PA (insensitivity to sensory rewards) was significantly associated with high cortisol responses to the NA reuptake inhibitor reboxetine ($p < 0.009$) as opposed to SA (lack of reward from social contact and feedback). But both, PA and FA, were characterized by a tendency to more immediate (= early) NA cortisol responses to reboxetine ($p < 0.10$).

High NA response amplitudes only observed in high PA individuals may point to a role in motivational goal-directed behaviour of NA [71] as opposed to mere lack of drive and energy as in high-scoring FA participants. This motivational aspect of NA is emphasized in animal research [72]. It is discussed that NA is a necessary condition for adding salience to rewarding stimuli by modulat-

Fig. 3. Summary of significant associations between size and time of transmitter responses and facets of depression. H, high response; L, low response; E, early response; D, delayed response. Numbers refer to levels of significance, and numbers in brackets = significance ($p > 0.05$); large brackets: interactions between sizes of 2 different TMs; $\leftarrow \rightarrow$ interactions between time and size of responses within a TM. DA, dopamine; NE, norepinephrine; 5-HT, serotonin; TM, neurotransmitter.

Transmitter response	Depression size	time	Phys. size	Ached time	Social size	Anhed. time	Fatigue size	time	Stress size	Ractiv. time
DA	size	L $\leftarrow \rightarrow$ D 0.015	L $\leftarrow \rightarrow$ D 0.016	0.039	L		L $\leftarrow \rightarrow$ D 0.008			
	time		0.027		0.030					
NE	size	(H)	H 0.009							
	time	(0.096)		E (0.093)			E (0.062)			
5-HT	size	(H)			L 0.011					
	time						E 0.001		E (0.056)	

ing DA in the nucleus accumbens [71, 73]. This may be explained by a higher sensitivity or density of post-synaptic noradrenergic alpha receptors possibly resulting from low production and release of NA. This corresponds to reports on upregulated noradrenergic receptors in depressed patients as confirmed in several studies and as evidenced by downregulation of receptors as one of the assumed therapeutic principles of antidepressant pharmacotherapy by noradrenergic as well as serotonergic drugs (see e.g., reviews [67, 68]).

Higher responses could also be explained by abnormalities of presynaptic alpha 2 receptors, as indicated by blunted growth hormone responses upon a challenge with the alpha 2 agonist clonidine, which, due to its inhibiting effect, leads to reduced NA output as shown in clinical studies on depressed patients [74–76]. Finally, high reboxetine-induced cortisol responses can also be ascribed to a more sensitive HPA system with upregulated CRH receptors, as evidenced by the DEX/CRH test in patients suffering from major depression in the first phase of disturbance [77–79]. The marginally *early NA response* to the uptake inhibitor in high PA and high FA could either point to a role of the NA transporter or to a relation with the HPA axis in view of the highly significant early cortisol responses also to the 5-HT uptake inhibitor citalopram by high scorers on FA and (less pronounced) by high scorers on SR (see Fig. 3) since both NA and 5-HT are indicated by cortisol responses.

The Serotonergic System: Responses to Differently Acting Serotonergic Drugs

Underlying processes of serotonergic disturbances in depression have been shown to be manifested by abnormalities of 5-HT synthesis, different receptor subtypes, and genetics [80–82]. Results of serotonergic challenge tests with SSRIs, however, are controversial [83].

The only facet of the ones discussed in the crossover study, related to *size* of 5-HT responses, is SA. This is marked by very low 5-HT responses, but only in combination with low responses to DA stimulation, which suggests kinship to schizophrenia characterized by the same pattern of TM activity [84].

The early responses to citalopram seem to be merely relevant for FA and SR (Fig. 3) (possibly due to sensitivity of the 5-HT transporter or of the HPA axis?). But *size* of cortisol response to the 5-HT reuptake inhibitor did not relate to the traits characterized by lack of activity (PA and FA). On the other hand, the 5-HT releaser d-fenfluramine tested by PRL responses (the most frequently used indicator of 5-HT release) tends to lead to blunted PRL responses in affective disorders (review [80] and [83, 85, 86]).

d-Fenfluramine was also successfully applied in a placebo-controlled crossover experiment [87] on 24 male students exposed to 15-mg d-fenfluramine and tested by Cloninger's Questionnaire (TPQ) [61]. Blunted PRL responses were obtained in high scorers on the scale of HA which comprises the subscale FA (see above), apart from other subscales of depressiveness and anxiety. A second placebo-controlled study on the

same participants was performed which used cortisol responses to 10 mg of the 5-HT_{1a} partial agonist ipsa-pirone. This did not show associations with the total score of HA but did yield significantly lower cortisol responses in high scorers on the subscale FA. This would indicate that low release, as suggested by the blunted PRL response to the releaser d-fenfluramin is possibly accompanied by subsensitivity of presynaptic 5-HT_{1a} receptors, leading to lower release of cortisol. Subsensitivity of 5-HT_{1a} receptors has frequently been claimed to be associated with depression [88] as opposed to supersensitivity of these receptors in anxiety disorders [89]. This result demonstrates that by using different challenge substances with different mechanisms of action in the same individuals, it may be possible to elucidate which particular steps in TM abnormalities are characteristic of a specific facet of depressiveness, in this case the low-energy subtype fatigue.

The Dopaminergic System: Interactions between and within TM Systems

The role of DA in affective disorders has received less attention than the serotonergic and noradrenergic systems [90]. Evidence from experiments on animals as well as on healthy humans and patients, however, points to an important impact of DA.

- Chronic mild stress in animals leading to depression-like symptoms is related to DA depletion and can be compensated by dopaminergic drugs [91, 92].
- A reduced PRL response to dopaminergic stimulation by apomorphine has been observed in depressed patients [75, 93].
- Lack of drive and increased fatigue as well as deterioration of performance is observed in healthy persons treated with alpha-amino-methyl-paratyrosine, which induces DA depletion [94].
- Euphoria and increased drive observed in mania may be antagonized by DA antagonists [95], and the same applies to euphoria induced by amphetamine or methylphenidate [96].
- Higher DA receptor binding is observed by SPECT analysis in the striatum of depressed patients which would indicate a reduced striatal DA function [97].
- DA has been shown to be involved in all kinds of appetitive and motivational behaviour (e.g., [98]), and there is evidence that low DA release or levels may be a biomarker of affective disorders [90, 99, 100].

DA activity is reliably represented by decrease of PRL upon agonistic and increase upon antagonistic stimulation.

Including time of onset of hormone responses into the evaluation of DA responsiveness in the 4-fold crossover study mentioned above, a particular feature of depression-/neuroticism-related temperament/personality traits was revealed. The significant interaction between time and size of DA-induced PRL responses computed for each trait indicated that low and late responses to the D2 agonist bromocriptine were reliably associated with traits characterized by low energy and motivation: general depressiveness, PA, and FA [101, 102]; see Figure 3 above ($p = 0.015$, $p = 0.039$, and $p = 0.009$, respectively, for depression, PA, and FA).

Low response to DA agonists evidently results from low DA production as evidenced by higher DA receptor binding observed by SPECT analysis in the striatum of depressed patients which would indicate an upregulation of DA receptors due to reduced striatal DA function [97] resulting from low DA synthesis [103]. The late response would then indicate that upon DA stimulation, a longer time is needed for full receptor occupancy required for eliciting endocrine responses [104]. The delayed response may also result from low NA availability (higher sensitivity of NA receptors). This could indicate the relevance of NA in goal-directed and motivational behaviour [71] and would match the finding that prefrontal cortical NA transmission is a necessary condition for attributing salience to stimuli of reward by modulating DA activity in the nucleus accumbens [73, 105, 106].

Furthermore, a significant interaction between size of DA and NA responses in the crossover study ($p = 0.027$, Fig. 3) resulting in high NA and low DA responses for PA indicates that the supersensitive NA receptors resulting from low NA supplies (see above) in association with low DA responses would support the general catecholamine hypothesis [64] specifically for PA and would indicate the relevance of NA in goal-directed and motivational behaviour, which modifies the general motivation-directed activity of DA and could be a specific feature of individuals lacking sensitivity to sensory rewards as assessed by the PA scale. The NA/DA relationship could also point to the functional relationship of the 2 catecholamines; since NA is converted into DA by DA- β -hydroxylase, low supply of NA (= high response in the experiment) would also result in low DA levels in case of a normal function of the converting enzyme DA- β -hydroxylase.

In summary, depression-related traits in healthy persons are more distinctly characterized by low and delayed dopaminergic activity than by abnormalities of the serotonergic system. This emphasizes the importance of de-

fining responses also by time of response onset. Furthermore, a combination of low DA and high NA responses is suitable for distinguishing between TM affinities of depression-related PA from the schizophrenia-related social anhedonia, which reflect different temperament traits.

Impulsivity-Related Traits and TM Responses

Aspects of Impulsivity

As depression, impulsivity-related disturbances are composed of different facets as demonstrated in psychopathology, animal research, and questionnaires: impulse-control disorders like ADHD and addictive and compulsive disorders are the models from which animal and human experiments have derived their behavioural models which may be categorized on the basis of reviews like the one by Dalley [107, 108] as follows:

Behaviours related to quick or premature responding “can’t stop” [109]:

- on the motor level: manifested by commission errors (lack of inhibition of initiated actions)
- on the cognitive level: inattention (wrong decision, lack of error control, lack of premeditation)
- on the affective level: lack of affective restraint (inappropriate emotional response, irritability, aggression). Behaviours related to reward “can’t wait” [109]:
- for expected positive reinforcers (delay discounting)
- for negative reinforcers (lack of perseverance with unpleasant tasks)
- rewarding goal-directed actions (e.g., gambling).

The first set of behaviours is predominantly represented in ADHD and the second set rather in addiction-related disturbances. TM abnormalities have been reported for most representatives of psychopathological impulse-control deficiencies described below.

The Serotonergic System: 5-HT Deficiency

One of the most reliably confirmed findings in biochemical neuropsychiatry is that impulsivity is characterized by low release of 5-HT as first hypothesized from low 5-hydroxy-indole acidic acid levels in suiciders [110, 111]. Since then, a large batch of studies was conducted in the context of violence and aggression (see review [112]) but also studies related to addicted behaviours like drug abuse, gambling, and eating disorders confirmed the phenomenon of low 5-HT levels by blunted PRL responses to d-fenfluramine in several impulsivity-related disorders [113, 114] and were sometimes complemented by

Fig. 4. Possible mechanisms for explaining responses to serotonergic drugs in impulsivity. Arrows indicate increase and decrease, respectively; (), blunted response.

findings on the role of presynaptic 5-HT_{1a} receptors in modulating impulsive responses since 5-HT_{1a} agonists tend to decrease impulsive behaviour [115].

The approach of attempting to identify biomarkers of impulsivity as a trait by drug challenge tests is, of course, inverse to the animal and clinical studies: the question raised in the present approach is not “What type of impulsive behaviour or disorder is induced or reduced by manipulation of TM levels,” but “How do persons showing differences in their levels of impulsivity as a trait differ in their TM-related responsiveness.”

A model depicting possible mechanisms suitable to explain the association between impulsivity and low levels of 5-HT described above for studies on impulsivity is given in Figure 4. The model, however, has to be modified according to subtypes of impulsivity and according to modes of drug application as indicated by results described below:

Studies in animals show that only acutely as opposed to chronically administered 5-HT_{1a} receptor agonists increase reward-related impulsivity (delay discounting = choosing a small reward immediately as opposed to choosing a delayed large reward) [116, 117]. Experimental reduction of 5-HT synthesis by depletion of tryptophan, the 5-HT precursor, has led to an increase in aggressive and impulsive behaviour [118–120]. Lowering 5-HT by 5-HT inhibiting drugs in rats tends to increase premature responding but not reward-dependent behaviour like delay discounting (for review see

[107]). This indicates that different behavioural subsets of impulsivity may reflect different neurochemical mechanisms.

Therefore, for further analysis of impulsiveness-related transmitter responsiveness in the range of healthy persons, the scale “Disinhibition” (subscale of the Sensation Seeking Scales [SSS] [121]) was selected to represent the reward-related aspect of impulsivity, and the 2-component characteristic of ADHD, “Cognitive” (Attentional) and “Motor Impulsivity” defined by the BIS 11 Barrett scale [122], were selected to represent attentional and motor premature responding. The global trait of impulsivity measured by the Eysenck Impulsivity Scale I7 [123] was included.

TM responsiveness was assessed in the 4-fold crossover study with the 3 TM-related drugs for serotonergic, dopaminergic, and noradrenergic responsiveness and placebo (see above) determined by cortisol responses for 5-HT and NA and PRL responses for DA. Time and size of responses were defined as above and used as independent variables with the impulsivity questionnaire scores as dependent variables for analyses. Results of TM-related hormone responses for facets of impulsivity are depicted in Figure 5.

Inspecting results for 5-HT, there was no indication of the expected low 5-HT responses in impulsivity-related traits, but this may be due to the fact that in this sample of healthy young males, no violent impulsive highly aggressive participants had been included because there is evidence that low 5-HT is mostly associated with the aggressive aspect of impulsivity [112] (see above). This is also evidenced by low plasma levels of monoamine oxidase B as an indicator of low 5-HT in violent offending adolescents [124, 125]. However, when including time of onset of the hormone response, the relevance of 5-HT responsiveness for disinhibition was revealed by a significant interaction between time and size of 5-HT responses ($p = 0.043$ [126]) showing that low and early as well as high and late responses may be observed, indicating that the Sensation Seeking subscale Disinhibition (defined by liability to alcohol and drug abuse as well as by ignoring social norms) is not an entity in itself but may be represented by 2 different serotonergic processes: low production of 5-HT + supersensitive pre- and post-synaptic 5-HT receptors or a sub-sensitive transporter system could lead to the early but low cortisol response to citalopram (see Fig. 4) in disinhibited persons, while in other participants, the transporter could be sub-sensitive to the reuptake inhibiting drug citalopram resulting in high and late responses.

The Dopaminergic System: High DA Activity

High dopaminergic activity has been reported to indicate impulse-control deficiency as in violent offenders [127] or addictive patients [128, 129] as well as in healthy persons scoring high on scales of impulsivity [130]. On the other hand, patients suffering from ADHD are successfully treated by dopaminergic and noradrenergic substances like methylphenidate and atomoxetine, indicating a deficiency of catecholaminergic brain activity in this disease. As in many transmitter-related diseases, both abundance and deficiency (TM hyperactivity and hypoactivity) may be responsible for different types of dysfunction (e.g., schizophrenia vs. depression). In addition, as outlined above for DA and flexibility, drug effects often follow an inverted U-shaped function depending on differences in initial levels of the transmitter [54]. Furthermore, subtypes of impulsivity are differently affected by treatment or condition: increasing DA leads to increase in premature responding but to decrease in reward-related (delay discounting) behaviour [107, 131]. This is also evidenced by brain lesion studies in rats indicating that lesions either in the nucleus accumbens or in the medial striatum selectively increase delay discounting and premature responding [132–134]. DA research on impulsivity as compromised plasticity of behaviour was summarized in the neurochemical model FET [5].

Results from the 4-fold crossover study (Fig. 5) show the expected high DA activity for the total score of Imp I7 ($p = 0.048$), for Disinhibition ($p = 0.009$) and Cognitive Impulsivity ($p = 0.032$), but low DA responses for Motor Impulsivity ($p = 0.040$ in interaction with low NA). This has to be interpreted in combination with the observation that Disinhibition as well as Motor Impulsivity and, to a minor extent, Cognitive Impulsivity show significant interactions between DA and NA activity resulting in high DA, low NA responses for Disinhibition ($p = 0.031$), low DA, low NA responses for Motor Impulsivity ($p = 0.040$), and high DA, high NA for COG (not significant $p = 0.190$). The nature of the differential interaction between DA and NA requires considerations on the role of NA.

The Noradrenergic System: Low NA Responses

Although NA deficiency has primarily been reported for affective disorders mostly discussed in combination with DA (see above [63, 64]), low levels of brain NA inferred from low cerebrospinal levels of its metabolite 3-methoxy-4-hydroxy-phenyl-glycol have been assumed to characterize people scoring high on impulsive

Fig. 5. Summary of significant associations between size and time of transmitter responses and facets of impulsivity. H, high response; L, low response; E, early response; D, delayed response. Numbers refer to levels of significance, and numbers in brackets = significance ($p > 0.05$). Large brackets refer to interactions between 2 different TMs; $\leftarrow \rightarrow$ refers to interactions between time and size of responses within a TM. *, interaction between time and size of 5-HT responses (low and early as well as high and late responses). DIS, disinhibition; SSS, Sensation Seeking Scales; MOT, motor; COG, cognitive; DA, dopamine; NE, norepinephrine; 5-HT, serotonin.

Transmitter response	Impulsivity (Eysenck, I7)		Disinhibition, (SSS, Zuckerman)		Motor Impulsivity (Barratt BIS 11)		Cognitive Impulsivity (Barratt BIS 11)	
	size	time	size	time	size	time	size	time
size DA	H 0.048	(0.095)	H 0.009	0.031	L	0.040	H 0.032	(0.190)
time DA								
size NA	L	(0.058)	L (0.058)	D 0.038	L 0.031		H	0.030
time NA								
size 5-HT			L $\leftarrow \rightarrow$ E 0.043 *)				H	
time 5-HT			H $\leftarrow \rightarrow$ D					

sensation seeking already in 1983 [135, 136]. Low NA in combination with high DA activity is represented in Zuckerman's neurochemical model of impulsivity [137, 138]. Different roles of DA and NA are also suggested by individual differences in therapeutic responses to the DA and NA reuptake inhibitors methylphenidate and atomoxetine in treatment of ADHD [139–141]. This is furthermore supported by the findings that DA 2/3 receptor density, the DA target, is higher in the striatum and distribution of alpha 2 receptors, the target of NA agonists, is higher in the prefrontal cortex which is in line with the predominance of effects on rather motor- versus attention-related functions [142]. In many studies and experiments, noradrenergic stimulation has been shown to decrease impulsive behaviour [143, 144].

Inspection of Figure 5 would suggest that low NA responses characterizing high Disinhibition ($p = 0.058$) and high Motor Impulsivity ($p = 0.031$) reflect low inhibitory power of NA on impulsive behaviour considering that noradrenergic stimulation can reduce impulsive behaviour [141]. In high Disinhibition, low NA response is related to a significantly elevated DA response ($p = 0.009$), representing the expected impulsivity feature (interaction DA $\times$ NA: $p = 0.031$). This is reflected by an opposite pattern of high NA ($p = 0.083$) and low DA responses ($p = 0.038$) obtained in persons scoring high on the scale of Restraint (subscale of the MPQ [62, 145]).

As opposed to Disinhibition, representing reward-related impulsivity, low NA in Motor Impulsivity is associated with low DA responses (interaction DA $\times$ NA re-

sponse: $p = 0.040$). This would rather suggest that in addition to lack of inhibitory effects related to low NA, low DA reflects the assumption of DA deficiency in patients suffering from ADHD in view of the therapeutic benefit from treatment by the DA reuptake inhibitor methylphenidate in particular for hyperactivity [146]. It is interesting to note that Cognitive (= attentional) Impulsivity is represented by rather higher dopaminergic responses combined with significantly higher serotonergic responses (interaction DA $\times$ 5-HT response: $p = 0.030$). This may correspond to differences in DA activity in the prefrontal and the striatal area of the brain resulting rather in attention deficit or hyperactivity-related impulsivity [134]. Moreover, the interaction with 5-HT responses may result from the fact that NA reuptake inhibitors like atomoxetine and possibly also reboxetine have a slight additional affinity to the 5-HT transporter. Actually, the interaction indicated in Figure 5 revealed an additive effect of DA and 5-HT responses on Cognitive Impulsivity scores (highest scores with high DA + high 5-HT responses).

These differences between Cognitive and Motor Impulsivity may reflect the finding that scores on Motor Impulsivity as opposed to Cognitive Impulsivity are highly positively correlated with scores on Disinhibition ($r = 0.486$, $p < 0.01$) as well as with scores on a scale related to Adventure Seeking Exploratory Excitability (MPQ, 62) ($r = 0.550$, $p < 0.01$) and with Addiction defined by the DSM IV-based Interview CIDI [147] ($r = 0.353$, $p < 0.01$). By contrast, Cognitive Impulsivity shares variance with behavioural inhibition (BIS scale [148], $r = 0.450$, $p <$

0.01), Neuroticism (FPI [36], $r = 0.485$, $p < 0.01$), and general depression [59] ($r = 0.378$, $p = 0.05$), as opposed to Motor Impulsivity [145]. This affinity of Cognitive Impulsivity to 5-HT responses and depression is also reflected by high 5-HT responses to Depressiveness (see above, Figure 3) and to the clinical relationship between impulsivity and depression [149].

These partly hard-to-interpret, mostly unreliable findings due to low sample sizes may yet give rise to further hypotheses and lead to the following summary:

- Reward- and premature responding-related impulsivity represented by personality scales in healthy persons can be separated by patterns of hormone responses in drug challenge studies.
- The same holds for discrimination between the cognitive and motor aspects of ADHD-related personality traits.
- Although 5-HT has primarily been regarded as the transmitter which inhibits impulsive behaviour and DA-related activation as postulated by Depue's model [4], it must be recognized that NA, besides its functions in attention, goal-directed behaviour, and emotional arousal, may also exert an inhibiting function by inhibition of spontaneous actions in depression-related traits and by inhibiting impulses for inappropriate actions in impulsivity-related traits.
- The opposite association between responses to the NA reuptake inhibitor in depression-related traits (Fig. 3 NA high responses) versus impulsivity-related traits (Fig. 5 NA low responses) may depend on differences in disturbances between either low NA production or alpha 2 receptor subsensitivity.

Conclusions, Limitations, and Future Recommendations

Disturbances of adaptability, in this paper conceived as a major principle inherent in depression-related as well as in impulsivity-related disturbances and psychological traits, may not only be found to be related to endocrinological disturbances but also to TM responses assessed by pharmacological challenge tests in healthy humans. Pharmacological challenge tests may appear to be outdated in view of modern developments of neuroimaging techniques with the possibility of localizing brain activity in specific areas and to assess connectivity, and the development of molecular genetics with the technique of genome-wide association studies (GWAS) based on big data sources. Yet, from the results report-

ed, some hypothesis generating conclusions may be drawn:

Healthy persons with temperament traits representing psychopathological disturbances may exhibit similar TM response patterns to the corresponding psychopathological disturbances. Challenge tests performed consecutively on the same individuals may provide hypotheses for specific patterns of NT responsiveness associated with separate facets of depression-related as well as impulsivity-related disturbances. The inclusion of the temporal aspect (time of onset of endocrine response to drug stimulation) enhances the possibility to discriminate between facets of larger groups of disturbances and traits.

Limitations are, of course, that

- sample sizes are too small for drawing valid inferences, so that results may in principle serve as hypotheses for further research;
- no data from neuroimaging for localizing the TM activity and no data from molecular genetics have been included for tracing TM responses to specific sources;
- merely 3 transmitters and no peptides have been included, ignoring acetylcholine, GABA, opioid receptors and many others;
- merely rough dichotomies instead of continuous measurements of TM responses (used as independent variables) have been applied;
- no replication studies of experiments from the author's laboratory have been performed.

Future directions:

- Neurochemical, neuroimaging, and molecular genetic methods of assessment in the same individuals are recommended. It is deplorable that so few studies using challenge tests or biochemical biomarkers have examined their molecular genetic basis and only a few use neuroimaging and neurochemical biomarkers in the same individuals.
- Constellations of transmitter responses in the same individuals should be applied rather than single TM analyses.
- Time of onset should be included in evaluations, supported by knowledge of basic research on kinetics of TM release.

Finally, using TM responses as independent measures may serve to identify clusters of psychological traits, that is, defining biochemically based taxonomies of temperament in the future.

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Statement of Ethics

Approval of the Ethics Committees of the Psychological and Medical Faculties of the University of Giessen had been obtained for the individual papers cited from our own laboratory. Respective confirmations are mentioned on the respective publications.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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