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Benefits and limitations of drug studies in temperament research: biochemical responses as indicators of temperament

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This paper presents a discussion of principles and problems of neurotransmitter challenge tests using examples of experiments, most of which were performed in the author's laboratory. Drugs targeting synthesis, release, receptors or reuptake of dopamine, serotonin and noradrenergic transmitter (TM) systems were used for characterizing or discriminating certain temperament or personality traits and their sub-factors. Any personality or temperament trait is characterized by multiple TM responses, thus constellations of hormone responses to drugs acting on different TM systems or on different sources of TM activity were investigated within individuals in crossover designs. The major conclusions are: (i) intra-individual patterns of hormone responses to different TM-related drugs, or to agonists and antagonists, can help to discriminate subtypes of temperament dimensions, and (ii) the latency and shape of response curves may help specify processes of biological responses related to psychological dimensions and reveal common TM sensitivities in clusters of traits. TM sensitivity, defined by hormone responses, does not always correspond to accompanying behavioural indicators, but may provide more specific information on underlying mechanisms. Additional consideration of drug doses and experimental induction of stressors may serve to identify temperament-related susceptibilities to certain drugs. Limitations of the challenge approach and recommendations for future research are discussed.

This article is part of the theme issue 'Diverse perspectives on diversity: multi-disciplinary approaches to taxonomies of individual differences'.

1. Introduction

This Opinion paper discusses approaches to biological research on temperament, and the benefits and limitations of drug trials (in particular, pharmacological challenge tests) in the study of temperament. Space does not permit expanding it to a full review. Therefore, findings and shortcomings of previous psychopharmacological experiments will not be discussed. Rather, studies conducted in our laboratory over the past 30 years are presented to provide hypotheses and approaches for future research on the neurochemical bases of temperament traits.

2. Concept of temperament

Attempts to define temperament have resulted in heated debates about the differences between personality traits and temperament. Although many discriminatory features between temperament and personality factors have been put forward [1–3], some personality traits, in particular neuroticism and extraversion in Eysenck's model [4], mirrored by the Big Five [5], as well as dimensions of novelty seeking or impulsivity defined by subscales in Zuckerman *et al.*'s [6] or Cloninger *et al.*'s [7] models, also cover 'temperament traits'—neuroticism, sensation (novelty) seeking, impulsivity, sociability (social–verbal endurance).

Therefore, in this paper, we use the word 'traits', referring to both personality and temperament traits.

Temperament traits as represented in major theories of temperament (in spite of partial overlap) can roughly be grouped into *activity*-related dimensions (e.g. activity: Strelau [8,9], Buss & Plomin [10], Windle [11]; ergonicity: Rusalow [12]; intensity: Chess & Thomas [13]); *speed*-related dimensions (speed, tempo: [9,12]), dimensions of *adaptatability* (flexibility [11], mobility [9], adaptation [13], plasticity[12]); a dimension of *rhythmicity*, [8,9]; dimensions of *endurance* (persistence, endurance [9], distractability [11,13]); dimensions of *reactivity* [9,11,12]. Some theories, however, still include content-related dimensions, such as approach–withdrawal or negative versus positive mood [12,13]. Moreover, it turned out that dimensions had to be subdivided: for example, speed into premature actions related to impulsiveness and tempo related to activity and alertness [10], reactivity into sensory, emotional and motor reactivity [9] or endurance into endurance against fatigue and against distraction [8,9].

Problems arise when researchers, trying to identify biological correlates of temperament, attempt to represent temperament traits as independent dimensions.

(1) Temperament traits are not independent. For example, even the main dimensions of temperament—activity and emotionality—showed significant positive correlations. This was observed for emotional and general endurance, and significant negative correlations were found between endurance and emotional sensitivity when the Strelau FCB-Temperament Inventory was used [8,9]. Thus, biochemical correlates of activity and reactivity will show large overlap and can hardly be investigated without hitting aspects of positive/negative affect or approach/withdrawal.
(2) Temperament traits are partly very heterogeneous concepts, e.g. decreased activity and speed may be observed in old age, depression or fatigue, all of which may be related to low-dopamine activity. Thus, in order to separate sources of similar behaviours or overlapping dimensions, consideration of additional biological markers within the same individual will be required.
(3) Temperament dimensions may differ when exhibited in different conditions and in different areas of behaviour (e.g. physical, social or mental [3]; spontaneous activity or activity induced by the social environment [14]; activity measured with or without application of stressors [15]).
(4) Finally—and this may be controversial—how closely do the temperament dimensions measured by questionnaires on the one hand, and mental performance or motor behaviour on the other, represent the same temperament trait? Which of these is the more valid measure? Do these indicators of a specific temperament trait show corresponding biochemical correlates? The psychophysiological research that uncovered the inter-connectedness of temperament traits suggests that a search for independent dimensions, common in psychometric practice, might not be the best approach to the development of classifications of types of nervous systems [16]. The ultimate goal would of course be to show that the biochemical findings are reflected in findings from neuro-imaging and molecular genetic studies, a question to be answered by inspection of all the contributions to the present issue.

3. Basic considerations and biochemical approaches in the study of temperament

The first approaches to investigating the biological correlates of temperament were based on concepts of activating and inhibiting arousal systems of the central nervous system, assessed by physiological measures and performance [17,18]. Biochemical measures as indicators of the autonomic sympathetic nervous system, adrenaline (A) and noradrenaline (NE), measured first in urine, later in plasma, yielded findings that the catecholamines are related to activity (performance) as well as to emotionality, (mostly stress-induced arousal) [19]. But it is clear that peripherally measured biochemical variables do not truly reflect brain activity, because they are also produced in peripheral tissues such as in the adrenal medulla (catecholamines) or in the gut (serotonin).

Hormones of the hypothalamo–pituitary–adrenal (HPA) axis, ACTH and cortisol, measured as stress responses mostly in saliva, could be shown to indicate individual differences in emotional reactivity associated with neuroticism [20,21]. But those indicators of affective states are also not convincing links to neurotansmitter activity.

Evidence for the relevance of biochemical processes in the central nervous system for temperament came from psychiatry: observations from drug treatment revealed the role of serotonin (5-HT), NE and dopamine (DA) for affective, psychotic or impulse control disorders [22] and psychopharmacological drug studies were started [23]. In the search for sources of variability in therapeutic responses to treatment [24], the role of temperament, e.g. anxiety and activation orientation [25,26], was discovered.

Psychologists adopted the use of drug trials from psychiatry, (a) to explore the biological basis of psychological functions like attention, memory and learning (elements of temperament) [27], and (b) to use drugs as research tools for detecting hidden dispositions (such as susceptibilities to sedative or stimulating drug effects on behaviour) as indicators of neuroticism or extra-/intro-version [27,28]. From these drug studies, we learned that neurotic, anxious and disturbed persons show improved performance and stabilized mood with the use of sedatives as opposed to non-neurotics [28,29] and that highly activated persons benefit less from stimulants and get worse from sedative drugs due to the inverted U-shaped response curve postulated by arousal theory [27]. Later, drug studies were enriched by the use of more specific neurotransmitter-related drugs [15,29,30].

In one experimental approach (here called *Approach 1*), the steps are: (1) measure a temperament trait by means of a questionnaire, (2) define performance/emotional states relevant to that trait, (3) apply a drug of known antidepressant, antipsychotic, sedative or stimulant effect or of known transmitter (TM) related activity, (4) measure changes of the psychological output variable from pre- to post-drug application, (5) either correlate the change with the temperament trait or compare the change in high and low scorers on the temperament trait. *Inference*: the drug has disclosed a hidden susceptibility of the temperament trait to the specific

drug qualities indicated by higher change scores of behaviour/affect. These steps are often modified by experimental conditions such as induction of stress, manipulation of information given to the participant or adjustment of the dose of the applied drug [15,28,29]. It is evident that this approach does not disclose which biochemical mechanisms in the brain are responsible for changes in psychological responses.

Pharmacological challenge tests (here called Approach 2) have also been adopted from psychiatry and follow a similar approach as above, but use a biochemical drug response as a marker of a hidden disposition of susceptibility of a temperament trait. That is, they serve as a diagnostic tool for detecting a disposition, which is invisible in unstimulated conditions, just like an allergy test.

They make use of the fact that TMs in the limbic system act on hypothalamic peptide-releasing hormones, which induce pituitary hormones such as prolactin (PRL), growth hormone (GH) and glandotropic hormones like ACTH, leading to cortisol release. These hormones can be measured in blood or saliva and can serve as indicators of TM activity (electronic supplementary material, S1). Examples of challenges of the three most behaviourally relevant TM systems DA, 5-HT and NE [31 p. 654] (electronic supplementary material, S2) demonstrated that each of these three systems can be manipulated at several steps from synthesis to degradation, that in many cases the same drug may elicit several different hormone responses, and that the systems can be targeted by drugs related to different receptor subtypes, and by agonistic and antagonistic procedures (for more thorough reviews, see [32]).

There is uncertainty about the basic processes involved in drug challenges.

(1) The hormone responses may indicate different underlying mechanisms (disturbance of TM synthesis or release, receptor sensitivity and subtypes, activity of transporter or catabolizing enzymes) (electronic supplementary material, S3).
(2) The induced hormone responses may depend on changes in sensitivity of the hormone system itself (e.g. the HPA axis) and on compensatory and feedback mechanisms, like up- and downregulation of receptors depending on the previous frequency of stimulation, as in addiction, and the availability of TMs depending on age or state of health,
(3) Several drugs, like 5-HT agonists, nicotine, alcohol or benzodiazepines, show inverted U-shaped biphasic actions (initial stimulant, followed by sedative effects), which may result from timing effects, from binding to pre- and postsynaptic receptors, or from the dose of the applied drug.

As a consequence, when using drugs with several modes of action, the effects of different doses as well as the temporal course of the response should be assessed in the same individuals.

There is also ambiguity in TM–behaviour relationships.

A major problem is that any performance, emotion, motor response or temperament dimension is related to several neuroTM (see [33], p. 388), and every single TM system is responsible for a variety of functions (e.g. serotonin for sleep, body temperature, feeding, aggression and depression, depending on receptor subtypes) [34].

As a consequence, it is essential (a) to analyse one behaviour or temperament dimension in relation to a number of different TMs in order to test for additive and interaction effects, and (b) to correlate a specific TM disturbance to a number of psychological functions or personality/temperament traits. It is clear that applying the test to the same individual at different times across their lifespan might reveal different susceptibilities according to changing TM availabilities and sensitivities.

4. Aims and approaches in research with TM challenge tests

Following the principles listed above, TM challenge tests may help to identify temperament dimensions or to separate subcomponents of temperament by

(1) the combination of TM challenges to different systems (e.g. stimulation of 5-HT-, DA-, NE-systems) in the same individuals,
(2) the combination of responses to different challenge drugs representing different principles of drug action on the same system (e.g. agonists and antagonists or uptake inhibition and receptor stimulation),
(3) the combination of different response parameters like time of onset and size of responses, and
(4) comparing different hormone responses to the same challenge, which may indicate different mechanisms and receptor sensitivities in response to the same drug (e.g. GH, PRL).

These tests may serve heuristic purposes, for example, by identifying clusters of personality or temperament characteristics on the basis of certain biochemical response characteristics. They also may help to elucidate the mediating or moderating role of the biochemical responses for the behavioural responses to the challenge drug.

In some of the following examples of Approach 2, drug-induced hormone responses will be defined as independent variables and personality or temperament traits or related behaviours as dependent variables. This may serve future attempts to classify temperament on a neurochemical basis.

5. Some results from using drugs as research tools

Some experiments on drugs and personality factors performed at the University of Giessen are listed in tables 1 and 2, grouped according to the three major neuroTM systems. DA, 5-HT and NE drug studies on alcohol (GABA receptor-related) and nicotine (acetylcholine receptors) are not listed in the table, but will be mentioned in order to demonstrate the role of differences in habituation or dose effects for inferences on temperament-related susceptibilities.

The personality traits targeted are listed within the TM categories according to major temperament domains such as traits related to activity, speed, novelty seeking, impulsivity/aggression, neuroticism/depression. Many of them have been studied with respect to more than one TM system. Therefore, results from studies using more than one drug category are presented in different sections.

Table 1. Summary of studies with ***dopamine***-related challenges and various traits conducted in the Department of Psychology, University of Giessen, Germany. *Note:* std N: ID number of the study presented; Ap: experimental approach (1: without, 2: with assessment of biochemical variables); ref: reference number indicates the number in the reference list related to the study; #: studies using drug hormone responses as independent variables; L-DOPA: L-3,4 dihydroxyphenylalanin; AMPT: alpha-methyl-paratyrosine; DA: dopamine; D1 D2: dopamine receptors 1 and 2; RT: reaction time, CFF: critical flicker fusion frequency, HVA: homovanillic acid (metabolite of dopamine), PRL: prolactin, GH: growth hormone. *For column 6, questionnaires, with reference numbers in reference list:* Anhed Scale: Chapman Anhedonia Scales [35]; BIS 11: Barratt Impulsivity Scale [36]; BIS/BAS: Gray Behavioural Inhibition and Activation Scale [37]; EPQ: Eysenck Personality Questionnaire [4]. FPI: Freiburg Personality Inventory [38], HHF: Hypo- Hedonie – Fragebogen [39] (olf: olfactoric subscale); MPQ: Multidimensional Personality Questionnaire [41], SSS: Sensation Seeking Scales [6] (BS: Boredom Susceptibility, TAS: Thrill + Adventure Seeking); STAI: State Trait Anxiety Inventory [42]; TPQ: Three-dimensional Personality Questionnaire [7][a]). *Column Results:* MP: mental performance; ↑ ↓: increase/decrease of dependent variable induced by the drug as compared to placebo or pre-drug value; high/low scorers had their scores above/below median value on a respective scale. ESM, electronic supplementary material.

std *N*	temperament or personality trait	TM action	substance	dependent variables	scales for traits	results	Ap	ref.
1	extraversion (E)-introversion (I)	D2 antagonist DA precursor DA synthesis inhibitor	haloperidol L-DOPA AMPT	RT, CFF HVA	EPQ	halo challenge: both E & I equally reduced performance L-DOPA challenge: E & I: no change in performance, AMPT challenge: I clearly reduced performance, none in E HVA: no change, I & E	1/2	[43]
3	extraversion (E)-introversion (I)	DA synthetic inhibitor	AMPT	Subj state HVA	EPQ	E reported more drowsiness than I but their HVA did not differ	1	[44,45]
6#	extraversion (E)-introversion (I)	D2 antagonist D1/2 agonist	fluphenazine lisuride	Smoking urge PRL	EPQ	high E were PRL antagonist responders, E was not related to PRL agonist response[a]	2	[46]
5	Behav. Activ.(BAS)	DA reupt. inhib	mazindole	PRL	BIS/BAS	no diff in PRL change between persons with high and low BAS scores	2	[47]
2	thrill and adventure seeking (TAS), boredom susceptibility (BS)	D2 antagonist DA precursor	haloperidol L-DOPA	mental performance (MP) Subjective state	FPI SSS	halo challenge: High TAS and high BS subjects. tension ↓, MP ↑ or no difference; low TAS and low BS subjects: tension ↑, MP ↓ L-DOPA challenge: High TAS and high BS subjects: MP ↓, no change in tension; low TAS and low BS small MP ↑, tension ↓	1	[48]
5	novelty seeking (NS)	DA reupt. inhib	mazindole	PRL	SSS	PRL response in high NS > low NS subjects	2	[47]
6#	thrill and adventure seeking (TAS)	D2 antagonist D1/2 agonist	fluphenazine lisuride	smoking urge, PRL	SSS	high TAS and high ES were PRL agonist responders, no relation of TAS and ES to PRL antagonist response[a]	2	[46]
18	experience seeking (ES) disinhibition (DIS)	D2 antagonist D1/2 agonist	fluphenazine lisuride	affect. state, PRL, cortisol smoking urge	SSS	for both DA challenges high ES and high DIS subjects had identical blunted PRL responses but smoking urge was larger in high ES than in high DIS	2	[49]
7#	disinhibition (DIS)	D2 agonist	bromocriptine	PRL, GH	SSS	subjects with high DIS had higher GH than PRL responses	2	[50]

(*Continued.*)

Table 1. (*Continued.*)

std *N*	temperament or personality trait	TM action	substance	dependent variables	scales for traits	results	Ap	ref.
19#	motor and cognitive impulsivity (Imp)	D2 agonist SNRI (NE)	bromocriptine reboxetine	PRL, cortisol	BIS 11	persons high in Motor Imp. had low DA-induced PRL response combined with low NE-induced cortisol response persons high in Cognitive Imp. had high DA-induced PRL responses combined with high NE-induced cortisol responses	2	[51], ESM S4
2	aggression (Agg)	D2 antagonist DA precursor	haloperidol L-DOPA	MP: mental performance	FPI	halo challenge: in high Agg subjects: Tension ↓, MP ↑ or no change, in low Agg subjects: Tension↑, MP↓. L-DOPA challenge: in high Agg subjects MP↓, no change in tension; low Agg subjects: little MP↑, tension↓	1	[48]
4	olf. hedonic tone aggression	D2 antagonist D1/2 agonist	fluphenazine lisurid	urge to smoke	HHF	high-Agg and low-HHF-olf subjects: smoking urge ↑ with D1/2 agonist more than with D2 antagonist; low-Agg and high-HHF-olf. subjects: smoking urge ↑ with D2 antagonist more than with D1/2 agonist	1	[52]
20#	anxiety, depression	D2 agonist	bromocriptine	PRL (tme/size)	STAI, MPQ,	highly anxious and depressed subjects had low and late PRL responses	2	[50]
19#	phys anhedonia (PA)	D2 agonist	bromocriptine	PRL (size/time)	Anhed Scale	high PA subjects responded by low and late DA-induced PRL decrease	2	[53]
20#	fatigue (FA)	D2 agonist	bromocriptine	PRL (size/time)	TPQ HA4	high FA subjects respond by low and late DA-induced PRL decrease	2	[54]

[a]For definition of responders see §4.2. of the text, Study 6.

Table 2. Summary of studies with ***serotonin***- *and* ***noradrenaline***-related challenges and various traits conducted in the Department of Psychology, University of Giessen, Germany. *Note:* std *N*: ID number of the study presented; Ap: experimental approach (1: without, 2: with assessment of biochemical variables); ref: reference number indicates the number in the reference list related to the study; #: studies using drug hormone responses as independent variables; 5-HT: serotonin, 5-HT 1a and 5-HT 2: serotonin receptor subtypes 1a and 2; LSD: d-lysergic acid diethylamide; NE: norepinephrine (= noradrenaline); SNRI: specific noradrenaline reuptake inhibitor; RT: reaction time, CFF: critical flicker fusion frequency, PRL: prolactin, *For column 6, questionnaires, with reference numbers in reference list:* Anhed Scale: Chapman Anhedonia Scales [35]; BIS 11: Barratt Impulsivity Scale [36]; EPQ: Eysenck Personality Questionnaire [4]. EASI: Emotional Activity Sociability Impulsivity Scale [10] FPI: Freiburg Personality Inventory [38], IVE: Impulsiveness Venturesomeness Empathy Inventory [40]; MPQ: Multidimensional Personality Questionnaire [41], SSS: Sensation Seeking Scales [6] ES: Experience Seeking; STAI: State Trait Anxiety Inventory [42]; BDHI: Buss Durkee Hostility Inventory; TPQ: Three-dimensional Personality Questionnaire [7][a]). *Column results:* ↑ ↓: increase/decrease of dependent variable induced by the drug as compared to placebo or pre-drug value; high/low scorers had their scores above/below median value on a respective scale. ESM, electronic supplementary material.

std *N*	temperament or personality trait	TM action	substance	dependent variables	scales for traits	results	Ap	ref.
		Serotonin						
9	extraversion (E) neuroticism (N)	5-HT2 agonist	LSD	disturbed affect and thinking, blackouts	EPQ	LSD caused all three disturbances in high E + high N subjects and a single symptom each in either high N or high E or low E + low N subjects	1	[56]
11	extraversion (E)-introversion (I)	SSRI reupt. inhib. 5-HT2 antagonist	fluoxetine ritanserin	CFF, RT	EPQ	SSRI challenge: in E: performance↑ in I performance ↓ 5-HT2 antagonist: no effect in both, E & I	1	[57]
12	tempo	5-HT1A agonist. same + induction of aggression	ipsapirone	anger (subj. state) aggr. behaviour. PRL, cortisol	EASI	5-HT 1A agon.challenge: In high Tempo subjects: anger and aggresion↑, in low Tempo subjects aggression ↓; 5-HT1A challenge and induction of aggression: In high Tempo subjects anger ↓, in low Tempo subjects: no change. Both high and low-Tempo ss had blunted cortisol and PRL responses	1/2	[58] [59]
11	sensation seeking (SS)	5-HT2 antagonist	ritanserin	CFF, RT	SSS	5-HT2 antagonist improved RT in high SS subjects more than in low-SS	1	[57]
18	experience seeking (ES)	5-HT1A agonist	ipsapirone	affect, PRL, cortisol	SSS	5-HT1A agonist: High ES subjects had blunted cortisol response	2	[49]
12	impulsivity (Imp)	5-HT1A agonist +Induction of Aggression	ipsapirone	aggr. behaviour PRL, cortisol	EASI	5-HT1A agonist: In high-Imp-subjects aggression ↓; in low Imp. subjects aggression.↑; 5-HT1A agon. + induction of aggression: in high Imp subjects aggression↑, in low Imp.ss: no change blunted PRL in high-Imp subjects	1/2	[58], [59]
13	aggression (Agg) impulsivity (Imp)	5-HT1A antagonist	pindolol	PRL	FPI BIS 11	5-HT1A antagonist in high-Agg and high-Imp subjects: blunted PRL response	2	[60]
14	impulsivity (Imp)	5-HT1A antagonist 5-HT1A agonist	pindolol ipsapirone	core temperature	IVE	5-HT1A agonist and antagonist both decreased body core temperature in high impulsives more than in low impulsives	1	[61]

(*Continued.*)

Table 2. (*Continued.*)

std *N*	temperament or personality trait	TM action	substance	dependent variables	scales for traits	results	Ap	ref.
16	aggression (Agg) psychoticism (P)	5-HT1A agonist 5HT releaser	ipsapirone d-fenfluramin	affective state, cortisol, PRL	FPI R EPQ	5-HT1A agonist induced: cortisol ↑ and the 5-HT releaser blunted PRL ↑ in high-aggressives; Both, 5-HT agonist and releaser led to blunted PRL and cortisol ↑ in subjects with high Psychoticism scores	2	[62]
17#	aggression (Agg)	SSRI	s-citalopram	aggressive behaviour; cortisol	BDHI	SSRI challenge led to high aggressive behaviour in high-aggressives with high testosterone + high SSRI-induced cortisol responses	2	[63]
10	neuroticism (N)	SSRI	fluoxetine	RT, negat. mood	FPI	SSRI challenge: in high N subjects: Performance ↓ and neg.mood ↑	1	[64]
15	harm avoidance (HA)	5-HT1A agonist 5-HTreleas + SSRI	ipsapirone d-fenfluramin	cortisol, PRL	TPQ	High HA subjects were identified by high 5-HT1A agonist induced high cortisol responses + 5-HT releaser induced blunted PRL response	2	[55]
19#	social anhedonia (SA)	5-HTuptake inhib D2 agonist	citalopram bromocriptine	cortisol PRL	anhedonia. Scale	SSRI challenge: in high SA subjects: high cortisol response, in particular when combined with low DA agonist-induced PRL responses	2	[53]
20#	fatigue(FA)	SSRI	citalopram	cortisol (time/size)	MPQ	5-HT reuptake inhib. challenge: high-FA subjects show fast cortisol resp	2	[54]
		Noradrenaline						
8	harm avoid. (HA)	SNRI (NE)	reboxetine	cortisol	TPQ	SNRI challenge: cortisol ↑ more in high-HA than in low-HA subjects	1	[65]
19#	physical anhedonia (PA),	5-HT uptake inhib D2 agonist	reboxetine bromocriptine	cortisol, PRL	anhedonia scale	SNRI challenge: high PA subjects show cortisol ↑, in particular when combined with DA agonist induced high PRL ↓	2	[53]
20#	stress reactivity (SR); fatigue (FA)	SNRI (NE)	reboxetine	cortisol (time/size); smoking urge.	MPQ SR TPQ HA4	SNRI challenge: increase in smoking urge in high-SR subjects, but no change in their hormone responses High-FA subjects reacted by fast SRNI induced cortisol ↑	2	[54]

[a]The scales Harm Avoidance (HA) and its subscale Fatiguability (FA) are more consistent than the other scales in Cloninger's TPQ and later TCI questionnaires [55].

The dependent behaviour variables were selected because they reflect known basic biological effects of the TM-related drugs applied. For instance, critical flicker fusion (CFF) and reaction time (RT) refer to attention, speed and vigilance (studies 1, 2, 11). Craving (studies 4, 6, 19, 20) is a dynamical disposition based on neurochemical imbalance. Therefore, these measures are considered to serve as indicators of temperament.

The major conclusions from these studies are: valuable information on temperament and personality-related differences in TM affinities can be obtained 1. from crossover studies and 2. from the analyses of intra-individual constellations of

— drug effects on different functions and traits,
— different drugs applied to the same individuals,
— different response parameters of drug effects,
— different hormones released from the same drug.

Here is a summary of the main results.

1. Interactions between drugs and psychological functions or personality/temperament traits suggest

Studies 1 and 3: Extraverts were more susceptible with respect to states of drowsiness, introverts more with respect to decrease in performance by the DA synthesis inhibitor AMPT (alpha-methyl-paratyrosine) [43–45]. *Study 12:* Persons scoring high on tempo became more aggressive than low scorers upon 5-HT stimulation by ipsapirone, while the drug reduced aggressive responses in those scoring high on impulsivity compared to low scorers [58,59]; *Study 5*: High novelty seekers showed higher PRL responses induced by the DA uptake inhibitor mazindole than low scorers, while there was no difference between persons high and low in activation [47]. *Study 9:* Intra-individual constellations of traits: groups defined by high/low neuroticism and high/low extraversion (E + N+, E + N−, E-N+, E−N−) exhibited different types of mental disturbances elicited by the hallucinogenic 5-HT2 agonist LSD [56].

2. Responses to agonists and antagonists acting on the same TM system can demonstrate individual differences in susceptibility to deprivation from or stimulation of a neuroTM:

(1) *for the 5-HT system: Study 14*: Pindolol and ipsapirone, antagonist and agonist respectively to the 5-HT1A receptor: High impulsives were more susceptible to both ipsapirone and pindolol than low impulsives [61]. *Study 11:* Fluoxetine (SSRI) and ritanserin (5-HT2 blocker): the agonist agent separated extraverts from introverts, the antagonist high from low impulsives [57].
(2) *for the DA system: Studies 1 and 2*: L-dopa (DA increase) and haloperidol or AMPT (DA decrease): High aggressives as opposed to high novelty seekers were more affected by DA stimulation than by its blockade [43,48]. *Study 6*: Lisuride and fluphenazine: Types of PRL responders defined by the size of PRL responses to the DA agonist (lisuride) in relation to the DA antagonist (fluphenazine) were differently associated with personality traits: Agonist responders were found to be rather action-oriented adventure seekers, antagonist responders more addiction-prone extraverts [46]. *Study 4:* Lisuride and fluphenazine: participants low in hedonic tone and high in aggression developed an increase in cigarette craving with the agonist and a decrease with the antagonist, whereas low aggressives and high-hedonic participants exhibited the opposite pattern [52].

3. Responses to drugs with different modes of action within the same transmitter (TM) system might reveal the underlying specific vulnerability or may identify personality/temperament dimensions by combined vulnerabilities:

(1) *for 5-HT-stimulation: Study 15* showed that persons of low-habitual activity (fatigue = HA 4 on TPQ) could only be identified by the combined effects of subsensitivity to the 5-HT 1a receptor agonist (blunted cortisol response to ipsapirone) and of reduced 5-HT release to d-fenfluramine (blunted PRL response) measured at repeated sessions in the same individuals [55]. *Study 16* showed that differences in responsivity to the 5-HT1a agonist ipsapirone and to the releaser/uptake inhibitor d-fenfluramine were able to discriminate irritable impulsive aggressiveness (Ag) from 'psychoticism' associated 'cold' aggressiveness (P). High Ag exhibited higher susceptibility to the 5-HT1A agonist, indicated by increases of hormones; high P scorers responded by the well-known blunted hormone release to both substances [62].
(2) *for DA inhibition: Studies 1 and 3* showed that extraverts (E) and introverts (I) were differently susceptible to DA depletion by the synthesis inhibitor AMPT (E showed a higher state of drowsiness than I) and the D2 receptor blocker haloperidol (E showed less decrease of mental performance than I) [43,44].

4. Responses of different hormones to the same TM stimulation may reveal different pathways of TM stimulation:

Stimulation of D1 and D2 receptors leads to DA effects on the hypothalamus causing (a) cortisol increase via ACTH release from the frontal lobe of the pituitary, (b) GH increase from the posterior lobe of the pituitary via release of somatostatin and (c) activation of the tuberoinfundibular system leading to PRL release from the posterior lobe of the pituitary [66]. Similar mechanisms apply to the 5-HT system. So the relation of hormone responses to the same challenge drug may indicate underlying differences in affected systems related to traits.

Study 7 showed that persons with high DIS scores (disinhibitors) responded by higher PRL than GH responses to the DA agonist bromocriptine [50]. *Study 16:* Intra-individual differences between cortisol and PRL responses to both 5-HT stimulating substances, the 5-HT 1a agonist and the 5-HT releaser and uptake inhibitor, were observed within both types of aggressiveness [62].

5. Patterns of responses to different TM systems

As emphasized in §1 [33], each temperament trait is characterized by several TM systems. This is also demonstrated by

Study 18: High experience seekers (ES) could be separated from high disinhibitors (DIS, SS) by their responses to stimulation of the 5-HT and DA systems in three different experiments [49]. However, only crossover experiments can identify the intra-individual relationships between responsiveness of different TM systems suitable to discriminate temperament sub-systems.

Study 19. In a fourfold placebo-controlled balanced crossover study, hormone responses to stimulation of the 5-HT

system by the reuptake inhibitor citalopram, the NE system by the reuptake inhibitor reboxetine and the DA system by the D2 agonist bromocriptine, were used as independent variables, each divided into high and low responders according to the size of cortisol responses to 5-HT and NE stimulation and according to the decrease of PRL upon DA stimulation (these hormones had been identified to be the most reliable ones for each TM system). The study showed that facets of low-emotional responsivity, physical (PA) and social anhedonia (SA) [35] could be discriminated by responses to the three TM systems: low DA + high NE responses were characteristic for high scorers on PA as opposed to low DA + low 5-HT responses for high scorers on SA. This revealed similarities to patterns described for pathological diseases: PA reflecting the pattern of major depression and SA that observed in schizophrenia. A similar discrimination between facets of impulsivity has been tried: motor and attentional impulsivity, which have been distinguished in the clinical syndrome of attention-deficit hyperactivity, were assessed by the Barratt impulsivity scale [36] and could be discriminated by patterns of TM responses computed from data of *Study 19*

— motor impulsivity was characterized by low NE combined with low DA responses and
— cognitive (=attentional) impulsivity by low DA combined with high NE responses [51].

Results confirm the clinical observation of low DA in the attention deficit hyperactivity syndrome (ADHS), but also revealed a possible role of NE for inhibition and constraint (see electronic supplementary material, S4).

6. Patterns of response parameters within the same TM system

Most often only levels and magnitudes of responses are used in psycho-biochemical studies, but it is advisable to include further aspects of response curves, like latency of response, trying to match this to the speed component in questionnaire-based temperament traits. Therefore also early and late (=fast and slow) responses were defined for all three TM responses (for the method, see [54]). *Study 20:* The two components of depression: lack of activity+low endurance defined by fatiguability (FA) [7] and emotional reactivity and irritability defined by stress reactivity (SR) [41] had been expected to be differentially related to speed (FA to slow tempo, and SR to fast responses because of its affinity to impulsivity and emotional reactivity). Furthermore, since both components of depression are known to be related to disturbances of the 5-HT and NE [67] as well as of the DA system [68], high/low sizes of responses (see study 19) were combined with early versus late drug responses (onset of PRL declines in response to the DA agonist and increase of cortisol in the responses to the 5-HT and NE uptake inhibitors). Size and time of onset of response were used as separate independent variables, with questionnaire scores on FA and SR as dependent variables [54].

Discrimination of the two facets revealed: Late and low responses to the DA agonist challenge were observed in high as opposed to low scorers on FA, whereas no relations with DA responses emerged with the SR scale.

The underlying physiological mechanism of low and slow DA responses may be upregulation in numbers of DA receptors due to low DA production, so that longer time is taken for full-receptor occupancy with the DA agonist, leading to delayed PRL release via the tuberoinfundibular neurons [69].

Differences in responsiveness of the NE system only became evident from higher induction of smoking urge by NE stimulation in highly stress-susceptible individuals as opposed to low SRs, which reflects the higher psychological responsiveness of SR to NE increase induced by stress. Identical responses in the two facets were reflected by short response latencies to 5-HT stimulation in both high FA and SR scorers. This may point to either a common high postsynaptic 5-HT receptor sensitivity (perhaps resulting from low production of 5-HT), or to hypersensitivity of the HPA system, since receptors for corticotropin-releasing factor have been found to develop hypersensitivity in depression [70].

The broader relevance of low and late responses to DA stimulation could be shown by screening further personality traits with respect to this response pattern, which revealed that not only activity but also negative emotionality (neuroticism-related) aspects of temperament are characterized by DA deficiency combined with slow release [50] (electronic supplementary material, S5). This reflects the observation that on the positive end of the DA speed continuum, fast release as achieved by, for example, amphetamine-like drugs is associated with euphoric and activating effects, whereas slowly acting drugs like precursors (L-dopa) do not induce euphoria in healthy persons [71].

7. Shape of response curves as an example of heuristic aspects

Studies 7, 19, 20: Inspection of individual PRL response curves to challenge by the DA agonist bromocriptine showed an additional short-term PRL increase prior to the start of PRL decline in some of the participants. Dividing the sample according to those with and without this primary PRL increase [50] revealed that the PRL peak was associated with activity-related traits on a number of scales BAS (BIS/BAS) [37], achievement motivation (FPI [38]), but also with disinhibition (DIS, SSS [6]) and impulsivity (BIS11[36]), whereas persons without this phenomenon scored high on inhibition (FPI), constraint (MPQ [41]) and timidity (TPQ HA3 [7]) [50] (electronic supplementary material, S6). So far, it is not clear if this initial PRL peak reflects hypersensitivity of pre-synaptic D2 receptors or if there are extra PRL agonistic DA neurons, as hypothesized by Burris *et al*. [72]. Further screening revealed that this PRL peak also characterized traits related to extraversion (FPI), positive emotionality (MPQ) and attachment (MPQ). This indicates that just like in temperament questionnaires, specific aspects of DA activity may also indicate overlap between positive emotionality and activity on the one hand and between activity and impulsivity on the other.

6. Hormone responses as moderators or mediators of drug-induced behaviour?

As shown by the early psychopharmacological studies [27–29] and our studies following Approach 1, a characterization and discrimination of temperament traits by TM-related drugs can also be obtained by assessing respective drug- and temperament-related behaviours like RTs, vigilance or ratings on affective state. Therefore, the question has to be raised: do we have to bother with the neurochemical responses in order to understand TM–behaviour

relationships in temperament research? (In other words, is the behavioural indicator moderated or even mediated by the neurochemical response?)

In two of our experiments using Approach 2, the hormone responses assumed to indicate TM sensitivity showed a closer relationship to the drug-related behaviour change than the drug itself or were able to modify the behavioural drug response:

Study 6: Additional evaluations indicated that there was no general difference between high and low extraverts or novelty seekers in smoking urge under the condition of the DA agonist (lisuride) or the antagonist (fluphenazine) but that dividing participants into high and low PRL responders to DA stimulation and DA blockade, respectively, disclosed that the biochemical and behavioural responses were correlated depending on the specific susceptibility of the individual to increased or decreased DA activity [46]. In the condition with the agonist lisuride, high agonist PRL responders developed more cigarette craving than lows, and in the condition with the antagonist fluphenazine, high antagonist PRL responders developed more cigarette craving than lows. This means the biochemical response may be a prerequisite for the psychological change only in highly susceptible individuals. This was also supported by the fact that individuals responding by equal PRL responses to both drugs also did not differ in smoking urge in the lisuride and fluphenazine condition. This indicates that manipulations of the TM systems by stimulation and blockade cannot only help to trace specific temperament-related susceptibilities, but also provides some information on the question under which conditions a possibly causal relationship between the biochemical and psychological indicator of TM activity may become manifest.

Study 20: An additional evaluation indicated that an expected overall effect of the DA agonist bromocriptine on smoking urge according to incentive stimulation theory [73] was not observed. However, dividing participants into high and low DA PRL responders revealed higher smoking urges among PRL high responders, indicating higher relevance of the biochemical marker for supporting the incentive stimulation theory of DA than the drug itself [54].

In an additional evaluation of these data, a significant interaction of the DA PRL response with stress responsiveness (SR) indicated a modifying role of the temperament trait SR: high SR scorers with low PRL response (indicating low DA supply) developed a decrease in smoking urge, whereas in non-stress reactive (low SR) low PRL responders smoking urge seemed to be unaffected by DA availability. This may lead to the hypothesis that for high SR individuals suffering from low DA supply, the DA challenge might rather have served as a DA substitute 'pacifying' their smoking urge just like smoking a cigarette in everyday life, since nicotine is known to release DA. This would match the DA deficiency (substitution) theory [74], whereas high SR high PRL responders react according to the incentive motivation theory [73].

So these examples suggest that the hormone response may sometimes be more helpful for discriminating temperament traits and related behaviour than the drug itself, and that depending on personality-related susceptibilities, the biochemical responses might be correlated with the psychological changes or even turn out to be their prerequisite.

7. The role of additional experimental factors

(1) *Stressors as adjunctive tools for temperament discrimination*. As demonstrated in a number of psychopharmacological experiments, additional application of stressors in drug studies may disclose their modifying effect on differences between high and low neurotic or high and low extraverted participants [15,27,29]. For example, in *study 12*, experimental induction of aggression did not change the drug-induced differences between high and low scorers on tempo but abolished the ipsapirone-induced decrease of aggressive response in impulsives [59]. The detection of temperament-related susceptibility to the GABA-ergic substance alcohol indicated that additional application of stress was suitable to increase the difference in plasma catecholamine responses between extraverts and introverts and between personality-related drinking habits [75,76].

(2) *Drug doses for detecting temperament-related susceptibility*. A promising approach is the use of drugs with biphasic actions (first phase stimulating, thereafter sedative effects) such as alcohol and nicotine. This biphasic action is also reflected by different dose levels. By this approach, individual differences in the point of shift from stimulating to sedating effects at different dosages could, for example, be detected by testing vigilance (CFF) at two doses of nicotine and placebo in the same individuals. The point of shift indicating difference in susceptibility to stimulating and sedating effects was found to be related to suggestibility, a trait sharing aspects of mental activity and flexibility in temperament research [77,78].

(3) *Information provided to participants along with drug application*. Information about the actions or side effects of drugs are widely known to modify placebo or drug-induced behaviour changes [29,79], but have also been shown to affect interactions between drugs and personality traits as shown by a study on the oral application of nicotine [80]. The information of receiving either nicotine or a placebo modified performance outcome differently in extraverts and introverts. Even biochemical responses have been shown to be modified by the accompanying information given with the drug [81].

8. Limitations and conclusion

Different approaches to the use of drug studies in research on biochemical correlates of temperament have been illustrated by some experiments of our group in Giessen. Briefly reported results were intended to provide hypotheses for further research in this field. A special emphasis was put on the assessment of intra-individual constellations of TM responsiveness to different TM systems, because this can provide information on imbalances between the systems within the individual. Furthermore, using the biochemical responses as independent variables in temperament research may provide future ideas for the classification of personality and temperament traits.

The present considerations on neurochemical indicators of temperament have their *limitations*.

Replications by other research groups are limited to experiments targeting single TMs, but studies aiming at

intraindividual configurations of neurochemical variables by repeated measurement designs have not yet been replicated. Further limitations are low sample sizes due to crossover requirements, missing tests of dose response effects, neglect of specific brain areas and missing proof of specificity of results by experimental variations with similar output variables and performed in samples of different age and gender. Furthermore, additional neurotransmitters like GABAergic or NMDA receptor-related TMs or peptides interacting with TMs have not been considered. Finally, last but not least, these studies applied mostly personality scales instead of tests measuring specific temperament dimensions.

However, the major intention was to illustrate approaches for further neurochemical research on temperament rather than to provide unassailable results. The following *conclusions* may be drawn, nonetheless:

(1) The inclusion of biochemical responses into research on personality–drug response relationships may provide useful additional information on underlying mechanisms of personality differences in drug-induced changes of behaviour or affective states.
(2) The use of biochemical responses as independent variables can, on the one hand, help to identify clusters of personality or temperament traits and, on the other hand, help to discriminate sub-dimensions of personality or temperament traits.
(3) The inclusion of additional response parameters like latency and shape of the response curve may reveal common underlying mechanisms of TM sensitivity in clusters of traits.
(4) Configurations of responses to different neurotransmitter systems are suitable to illustrate interactions and mutual dependence between TM systems in predicting temperament traits.

Future research should be directed to:

(1) comparing specific temperament dimensions manifested on cognitive, behavioural and emotional levels with respect to common or discrepant biological correlates;
(2) neuroimaging, in particular PET studies, should try to allocate the biochemical indicators of TM activities to different brain areas where TMs and their receptor subtypes are differently distributed and serve different functions;
(3) molecular genetic studies targeting the same system as the challenge drugs performed in the same individuals are rare at present but could verify and specify the hypothesized biochemical personality-related mechanisms by relating them to specific enzyme or receptor polymorphisms;
(4) finally, neglected approaches to study biochemical correlates of temperament traits like adaptability and rhythmicity should be taken up by relating these temperament facets also to endogenous rhythms of hormones (e.g. to the ability to shift one's cortisol circadian rhythm [82,83]) or by relating disturbances of the menstrual cycle to disturbed behavioural adaptability assessed by questionnaires [84].

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