Contingent Tunes of Neurochemical Ensembles in the Norm and Pathology: Can We See the Patterns?

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Keywords

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Abstract

Background/Aims: Progress in the development of DSM/ICD taxonomies has revealed limitations of both label-based and dimensionality approaches. These approaches fail to address the contingent, nonlinear, context-dependent, and transient nature of those biomarkers linked to specific symptoms of psychopathology or to specific biobehavioural traits of healthy people (temperament). The present review aims to highlight the benefits of a functional constructivism approach in the analysis of neurochemical biomarkers underlying temperament and psychopathology. **Method:** A review was performed. **Results:** Eight systems are identified, and 7 neurochemical ensembles are described in detail. None of these systems is represented by a single neurotransmitter; all of them work in ensembles with each other. The functionality and relationships of these systems are presented here in association with their roles in action construction, with brief examples of psychopathology. The review introduces formal symbols for these systems to facilitate their more

compact analysis in the future. **Conclusion:** This analysis demonstrates the possibility of constructivism-based unifying taxonomies of temperament (in the framework of the neurochemical model functional ensemble of temperament) and classifications of psychiatric disorders. Such taxonomies would present the biobehavioural individual differences as consistent behavioural patterns generated within a formally structured space of parameters related to the generation of behaviour.

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Functional Constructivism in the Search for BioBehavioural Taxonomies

Challenging Complexity in Tracing Neurochemical Biomarkers for BioBehavioural Traits

The idea that biochemical systems are underlying factors in individual differences in behaviour is not new and has a long history of validation. It was proposed over 2,500 years ago as a concept of “temperamentum” (i.e., chemical “mixtures”) by Hippocrates and then Galen. Extensive studies in neurochemistry and psychopharmacology, as well as the long-established cultural practice of

using psychostimulants, provided a “proof of concept” for that idea. Despite the age of this theory, the long search by humanity for magic potions that could change someone’s behaviour, and modern advances in neurochemistry, the exact functional contributions of various chemicals to behavioural regulation remain elusive [1]. The search for biochemical correlates of biobehavioural traits was eventually confronted with the necessity of sorting out the functionality of neurotransmitters (NTs). This sorting task, however, appeared to be far from trivial because of the following:

- More than a dozen non-peptide and over 100 peptide NTs were identified, all having multiple functionalities and distributions in the nervous system; the multiplicity of single-NT functions suggests a category error for models describing one-to-one correspondence between any NT system and specific trait/symptom/function.
- Many of these NTs were found to have a diversity of receptors, each having different functionality and location pattern. For example, there are (so far discovered) 5 types of dopamine (DA) receptors, 9 types of adrenergic receptors, 14+ types of serotonin (5-HT) receptors, and 2 families of acetylcholine (ACh) receptors (each having 5–12 subtypes). A similar diversity of receptors has been found for histamine, gamma-aminobutyric acid (GABA), glutamate (Glu), and the endogenous opioids.
- Different brain structures with neurons containing the same types of NT have been found to differ in terms of distribution and types of receptors [2].
- Differences have been found in receptor distributions between mammalian species [3–5], limiting the benefits of comparative studies.
- NT appeared to regulate one another’s activity in a contingent manner via several mechanisms [2, 6–9]. The same 2 NTs can be rivals under one condition (or location), suppressing each other’s release, or partners under another condition/location, having a co-release. In fact, in most cases of neurotransmission, there is a co-release of NTs of different families (i.e., monoamines, neuropeptides, and amino acid NTs); however, the coupling of NTs in such co-release is highly specialized between brain structures and projections [2, 6, 8].
- Receptors known to be primary for specific NTs occasionally showed affinity to the “wrong” NTs [7, 9–11].
- ACh and monoamine NTs often employed so-called “volume transmission” (i.e., transmission in which NT is released into the extracellular space and acts on whatever neurons there are receptive to it) [3, 12, 13].

The “messy” nature of neurotransmission and the mutual regulation between NTs limits progress in identifying neurochemical biomarkers of behavioural traits and symptoms of psychopathology. This review highlights the benefits of using a functional constructivism (FC) approach [14, 15] in the analysis of contingent relationships between the main neuromodulating NTs. The functionality of neurochemical systems and their relationships are labelled here with formal symbols to facilitate a more compact analysis of the functionality of regulatory NT systems. The text, admittedly, looks strange with these symbols but the complexity of neurochemical biomarkers and the wealth of findings in neuroscience calls for the development of a formal language to facilitate scientific discussions on this matter.

This review uses only those findings in the neurochemistry and neuroanatomy of leading neurotransmitter systems that are relevant for arguments on the functionality and contingent relationships between neurochemical systems. This review does not include all details about the neurochemistry and neuroanatomy of NT systems that can be found elsewhere in handbooks on these subjects [16–19].

Variations within neurochemical systems underlie both temperament (according to its definition) and psychopathology (as seen in the progress of psychopharmacology), and here we show the possibility of a common taxonomy of these neurochemically based individual differences based on the formal framework proposed herein. Temperament traits are considered as consistent behavioural differences in mentally healthy people, whereas psychopathology and, in some cases giftedness [20], are represented as extreme deviations of these differences. For simplicity, we abbreviate consistent behavioural patterns as CBP, referring to these 3 types of biobehavioural individual differences. The approach that we found useful for such analysis can be called functional constructivism [15, 21, 22].

Constructivism in Biobehavioural Sciences

The main principle of constructivism is that all behavioural elements are neither reactive nor proactive but constructive. All processes and actions are generated through the integration of behavioural alternatives selected and sequenced for their relevance. According to the dictionary of the American Psychological Association, *behavioural integration* refers to the combination of separate individual behaviours into a synchronized or coordinated behavioural unit. The idea that psychological phenomena have a constructive nature is not new. It was

first experimentally demonstrated in the work of Bernstein [23–25] and Bartlett [26] in the mid-1930s in psychology and by Anokhin in psychophysiology [27]. Bernstein derived his model based on the use of his pioneering devices for tracking the construction of actions by learners versus experts – techniques that are now used in modern kinesiology. Anokhin's experiments involved neurophysiological measurements of the behaviour of cats whose muscles and nerve endings were surgically rewired in opposite directions (i.e., switching the position of flexor-extensor muscles, and afferent-efferent nerves). Both experimental schools and subsequent research clearly demonstrated that behaviour is a result of selection from multiple alternatives (“degrees of freedom,” or df) for perception, attention and elements of observable actions. In other words, behaviour cannot simply start from a stimulus because there are too many stimuli and too many ways to react to each stimulus. The concept of df was adopted since 1930s in many sciences, including physics, chemistry, engineering, and cybernetics. In psychology, the concept of df suggested that behaviour is a sequence of choices from multiple alternatives and a number of factors influence these choices (from genetic to sociocultural). The concept of df is used in psychological experiments on animal behaviour in labyrinths, serving as simplified decision-making models. Bernstein was credited for describing the *degrees of freedom problem* in motor behaviour [23, 24], which later was expanded to degrees of freedom in neuronal activities. The problem refers to the fact that the same result of actions can be reached by multiple ways in moving parts of the body; vice versa, the same motions can be employed in reaching different results. An excess of df was noted in neuroscience, in the behaviour of neuronal ensembles and in the multiple chemical processes involved in neurotransmitter release.

The generative, constructive nature of behavioural regulation and the “df problem” were noticed in different biobehavioural sciences, including kinesiology, psychophysiology, cognitive, developmental, ecological, and educational psychology, psychological modelling, and psychology of emotions (see [15] for review). At the neuronal level of behavioural regulation, it has been shown that brain connectivity is very plastic and that neuronal ensembles of the brain re-organize themselves with a change in situational contexts and tasks [28–33]. At the cellular-receptor (i.e., molecular) level, studies in neuroscience have described multiple phenomena confirming the FC principle. For example, the release of monoamines happens in several stages, and each stage involves a cascade

of contingent transformations regulated by mediators such as GABA, Glu, G-protein-coupled receptors, transcription and neurotrophic factors, enzymes, metabolites, ATP, calcium, and other chemical systems, including the regulatory impact of other monoamines [18, 34]. Similar complexity and contingent construction was described in the action of opioid receptors (ORs) [21, 35]. After transmission, the molecules of NTs are quickly metabolized at their releasing sites and therefore must be generated all over again later. During the construction and disassembling of NTs in the brain and gut, the availability of the chemical substrates, as well as variations in composition, can be affected by genetics, environmental factors, physiological state of the body, state of the supporting microglia cells, and the state of the brain cells themselves that manufacture the needed components.

Nervous systems solved the df problem in behaviour by having several “parallel processing” systems, each taking care of specific aspects of selection of these df. In fact, the functionality of most nervous system components can be described as select, select and select, suppressing irrelevant df. The final choice of what direction a hand should move to or what words should be said, out of a vast space of potential moves and words plus the sequencing of these actions in a specific order, has been referred to as “*programming of behaviour*.” Both Bernstein and Anokhin highlighted several information-processing “blocks” that precede the “block of programming,” and multiple subsequent models of behavioural construction converged to this idea. Despite differences in the architecture and names of the blocks in these models, they identified pre-programmed “blocks” related to motivation, executive capacities, memory and trigger stimuli. These blocks should be processed and integrated during the stage of programming of actions and then gradually sharpened with more detailed units, with feedback from the execution of actions. Similar functional “blocks” or stages in the construction of behaviour have been commonly described since the mid-twentieth century in constructivism theories in kinesiology [24, 25], functional neurophysiology [36], clinical neuropsychology [37], and behavioural cybernetics.

FC Approach in Classification of Neurochemical Biomarkers

A majority of neurochemical systems described in this review were previously identified in neuroscience by their distinct neurochemical processes and connectivity. The most commonly described networks that were differentiated based on their functional connectivity are the hypo-

Table 1. The 8 regulatory Systems, with their notations, contribution to development of the program (choice) of actions and examples

Sign	System	Space range	Time range	Novelty range	Contribution to programming	An example: next behaviour when writing a paper...
O	Maintenance	In-body	Now	Keep sustain	Dependence of the program on body's endurance, constitution, health, and microbiota	A person's decision to continue will depend on physical endurance required to maintain physical posture, typing, and using physical distractions (walking and cleaning) to stimulate writing
\\//	Probabilistic procesg	In-context	Ever	Keep collect info	Adjustment of the program to the context, and gathered info about external regulators (memory)	Context processing and social expectations will affect the schedule of writing, the choice of topics, structure, and words in the text
OO	Contextual tuning	In-context	Now	Keep monitor	Sustained attention in monitoring df	Monitoring the progress in writing and appropriateness to the task
/\	HPA, HPG, HCA	In-body	Now	Change, incl. past df	Generation of actions based on patterns in stress & sex hormones	Stress related to deadlines and sex drive might affect the schedule and even the content of writing
//\	Orientation expansion	In-context	Now	Search/process new df (change)	Assessment of the context in terms of novelty and changes, including a search for new df in behaviour	Inability to proceed with writing using the current resources will trigger the search for new options & information. Also, unexpected information will activate this System and pause []
?!	Emotional dispositions	In-body	Ever	Keep expect	MOR-based sense of approval (!), KOR-based mobilization (?) of//\, or DOR-based initiation of actions (I) create OR biases in behav. programming	OR systems generate dispositional (MOR-based) security and optimism about paper's outcomes, (KOR-based) perceptual mobilization, and (DOR-based) readiness for writing. These dispositions affect the choices and sequences in writing
[]	Integration of a program	In-context	Ever	Change, incl. past df	The choice of actions and their sequencing based on biases from the other 7 Systems	Integration of "votes" from all 7 Systems generates the final choice of actions and their sequences, with choices for plan-A and B in case of failure
[[]]	Skills development & usage	In-body	Ever	Reintegrate change	Previously composed units of behaviour have a priority for inclusion into a new program of actions	After producing some writing, the choice of wording, use of computer, colour markers, pencils, and the production of similar expressions becomes easier and faster

Shadowed rows relate to the integration of actions: the []-System as an integration of new actions and the [[]] System as an integration of well-learned actions. The last row also contributes to the integration of a new program. The column "System" lists the names of neurochemical Systems for the column "Sign." Time range contrasts behavioural aspects requiring immediate regulation ("now") versus all time-related degrees of freedom ("ever"), including past experience, future possibilities, and "now." HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; HCA, hypothalamic-catecholamine axis; MOR, mu-opioid receptor; DOR, delta-opioid receptor; KOR, kappa-opioid receptor.

thalamo-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal (HPG) axis, "hypothalamic-catecholamine axis" (HCA), "limbic system," "attentional networks," "sensory-motor networks," default network," and "reward network." There are multiple opinions concerning how these regulatory systems should be partitioned and named, and the Functional Ensemble of Temperament (FET) model offers one such functional partitioning called "*functional constructivism*" (FC, i.e., a constructivist approach with the focus on functional dif-

ferentiation in biobehavioural systems) [21, 22, 38, 39]. This review uses the FC approach linking the functionality of neurochemical systems to the universal architecture of generation of behaviour as described in constructivism models.

Following constructivism models, the FC differentiates between preprogramming selection, programming, and post-action processes. The first 5 "parallel processing Systems," which are described below, trim and select behavioural alternatives forming a preprogramming stage

of action selection, and the post-action processes following execution of the program also contribute to this selection (Table 1). In many situations, a new program of actions is not required; however, exchanges between these pre- and postprogramming Systems continue as short-chain interactions. When a new program is required due to the novelty or complexity of a situation, it also can be generated subconsciously, on the fly, without subjective awareness of this process. The “construction” or generation of behaviour is, therefore, a mainly unconscious process, and the “programming” of behaviour is most often not a goal-directed process. Instead, it is a gradual narrowing of options to a small set of plan A, plan B, plan C, and a no way plan that a person uses for mostly routine-based behaviour. Having said that, in this review, we trace the most complete chain of involvement of neurochemical systems of behavioural regulation, namely, how a goal-directed behaviour is being constructed for a new action (Table 2). The multiplicity of options for each action facilitates flexibility of behaviour that can be *contingent* (i.e., dependent) on a situation. Similar contingencies exist at the neurochemical level in relationships between the Systems described below.

Bernstein’s and subsequent models are heavily used in cybernetics, however there is an important difference between cybernetic and natural contingencies. In cybernetic models, all networks are viewed as ever-present blocks, each with a specific functionality and where each block executes its function on demand from other blocks. In contrast, natural contingencies follow the natural selection principle, in which demands of one System on another are not honoured unless they are compatible with the state of that System [38]. In this sense, our model considers the relations between neurochemical systems as natural contingencies that are based on the compatibility and complementarity of their states [40–42].

The functional roles of multiple NTs in generating consistent behavioural patterns (temperament) was proposed earlier in our neurochemical model FET [20, 21, 38, 39]. This model summarized experimental evidence from neurochemistry, differential psychology, psychiatry, endocrinology, and addiction research. Due to the complexity and multidisciplinary nature of the subject, the FET can be viewed as a framework hypothesis for the functional partitioning of biochemical biomarkers of behaviour. In this review, the FET model represents CBPs (temperament traits and symptoms of psychopathology) as the product of contingent interactions between 8 neurochemical systems. The functional aspects of behavioural construction regulated by these systems (Table 1) can be mapped into

a three-dimensional space (Fig. 1) (the dimensions of social functioning were excluded).

Neuroanatomic Structure-Based Connectivity and Neurochemical Functionality Provide Different Partitions of Biomarkers

Since this paper looks for function-based partitioning and classification, the functions assigned to neuroanatomic networks might be different from the partitioning of functions proposed in the FET for neurochemical systems. Here are a few important notes in this regard:

- Multiple neurochemical systems are found in every brain structure, and vice versa, every neurochemical system are found in multiple brain structures. In this sense, we should not expect a strong correspondence between neuroanatomic and neurochemical partitions.
- There is a mismatch between the most dense location of receptors and the sites with the release of the NTs that bind to those receptors [2].
- As noted, all neurotransmitter systems, including ACh and monoamine NTs often use “volume transmission” (i.e., transmission in which the NT is released to the extracellular space and diffuses to other neurons), some of which are receptive to it [3, 12, 13]. The localization of functions to specific neuroanatomic structures, in this case, is not possible.

We, therefore, do not argue against a functional partitioning proposed from neuroanatomic analysis but suggest that the functional partitioning of neurochemical systems will likely be different from the classification of neuroanatomic networks. This review, therefore, does not use the term “network,” leaving this term to neuroanatomic models of brain structural connectivity. Instead, we used the term System, capitalizing the first letter and referring to neurotransmitter systems operating across various brain structures.

Embodiment – Homeostatic Maintenance O-System

Neurochemical Components of the O-System: 5-HT and Neuropeptides as Major Players

The following systems are considered here as a part of homeostatic maintenance System:

- Hypothalamic neuropeptides (NP) and Histamine.* The chain of behavioural construction starts from the awakening of the body, and so we start the list of Systems from NP such as orexins (also known as hypocre-

Table 2. Brief information and contingencies in seven out of eight regulatory Systems

Systems	O – Embodiment, maintenance of cycles	\\// – Context-tuning & probabilistic processing	//\ – Expansion (orientation)	?! Dispositions, 1st draft of a program	[] – Programming-Integration	[[[] Sorting-storing the integrated units
Logos	[[[] → O-\\// ← \\//\	O → OO,\\// ← //\	OO,\\// → //\ ← ?!	//\ → ?! ← []	?! → [] ← [[[]	[] → [[[] ← O
Main NTs	5-HT, NP, gut biota	ACh, Glu-GABA	NE, Glu	MOR-KOR	DA, DOR-MOR	ACh, GABA-Glu, 5HT
Partners	H, ORE, MOR	5-HT (cortex)	ACh, hormones, KOR	NE, DA	ACh, GG, SubP	DA, A, SubP, NP
Lead structures	RN, HT, microbiota, immune system, glia	BF, Cortex	LC, HT, AM, Th	VTA, NAc, AM, micro-biota	mPFC, NAc, Caud, Put	GP/SN, STN, PPN, Crbm; cRN; HC, dLTA
Transitions	Homeostatic 5-HT & ANS cycles manage well-defined behavioral elements in tune to context (\\//) until their set is not sufficient and new alternatives (change) are needed (//\)	Context analysis (\\//) and monitoring of d.f. (OO) summarizes environmental options for busting Capacities & responding to the Needs, comparing it to body's capacities (O)	The hormonal (//) and NE-based (\\//) arousals search for new behavioural alternatives. This search is influenced by C/N context (//\) and OR-based dispositions	The appraisal of the external (\\//) and internal (O) C/N generates rough behavioral directionality (emotional dispositions) and 1 st sketch of the program	A program of actions is integrated based on the OR-supplied summary, contextual information and previous experience, habits and skills	Performance of actions creates LTP/D and metabolic mechanisms to provide motor and cognitive readiness and facilitate sequencing of actions
“←” L (left) types of CBP	O-\\// ← OO, \\//\ (1L) Context requires adjustment in local metabolic loops maintaining the stereotyped behaviour but within the limits of learned alternatives	OO, \\// ← //\ (2L) Context analysis (\\//) and monitoring of d.f. are influenced by attention to novelty that overshadows other contextual information.	//\ ← ?? (3L) The NE AM-TH-cortical system, with KOR > MOR imbalance, signals a poor N/C fit so a further search for alternatives and for guidance of behaviour is requested	?! ← [] (4L) The programs sketched by the ventral striatum are too challenging, so a revision of the directionality by the (?) system is needed (KORs suppress MOR & DA)	[] ← [[[] (5L) The sequence and content of actions cannot be implemented and should be revised, after the attempts by the habits-system to proceed with it	[[[] ← O (6L) The metabolic 5-HT and HT systems, cerebellum and ACh PPN send negative feedback due to inability to learn (or their incompatibility)
“→” R (right) types of CBP	O-\\// → OO, \\//\ (1R) Homeostatic maintenance cycles determine the focus of attention, supporting stereotyped behaviour & suppressing attention to novelty	OO, \\// → //\ (2R) The cortical-HC ACh-GG processing of context directs the search for novel information	//\ → ?! (3R) The lower arousal in NE AM-TH-cortical system, with MOR-KOR, signals a good N/C fit of capacities, calling off the search for new alternatives	!! → ?! (4R) The ventral striatum approves the program with an activation of MOR and deactivation of KOR, all leading to the DA release	[] → [[[] (5R) The chosen program is trimmed to the detailed implementation by the basal ganglia & by the existing skills set (incl. Cerebellum)	[[[] → O (6R) The metabolic 5-HT and HT systems and ACh PPN create positive feedback from the attempts to execute actions and store them as learned skills
FET mapping	O //\ [] OO \\// [] O\ //\ /\\[] O //\ [] !! ?? I	O //\ [] OO \\// [] O\ //\ /\\[] O //\ [] !! ?? I	O //\ [] OO \\// [] O\ //\ /\\[] O //\ [] !! ?? I	O //\ [] OO \\// [] O\ //\ /\\[] O //\ [] !! ?? I	O //\ [] OO \\// [] O\ //\ /\\[] O //\ [] !! ?? I	O //\ [] OO \\// [] O\ //\ /\\[] O //\ [] !! ?? I

The second row gives the names, labels and interactive teams of these Systems lined up in the one of possible sequences of their interaction (in the case of goal-directed behaviour); arrow point to the named System (at the middle) that mostly interacts with two (sides) Systems. The subtables in the last row correspond to the 12-components-structure of the FET shown in the Table 3. The 3rd row in these FET subtables correspond to social temperament traits, in which hormonal systems are suggested to play an important role. However, these systems are not discussed in the current review. Note: the \\// column includes the sustained attention system OO, and the //\ column includes the ^-System of hormonal regulation. 5-HT, 5-hydroxytryptamine (serotonin); ACh, acetylcholine; NE, noradrenaline; DA, dopamine; NP, neuropeptides; Glu, glutamate; H, histamine; A, adenosine; ORE, orexins; SubP, Substance P; KOR, MOR, DOR; kappa-, mu- and delta-opioid receptors correspondingly. Brain structures: RN, raphe nucleus; mPFC, medial prefrontal cortex; HT, hypothalamus; HC, hippocampus; BF, basal forebrain; LC, locus coeruleus; (dL, V)TA, (dorsolateral, ventral) tegmental area; Th, thalamus; AM, amygdala; NAc, nucleus accumbens; Caud, caudate nucleus; Put, putamen; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; Crbm, cerebellum; GP, pallidum; SN, substantia nigra.

Fig. 1. Eight neurochemical Systems (described in text and presented by their labels and titles, in boxes) that regulate 8 different aspects of behavioural construction. They differ in dealing with different degrees of freedom (df) in terms of novelty, time range, and space range of df. The colour gradient contrasts the differ-

ences in df: the darker the colour, the more df the system processes. Darker colours include the df that are assumed in the lighter colours. 5-HT, serotonin; ACh, acetylcholine; NE, noradrenaline; DA, dopamine; NP, neuropeptides; Glu, glutamate; GG, GABA and Glu; OR, opioid receptor systems.

tins) and a serotonergic “cousin,” melatonin that play key roles in sleep-wake cycles and behavioural arousal [43]. Histamine neurons, which are also concentrated in the hypothalamus (HT), also provide behavioural arousal. Other hypothalamic NP (including hormones) regulate multiple bodily cycles, physical endurance, stress response, and other endocrinal aspects of behaviour, as well as co-release with lead neuro-modulators [26, 44].

- b. *Serotonin (5-HT)* as a maintenance manager is present in all regions of the body and the brain, having seemingly full control over them. The nuclei that have 5-HT-producing neurons are located in the brainstem, forming a widely spread group called the raphe nuclei (RN). Serotonin is not stable and must be manufac-

tured by 5-HT neurons from tryptophan before its use and then quickly decomposed. Neither brain nor body make their own tryptophan and so both rely on the tryptophan supplied by gut microbiota or by food [45, 46]. This makes gut microbiota an important player in the O-System [47]. Moreover, 90% of tryptophan serotonin production is used by the body, not the brain, for the regulation of many internal organs, including blood vessels and primary sensory areas. Considering its distribution, 5-HT, therefore, can be called “a body neurotransmitter.” In contrast to the 5-HT in the body, the release of 5-HT in the brain is often mediated by GABA-Glu (GG) NTs via co-localization and co-release of these transmitters and/or volume transmission [8, 48]. The dorsal RN also express practically all

leading NTs, which are released from coming projections to it and by volume transmission: GG, DA, NE, nitric oxide synthase, enkephalin, substance P, neuropeptide Y, galanin, and corticotropin-releasing factor (CRF) [49]. Many 5-HT neurons in the dRN have colocalization and co-release with neuropeptides. Finally, there is a direct managerial position for 5-HT in the regulation of wake-sleep (circadian) cycles, which are the product of complex relationships between several neurochemical systems [43, 50, 51]. In contrast to the other monoamines, the regulation of 5-HT neurons in the dorsal raphe nucleus by orexins is likely state dependent [52] and bidirectional, in the form of a direct excitatory action and an indirect inhibitory one [53].

- c. The gut-brain cooperation is covered in detail in other reviews [47, 54, 55].
- d. The *immune system* contributes to the development and plasticity of synapses, regulates many NT systems, and its dysregulation impacts psychiatric health [56–58].
- e. *Glia* are the neuron's service stations and middle man between brain cells and blood vessels. Glial cells serve as precursors to neurons in the brain, provide a scaffold for their radial migration ([59], p. 1,190), provide repairs of synaptic connections, respond to injuries and infections, and also monitor the electrical activity of neurons [60, 61]. Moreover, the most prevalent neurotransmitter in the brain (90%+), Glu, is synthesized not by neurons but by glial cells (astrocytes) and then transported to and from neurons by a special transporter. This makes the glia an important diffuse system which regulates behaviour.

Functional Patterns of Neurochemical Connectivity of the O-System

Serotonin, hypothalamic neuropeptide, immune, glial, and endocrine systems are all linked to the homeostatic maintenance of nervous and body processes [26, 45, 57, 61, 62]. Since these processes operate in the form of internal cycles of composition and decomposition, we use the notation “O”-system for this neurochemical network. These cycles operate to support a massive amount of stereotypical background actions that constitute much of behaviour (well-learned habits and skills and also the simplest actions such as walking, listening to background noise, maintaining posture, chewing, etc.). The connectivity of the O-system is difficult to trace due to its global and diffuse nature. Still, several brain and body systems can be identified as the headquarters of this system.

One of the most prominent brain structures of the O-System, the HT is known as the centre of cooperation between endocrine and nervous systems. It manages energy metabolism, endurance, adenosine-based arousal, appetite, and other homeostatic functions. Histamine and orexin cells in the HT project to almost all brain areas and provide behavioural arousal [50, 51, 63–67]. Not only all brain structures but also all neurotransmitter systems “consult” the HT via neuroanatomic and neurochemical mechanisms, almost all of them having two-way projections between the HT and all NTs' nuclei and specific interactions with hypothalamic NPs. Moreover, the HT also has a less strict blood-brain barrier in comparison to other brain structures, and so the HT can direct behaviour depending on the content of the blood supply and status of the body. Indeed, hunger, sex drive, fever, or infection-caused inflammations affecting blood content contribute to a pro-body biased choice of actions and thoughts. This makes the HT truly a “body agent,” adjusting the state of the body to the parameters of actions and, vice versa, inducing a pro-body bias in the integration of behaviour.

Serotonergic RN could be seen as another structural headquarters of the O-system. In comparison to other NTs, the brain makes, and has, a very modest amount of serotonin, and 5-HT-neurons in the RN represent only one-millionth of the total population of neurons [68, 69]. However, this small group of neurons in the RN could be considered as a maintenance hub CEO of the brain: they project to almost every brain structure and receive inputs back from other NTs' nuclei: from dopaminergic SN, VTA, noradrenergic LC, cholinergic superior vestibular nucleus, and epinephrine nucleus of the solitary tract [46, 68]. 5-HT neurons provide the background homeostatic maintenance for repetitive elements of behaviour and, unlike other NT systems, release 5-HT on an “as needed” basis. Primary sensory organs also have significantly more 5-HT than other neuromodulators; however, the sensory-integration centre, thalamus, has significantly less 5-HT but more NE [70]. This suggests that 5-HT is not involved in information processing but is involved in the maintenance of homeostasis of different parts of the nervous system. The RN also projects and receives inputs from the hubs where all 4 neuromodulators meet: the HT, amygdala (AM), hippocampus (HC), and cortex [45, 46, 68]. Altman [3], after comparing brain structures in different species, pointed out that the cell bodies of the serotonergic neurons occupy virtually the same location in the brainstem of every vertebrate brain and are even in the same spot in the central nervous system of amphiox-

us, a primitive chordate. Since the processes of homeostatic maintenance in behaviour are more universal between animals than information processing in the integration of programs of actions (highly variable among species), this suggests that functionally 5-HT likely relates to homeostasis and not to the orientational or integrational aspects of behaviour.

Serotonergic axons do not often make permanent synapses, counting on volume transmission, especially in cortical, forebrain, and basal ganglia areas. However, when it comes to regulation of the hypothalamic wakefulness control, the 5-HT system is less fuzzy and much more organized [68, 69]. Innervations from serotonergic nuclei in the RN hold several HT nuclei “by the neck,” having well-defined and dense synapses, for example, to the suprachiasmatic nucleus, a manager of circadian rhythms. Melatonin (sleep-inducing hormone) is synthesized directly from 5-HT, and the pineal gland contains all the enzymes necessary to synthesize 5-HT from tryptophan as well as 2 additional enzymes required to convert 5-HT to melatonin. This allows the 5-HT system to directly moderate and inhibit the impact of excesses of light on circadian activity but maintain the daily rhythm of corticosterone for optimal arousal and sleep when activity is not necessary. There are also direct synaptic connections between 5-HT terminals and CRH-containing neurons in the paraventricular nucleus of the HT.

Any action involves multiple chemical transformations in the body and brain, leading to temporal imbalances within various systems. The functionality of the 5-HT system in homeostatic maintenance of behaviour seems to relate to the control of the optimal boundaries in variability of these chemical cycles and not to a blind arousal or inhibition of some processes. For example, in the body, it is in control of both expansion and contraction of blood vessels. In monitoring food consumption, 5-HT innervations to the hypothalamic PV nucleus tune this consumption to the need of the organism, preventing overeating by modulating gastric activity, controlling macronutrients in the diet, and influencing responses to the taste qualities of food [46]. During this, postsynaptic 5HT1B receptors are involved in regulating the size of meals, whereas 5HT2C receptors influence the rate of eating. In monitoring wakefulness, 5-HT neuronal firing is minimal during drowsiness, silent during sleep, and maximum during repetitive motor activity, such as chewing or grooming. Moreover, in the HT, 5-HT stimulates hormonal release from the anterior pituitary and adrenal cortex when mild behavioural activation is required [46]. It has been shown that intravenous administration of L-

tryptophan (5-HT precursor) increases plasma concentrations of prolactin and GH (i.e., endurance-related hormones) but not ACTH or cortisol (stress hormones). This suggests that 5-HT release itself does not participate in stress arousal; however, it controls the variations of ACTH and CRH, again highlighting the 5-HT's role in homeostatic maintenance. 5-HT neurons themselves do not increase their activity during stressful turns of events causing autonomic arousal; in fact, they do quite the opposite. Sudden demands for changes in behaviour and novel actions decrease 5-HT firing and vice versa – in stereotypic actions, there is an increase of 5-HT neuron firing [45, 71]. 5-HT neuron firing inhibits the alertness and information processing that is activated by NE-based afferent systems [71], consistent with the idea that maintenance of routine actions and orientation are managed by different networks.

Systems of OO-Context-Based Trimming and \\/-Probabilistic Processing of Behavioural Alternatives

Neurochemical Components of the Context-Trim and Probabilistic Processing Systems: ACh as Lead

The system selecting behavioural alternatives in favour of environmental context provides close monitoring of this context and is known as sustained attention (labelled here as OO, to highlight the engagement of the body's performance into environment-driven cycles). This System trims the combinations and sequencing of actions in line with the previously developed program in changeable contexts. The strongest consensus on the functionality of the ACh brain system points to its role in sustained attention, cue detection, context processing, and memory [72–77]. Extensive studies, especially those led by Prof. Sarter, show that the central ACh system modulates the activity of GG neurons in the cortex, basal forebrain (BF), and HT and provides basal ganglia modulation of DA-GABA activity. Most of the intracortical ACh, however, acts rather diffusely by its release into the extracellular space via volume transmission mechanisms and not through release at synaptic contacts [12, 78]. Synaptically, ACh is released from the boutons of axons that originate mainly from neurons in the nucleus basalis of Meynert in the BF [79–82] but also from several other locations. Rarely, ACh acts postsynaptically, in a one to one manner to specific synapses. Excitation of the postsynaptic cell, either by non-synaptically or synaptically released ACh, occurs after activation of postsynaptic/

dendritic receptors [83]. There are 2 types of ACh receptors – the slowly acting G-protein-coupled receptor type of transmission (GPCR) muscarinic (mACh) and fast-acting (ligand-based) nicotinic (nACh) receptors, and most brain ACh receptors are mACh. Modulation of all mACh receptors affects the selectivity in information processing, facilitates or suppresses intracortical neuronal response, contributes to attention [84], enhances cortical coding capacity and attention, whereas nACh receptors play a key role in sensory gain modulation [85]. Excitatory mACh M1, M3, and M5 receptors enhance Glu-based neurodynamics (except the cortical layer V), highlighting the most consistent or most special features of the environmental context and increasing the neuronal optimal spatial frequency [84, 86]. The GPCR mACh M2 and M4 receptors are inhibitory and when located on the cell bodies and terminals of GABA neurons in cortical layers IV and V, they suppress irrelevant information, providing fine-tuning of long-term potentiation (LTP) as part of the \\\/-System.

Several sources note that ACh-producing cells contain 2 distinguishable form of storage of ACh [83]. Only one of these forms is readily available for release (“depot pool”) as it consists of vesicles positioned near the plasma membrane of the axon terminal, rapidly responding to axonal depolarization. The second (“reserve” or “stationary”) pool is likely present in more distant vesicles and refills the depot pool as it is being used. However, the reserve pool is used truly as a last resort as the vesicles are refilled first with the newly synthesized ACh from the depot pool and only then use the reserve pool for the refill. This double-storage feature and LTP/D gating [87, 88] allows ACh systems to play a key role in sustained attention and probabilistic processing of events before, during, and after their unfolding. Another feature of ACh storage contributing to its role in sustained attention is the use of a neurotrophic factor that supports cell functioning and that changes very slowly in ACh cells [3]. The ability of ACh to stay longer within a cell and vesicles without being decomposed and the double-storage setting likely contribute to its key role in memory, learning, and attention.

Another system relates to information gathering and processing of probabilities of events (labelled here as \\\/-). These functions were linked to the memory capacities of the HC and to the abstract learning capacities of the cerebral cortex. As noted by Arbib and Erdi [89], the HC is involved in declarative rather than procedural memory and in episodic rather than skill learning. Long-term potentiation or depression (LTP/D) in HC and cerebellum, associated with synaptic plasticity and learning, was

linked to the interplay between cholinergic mACh and nACh receptors [87, 88], enabling the nervous system to store information about past events. The HC uses volume transmission and M1, M2, and M5 receptors. As noted, neurochemically, ACh cells have the ability to maintain their NT for a longer duration without being decomposed using their double-storage mechanism [87, 88]. Such a capacity to prolong the transactions and LTP/D allows the ACh networks to highlight the dynamics of unfolding events (i.e., their speed, frequency, and duration) and preserve this information for future use. Projections from the midbrain Ch1–2 area to the HC and to the cerebellum are complemented by projections to HT from the same location [80, 87, 88, 90, 91]. Since the HT gives a constant update about the present state of the body’s needs and capacities, such a combination creates a holographic image of past-vs-present states of the body. Another set of cholinergic projections arises from Ch3–4 midbrain area to the thalamus, AM, latero-dorsal forebrain, and cortex (i.e., brain structures producing a holographic impression of present-vs-future capacities, needs, and environmental context) [80, 90]. Such holography is convergent with the horizontal, cortical-to-cortical projections, allowing a past-present-future comparison in the assessment of the context of the situation and in developing a course of action. The ability of ACh systems to model a timeline of events facilitates the analysis of their frequency, duration, changes, and associated causes and outcomes. As has been shown in the experiments of Hasselmo’s group, the same neurons in entorhinal cortex and HC encode both time and space in the construction of actions [73, 92]. There are “split” neurons that are active in ambivalent contexts when a choice should be made and “grid” neurons that maintain the information processing about the background context [73, 92]. Overall, the brain connectivity of ACh neurons, the functional segregation and task-driven overlap in ACh projections, volume transmission, and the double-storage intra-cellular mechanism, give the \\\/-System the ability to model a timeline of events, as a holographic comparison of the past, present, and projected future. mu-opioid receptor (MOR) and delta-opioid receptor (DOR) actions in the HC are both excitatory as they suppress GABA and ACh in this region but activate the DA and 5-HT release. This likely induces positive emotionality when previously learned elements are recognized or should be approved during the construction of actions [93–95]. There is a pattern of functional differentiation within the brain’s ACh system that lies along the differentiation between \\\/-, /\/-, []-, and [[]]-Systems described in this paper.

Functional Patterns of Neurochemical Connectivity of the \\\-System

Cooperation of O, OO, and \\\ Systems in Regulation of Long-Term Features of Behaviour

Cortical Ach, Glu (as \\\ system), and 5-HT-NPs (as O system) are all ancient NTs that established a working partnership in the regulation of the organism's comfort within 2 different aspects of sustainability: within-the-body, immediate state (O System) versus a wide-range environmental context for behaviour, using a wide time range (from immediate to potential) degrees of freedom (\\\ System). The FET framework distinguishes the cortical GG-ACh-based system as a probabilistic processing system in behavioural regulation (\\\), sustained attention that trims actions according to subtleties of the context (OO), and \\\-System of parasympathetic ANS activity. Massive system of filtering information by glutamate and GABA cortical neurons should get a credit for doing the most work in contextual processing; however, the ACh modulation of this process provides proper trimming and also sustainability of information for prolonged analysis.

The 5-HT systems in frontal, entorhinal, and cingulate cortices support contextual information processing since these regions have the highest 5-HT presence out of all cortical areas [2, 69, 96]. A high density of 5-HT terminals and volume transmission of 5-HT in the frontal cortex likely assist monitoring functions of the OO-System by selective and timely suppression of attention to irrelevant elements of environment [96]. There is a high density of ACh projections in the OFC [70], suggestive of mutual regulation of cortical OO-\\\ Systems. There is also a 5HT-ACh-opposing influence on Glu-pyramidal neurons in cortical layer VI in the medial prefrontal cortex (mPFC) that provides feedback stimulation to the thalamus and forward stimulation to other cortical neurons [96]. 5-HT suppresses this stimulation, which is in agreement with the concept that the maintenance O-System opposes the orientational \\\-System. ACh release does the opposite in this area, selectively inducing the thalamic and cortical stimulation.

OO-\\\ regulation is not limited to the cortex as noted from the cholinergic pedunclopontine nucleus (PPN)-hypothalamic projections, projections from ACh neurons in dorsolateral tegmental nucleus (dLTA) to the RN and from the RN to HC, BF, and the cortex. These projections and noted 5-HT-ACh cortical interactions can generate a "pro-body bias" in perception and information processing known as *embodiment in cognition*. This is what we indeed observed in our experimental

studies of the impact of endurance-related temperament traits on semantic perception [97, 98], calling it "*projection through capacities*." Participants with lower physical and social endurance in our experiments estimated abstract neutral concepts as less positive and less detailed terms than participants with higher physical and social endurance. In other words, individual differences in endurance systematically affected meaning attribution (i.e., highest cognitive processing of individuals) and likely their decision-making associated with their behaviour.

ACh-NE Assistance of Context Processing \\\ $\leftrightarrow$ \\\, or \\\

Neurochemically, ACh volume transmission in the cortex interacts with 5-HT and NE systems, including volume transmission in those cortical layers, and this cortical interaction illustrates the \\\-\\\ and OO-\\\ relationships. It appeared that there is a preferential distribution of nAChRs in more sensory-processing areas, such as thalamic input layers and a preferential presence of mAChRs on the cortical inhibitory interneurons. The explanations of different nACh versus mACh receptor functionalities included the hypothesis that mAChRs provided tonic recruiting of excitatory circuitry necessary for sustained attention for slowly unfolding events. In contrast, nAChRs were suggested to mediate phasic ACh release in attentional cue detection for fast-unfolding events that would generate interference in information filtering process [99–101]. However, Hasselmo and Saper [73] pointed out that specific types of nACh receptors ($\alpha 4\beta 2$) might actually act slowly on the Glu terminals in the PFC modulating the gain of Glu-ACh interactions and so result in prolonged tonic "readiness for input processing." A similar role of nAChR in enhanced visual pre-attention was reported in ACh activity in the thalamic input layer of the visual field V1 [102]. This led to the hypothesis that the action of mACh relates to monitoring of expected and valid cues, whereas the action of nACh receptors provides monitoring of competing and "invalid" clues, complementing mACh activation. For example, using experiments on the genes for the nACh and mACh receptor, Greenwood et al. [101] found a significantly higher effect of mACh than nACh genes on performance in visual attention tasks. This difference was not, however, found in working memory tasks which normally include fast-unfolding learning material.

Neuroanatomically, BF cholinergic neurons receive ascending brainstem input from adrenaline containing neurons of the medulla and NE neurons in LC, and synapses with the afferent from AM and HT nuclei [82].

These projections contribute to the interaction of the $\backslash\backslash$ -System with the Orientation-Expansion System described below. The interaction between these systems continues at the cortical level which is diffusely innervated by the BF's Meynert nucleus and where both ACh and NE commonly use volume transmission. The selective and tonic influence of cortical ACh activity assists in early stages of goal-setting and probabilistic estimates for possible successes, failures, and other potential outcomes of events. This informational-motivational impact of knowledge contributes to the choices of behavioural alternatives (integration of behaviour) known as mesolimbic-BF interactions [75–77]. This way $\backslash\backslash$ -contextual probabilistic processing directs the focus of attention via the power of motivation, gating accordingly the prefrontal Glu-ACh potential [87, 88]. Projections from the cholinergic cells in the BF and cortical interneurons dominate the cortex, HC, and cerebellum (i.e., brain areas that are most associated with cognitive functions) [83, 91]. They have extensive axons building up horizontal cortical interconnectivity [2, 91, 103] combined with and bottom-up [“vertical”] projections from the thalamus to cortical layer IV [86]. This interconnectivity allows a simultaneous “crosstalk” between different cortical areas and layers during the cholinergic trimming of excitation of pyramidal neurons. The ACh system also combines well-defined topographic segregation of BF projections [82] with the overlaps in these projections on specific target cells [2, 85, 86, 103] highlighting cross-cortical modulation of sensory gains. The ACh projections can adjust the size of perceptive fields and so change the focus on specific details of the situation [104]. With repetitive training, the responsiveness of neuronal groups that processed specific properties of the context enhances, and the long-term modulation provided by mACh receptors helps to strengthen the lateral connectivity between similarly tuned neurons [86].

Systems of Orientation-Expansion $\backslash\backslash$ of Behavioural Alternatives

Neurochemical Components of the Orientation-Expansion System: NE as the Lead

The brain's NE systems have been linked to cognitive arousal, orientation, and attention to novelty [105–108], supporting the idea of the “expansion” and “exploration” functionality of these systems offered by many authors [16, 38, 109–111]. There is a variety of opinions on the term orientation. Posner and colleagues, for example

used “orienting” to distinguish ACh functionality from the “alerting” functionality of the NE system [112]. As noted before [113], both FET and Posner's models converge on the idea that ACh systems maintain attention to established elements of situations, whereas NE systems regulate attention to novel aspects of situations as well as many other aspects of behavioural sensitivity. The word “orientation” refers here to the expansion of behavioural alternatives in the situations of either occurring novelty or when the current situation cannot be handled and a search of novel alternatives in behaviour is needed. This System is led by the NE networks and differs from the System processing assumed or known context (featured in the cortical GG-ACh system).

The components of the Orientation-Expansion System (labelled here as $\backslash$ for its sympathetic ANS part and as $\backslash\backslash$ for brain activity) are not limited to the NE system and include other hormones, neuropeptides, and likely kappa-opioid receptors (KORs). However, NE is seen here as the leader of this neurochemical team when it comes to the selection of behavioural alternatives during the construction of actions. NE binding adrenergic receptors (adrenoceptors) are all of GPCR type. The excitatory $\alpha 1$ and inhibitory $\alpha 2$ receptors work in pairs in many areas of the brain, but there are differences in their distributions. For example, NE projections from the nucleus LC (located in the pons) to the thalamus, cortex, and VTA, use excitatory Glu release and excitatory $\alpha 1$ receptors more than $\alpha 2$ receptors. NE projections from the LC to AM use excitatory $\alpha 1$ and β -adrenergic receptors, and reciprocal AM-to-LC projections use inhibitory $\alpha 2$ receptors.

Functional Patterns of Neurochemical Connectivity of the $\backslash\backslash$ -System

The main function of this network is proposed here as being an expansion of behavioural alternatives when the N/C balance is no longer possible, by analogy with the ancient wisdom “If you can't accept it, change it.” This normally happens in the presence of novelty, which creates uncertainty about an individual's capacity to handle a situation. The brain's NE system indeed is most active in stress, in darkness, in tasks requiring attention to fluid, changing situations and orientation, especially upon the occurrence of unexpected sensory events [114, 115]. The response of NA neurons to novelty is so specific that when threatening stimuli are presented repeatedly, they gradually evoke less and less NE neuronal firing [116, 117]. Experiments on rodents showed a key role of NE networks in the PFC in attentional set-shifting tasks [114,

118, 119]. A deficit of NE was linked to ADHD and to difficulties in learning new information [111, 114, 118–120].

The main source of NE projections in the brain is the locus coeruleus (LC). These neurons project to multiple regions, with the densest projections to those areas associated with attention and sensory processing such as the thalamus, parietal cortex, the pulvinar nucleus, the superior colliculus, and AM, mainly avoiding the striatum. The LC also receives inputs from many brain areas and has molecular heterogeneity, likely facilitating the segregation of these inputs [121–123]. The multiplicity and heterogeneity of NE projections, as well as the fast action of NE as a neurotransmitter, allows the NE system to highlight novel degrees of freedom in behaviour in a timely manner. The majority of noradrenergic varicosities in the cerebral cortex, however, do not make synaptic contacts [12] and so NE action in the cortex uses volume transmission to interact with other systems.

There is a strong NE-ACh entanglement in attention processes, in which alertness to novelty is provided by NE modulation and sustained attention and context sensitivity is regulated by the cortical ACh activity [16, 105, 110, 112, 114, 115]. This entanglement likely starts from strong NE-ACh connectivity at the autonomic level of regulation, and mutual projections between NE-gic LC and ACh-gic dLTA in the brainstem, and ACh neurons in the PPN which send excitatory projections to the LC [122, 123]. The cholinergic neurons in the dLTA have inhibitory α_2 receptors, and vice versa, there are excitatory nACh receptors on the NE-gic LC neurons [124, 125]. At higher cortical levels, LC projections to cholinergic HC and BF use mostly inhibitory GABA release and α_2 receptors, even though excitatory α_1D receptors were also found in the HC [120–123]. The NE-gic α_1 receptors on ACh neurons in the BF stimulate ACh release [121, 122]; however, the same receptors in the PFC can interfere with PFC function, whereas adrenergic inhibitory α_2 receptors on PFC neurons improve PFC functioning [85]. As noted, both NE and ACh use volume transmission in the cortex, and there is likely a subtler level for their mutual regulation. For example, there is an abundance of common peptides in NE and ACh cells that control the co-release of NE and ACh and perhaps even the neurotransmitter profile of neurons [2, 126].

At first glance, the functional contribution of NE systems to behavioural construction is minimal if we consider only their role in attention to novelty since novel situations are rare. If 90%+ of behaviour is constructed out of known alternatives, then it looks like most behavioural construction seems to be regulated by the other

neurochemical systems. Indeed, when it comes to behavioural construction, DA is the lead neurotransmitter in the integration of actions, and there are almost antagonistic relationships between NE and DA. Neurochemically, NE and DA represent the same catecholaminergic system sharing one pool of regulatory peptides [127], literally giving behaviour a choice between stopping the behavioural integration and orienting for additional alternatives, or stopping the expansion of alternatives and continuing with the integration using known options.

However, this minimal contribution of the NE system changes sharply into complete control over behaviour in situations of novelty, uncertainty, and/or danger. Noradrenergic LC and cholinergic IdTA and PPN nuclei in the brainstem project widely into both autonomic and central nervous systems [122, 123, 128]. This allows the NE system to be a key player in fight-flight-freeze behaviour when the N/C imbalance of the situation is extreme, and capacities to assist this imbalance are not immediately available. In a stressful situation, the N/C -System uses its direct management of the sympathetic ANS N/C -System and its NE-adrenergic transformations to activate the HPA axis. The action of the HPA system prepares the body for drastic differences in behavioural alternatives, changing the heart rate, blood pressure, suppressing digestion and even the performance of routine actions. Expansion of behavioural alternatives, activated by this N/C -System at the ANS level and by the N/C -System at the brain level, therefore, includes not only the provision of attention to novelty but also a search for alternatives in actions that were not included into consideration before. This is experienced subjectively as acute stress when all planned and known elements of behaviour are brought into question by their appropriateness to a suddenly changed situation.

In the brain, the activation of NE can abruptly interrupt the activity of neural networks and re-organize them, facilitating rapid behavioural adaptation to changing contexts [129]. NE has a privileged way to regulate and, if needed, literally shuts down all other systems at many brain levels. As noted, this can be easily done with the tight relations between N/C - N/C Systems (we can use the notation N/C for that) and N/C -[], NE-DA systems. The NE system can also halt or selectively boost the performance of the serotonergic system at the very fundamental layer of brain activity, whereas the O-system does not have such direct control in return. There are NE-gic excitatory α_1 receptors all over the 5-HT-gic RN and a presence of inhibitory α_2c receptors [2, 49, 122]. These adrenergic receptors located on the 5-HT neurons of the RN

give a chance to the NE system to either increase or decrease 5-HT neuronal activity [122, 123, 130]. Some authors report that dRN bears one of the highest densities of $\alpha 2$ -adrenoceptors in the brain [130, 131] suggestive of the main inhibitory influence of NE system on 5-HT release [130]. The main ways for the O-system to “return the favour” and influence the $\wedge$ system mainly relate to slow-acting systems, such as via HT and cortex. The HT has mutual projections with the LC, and the hypothalamic paraventricular nucleus is in a closed efferent-afferent loop with both the sympathetic and parasympathetic systems. Thus, if the RN has to stop the dictatorship of NE, it should “complain” to the HT. Such antagonistic NE versus 5-HT relationships can explain the common observation that orientation stops stereotypic actions and, vice versa, stereotypic actions decrease orientation. This relationship have been observed experimentally in recordings of NE and 5-HT neuronal activity [71, 116, 132]. In agreement with ancient Chinese wisdom, it seems that the O-System control over the construction of behaviour using slow-acting NPs and 5-HT can influence all regulatory systems in a “give away slowly” manner whereas the hormone-based $\wedge$ -System pauses the planned construction in a “take away quickly” manner.

The Roles of OR in Dispositions as a First Sketch of Directionality of Behaviour: The “?!“-System

Neurochemical Components of the ?!“-System: Three Types of or Receptors

The system that is discussed in this section generates pro-body dispositions for behaviour when the events have not yet occurred. Findings in neuroscience and cognitive psychology indeed showed that decision-making, and cognition, likely starts from the stage of emotional processing and that emotional biases affect the generation of behavioural responses [31, 133]. The FET model has suggested that the first, “emotional” sketch of the directionality in the behavioural program (marked here as “?!“) is induced by the endogenous OR binding peptides that normally are produced by the body and the brain [21, 38]. The OR belong to the GPCR, and regulate the release of lead NTs. Dozens of endogenous ORs have been found and classified into three-plus groups: MORs, which bind endorphins; KORs, which react to dynorphins; and DORs, which bind enkephalins. This “specialization” in binding is not strict since ORs often inter-bind each other’s peptides. The “plus” group unites “orphan” receptors that do not have specificity for binding agents [93, 134].

The complex GPCR mechanism of ORs makes their density a very plastic system, having several possible states [134]. The density of OR ligands can increase (upregulation) or decrease (downregulation and desensitization) depending on the supply of the peptides binding to them and the sensitivity of the receptors themselves. A single administration of opiates often triggers a set of changes that usually is restored by a chain of recovery mechanisms. Downregulation of receptors is observed mostly after chronic overuse/overproduction of these receptors’ agonists as a protective feedback mechanism, and upregulation develops in cases of consistent deficit of needed peptides (due to their underproduction) [93, 134–144].

OR can contribute not only to emotional but also to other aspects of behaviour by regulating the release of all main NTs. They also are often co-released with NTs and with many hormones and neuropeptides, including CRF, prolactin, neuropeptide Y, or substance P [2, 26, 145–147]. This makes the OR systems neuromodulators and even “modulators of modulators.” Moreover, ORs bind peptides in an “interexchange” manner (for example, DORs and MORs often bind each other’s peptides). They are also often heteromers (i.e., act in heterogeneous teams rather than as isolated systems) [7–11, 93]. Locations with a high receptor density of a specific type do not match locations with a high presence of their binding peptides [2, 148]. Plus, the effect of OR activation greatly varies depending on their location, type, pre- versus postsynaptic position, and co-releasing NTs, so the functionality of OR likely goes beyond merely inducing positive-negative affectivity. Due to this complexity, any reasoning on the functionality of any member of these neuromodulatory ensembles should be done with caution: their functionality is likely the product of co-release or reciprocal suppression by other neurochemical systems. Sorting out this complexity is a work in progress, and we do not claim to have sorted out the OR “soup.” However, the FET summarizes the most basic OR functionality that was consistently found in experiments [21, 38, 39, 149].

In terms of locations, the OR systems are diffuse and not mapped into the brain connectivity. Many brain structures were found to have at least some ORs and peptides that bind to them, so it is more informative to look at the highest density of receptors or binding peptides: these high-density locations might highlight a non-random regulatory tendency. It appeared that despite the presence of ORs in many brain structures, only a few brain structures have all 3 types of receptors present: HC (MOR-DOR) are most present on CA1 cells and the dentate gyrus, whereas KOR are present on CA3 cells ([95],

p. 86), AM, NAc-Caudate, and cortical layers III, V-VI [2, 148, 150–152]. This can be viewed as possible indirect exchanges between the \\\-System (HC, cortex), /\-System (AM, cortex), and the []-System (NAc-caudate) using the OR action since the OR regulates the release of ACh, NE, and DA in these structures. Interestingly, the HT, LC, and VTA, traditionally assigned to the limbic complex, could not be included in this set as they miss one or 2 types of OR.

Functional Patterns of Neurochemical Connectivity of the \-System (KOR-MOR)

The differences in OR distribution in functional areas of the brain and their effects on the release of major neuromodulators suggest that their functionality relates to at least 3 different biases affecting the choice of actions: MOR is involved in “coping approval” of current selections of alternatives, KOR enhances perceptual arousal and sensitivity, and DOR regulates the speed of integration and initiation of chosen actions. Despite frequent overlap of the 3 OR types in various brain structures, there is a gradient in their distribution from a prevalence of MOR in the O-System and []-System locations; a prevalence of KOR in brain structures related to the /\-System, and a prevalence of DOR in brain structures related to the []- and [[]]-Systems. Here are some details.

MOR activation was linked originally to positive emotionality and relaxation but also associated with affiliative behaviour [153, 154], indicating that MOR’s functionality might not be limited to positive affectivity alone. After all, MOR agonists in humans reportedly decreased pain but also decreased mood (i.e., induced persistent dysphoria) [56, 155]. There are links of MOR to the O-System of homeostatic maintenance that includes restoration of homeostasis after stressful events and in pain. It has been shown that MOR (but not KOR or DOR) agonists inhibit 5HT in the HC [149, 156], and out of all ORs only MORs develop heterometric complexes with 5-HT₁ receptors [157]. Mostly, MORs and their binding peptides, endorphins (but not KORs and DORs) are highly prevalent in the gut (being produced by microbiota) and in the HT, PAG, Golgi cells in the cerebellum, and in reticular, vagus, and other nuclei downstream in ANS regulation, all linked to pain suppression [2, 148, 150–152]. Gut endorphins have the capacity to suppress stress-related HPA arousal providing an individual with the ability to cope with the current state of events. Hypothetically, MOR action can be summarized as inducing a feeling of lower needs, to reach a needs/capacities balance, as a combination of the following:

- Enhancing coping with pain (analgesic effects), both physical and emotional [93, 158]. Stefano also pointed out that MOR evolved initially as part of the immune system due to MOR’s ability to suppress pain and neutralize an aggressive immune response to injuries and other health challenges: otherwise pain-related shock can lead to death [56].
- Enhancing the ability to cope with stress by the suppression of HPA axis arousal (stress hormones release) [93, 159–162].
- Suppression of attention to novelty via the inhibition of NE release [159, 160, 163–166] that would enhance a sense of predictability of the surroundings and of the capacity to handle it.
- Suppression of contextual processing that potentially could highlight new needs and lack of capacities; this suppression is combined with a calming effect inducing a feeling of a safe and predictable context. This effect is seen in MOR’s inhibition of cortical ACh [93, 167].
- Facilitation of 5-HT, BDNF production in HC [149], DA release by suppression of GABA in the VTA-NAc [168, 169] and working as heterodimers with DOR in the striatum. In human post-mortem studies, a high density of MOR was found in anterior-ventral parts of several brain structures: anterior AM, anterior thalamus, anterior cingulate, anterior-ventral putamen, caudate, and STN – areas that are involved in shaping goal-setting and the sequence of actions (i.e., programming, labelled here as I! → [] relation). MOR activation, therefore, “sweetens the deal” in development of the program of actions, making it more detailed to give the near future more transparency and predictability. This signals sufficient capacities to meet future needs. No wonder that the DA VTA-NAc networks are often called “reward circuits”: planning of actions and their anticipation gives an individual a capacity to control the future, and MOR adds positive affectivity to it.

Upregulation of MOR was linked to extreme dysphoria and irritability as seen in the borderline personality disorder and attachment disorders [154, 158, 170–172]. We can hypothesize that MOR downregulation, when there is an excess of endogenous endorphins, can be experienced as dispositional, often negligent satisfaction with “life as is,” low productivity, high agreeableness, and dispositional positive mood.

The KOR system has been linked to sensory mobilization processes, aversion, chronic anxiety, hallucinations, and malaise, and there is an association between KOR activation and HPA axis arousal [93, 168, 169, 173–176].

Neurons in the most prominent hypothalamic-pituitary nuclei (paraventricular and supraoptic) contain high amounts of dynorphins binding KOR [177]. It has been shown that the same NE axons that respond to dynorphin co-localize with excitatory Glu as well as stress-related CRF [178]. KORs activate NE release, contributing to the attentional capacities of the NE system [93, 179]. KOR activation in the LC suppresses Glu and uses CRF as a co-transmitter [180], and the anxiogenic effects were associated with dynorphin and CRF co-release in the basolateral AM [171, 173, 176, 181]. KOR has direct effects on Glu-gic NMDA receptors that make them a key player in the control of excitatory processes in perceptual and limbic systems. Presynaptic KOR activation reportedly depresses GABA and facilitates Glu transmission in the NAc [169, 182], likely making NAc more responsive to adverse, not positive stimuli [183]. The same effect of KOR was found within the bed nucleus of the stria terminalis – the brain region linked to anxiety, likely indicative of dysregulation of the KOR system [184]. It is not a surprise, therefore, that in studies of psychiatric disorders, upregulation of KOR was linked not only to addiction [185] but also to dispositional and chronic anxiety [173, 175]. In KOR-absent animals, the expression of stress-related hormones is significantly reduced [163, 179]. Despite its involvement in HPA arousal and the co-release of CRH, KOR systems were not linked to acute stress [179, 186] or specific phobias [173, 175, 179, 187].

The functionality of the KOR system also likely extends beyond emotional (such as anxiety) aspects of behaviour, as in many cases, alteration of KOR receptors does not lead to changes in anxious behaviour [179]. Studies on animal models have shown that KOR antagonists decrease avoidance and anxious dispositions [93, 179, 188]; however, KOR agonists do not produce an elevation of anxiety. Instead, they produce perceptual distortions of sensory stimuli, depersonalization, speech processing problems, and thought disorganization (i.e., features of perceptual hyperarousal) [175, 176]. There is significantly less KOR than MOR in the brain in general; however, the anterior and lateral nuclei of the thalamus (i.e., the brain area integrating sensory information), has a significant presence of KOR in comparison to other brain structures [148, 150, 151, 189]. Dynorphin that binds to KOR was found in GABA neurons in the central nucleus of the AM, and lateral and medial HT [176], and high KOR density was found also in the lateral AM, HT, ventral striatum, and PFC (especially layer VI) [151] (i.e., in the structures that, in addition to the thalamus, strongly contribute to perceptual and orientational mobiliza-

tion) [148, 150, 151, 189]. Moreover, it has been shown that only high doses of KOR agonists induce anxiety, while low doses act as an analgesic and very low doses may induce positive mood states [93, 179, 190]. Also, comparison of the distribution of OR revealed that rats have significantly less KOR (9%), in comparison to humans (37%) whereas the remainder of the OR numbers is divided relatively equally between the other 2 types of receptors (MOR and DOR) [167]. This suggests that KOR functionality does not relate to just emotional aspects such as stress or anxiety, which would be present in the life of many mammals; otherwise, the human brain should have a similar amount of KORs as a rat brain. The higher presence of KORs in the human brain can be explained by the complexity of human activities that requires much more information processing in comparison to rats. Such specificity towards orientational aspects of behaviour in KOR action might explain why some studies using non-orientational behavioural markers reported no anxiolytic effects of KOR [187].

There is a reciprocal suppression of MORs and KORs in many areas of the brain, whereas MORs and DORs often work in one direction [93, 134]. The brain structures having high receptor density and/or high presence of relevant peptides for MORs and KORs, but not for DORs, are known as the main limbic structures for emotional processing: NAc, AM, HT, Th, intralaminar nucleus [148, 150], SNc, RN, granular layer of the cerebellum, PAG [2, 152, 191], and, to some extent, LC. The MOR-KOR antagonism especially shows in their regulation of the leading NTs. MORs often suppress NE release [165, 166], whereas KORs induce it [93]. MORs were found only on the small-sized LC's pars alpha neurons of the LC, whereas KORs were seen on the medium-large sized neurons [152]. MOR agonists induce both endocytosis and desensitization changes in striatal neurons but not in those of the LC [192]. Moreover, in the VTA, MORs activate whereas KORs suppress DA release [168, 169, 173]. A similar action of KORs on DA likely occurs in the dorsal striatum [193, 194] and the NAc where KOR's suppression of DA synaptic transmission leaves more DA in extracellular space [194–196]. It has been shown that KORs inhibit only those DA neurons in the VTA that project to the mPFC but not to the NAc [169] and this helps to avoid aversive stimuli [176]. Even though both MORs and KORs were found in the NAc, some studies showed that KOR might have a higher density in ventral than dorsal striatum, whereas MOR have a higher density in dorsal than ventral striatum [151, 197, 198]. This pattern suggests that KOR can pause the []-process of integration of

action for unfavourable alternatives, suppress the \V/-process of contextual analysis of known alternatives but boost the search for new alternatives using NE release in the AM and cortex. MORs, on the other hand, suppress this new search (also the contextual analysis) and “approve” the existing alternatives in actions. Both systems contribute to what is called “emotionality-driven” behaviour as both of them suppress cortical and striatal ACh activity but activate ACh activity in the HC. Chronic exposure to opiates that downregulates MOR system (decreases the OR density), which, in turn, disrupts the 5-HT turnout and can cause a decrease in energetic aspects of behaviour [93, 149].

Functional Patterns of Neurochemical Connectivity of the I!-System as a Bridge to the []-System

The action of DORs has a distinct association with those structures that integrate a concrete program and sequence of actions. Enkephalin (i.e., the activating DOR-binding peptide) was found to be one of the key regulatory peptides in the basal ganglia and in the interaction between striatosomes and matrix in the striatum [199]. Originally linked to positive emotionality, DORs also appeared to play a role in behavioural mobility, speed of generation of actions, including its premature generation (i.e., impulsivity) [21, 38, 200] or compromised motor control (as in Parkinson’s disease) [200, 201]. In contrast to KORs, the highest density of DORs was found not only in the NAc but also caudate, putamen, and other basal ganglia [2, 148, 150–152, 168, 202–204] (i.e., in the DA-rich striatum structures that are all involved in shaping the sequence and details of an action rather than processing emotionality or orientation). Vice versa, DORs are not present in “sensory” and “maintenance”-related brain structures, such as the thalamus, LC, RN, and HT [2, 150, 152, 202, 204]. The DOR-MOR are heteromer complexes [157, 205] that facilitate DA release in striatum, whereas KOR action was proven to be minimal in that important locomotor control region [167, 206]. DOR agonists stimulate and initiate locomotor activity in swimming and climbing behaviours in rodents [200, 207], and high dosages of these agonists induce convulsions (i.e., uncontrolled motor actions) but not changes in mood [208, 209]. Mice lacking the DOR-1 genes showed higher levels of motor activity and impulsivity, but lower plasticity (a deficient control over when the behaviour should start and stop) [210], and lower behavioural mobility [187]. DORs facilitate the release of DA [93] and the high DOR density in basal ganglia [2, 198–200, 202, 211] points to its significant role in the integration of motor behaviour.

Moreover, high MOR density in the AM suppresses alertness of the NE systems there and its high density in dorsal striatum promotes action (marked here as “!”).

In the cortex, all ORs suppress ACh (i.e., the \\\-System), which is in line with the idea of a reciprocal suppression of rational context processing and emotional dispositions in the generation of behaviour. Interestingly, when it comes to ACh, it is KOR but not DOR that inhibits ACh in the striatum [206], also likely as a way to suppress contextual orientation. If DOR’s trimming of the activity of striatal neurons fails but KOR’s suppression of contextual processing continues, then it can speed up the integration of actions regardless of contextual appropriateness. It is possible that the DOR system assists in speeding up the behavioural integration as seen in healthy tempo of actions. However, when cortical and ventral striatum guadnace is compromised, and with an increased /\-arousal of hormones-based systems, the DOR activation can lead to impulsive behaviour (the tendency marked here as I!). The DOR facilitation of DA release can be one explanation of why impulsivity was linked to the striatal DA system [208–210, 212].

There are, therefore, functional bridges between the MOR-DOR-based I!-System and the DA-based []-System, on the one hand, and between the and NE-based /\-System and the KOR-based ?-System, on the other hand. The mismatch between the supply and demands of binding peptides to OR systems generate biases in the directionality of future actions (either to approve-relax or to search for alternatives). This dispositional directionality is experienced as an emotional state in goal-setting, planning, and anticipation of the outcomes of behaviour. The interplay between MOR-KOR in the AM, HT, and NAc builds up the ?I-System that helps to contrast and heighten the directionality in behaviour by controlling the release of neuromodulators in a calibrated manner. The NAc, which could be considered a bridge between the ?I-System and the []-Programming System has a high density of KOR and a high presence of dynorphins and enkephalins whereas the dorsal striatum has a higher presence of MOR and DOR [151, 197, 198]. These 3 OR systems likely facilitate the first draft in the directionality of actions (goal-setting), each contributing their specific aspects. KOR likely enhances perception to the sensation and adverse features of the environment [176], whereas MOR adds positive affectivity and a sense of approval of choices. KOR underperformance (due to upregulation of receptors) might lead to a sense of “deflation,” lack of interest, and low perceptual arousal. For example, George Koob described a special state of patients suffering from

Table 3. The comparison of T-CBP, C-CBP, and G-CBP-related consistent behavioural patterns in the framework of the neurochemical model FET (shown here as T-CBP)

	Maintenance of construction O-class	Behavioural orientation to types of reinforcers, //\\	Preferred speed of integration of actions, []-[[]] class
Implicit, more probabilistic mental aspects ("cortical")			
T-CBP	Mental (intellectual) endurance, ERI	Orientation to probabilistic processing, PRO	Ease of changing a course of actions: plasticity, PL
C-CBP	Inability to focus, low concentration	Learning disabilities & low IQ	Rigidity (e.g., rituals in OCD) or excessive start-ups without finishing them (e.g., in mania)
G-CBP	High sustained attention	High ability to learn causality and probabilities of events	Creativity
NTs & labels	ACh , 5HT O → OO ← \\//\\	Glu , ACh, NE OO → \\// ← //\\, ?	DA + ACh , 5-HT, Glu \\//\\, ! → [] ← [[]]
Explicit, more deterministic social-verbal aspects			
T-CBP	Social endurance, ERS	Empathy, EMP	Social tempo, TMS
C-CBP	Social withdrawal	Autistic disorders	Expressive language problems
G-CBP	Ability to sustain prolonged communications	...to others people's motivation and feelings	High verbal speed
NTs & labels	5-HT + Estr , H, OXY [[]] → O-\\ ← \\//	NE + OXY , VSP \\// → //\\ ← ?	DA + Estr , OXY [] → //\\[[]] ← O-\\
Explicit, deterministic physical-motor aspects			
T-CBP	Physical endurance, ERM	Sensation seeking, SS	Physical tempo, TMM
C-CBP	Fatigability	Antisocial behaviour just to increase the HPA arousal	Motor retardation
G-CBP	Athletic ability for endurance	Ability to act in high-risk settings	Athletic ability for motor speed
NTs & labels	5-HT + ORE , H, NP(GH) [[]] → O ← OO, \\//	NE/α1 , NP/SubP O-\\ → //\\ ← ?!	DA + GABA , ACh, NP, DOR, A [] → [[]] ← O, OO
Emotional amplifiers			
T-CBP	Disposit. Satisfaction, SF	Neuroticism, alertness, NEU	Impulsivity, IMP
C-CBP	Too relaxed dispositions, idealistic expectations versus pessimism & low confidence	Low tolerance to novelty and uncertainty, perceptual alertness	Premature integration of actions, behavioural reactivity
G-CBP	Emotional stability	High tolerance to uncertainty	Strong impulse control
NTs & labels	MOR → DA , MOR > KOR O → !! ← []	KOR → NE-HPA , KOR > MOR //\\ → ?? ← \\//	DOR → (DA, MOR) hormones [] → ! ← //, [[]]

The labels of Systems: O – homeostatic maintenance; OO – sustained attention; \\// – probabilistic processing; //\\ – expansion (orientation); "?! " – emotional dispositions; [] – new integration; [[]] – established integrations. Bold font indicates leading NT systems in the given CBP; grey font indicates supporting mediators. T-CBP, temperament-related consistent behavioural patterns; C-CBP, clinical-related consistent behavioural patterns; G-CBP, giftedness-related consistent behavioural patterns; FET, functional ensemble of temperament; 5-HT, serotonin; DA, dopamine; NE, noradrenalin; ACh, acetylcholine; GH, growth hormone; SOM, somatostatin; PRL, prolactin; OXY, oxytocin; Estr, estrogen; SubP, substance P; NPY, neuropeptide Y; H, histamine; NP, neuropeptides; α1, alpha-1 adrenergic receptors; KOR, kappa-opioid receptor; MOR, mu-opioid receptors; DOR, delta-opioid receptors.

addiction that he called “hyperkatifeia” (i.e., a general malaise, irritability, and despair) [185]. The MOR-DOR heterodimers in the striatum and other basal ganglia facilitate DA release and, with the support of ACh interneurons, shape the program of actions. As discussed earlier [21], subjective experience of $N(eed) > C(apacities)$ induces negative while $N < C$ induces positive emotional valences under the condition of optimal arousal. The DOR-MOR activation as an approval of the program of actions suppresses a feeling of needs by suppressing NE and cortical ACh and activating DA release, signalling a capacity to handle a situation. This might explain why planning where the options are certain is often accompanied by positive emotions and by activation of the limbic structures assigned to the “reward networks,” with the high presence of MOR (VTA-Nac).

Since the binding peptides are produced internally by microbiota and several sites in the brain that vary among people, the degree of any imbalance between the supply of these peptides and their corresponding receptor's density can determine whether or not CBP will emerge as a temperament trait or as a symptom of psychopathology (Tables 3, 4, as example). Regardless of the degree, the

dynamics of the OR activation cycles can be a factor in emotional behavioural dispositions that persist even in the absence of triggering events that could explain them [170, 172, 173, 179, 192, 213]. Here, we can see at least 3 OR-driven CBP: neuroticism (as KOR suppression of MOR systems), dispositional satisfaction (as an opposite pattern), and impulsivity (as DOR dysregulation) [21, 38].

Behaviour Is Construction, Not Reaction: DA-GG-Based []-System of Behavioural Integration

Neurochemical Components of the []-System: DA and DOR as Main Players

The integration of a behavioural act is the selection of alternatives, labelled here as the []-System. This selection of behavioural alternatives is influenced by all other Systems: O-System signalling the body's needs and capacities, \\// -System unfolding the environmental context for actions, //\\ -System highlighting changes and novelty that should be dealt with, and (discussed later) the [[]] -System providing cognitive and motor memory for

Table 4. Summary of results of clinical studies using the FET-related test STQ-77 [214–219]

	ICD code	NEU	IMP	SF	SS	TMM	ERM	PRO	PL	ERI	EMP	TMS	ERS
Depression [214, 215, 218, 219]	6A7Z	↑	↑	↓		↓	↓		↓	↓		↓	↓
Hypomania [215]	6A60.2		↑	↑	↑	↑		↑				↑	
GAD [214, 215, 217]	6B00	↑	↑					↓				↓	↓
PTSD [215]	6B40	↑	↑						↓	↓		↓	↓
Adjustment disorder [215]	6B43	↑	↑	↓		↓	↓	↓	↓			↓	↓
Schizophrenia [214, 216]	6A20.Z	↑	↑	↓		↓	↓		↓	↓		↓	↓
Delusional Dis [216]	6A24.Z	↑							↓	↑			
Paranoid PD [215]	6D10.Z	↑		↓					↓	↓	↓		↓
Borderline PD [215]	6D11.5		↑	↓						↓			
Antisocial PD [215]	F60.2		↑		↑	↑						↑	

The abbreviations of the STQ-77 scales that are used in the heading of the Table relate to the scales shown as 12 T-CBP (temperament components) in Table 3. Numbers in the first column indicate references for the studies. FET, Functional Ensemble of Temperament model; STQ-77, Structure of Temperament Questionnaire.

units of behaviour that were integrated previously. The DA-GG networks, with full support of Ach, were identified as the lead systems in the integration of actions. Moreover, in the cortex, the release of DA appeared to be under the close supervision of the NE system. In fact, most cortical DA comes not from DA-producing neurons in the VTA and SN but from NE neurons [7]. NE is more prevalent in the cortex than DA, whereas DA is more prevalent in the striatum as NE neurons from the LC do not project there. It seems that in the striatum (i.e., the areas that are involved in the preparation of motor programs and selection of action), NE passes the lead of highlighting priorities to its by-product DA, whose release dominates the integration of behaviour. DA is co-released from NE neurons when NE release is triggered and is recaptured back by the NE, and not the DA, transporter [7]. Most of the interaction between cortical DA and NE happens within the extracellular space, as volume transmission, where they compete for each other's transporters. As [7] pointed out, the NE transporter displays a higher affinity for DA than for NE itself in vitro, and the NE transporter is more expressed in the areas of high DA innervations.

Yet, in the striatum, DA acts independently from NE and instead uses ACh interneurons, selectively suppressing ACh release when sorting out the integration of actions. In the caudate nucleus (i.e., the part of the ventral striatum that was linked to the main goal- and program-setting stage of construction of action [220]), DA and ACh release is complemented by 5-HT release from projections from the dRN [46], providing additional sustainability during processing of wide range of df [221–223].

Behavioural plasticity would not be possible without coming from Glu-GABA networks that using complex mechanisms of filtering the signal [29], facilitate selection of df and information processing. All of these play a key role in the plasticity of behaviour as it allows for the simultaneous activation and editing of several scripts of actions [221, 222], prolonging the availability of these scripts and making available multiple options for relevant combinations. These differences in the neurochemistry of prefrontal and striatal DA systems can explain their reciprocal influences [222]. NE-DA differences in cortical versus striatal systems suggest catecholaminergic continuity and a gradient in their behavioural regulation, where the highlighting of novelty in the environment is provided by NE and the highlighting of priorities under the condition of multiple alternatives (in diverse environments) is handled more efficiently by DA systems.

As noted, the highest DOR density was observed in the ventral striatum – NAc, caudate, and ventral putamen – exactly the structures that were linked to the generation of behavioural programs [198–200, 211]. Both MOR and DOR facilitate DA release in the striatum [19, 93], making them a part of the []-System.

Neurochemically, the []-System is only led by DA but is not based solely on this NT, using the assistance of the OR-based ?I!-System (as described above), the ACh-based //\\-System of interneurons, GG, and several other neurochemical systems of the striatum. The ACh interneurons and GABA inhibitory neurons basically are the striatum, as they represent over 95% of striatal cells in humans [222, 224], and DA is just the lead modulator of these cells. The cholinergic and DA-gic systems in stria-

tum are inhibitory, as integration of a program of actions requires extensive trimming (i.e., rejection of multiple df in behaviour in favour of the final few trajectories of actions). DA selectively inhibits the activity of ACh interneurons and also stops Glu from excessive release to the spinal cord in the regulation of action, and this trimming helps to let only non-inhibited neurons go ahead with producing an action. When this process is compromised, it leads to dyskinesia as the production of unnecessary actions [200, 201].

Interestingly, there seems to be a functional segregation between 5-HT-pre-[] and 5-HT-[] regulation based on the differences in axonal morphologies and synaptic connections between the medial and dorsal RN [46, 68]. The medial group has large varicose axons-forming arrays around the soma and proximal dendrites of neurons. The dorsal group has small varicose axons with fibres of synaptic boutons operating through volume transmission mechanisms. These 2 5-HT forebrain systems cross in the caudal HT, then continue relatively independently to the cortex, where they partially overlap again using their different mechanisms of transmission [46]. The mRN seems to project more to HC, HT, septum, and cortex (i.e., areas related to information processing and sustainability of established cycles) but not striatum, whereas the dRN – to catecholamine-rich areas involved in the []-System of behavioural integration, such as VTA and striatum.

ACh Assistance to DA during Programming and Trimming of Actions

The cholinergic system, in addition to cholinergic projections in the cortex implicated in sustained attention, has a second subsystem and cell type: interneurons in basal ganglia where most programming of behaviour is happening (regulated by DA-ACh cooperation). This validates the idea of separation of /\- and []-Systems, each of which the ACh system apparently assists but by a distinctly different cellular morphology. Moreover, in contrast to the cortex using primarily M1, M2, and M4 receptors, there are predominantly M5 mACh receptors on DA neurons in the SN, and almost 30% of presynaptic $\alpha 7$ nAChRs act extra-synaptically in the VTA [225]. The ACh interneurons are the main interneurons in the striatum and appear to have different functionality from projective BF cortical neurons. The large spiny neurons in the striatum that provide the cholinergic tone to local neurons are under the tonic inhibition of the SN dopaminergic system that is seen here as an [[]]-System for the prioritizing and sequencing of actions. Without this DA control, the tone for the execution of the action and even general direction-

ality would continue, but the reinforcement of beneficial and suppression of irrelevant alternatives would fail. Indeed, the loss of the inhibitory influence of D2 dopaminergic receptors in that region in Parkinson's disease is associated with high ACh concentration in the striatum. The BF cholinergic neurons also receive ascending brainstem input from dopaminergic SN and VTA and have afferents synapsing with the NAc [82]. As noted below, HC and cerebellum ACh systems also assist in trimming actions using combinatorics of cognitive (memory) pre-fab elements (as a part of the \\\-System). The segregation of the passes from the brainstem ACh neurons to mainly information processing (AM, Th, medial cingulate gyrus, and latero-frontal cortex), mainly hypothalamic and hippocampal projections [90] is in line with the separation of the 3 different neurochemical Systems, formally noted here as \\\-/\, [[]]-O, and [[]]-\\.

Functional Patterns of Neurochemical Connectivity of the []- and [[]] DA Systems

DA is often regarded as a “neurotransmitter of pleasure” and positive affect; however, there are numerous examples showing that this is not always true [226–229]. In fact, negative stimuli and situations enhance activity in the mesocortical DA system to a higher degree than do positive ones [227, 230]. An excess of extracellular DA was linked not to more positive moods but to schizophrenia [231–233], psychoticism [234] and, when combined with a 5-HT deficiency, to OCD [235–237]. The DA-gic VTA-NAc network is often called a “reward circuit” in the context of addiction research; however, this is likely not the best descriptor. NAc neurons are activated mostly in response to aversive stimuli and inhibited in response to rewarding stimuli [238]. Moreover, as noted above, the effect of the VTA-NAc projections in motivational processes could be largely explained by the high involvement of OR systems in these brain structures. This effect is highlighted here as the ?!-[] transition and known as a function of the mesolimbic DA network. Experimental studies led many neuroscientists to believe that the ascending DA system provides a spectrum of functions that are unrelated to positive or negative emotionality since DA release was linked to the following:

- Cognition, assigning significance and priorities to stimuli (saliency), both negative and positive [226, 228, 229], dysregulated in schizophrenia and other delusional disorders [231–234].
- Integration of goals and priorities as seen in motivational processes and planning, mostly linked to DA mesocortical networks [221, 239–241]. Indeed, In

comparison to cortical ACh, NE, and 5-HT projections, which are evenly distributed among cortical regions, there is a predominance of DA projections in the mPFC, anterior cingulate, rhinal and entorhinal cortices, (i.e., the “programming area of the brain”) [7, 242]. As noted, OR involvement in the mesolimbic DA network contributes to these motivational processes with the emotional component, whereas cortical ACh regulation contributes with the informational component.

- Quick re-integration (change) of the sequences, contents, and even goals of actions in changing, complex, or unknown situations known as the plasticity of behaviour and linked to the interaction between DA mesocortical and mesostriatal networks [39, 221, 222, 224, 230, 241, 243]. DA release in the caudate nucleus that is the lead in behavioural programming is combined with 5-HT release from RN projections to this structure, one of the rare striatal sites with a high 5-HT presence. Deficiency in behavioural plasticity (rigidity) seen in OCD was indeed linked to both DA and 5-HT systems [235–237]. Abnormal cognitive and behavioural plasticity was also noted in delusional disorders [216, 231–234], all linked to an excess of DA. Moreover, forebrain depletion of 5-HT has also been linked to premature initiation of actions (i.e., impulsivity) [212, 244, 245], indicative of the importance of 5-HT support of behavioural integration.
- Stereotypic integration of suppression-excitation of pre-learned (pre-fab) motor habits and skills needed for the maintenance of the tempo of activity and coordination of simple actions. It has been shown that unlike in plasticity, habit-based behavioural and impulsive types of integration both have weaker cortical activity. Unlike impulsivity, however, tempo of actions has healthy control over integration of actions from basal ganglia [222, 224, 243, 246, 247]. The loss of this DA function in basal ganglia does not lead to impulsivity but is associated with Parkinson’s disease [200, 201, 248].

Such diverse roles for DA release in behavioural regulation have one feature in common: all of them need prioritization of some behavioural elements and suppression of many others. This facilitates the choice of behavioural alternatives necessary for the integration of sequences of actions (whether perceptual-cognitive or motor). In fact, a recent study on the role of DA D2 receptors in reinforcement learning reported that a D2 receptor antagonist did not disrupt learning but rather induced profound impairments in choice performance [249]. It

has also been shown that D1 and D2 receptors may be stimulated optimally at different levels of DA presynaptic activity, which may improve some aspects of cognition and hinder others [230, 246]. This suggests that DA plays a key role in integration (including prioritization, sequencing, and programming) of actions.

The integration of actions appears to involve a transition from a general goal-setting stage to a stage of more detailed sequencing of action and activation of previously learned behavioural elements (such as habits and concepts). The transition between 2 stages of behavioural integration (noted here as $[] \rightarrow [[]]$) was traced to the transition between 2, ventral and dorsal, complexes in basal ganglia [220, 250, 251]. With the increase in transparency of the program of actions (with habit formation and more automatic integration), control over the integration of action is passed from the ventral to dorsal striatum. Conversely, with an increase in complexity of the task, control over integration is passed to ventral-striatal-cortical networks. This resembles the theory of multilevel control over the construction of action of Bernstein [23–25].

The first 3 DA functions listed here are proposed to be assigned to the $[]$ -Programming System traditionally described as the interaction between the mesolimbic and mesocortical DA networks. The last listed function of DA is assigned here to the part of the $[[]]$ -System which stores, activates, and sequences motor habits, amongst other learned elements of behaviour.

$[[]]$ -Systems of Sorting and Storing of Previously Integrated Units: Skills and Habits

The $[] \rightarrow [[]]$ Transition as Habit Formation and Habit Use for Future Integrations

The integration of action transitions from a more general program compiled in the anterior-ventral striatum and cortex to more detailed sequences of actions compiled by the dorsal striatum in a context-dependent manner [220, 243, 247, 250, 251]. The first complex was signified here as the $[]$ -Programming System, and the second one as the $[[]]$ -System, often named the “default” or/and “habit” network [222, 243, 247]. The $[] \rightarrow [[]]$ transition can be presented in the FC perspective as part of the production process that has features of diagonal evolution [14]. Similar to the phenomenon of “zone of proximate development,” known in developmental psychology, the nervous system approximates boundaries and the shape of the future behavioural outcome and then uses multiple back-and-forth interactions, gradually calibrating the final

set of actions and at the same time changing the environmental reinforcers, or plan of actions, if needed.

Instead of presenting behaviour as starting when the environment “kicks” the “bag of bones and muscles” of an individual to do something, behaviour is presented in the FC approach as a construction that starts from both extremes, the wide-environmental context (in line with the idea of extended phenotype [252]) and the deep physiological organization of the body. The interactions between these extremes in search of points of compatibility between needs and capacities create a more and more crystallized product that we see eventually as a behavioural act, contributing to the development of both these extremes (i.e., environment and body). These iterations on a “diagonal” of natural organization result in more and more organized structure as it is supported by multiple compatible factors. Indeed, the “sorting” of behavioural elements in striatum progresses not only using a change in neuroanatomic location but also at several other levels of neuronal organization. Firstly, within each part of striatum (ventrum versus dorsal) and cortex, there is functional differentiation between its structures (for example, core versus shell of the NAc), each having a different neurochemical signature [222, 223, 253, 254]. The striatum has a patchy neuronal structure known as the striosomes-matrix system [199], also having heterogeneous neurochemical markers and differential afferent or efferent connections. Moreover, within both []- and [[]]-Systems, heteromers and receptor mosaicism are common, in which local teams of receptors belonging to different NT families create regulatory complexes improving the calibration of the neuronal excitability of suppression [255, 256]. Moreover, there is functional differentiation within each NT system associated with a diversity of receptors and their mechanisms. All of this suggests that the [[]]-System works on more and more fine details of behavioural regulation in a fractal manner while staying within the sketched boundaries.

It is important to give credit to Bernstein, who, as noted, pioneered the constructivism approach. In addition to the concepts of df and the generative nature of behaviour, he demonstrated in his experiments in the 1930s that there are likely several levels of control over the construction of action. With learning, the control in action construction is passed from the upper levels (more conscious control) to lower (automatic) levels, but when the construction of action faces challenges, it shifts back from automatic to more conscious levels. Preservation of learned units of behaviour is known as habit formation and helps to optimize, to ease and to simplify the develop-

ment of new programs of actions. Habit formation takes the load off of conscious processing and transforms learned elements of cognition or action into ready-to-use habitual units labelled here [[]], which require just initiation for their use but no longer require new orientation and programming (i.e., involvement of //\\- and ?I!-Systems). As a result, an action can use a complex combination of pre-packaged elements from previous actions and still have sufficient resources for an optimal orientation and selection of actions during programming. Back in the mid-1930s, Bernstein suggested that different levels of control (he identified 5) are regulated by different brain systems, and this insight was later supported by neuroscience. The transition between several levels of control was noticed not only in the construction of motor behaviour as motor habits but also in cognition as memory, that is, units integrated into nervous systems and labelled here as [[]]. Therefore, the discovery of well-segregated systems in the basal ganglia gave additional validation to Bernstein’s experiments by showing a transition of integrational control from cortico-caudate and ventral striatum networks to dorsal striatum [220, 243, 247, 250, 251].

Motor and Mental Components of the [[]]-System

The neurochemical “signature” of the [[]]-System is hard to identify as it is proposed here to be based on diffuse NP (OR included) and GG systems entangled with DA, 5-HT, and ACh systems. Both 5-HT/NP and ACh are proposed to be the systems regulating the most stable features of behaviour (5-HT/NP – body-related, and ACh – context-related). DA/ACh regulation in the dorsal striatum contributes to the shape and sequence of actions, which is complemented by the parallel cerebellum-thalamic and RN-cerebellum networks for more automatic motor control, such as posture and balance [88, 257]. DA-GG regulation appeared to be important in LTP during habit learning and activation [222]. Due to space limitations, we cannot discuss the details of the endocrinology of behaviour and the role of GG, but they can be found in other sources [18, 26, 38, 44, 258]. For example, enkephaline binding DOR is co-expressed in GABA in the external globus pallidus, which is a member of an excitatory indirect pathway increasing the output of basal ganglia. The second, direct pathway via internal GP and substantia nigra reticulata has projections from spiny neurons of different chemistry, namely, substance P and GABA, and inhibits the output. As with the rule “if acting then stop orienting,” the first excitatory path for generating action suppresses thalamic control over sensory processing. However, as with the rule “give away slowly, take away

quickly,” the direct route has the privilege of suppressing the indirect route, activating the thalamus and sending direct projections to cortex, providing guidance when something does not work out. This interplay between excitatory and inhibitory routes allows a calibrated behavioural response, which is contingent on the capacity to perform the chosen program and the existence of necessary pre-fab elements. An imbalance between the activity of these 2 routes can lead to either hypokinetic (diminished motor ability) or hyperkinetic disorders. Indeed, a high DOR density in striatum and associated control of DA release were also linked to the preparation of motor actions and in pathology – to Parkinson’s disease – suggesting a role for the DOR-DA relation in motor sequencing [200, 201].

The 5-HT/NP and GG systems, coupled with ACh, contribute to the development of local metabolic cycles that help to store and maintain draft-elements of behaviour, summed under the label “[[]].” The trials and performance of actions create specific local intercellular loops within the locomotor and brain systems, which, as noted, often include DA-regulated motor readiness [230, 248]. The activation of this “habit” network likely starts from the caudate in the ventral striatum (during the []-Programming), where there is a significant presence of 5-HT projections from the dRN [46, 68] and proceeds to the dorsal striatum with more support of ACh interneurons than with 5-HT modulation. The transition continues, via direct and indirect routes, to the GP, STN, cholinergic PPN in the brainstem eventually reaching the cerebellum. The PPN has a direct projection to all leading structures involved in motor programming (i.e., to both GP nuclei, both parts of the SN, thalamus, and cerebellum), and receives projections from most of these structures, including the cortex, taking an active part in the control of fitting actions to context [80, 90]. This line of automatic integration of actions (habits) is complemented by another route to the cerebellum starting from the caudate RN and other brainstem 5-HT formations, to the cerebellum, where 5-HT, GG, and neuropeptides also regulate learning and motor behaviour [257]. 5-HT regulation in the cerebellum was linked to learning functions, which on the neuronal level include initial stimulation, establishment, but then suppression of dendritic growth, with maintenance of synaptic plasticity and occasional formation of synapses [257]. The cerebellum has internal loops of modulation during the integration of actions using ACh-based LTP/D [88] that likely facilitates the simultaneous availability of multiple drafts of actions. It also has a MOR presence, which modulates the activity of

cerebellar projections to thalamus. These projections likely provide updates on the readiness of the executive body systems and affect sensory processing. There is a segregation of thalamo-cortical projections between those that go to the cerebellum and those that go to the basal ganglia, favouring the idea that these 2 areas can be viewed as functionally distinct integration systems [80, 90].

The incorporation of learned physical actions into motor skills is, therefore, based on 5-HT-ACh-MOR-DOR cooperation at many levels. This interaction includes the cholinergic PPN-HT projections, projections from ACh neurons in the dLTA to the serotonergic RN and from the RN to HC, BF, and the cortex. The 5-HT and ACh systems “meet” in the cerebellum, being lead neuromediators there [90, 257, 259]. In contrast to the dorsal striatum, which does not have 5-HT projections, the HC has 5-HT-gic M-fibres from the mRN [46, 68]. The fact of such selectivity of projections from different parts of same RN system (dRN to DA-gic caudate, mRN to cholinergic HC-BF, and caudate RN to cerebellum) suggests a hidden functional differentiation.

Social Aspects of Behaviour Are Regulated by Different Systems than Physical Aspects

Several temperament researchers suggested an activity-specific differentiation of traits regulating physical, verbal-social, and mental aspects of tasks [217, 260–264]. The functional specificity of cortical areas for verbal processing, abstract thinking, and management of physical aspects of behaviour, as well as the role of oxytocin and vasopressin hormones in social-affiliative aspects of behaviour [65] support the idea of activity-specific differentiation between temperament traits. Due to the diverse nature of pre-fab elements of behaviour, the FET makes a distinction between the aspects that have well-documented neurochemical and neuroanatomic segregation of their regulation (physical-motor vs. cognitive vs. and social-verbal), following the *activity-specific approach* to taxonomies of temperament [20, 21, 38, 39, 217, 260–264].

Hormones are fast-acting neuropeptides and assist in the generation of behaviour for dealing with fast-changing aspects of situations requiring the highest behavioural plasticity. This property of hormones is crucial for “horizontal” (i.e., animal-to-animal interactions), interactions within the same level of complexity of natural systems (prey-predators, family members, dating, etc.). Such interactions include hunting and being hunted, socialization, mating, and taking care of

offspring. Hormones are the main family of neurochemical systems assisting these functions in many species. In humans, situations requiring a fight (defence)-flight (escape) or freeze behaviour are handled by the release of “stress hormones” (ACTH, CRH, cortisol, and adrenaline) and their HPA axis regulation. Maternal and affiliative behaviour also dealing with fast-changing situations has been linked to oxytocin and vasopressin; sexual behaviour – to gonadal hormones, competition, and aggression in mating – to testosterone, etc [145, 265–268]. The evolution of hormonal systems in animals often included advances in their own “chemical laboratories” (smell, taste) specifically tuned to hormones and excretions from other animals – something that was gradually suppressed in humans. We highlight the tighter association of hormonal systems with behaviour related to “horizontal” environments (i.e., peers, family, and prey-predator interactions) rather than with interactions related to non-living objects and higher-order societal regulation. It has been shown that both KOR and MOR (but not DOR) antagonists inhibit oxytocin release and the MOR system was found to be an important player in the perception of social support and affiliative behaviour [145, 265–272]. Moreover activation of the 5-HT_{2A} receptor in the HT reportedly increases hormonal levels of oxytocin [273], likely signalling sufficient capacities and promoting socialization. In Table 2, last row highlights how, according to the FET model, the temperament traits emerge as the result of the interplay between the described Systems [20, 21, 38, 39]. The table uses the notations O/\ for sociability as social type of endurance and /\[\] as socio-verbal tempo, considering the contribution of estrogen and other hormones to these capacities.

Towards Taxonomies of Contingencies in Neurochemical Construction of Behaviour

Mapping Eight Regulatory Aspects of Behavioural Constructions into 3D Space

The generation of behaviour can be mapped in a three-dimensional space related to specific requirements for the temporal range, spatial range, and novelty range in the generation of behaviour. Tables 1 and 2 and Figure 1 summarize the way in which the neurochemical Systems described above can be mapped into these categories:

- The temporal range for when a behaviour should be integrated (immediate, now vs. the full time range

[past, now, and potential events], i.e., eventual and ever).

- Spatial-extension range of selecting factors (from regulation of somatic processes, in-body, to regulation by the context of world-scale events that include an interaction with the body, in-context).
- Novelty range (using established df, marked as “keep” type vs. all range of novelty in df including established and novel that change established integrations).

We can, therefore, classify not only the functionality of neurochemical Systems, but also situations for generating behaviour, using the same “cube.” In the most urgent situations, behaviour is constructed differently than in situations in which an individual can use knowledge about a wide-range context of events. As known, in urgent situations, actions are driven by activation of the HPA axis, with stress hormones affecting hippocampal and cortical activity. Another hypothalamic-pituitary-gonadal hormonal axis that activates hormones related to sex and maternal behaviour also affects cortical and HC functioning. A third system (hypothalamic-catecholamine axis) is associated with the actions of catecholamines (NE, A, and DA) and, at the body level, mainly with NE, acting via sympathetic ANS and assisting in behavioural arousal. The hormonal-driven actions are labelled here as /\. When Systems of context processing and the integration of more thoughtful program of actions are compromised, the integration of behaviour becomes faster, “grabbing” whatever pre-learned elements available (known as impulsivity). DORs assist the speed of actions, similarly to their involvement in tempo of well-planned actions but they should not be considered as a sole system of impulsivity. Instead it is the failure of other systems that gives a way to hormonal systems to control the integration of actions, and DOR simply speeds up whatever was chosen. All 3 axes are suppressed by endorphins and enkephalins that bind to (and activate) MORs and DORs (marked here as “I!”) [93, 159, 160].

Postprogram stages of behavioural construction start from multiple []-\\// iterations making the program of actions more detailed and more relevant to the context, gradually transferring it from the []-System to the next Sorting-Storing System (labelled here as [\]). The activation of [\] networks supplies pre-integrated units of actions (habits and knowledge), assisting in the integration and execution of actions. The [\]-System also accommodates new experiences in the form of motor readiness for similar actions in the future (supported by the O-System) and episodic memories (supported by the \\//-System). Different sub-systems that secure and activate pre-fab

units of cognition and action are labelled here as [[]] (O and \\\).)

As noted, 6 preprogramming (O, OO, \\\, /\, /\, and !I?) and a post-action ([[]]) System, acting in a semi-parallel, semi-sequential manner, contribute to the selection of behavioural alternatives, which is finalized by the programming System []. Each of the 7 non-[]-Systems process specific range in degrees of freedom in actions, creating biases in the selection of the program:

- O – body bias as motivations affected by the “Now” needs and capacities of the body necessary to keep body’s homeostasis.
- OO – maintaining attention to specific df in actions that were determined by previously integrated program, that is, offering experience-biased now and in-context df.
- \\\ – capacities for probabilistic processing of events in a wide time range (including now, past, and possible events) and tunes an individual to sociocultural influences on program of actions (instructions, rules, and attitudes); this system is tuned to existing processes, to provide an individual with an informational map of the reality “what is normally there.”
- /\ – HPA- or HGA-related arousal and other hormonal systems contribute hormones, and in-body-now-based arousal to programming of actions.
- /\ – highlights novel df or launches a search for them if there the []-System cannot chose actions considering existing options.
- !I? – emotional disposition for events that have not happened yet contribute by biases towards approval of chosen df or further search for df.
- [[]] – this System favours an action out of habit, such as to open a fridge and grab food or drink that they should not;

The individual differences in these “selectors” of df plus the differences in the eighth, programming []-System that takes “votes” from these selectors can generate individual differences in CBPs.

Temperamental and Clinical CBPs Associated with Over-Under Performance of Described Systems

Table 2 provides a brief summary of related contingent elements of 7 out of 8 regulatory Systems described above and highlights the construction of actions according to one possible script of behavioural construction: goal-directed behaviour for a new action. As noted, most behavioural construction does not generate new programs of actions but runs on previously integrated programs, creating smaller loops between pairs and trios within the 7

systems (with exception of the []-System). The last column in Table 2 unites both components of the [[]]-System, and the last row highlights the correlates between the above Systems and temperament traits included in the current FET model (Table 3). As can be seen, none of the FET components (temperament traits) are proposed to be regulated by a single NT system. Instead, each component of the FET is linked to an interplay between specific sets of NT systems, similar to the composition of elementary particles by quarks. These NT systems work in teams, which are specific to each trait, with dominant NTs for each team.

Consistent weak or severe imbalances in transitions between the described Systems during behavioural construction, resulting in the dominance of some at the cost of weakness of others, can emerge, correspondingly, as temperament traits in healthy people or symptoms of psychiatric disorder in clinical populations. To make the analysis more formal, for every given pair of system-1 and system-2, we can expect at least 4 trends contributing to the types of CBP (Tables 2, 3):

L-trends: system-1 $\leftarrow$ system-2, with consistent behaviour of system-1 type and underperformance of behavioural aspects related to system-2 type (marked with left arrow).

R-trends: system-1 $\rightarrow$ system-2, with consistent behaviour of system-2 type and underperformance of behavioural aspects related to system-1 type. Either case with (L)eft or (R)ight directionality of dominance between these networks can create a behavioural pattern emerging as a temperament trait (T-CBP) in healthy people. The combination of 2 and more systems with overperformance of one and underperformance of others enforces such a temperament trait from both sides and makes a temperament trait more distinct: system-1 $\rightarrow$ T-CBP $\leftarrow$ system-2 (see Table 2; Fig. 1).

G-trends: system-1 $\leftarrow$ G-CBP $\rightarrow$ system-2, when both networks perform strongly ([G]iftedness) and create high-intensity fast exchanges showing up as overperformance in behavioural aspects related to both types [20].

C-trends: $\leftarrow$ system-1 – C-CBP – system-2 $\rightarrow$, when both networks underperform, passing the lead of behavioural regulation to other Systems. A C-CBP can show up as (C)linical symptoms of mental disorders, which can highlight the functionality of neurochemical biomarkers in behavioural regulation in the case of extreme deviations.

In these notations, we follow the hint “the tip of the arrow pulls the game” (i.e., the behaviour towards that system). Temperament traits listed in Table 3 do not cov-

er all possible healthy CBP – such as memory, some aspects of attention, and learning – but include only those related to dynamical features of behaviour. In most cases, consistent behavioural patterns are based on contributions from several Systems described here. In this sense, the FET groups the patterns not according to single Systems but according to the way they emerge as CBP, shrinking possible combinations of up- and downregulation into 12 temperament traits. The FET is organized in a 3×4 matrix where 9 out of 12 components represent temperament traits regulating endurance, integration, and orientation aspects of behaviour (3 columns of the FET model) [20, 21, 38, 39]. These formal dynamical aspects are regulated differently at several levels of contextual complexity of behaviour (i.e., physical, social, and mental aspects of actions). The division into these 3 rows is known as the activity-specific approach [217, 261–264]. The 3 emotionality-related traits (neuroticism, impulsivity, and [a disposition for] satisfaction) are considered in the FET as emotional dispositions that were linked to dysregulation of OR density.

This review commented on some links to clinical conditions associated with the C-CBP where possible, but due to the significant number of scenarios in these contingencies and limited space, we cannot comment on all of them. Here, however, a few examples show how the formal approach offered in this review could be used for CBP taxonomies.

The FET considers 3 temperament traits related to 3 types of endurance – physical (ERM) based on the O-System, social (ERS) based on $\backslash$ -O Systems, and mental (ERI, sustained attention), based on the OO-System. If context-processing capacities are low but endurance is sufficient or high, then behavioural regulation follows the $O \leftarrow OO \leftarrow // \backslash \backslash$ script, and an individual exhibits a low ability for information processing but compensates it by sustained performance of previously learned habits or simple actions. In the opposite contingency, if the information processing capacities are sufficient or high, and the body's maintenance cycles require changes (i.e., initiation of behaviour), then an individual shows the $O \rightarrow // \backslash \backslash$ behavioural pattern by underperforming in physical activities and engaging in observation and probabilistic analysis of the reality.

As noted, when any 2 regulatory networks underperform, passing the lead of behavioural regulation to other networks, symptoms of mental disorders may emerge. The underperformance of the O-System can emerge as low physical and social endurance (that is, fatigue, loss of sleep and appetite, social withdrawal), which are key

symptoms of major depression [214, 219]. Indeed, deficiencies in 5-HT transmission had so profound an association with depression that the serotonergic hypothesis of depression was well accepted in psychiatry for long time. The contribution of the immune system can be also a factor in dispositional emotionality, low endurance, comorbid depression, and other psychopathology during somatic illnesses [47, 56, 58, 60, 274]. It has been shown that inflammation can damage the body's reserves of the 5-HT precursor tryptophan, production of endorphins and binding OR receptors, functionality of glia and neurons. For the " $\leftarrow O \leftarrow C \leftarrow CBP \leftarrow // \backslash \backslash \rightarrow$ " case, when both endurance and context-processing aspects of behaviour are underperforming, this might emerge as depression with the symptoms of fatigue and apathy. For the " $\leftarrow [] \leftarrow C \leftarrow CBP \leftarrow [[]] \rightarrow$ " case, when both plasticity and use of skills are negatively affected, an individual might exhibit inability to integrate new actions, "sitting on the sofa all day long," as some say, even though knowing what should be done to feel better.

As another example, 3 temperament traits in the FET model reflect 3 types of orientational biases: sensation seeking (SS), empathy (EMP), and probabilistic reasoning (PRO), all found not only in humans but also in animals [20, 38]. When both "Orientation $\leftarrow \rightarrow$ Context trim" are strong, an individual might show high sustained attention (mental endurance), attention to novelty and processing of context (causes and probabilities) of events. This is known as intellectual ability and highlighted in the FET as the PRO trait (probabilistic processing) regulated by ACh-Glu and NE cortical systems [70, 77, 103, 106]. This trait emerges as a drive to differentiate and to categorize features of objects/events and to gather of probabilistic information related to reality (extreme events, possibilities of future events, frequency, commonality, causal relations between observed events, etc.). There is a common observation of a correlation between neuroticism and high intelligence, as both of these CBPs are based on functionality of the KOR and NE systems (but not only these) [20]. The underperformance of the Orientation-expansion network can emerge as preferences for stereotypic, familiar, or simple behavioural alternatives, stress resilience, and indifference to information or new events, accompanied by low HPA axis excitability. When 2 networks underperform in the " $\leftarrow$ Orientation – Context trim $\rightarrow$ " case, this might emerge as learning and intellectual disabilities, as an individual would have a deficiency in processing newly arriving information.

Several clinical studies have been conducted using the compact version of the Structure of Temperament Ques-

tionnaire [STQ-77] that is structured in line with the FET model [214, 215, 217–219, 275]. Table 4 summarizes the results of these studies highlighting the differential power of the FET model. The idea of the continuity between temperament and psychopathology was well confirmed: the symptoms of mental illnesses amplified temperament traits of a similar nature. More importantly, the FET model was able to show good differential power, exhibiting distinct “signatures” for all tested diagnoses. In contrast, such differentiation is very weak in clinical studies using the Big Five or positive-negative affect models that commonly show high neuroticism and low extraversion in many tested diagnoses. This weak differential power forced researchers to put many distinct diagnoses into one group of “distress disorders,” which is not very useful for psychiatric practice. The FET framework, on the other hand, highlights the differences between diagnoses of mental illness and can be used as a first step towards a common CBP taxonomy.

Conclusion

The present review highlighted the benefits of using a FC approach in the analysis of neurochemical biomarkers underlying temperament and psychopathology. In contrast to label-based DSM/ICD taxonomies and dimensionality-based models, the FC approach focuses on the contingent, context-dependent, generative, and transient nature of biomarkers that were linked to specific CBP. “Construction” of behaviour is a mainly unconscious process and is based on the interplay between multiple neurochemical systems and environmental conditions. There are at least 8 distinct regulatory Systems (neurochemical ensembles) that have been identified in neuroscience, and 7 of them are formally presented in this review. Where possible, neuroanatomic associations are also mentioned. The 8 Systems cover a three-dimensional space of behavioural construction related to *temporal range* (immediate vs. eventual), *spatial-extension range* (from in-body’s close proximity to a world-events context) and *novelty range* (construction of behaviour as combinatorics of previously integrated actions or as generating a new program of actions). None of the 8 neurochemical Systems assigned to the vertices of this space is represented by a single neurotransmitter and all of them work in ensembles with each other. Their interplay in the generation of behaviour is conjectured to lead to specific types of consistent behavioural patterns observed as temperament, clinical symptoms, or giftedness (noted here,

correspondingly, as T-CBP, C-CBP, and G-CBP). The functionality and relationships of these systems are presented here in association with their contribution to generation of the program (choice and sequencing) of actions and are labelled with formal symbols to facilitate a more compact analysis in the future. This analysis demonstrates the possibility of generational and unifying taxonomies of temperament and classifications of psychiatric disorders. Such taxonomies would present the biobehavioural individual differences as consistent behavioural patterns generated within a formally structured space of parameters related to the generation of behaviour. The literature is full of important additional examples of functional differentiation within neurochemical systems that we could not include here due to space limitations.

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