

Irina Trofimova\*

# Anticipatory attractors, functional neurochemistry and “Throw & Catch” mechanisms as illustrations of constructivism

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**Abstract:** This review explores several rarely discussed examples illustrating constructivism principles, generative and selective features of neuronal regulation of behaviour. First, the review highlights Walter Freeman’s experiments and mathematical analysis that uncovered the existence of anticipatory attractors, *i.e.* non-random dynamical patterns in neurodynamics. Since Freeman’s work did not extend to neurochemistry, this paper then points to the proposed earlier neurochemical framework summarizing the managerial roles of monoaminergic, cholinergic and opioid receptor systems likely contributing to anticipatory attractors in line with functional constructivism. As a third example, neurochemistry’s evidence points to the “Throw & Catch” (T&C) principle in neurodynamics. This principle refers to the pro-active, neurochemically expensive, massive but topical increase of potentials (“Throw”) within electrodynamics and neurotransmission in the brain whenever there is an uncertainty in selection of degrees of freedom (DFs). The T&C also underlines the relay-like processes during the selection of DFs. The “Throw” works as an internally generated “flashlight” that, contrarily to the expectations of entropy reduction, increases entropy and variance observed in processes related to orientation and action-formation. The discussed examples highlight the deficiency of structures-oriented projects and excitation-inhibition concepts in neuroscience. The neural regulation of behaviour appears to be a fluid, constructive process, constantly upgrading the choice of behavioural DFs, to ensure the compatibility between the environmental and individual’s individuals’ needs and capacities.

**Keywords:** attractors in neurodynamics; constructivism; mass action; neurochemical framework FET; “Throw & Catch” principle.

## Introduction to constructivism principles

The efforts in analytic, and not just experimental, work in neuroscience continue in order to make sense of the diverse and massive amount of experimental findings so we can “see the forest behind the trees” (Arbib and Erdi 2000; Bressler and Kelso 2001; Trofimova 2021a; Trofimova and Robbins 2016). The language of neuroscience that shapes research questions and methodologies makes a big difference in the interpretation of results, and so it is essential to highlight the outdated concepts and the promising principles.

Several principles that can fundamentally influence methodology and interpretation of results in neuroscience but are very difficult to study relate to the paradigm called “the constructivism”. *Constructivism* suggests that:

- Behaviour and all its psychological elements are not reactive but generated (constructed) every time afresh (Trofimova 2017, 2021a,b; Whiting 1991). The principle that psychological phenomena have a constructive nature was first experimentally demonstrated using original tracking devices in the work of the Russian psychologist Nikolay Bernstein almost 100 years ago (literally creating a new discipline of kinesiology) (Bernstein 1947, 1967; Bernstein et al. 1996; Hayashibe and Shimoda 2014). Paradoxically, even well-learned, stereotypical actions appeared to be generated anew, just at the lower level of behavioural regulation (Bernstein called it “repetition without repetition”). English cognitive psychologist Frederic Bartlett (Bartlett 2009) also proposed in the mid-1930s that memory has a constructive nature.
- Bernstein was also the first scientist who outlined and experimentally demonstrated “the Degrees of Freedom problem” back in 1930s (Whiting 1991) the key concept of constructivism. This problem since then has been

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\*Corresponding author: Irina Trofimova, Laboratory of Collective Intelligence, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton L8S 2T6, ON, Canada, E-mail: iratrofimov@gmail.com. <https://orcid.org/0000-0001-6758-1389>

well-recognized in neurobehavioural sciences and relates to the fact that there are too many stimuli around that our nervous systems can react to. There are also multiple ways to “react” in every behavioural act. Out of all possibilities, it is a great challenge for nervous systems to select what to be attentive to and suppress the majority of stimuli and possible actions (whether or not the action is a new or a learned one), and make this selection fast and, preferably, in advance. The “degrees of freedom” concept was well-adopted in statistical mechanics, especially in association with the concept of “entropy” (that could be simplistically translated to a common language as “number of possibilities”). Several researchers reflected that nervous systems work on decreasing the degrees of freedom (DFs), *i.e.* decreasing entropy in behaviour (Cieri et al. 2021; Friston and Buzsaki 2016).

- Experiments by Bernstein and later scientists demonstrated that there is a universal architecture (stages) that construction of actions follows in the suppression and selection of DFs, such as: gathering (orientation), integration (selection and sequencing) and maintenance of preferences (with suppression of deviations from the chosen sequences of actions) and feedback adjustments during these stages (Alexandrov et al. 2018; Bernstein 1947, 1967; Trofimova 2017, 2021b; Whiting 1991).
- Bernstein has demonstrated the existence of several neuronal “levels of control” of action construction, from conscious to automatic, and the transition of behavioural construction between these levels during learning processes. These findings were later fully supported by neuroscience.

The constructivism principle was described in a range of bio-behavioural sciences kinesiology, psychophysiology, cognitive, developmental, ecological, educational psychology, psychological modelling and psychology of emotions, neurochemistry, molecular neuroscience and endocrinology (see Trofimova 2017, 2021a,b for reviews). 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 (Alexandrov et al. 2018; Hebb 2014; Quartz and Sejnowski 1997). Similar generative processes were described since then in multiple phenomena in neuroscience, from molecular level to synaptic plasticity to construction of behavioural response by neuroanatomic or neurochemical ensembles. For example, neurotransmission, in most cases, requires the composition and decomposition of its components every time afresh (Siegel et al. 2006). There is, therefore, a disconnect between enthusiasm and scale of structures-

oriented projects, like brain-mapping Connectome, presenting brain activity as mechanical activation of stable brain structures by incoming information and transient, constructivism phenomena seen in neuroscience at molecular and neurochemical levels.

This review considers three rarely discussed examples illustrating the benefits of constructivism in neuroscience. First, the review gives credit to the fundamental and original work of neuroscientist Walter Freeman, our modest, polymath, hard-working colleague and a friend who would be 95 this year. Even though his recent death came with acknowledgement from the Cognitive Neurodynamics community (Kozma 2016), his work in the mathematical analysis of neurodynamics is yet to be appreciated. The other two examples of constructivism will involve the area of neuroscience that Freeman’s work did not involve but that could confirm the validity of his findings: functional neurochemistry. We will briefly mention the neurochemical framework summarizing the most conservative findings related to the specificity of neurotransmitters (NT), hormones and opioid receptors. The third example will highlight the convergence of described functionality of neurochemical systems with the mechanisms that could be summarized as the “Throw and Catch” principle.

More importantly, there is a key difference between the idea of “entropy reduction” and constructivism as the principles of neural regulation of behaviour. Constructivism aligns with “entropy reduction” in highlighting the trend for DFs reduction-selection but, unlike entropy reduction, it also points to creativity and self-generations of DFs within nervous systems. This internal generation of additional DFs is paradoxical considering how many levels of DFs selection and reduction are in the nervous systems – some are reviewed in the sections below. One of the examples of overproduction of DFs is mass action of neuronal potentials.

## Mass action principle in neurodynamics: weighing its costs and benefits

### Mass action in neurodynamics – is it too massive? It surely is neurochemically expensive

The mass action principle in neurodynamics relates to the fact that information transfer can hardly happen as neurotransmission between a single pair of neurons within a single synapse. In our view, one of the most comprehensive

works on mass action principle and the concept of neurodynamics was offered by Walter Freeman, an American neurophysiologist from the University of California in Berkeley in the 1960s–2000s (Freeman 1961, 2000b, 2001a,b, 2007, 2012). He was not the first author to point to the mass action of neurons in neuroelectrodynamics, but he was one of the lead scientists investigating the details of these processes. Freeman, like other authors, points out that it takes more than a hundred inputs to one neuron to make it fire (Altman 1999; Freeman 2000a; Liley et al. 2012; Stark and Abeles 2007) and that inputs to neurons contribute to the resulting electric wave from this neuron just like people contribute to political decisions by voting (Freeman 2001a). This is similar to the scenario when many blind wise men touch various areas of an elephant, and only the integration of their “reports” brings the whole “holographic” picture of the object. In fact, the “holographic” nature of mass action underlying human cognition was described by the American neuropsychologist Karl Pribram (1991). The transmission of signals within the same cortical cell uses different dynamical mechanisms, depending on the location of the transmitting site (dendrites vs axonal trigger point vs the cell body) and the shape of neurons.

There is a special part of science – sampling theory – that calculates “how many wise men”, or sensors should be used per unit of the coverage of the “elephant” to ensure a complete signal reception. According to this theory, to have full information about the object, there should be a double presence of “antennas”, or two wise men per each elephant spot (Dewdney 1998; Griffiths and Tavaré 1994). Moreover, statistical sampling theory recommends that, in order to obtain a more exact picture of the observed or measured phenomenon, it is crucial to decrease its variance (Fortmann-Roe 2012).

However, here is a problem: the nervous system does precisely the opposite of this recommendation. Instead, it conducts a massive overproduction of “reporting sites”, millions of “wise men” (synapses and brain cells) per each spot of the “elephant” (amount of relevant objects and events to be perceived). The number of potential stimuli (*i.e.* “elephant parts”) and degrees of freedom in actions for selection are numerous but still insignificant in comparison to the number of neuronal synapses and generated pulses in the brain (*i.e.* reporting “wise men”). More specifically, the average amount of synapses in the human brain is around 1000 trillion (if including glial cells), which is more than the estimated number of stars in the Universe. This is too dense a coverage of “wise men”, enormously exceeding the sampling theory rule “two wise men per spot”.

Moreover, there are more than twice as many excitatory glutamergic synapses in the human cortex as inhibitory

Gamma-Amino-Butyric Acid (GABA) synapses – and this would surely shift the “voting” during the wave-pulse generation in favour of an excitation if the mass action would be a simple matter of “voting”. Having twice as much excitation than inhibition only increases the entropy unless there are non-random and multiple mechanisms that trim the potentials.

Mass action by itself (“multiplicity of siblings”, or similar compositions) is useful for sustainability of compositions, as noted above. However, enormous over-production of mass action in neurodynamics with excesses in neurotransmission is somewhat puzzling if considering how neurochemically expensive and complex single neurotransmission is from one neuron to another. Most NTs and neuropeptides (NP) are not stored in synapses, ready for release. Instead, they are synthesised and immediately decomposed after use, with different mechanisms related to these cycles for each NT. NT release proceeds in several stages, and each stage involves a cascade of contingent transformations regulated by mediators such as co-releasing neurotransmitters, GPCR contingent mechanisms, transcription and neurotrophic factors, enzymes, metabolites, ATP, calcium and other chemical systems, as well as the regulatory impact of NTs and NPs on each other (Siegel et al. 2006). Each of these mediators has the capacity to disrupt or change the pace of neurotransmission. A similar complexity and contingent construction were described in the action of opioid receptors (OR) (Gupta et al. 2021; Waldhoer et al. 2014). 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.

Considering how complex, multi-stage and contingent the neurotransmission is (requiring multi-elements composition and decomposition of neurotransmitters every time afresh for neurotransmission to proceed), it is puzzling why the brain needs to overproduce such pricy neurotransmission in so enormous quantities. In this context, what looks even more strange is the well-documented spontaneous firing of many neurons at a rate of about five action potentials per second as a constant, highly irregular background activity. This background firing happens not only before but also after a stimulus; the only time it suppresses is when it is time to transfer a signal. It seems a waste of chemical components to build up and maintain this constant background excitation if at least 90% of them are never transformed into useful information.

The high neurochemical cost of this mass generation, maintenance and cleanup of the enormous number of seemingly useless excitations should be somehow justified by the benefits for the individual’s functioning.

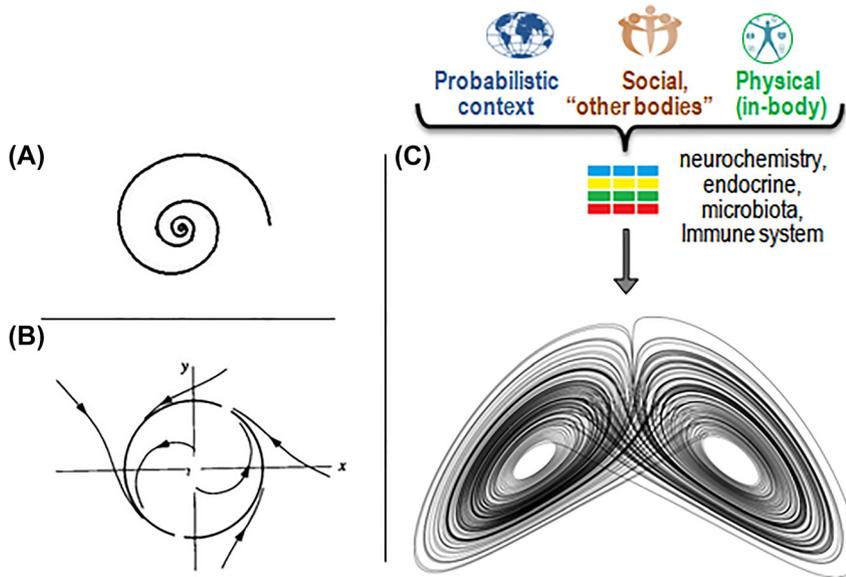
### Freeman’s anticipatory attractors illustrate the constructivism principle

One of the major contributions of Freeman’s work in the 1960s–2000s is the pioneering application of nonlinear dynamics methods to the analysis of neurodynamics. His analysis revealed more complex, contingent and structured dynamical patterns than just “voting for or against” the spread of neuronal pulses. Freeman described the presence of an *attractor* landscape with several adjoining basins of attraction, one for each class of learned stimuli. “Attractors” are mathematically plotted trajectories of a system in the space of its possible states. The system tends to follow these trajectories more often than others (*i.e.* to be “attracted to”) (Figure 1). Freeman described a transition between several dynamical patterns in neurodynamics: point attractor, limit cycle attractor and chaotic attractor (Freeman 2000a,b, 2001a,b, 2007, 2012; Freeman and Vitiello 2006). “Chaotic” sounds helplessly messy, but the concept of chaos in mathematics is not equal to randomness. It relates to complex but structured dynamics that are often driven by “clean” deterministic functions that generate unpredictable outcomes. The trajectory of a chaotic attractor, when plotted on a graph of states, travels along a set of similar nonlinear loops (“wings” of attractor) (Figure 1C) but at some point switches to a different set of loops and “stays” there till it switches to the previous set of loops. The name “chaotic” was given to such systems because their switches from one trajectory to another are unpredictable and incalculable (unless more variables are given). Chaotic attractors are patterns that were found in many natural systems that exhibit complex and seemingly unpredictable dynamics, like weather or other natural systems (Nation et al. 2002; Sulis and Combs 1996; Sulis and Trofimova 2001).

Freeman showed that neurodynamics of a chosen behaviour that can be plotted as a point- or limit-cycle attractor, when a system goes predictably around the same dynamical patterns (Figure 1A and B). However, active construction of behaviour generates a more complex “strange” (type of chaotic) attractor (Figure 1C). The selection of few behavioural alternatives happens during the most uncertain periods of chaotic attractors within the steady, chaotically structured “noise” of mass action of cortical neurons. Each of the sources of votes creates excitatory biases having very specific voting power when

the system approaches those flip-flop, sensitive points of potential switches between the “wings” of attractors. Cortical neurons continue exciting each other to ensure this background build-up of attractors until additional inputs are sent to make excitation go above the threshold, causing a neuron to fire downstream. During these most unstable points of strange attractors, it takes just a slight push by (semi-selected and semi-expected) stimuli to create a small imbalance in the voting of conflicting potentials for falling towards a specific “wing” of attractor (Figure 1C). How many additional inputs are needed to make this output, *i.e.* to push the neuron into a more certain state? According to the estimates of Abeles’ work discussed in detail by Altman (Altman 1999), an additional 25% of excitation, added to the existing amount of excitation, can make the neuron fire the output. This additional excitation can be provided by environmental trigger stimuli and by endogenously generated stimulation coming from the lateral hypothalamus and several neuromodulators (Trofimova 2021a; Trofimova and Robbins 2016).

Freeman’s acknowledgement of the generative nature of neurodynamical processes of cognition and behaviour is in line with the principles of constructivism. He made an important point that *“the attractors are not shaped by the stimuli directly, but by previous experience with those stimuli. These attractors and behaviours are constructions by brains, not merely read-outs of fixed action patterns”* (Freeman 2001b, p. 83). Moreover, chaotic attractors prevent the brain from falling into the stereotyped patterns of synchronous discharge that characterize seizures, prevent the convergence to previously learned patterns, and hence facilitate the emergence of new patterned activity if needed. So the chaotic background states provide the system with continued “open-endedness”, making it ready to respond to information without the requirement for an exhaustive memory search (Freeman 2001a; Freeman and Vitiello 2006). Freeman, therefore, presents perception as *“a steady-state dynamic pattern with multiple outcomes. It might not coincide with timing of stimuli or a preparation of an action. Perception often just screens the environment as preference, or ignores it as there is no interest to it. The arrival of stimuli confirms or denies the perceptual hypothesis”* (Freeman 2001a). Having these steady-state dynamical patterns creates anticipatory readiness for several behavioural alternatives and significantly speeds up the future selection of degrees of freedom. Therefore, the anticipatory attractors identified by Freeman are likely the neuronal correlates of perceptual and behavioural dispositions, *i.e.* readiness to perceive certain things and to act in a certain way. The presence of anticipatory attractors contrasts with the second recommendation from the statistical sampling



**Figure 1:** Types of attractors (trajectories of the states of neurodynamical systems) found by Freeman in the electrical activity of the brain. (A) Point attractor. (B) Limit cycle attractor. (C) “Strange” (type of chaotic) attractor, in which a system can loop around one wing (in one set of states) or suddenly switch to a completely different set of states (a second wing). Neuromodulators (monoamines, ACh, hormones and neuropeptides) affect the switch of the system towards specific wing, providing the bias in selection of degrees of freedom in line with sustainability cycles that the individual is involved. The neurochemical Functional Ensemble of Temperament framework (FET, depicted as 12-component coloured rectangle) identifies three phenotypic cycles (physical body’s maintenance; other-bodies interaction and wider probabilistic context) and a reproductive (genetic) cycles, not shown here but affecting all phenotypic behaviour.

theory – to avoid biases while sampling the data about reality (Fortmann-Roe 2012). Apparently, this recommendation is also totally ignored by the nervous system because it seems that there is nothing unbiased within the sampling processes of nervous systems.

The anticipatory nature of cognition was noticed in psychology before, especially since Neisser described them in his work as internally derived schemata, *i.e.* hypotheses created by the nervous system to be checked against selected aspects of reality (Neisser 1978). Only recently, neuroscience started uncovering the mechanisms behind the anticipatory nature of perception, with Freeman’s work showing some relevant neuro correlates. The pro-active, anticipatory attractor basins described by Freeman collapse multiple DFs in signal propagation to much fewer DFs, converting them to limit and point cycles.

### “Repetition without repetition” and learning: neurodynamic perspective

Now let us briefly come back to Bernstein’s paradoxical principle of “repetition without repetition”, which looks contradictory to the Pavlovian learning paradigm (“repetition establishes associations that later just REPEAT an action”). Cognitive psychology provides considerable evidence in support of the constructivist view first described in

memory research by Bartlett almost a century ago (Bartlett 2009). Learning as memorization appeared to use encoding based on the current context, features of the environment and the state of the body, and not just on the properties of items to learn (Quartz and Sejnowski 1997; Roberts 2019; Schmidt et al. 2021). A similar dependence of reconsolidation on the context and the state of the body was demonstrated for memory retrieval, including drugs-induced states (De Oliveira Alvares and Do-Monte 2021; Lee et al. 2017; Quartz and Sejnowski 1997; Walsh et al. 2018). Immune challenges or substance use altering body states were found to influence learning process (Dutcher et al. 2020; Giuliano and Dalley 2020; Jupp et al. 2020; Zarrindast and Khakpai 2020). Earlier consolidated memory often becomes labile and susceptible to modifications after being reactivated, explaining imperfections and variability of recall (De Oliveira Alvares and Do-Monte 2021; Lee et al. 2017; Walsh et al. 2018). Natural learning and recall, therefore, do not follow the computer metaphor, which considers memory as a storage collecting associations gained from experience. Instead, learning has the properties of any action construction, *i.e.* integration of its product as a choice of alternatives under the influence of context, subjective experience and state.

The multiplicity of DFs at behavioural and neuronal levels that creates the DF problem (*i.e.* how and what to choose from multiple possibilities in synaptic transmissions, in stimuli to attend and in shapes of actions) appears to be a

solution to the paradoxical principle “repetition without repetition”. Indeed, as we argued earlier (Trofimova 2016b, 2023), when there is a “multiplicity of siblings”, *i.e.* overproduction of similar compositions, this multiplicity can provide sustainability of the same composition, even though the actual “players” would be changing. This is similar to the BBC having a set of hosts (players) while producing previously established (“learned”) designs of the BBC channels. When one host is not accessible, another host is called to read the news and perform the routines. Each BBC issue is, in a way, unique and yet, it repeats the BBC tradition.

The multiplicity of neuronal connections underlying learning is created by either repetition of experience, where each repetition involves diverse neuronal ensembles or by a single experience that has an emotionally important context (expanding neuronal ensembles). In both cases, learning generates not one association but, considering the mass action of neuronal potentials described above, multiple ways for encoding, recall and performance of the habit. In addition to numerous modalities for encoding, each requiring involvement of a spectrum of sensory networks (visual, auditory, smell, proprioceptive), learning uses neuronal systems processing spatial, timing, social context and safety features of actions. Neurodynamically speaking, learning uses multiple candidates in synaptic pulses to generate chaotic anticipatory attractors to provide several DFs in encoding the experience. This process emerges as subjective exploration in learning: individuals that learn the same material or action perceive and interpret it differently because of the differences in their anticipatory attractors (which, in turn, depend on their previous experience, state of the body and differences in neurophysiology). With the progression of learning, as Freeman showed, the ambivalence of chaotic attractors (Figure 1C) is gradually reduced to a limit cycle attractor (Figure 1B) and then to the point attractor (Figure 1A), as limitations of DFs to a specific course of actions or perception. However, in changing context, previously learned habits are being revised for their DFs, and so the dynamics come back to more chaotic patterns, consistent with MRI studies (Zühlsdorff et al. 2022). Freeman’s discoveries of anticipatory attractors in electric neurodynamics of the brain’s waves and pulses highlight the proactive mechanisms of selecting behavioural DFs – an important aspect of learning even in the learning was enforced onto an individual. If perception is so pro-active even during the forced learning, then, regardless of existing stimuli, the nervous system stays mostly deaf and blind to them and “acquires” them only on as-preferred and as-needed bases. In this selective perception, only a specific, small portion of stimuli (most relevant for survival and current needs and capacities [N–C]) can be processed under

the condition of the existence of anticipatory attractors, ready to “swing” to specific scripts of action or elements of perception.

Local neuronal loops supporting attractors in neurodynamics are likely regulated by specific relationships between local neurotransmitter systems driven by the dispositions of the nervous system to receive specific signals or choose a certain action. However, statistically speaking, there would be millions of these attractors, so there should be additional mechanisms facilitating a further collapse of millions of DFs to a single sequence of actions. Further analysis of *neurochemical* mechanisms regulating the generation and transformation of these attractors could bring insights into the solution to the DF problem.

## Functional constructivism helps to sort out the neurochemical ensemble generating Freeman’s attractors

### Functional constructivism uses dynamical categories for classification of brain systems

Neurochemical regulation represents the basis of the nervous system’s activity, especially the brain’s electrical activity, including forming and transforming attractors described in Freeman’s work. The presence of neurotransmitters and their receptors varies dramatically in various areas of the brain, and this variation likely relates to their different functionality. However, analyzing the functional roles of neurochemical systems is complicated by their multiplicity, complexity and diversity. Therefore, when sorting through this complexity, one should be prepared to deal with a multiplicity and complexity of categories, mechanisms and functional aspects. All these aspects influence the selection of DFs in behaviour, so there are limits to how much they could be simplified.

Several neuroscientists pointed to the functional differences between neurotransmitter systems in behavioural regulation, but the most prominent work, in our view, was conducted by Trevor Robbins group at Cambridge University (Robbins 1997, 2010; Robbins and Everitt 1996). Robbins’ detailed analysis of the functional roles of monoaminergic and ACh systems offered in the mid-1990s coincided nicely with Bernstein’s model of an action construction. Using the integration between these two lines of research and review of models of bio-behavioural

individual differences, earlier, we proposed a summary of the functionality of some neurochemical systems, based on *Functional Constructivism* (FC) (Trofimova 2016a, 2018, 2019, 2021a,b; Trofimova and Gaykalova 2021; Trofimova and Robbins 2016). The FC suggests a classification of neuroanatomic and neurochemical systems based the stages (universal functional aspects) of the construction of behaviour (Figure 2). This approach is summarized in the form of the neurochemical framework, Functional Ensemble of Temperament (FET) (Trofimova 2016a, 2018, 2019, 2021a,b; Trofimova and Gaykalova 2021; Trofimova and Robbins 2016) (Figures 2 and 4).

### The overview of the neurochemical framework Functional Ensemble of Temperament

The FET framework represents consistent behavioural patterns (CBP, *i.e.* temperament traits and symptoms of psychopathology) as the product of contingent interactions among specific NTs, OR and hormonal systems. The FET acknowledges the diversity of receptors within each NT system and the specificity of these receptors, pointing, however, to the common features of their functionality within each given NT system. This differential functionality and differences in distributions of release and receptors contribute to

differences in functionality of brain structures (Trofimova 2016, 2021a; Trofimova and Robbins 2016, top row of Figure 4). The FET, therefore, suggests grouping brain structures by their neurochemical compositions and by their functional roles in action construction (Trofimova 2021a).

The 12-block structure of the FET organizes temperament traits and symptoms of mental illness in a 3 × 4 matrix and reflects the universal architecture of how an action is constructed out of millions of possible alternatives. It follows the three main aspects of action construction (three columns of Figure 2): expansion of degrees of freedom (orientation), selection/integration of a program of action, and energetic maintenance (including decomposition of unneeded degrees of freedom) – all associated with physical, social, mental and emotional aspects of actions (four rows of Figure 2). There is a contingent and mutual regulation between these three blocks during the selection of DFs in action and cognition. As discussed in previous publications (Trofimova 2016a, 2021a; Trofimova and Robbins 2016), the FET proposes that orientational aspects of behaviour and expansion of behavioural alternatives are led by the noradrenalin-related systems, with the cooperation of other neurotransmitters, neuropeptide and hormonal systems. Prominent research highlighted the roles of DA systems assisted by ACh and GABA in the integration and programming of behaviour and, with the progressing to automatic actions – the role of delta opioid receptors in basal ganglia in both adaptive and impulsive integration of behaviour (Robbins 1997, 2010; Robbins and

<i>Functional aspects:</i>	<b>Behavioural orientation to...</b>	<b>Speed of integration</b>	<b>Maintenance of cycles</b>
<b>Probabilistic aspects</b>	<i>Probabilistic processing</i> Glu + ACh, NE, DA	<i>Plasticity</i> (new integration) DA + ACh, 5-HT, GABA	<i>Intellectual Endurance</i> , (sustained attention) ACh + NE, 5-HT, GC
<b>Social-verbal</b>	<i>to others vs Self: Empathy</i> OXY, -VSP, -Tstr, NE	<i>Social-verbal Tempo</i> (learned integration) DA+Estr, NP	<i>Social Endurance</i> (sociability) Estr + 5-HT, H
<b>Physical-motor</b>	<i>...to sensations</i> <i>Sensation Seeking</i> -Adr+Tstr, -GC, NE-sANS	<i>Motor Tempo</i> (learned integration) DA + GABA, A, NP	<i>Physical-Motor Endurance</i> 5-HT + Tstr, NP (GH, SOM)
<b>Emotional dispositions/ amplifiers</b>	<i>Neuroticism</i> KOR, biota, cytokins → NE, HPA	<i>Impulsivity</i> (premature integration) ANS, DOR → (DA, MOR)	<i>dispositional Satisfaction</i> MOR, biota → (DA, 5-HT)

**Figure 2:** Neurochemical framework Functional Ensemble of Temperament (FET) summarizing the literature review related to the action of NTs on selection of degrees of freedom in behaviour. There is an interaction between neurochemical teams within each block and between the blocks. Three first rows relate to behavioural regulation within the cycles of different nature that a given action involves: physical (body), social (other bodies) and probabilistic (not immediately present and wider context). The last row relates to emotional amplifiers of behavioural orientation, integration and energetic maintenance. ACh, acetylcholine; NE, noradrenaline; 5-HT, serotonin; DA, dopamine; OXY, oxytocin, VSP, vasopressin, Tstr, testosterone; Adr, adrenalin (and its deficient cycles); GC, glucocorticoids (including cortisol dysregulation); ORE, orexins; NP, neuropeptides; Glu, glutamate; GG, gamma-aminobutyric acid and Glu; (M/D/K) OR, (mu/delta/kappa) opioid receptor systems; ANS, autonomic nervous system.

Dalley 2017; Trofimova 2021a; Trofimova and Robbins 2016). Energetic maintenance aspects of behaviour support three types of cycles associated with phenotype functioning:

- within-body cycles (“physical”),
- “social” (cycles that include interactions with other bodies such as peers, offspring, prey and predators) and
- “probabilistic” (cycles involved more extensive, not immediately present infrastructures).

The FET structure highlights that not only energetic but all three formal dynamical aspects (orientation, integration and maintenance) are regulated differently in relation to functioning within three types of cycles (*i.e.* physical, social and mental aspects of actions represented by the three top rows of Figure 2). The division of regulatory aspects into these three types is known as the *activity-specific approach* in differential psychophysiology (Rusalov 1989, 2018). Neuroanatomic and neurochemical partitionings of the hypothalamus and pituitary support the activity-specific approach: hormones regulating social-affiliative aspects (oxytocin and vasopressin), and physical aspects of behaviour (Growth Hormone and Somatostatin) are released from different parts of the pituitary and regulated differentially (see more on these components of the FET in (Trofimova 2021b) and Trofimova and Gaykalova (2021)). Three types of behavioural orientation relate to two more deterministic aspects of behaviour – orientation to sensations (physical, body-oriented type) or expectations of other people, empathy (*i.e.* social type) (Trofimova and Gaykalova 2021). The third, probabilistic type of orientation is known as contextual information processing and learning abilities (Trofimova 2019).

Probabilistic aspects of behavioural regulation highlighted in the FET assist an individual in handling the events that are not immediately present: mental endurance (sustained attention) is needed, for example in hunting, when the behaviour of the prey is not determined; plasticity is needed to adopt to not planned situations and probabilistic processing is needed to derive the causes and outcomes of past, future or distant events.

Finally, the FET framework summarized the functionality of three opioid receptor systems (using the “!!”, “?” symbols in Figure 4) as inducing dispositional emotionality or premature integration aside of the normal selection processes described above (Trofimova 2018, 2021a; Trofimova and Gaykalova 2021). The kappa opioid receptors system (KOR), coupled with the NE and Glu release, is seen as a limbic amplifier of sensory-orientational mobilization (but not general behavioural arousal); the mu-opioid receptors (MOR), coupled with 5-HT and DA, are considered within the

FET as an amplifier of approval of alternatives. Amplification of preferable alternatives and suppression of a future search for them can be subjectively experienced as relaxation, comfort and confidence. From this perspective, MOR-KOR teams provide significant assistance in selecting behavioural alternatives and forming directionality of behaviour, often associated with emotional experience and activation of “limbic” brain structures that have a high density of MOR and KOR. The third, delta-opioid receptor system (DOR), is coupled with DA and GG networks in the basal ganglia and often creates heterodimers with MOR, working in one direction and binding each other’s peptides. DOR can be presented as a system assisting the further selection and initiation of actions. Activation of these opioid receptors and possibly high presence of peptides binding to them can generate at least three emotional dispositions in behaviour that occur regardless of events, *i.e.* Neuroticism, dispositional Satisfaction and Impulsiveness (see the evidence reviewed in Trofimova (2018, 2021a) and Trofimova and Gaykalova (2021)) (Figure 4). As discussed in other reviews, these systems are entangled with immune and endocrine systems and, therefore, can generate body-biased dispositions in selecting DFs (Trofimova 2018, 2021a; Trofimova and Gaykalova 2021).

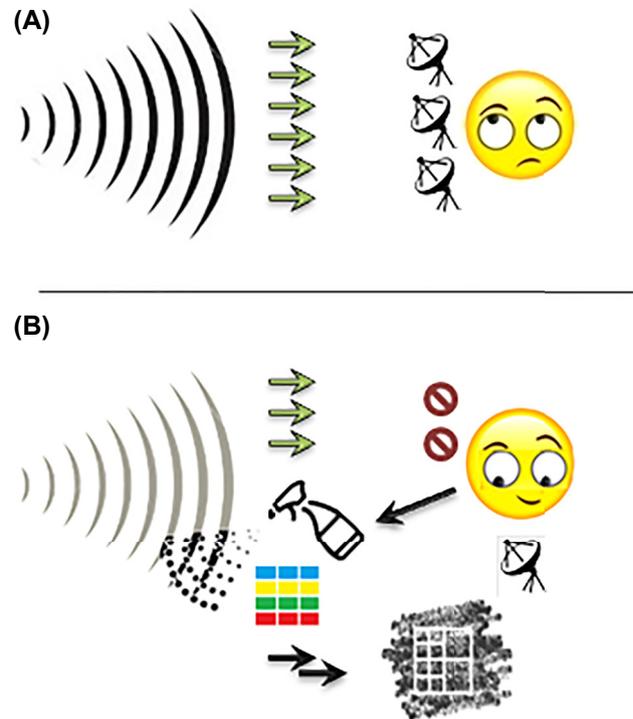
In every single neurotransmission, there are multiple mediators and components involved, and so it would be simplistic to classify their functionality taken off the context of this “ensemble” cooperation. Many neurotransmitter use heteromer complexes (cooperation between receptors that belong to two neurotransmitter systems) (Agnati et al. 2010; Altman and Bayer 1990; Borroto-Escuela et al. 2018; Fuxe and Borroto-Escuela 2016; Fuxe et al. 2010; Kenakin 2002). The FET, therefore, uses a “*multimarker*” approach, suggesting that there is no one-to-one correspondence between specific behavioural patterns and any single neurochemical system. Instead, every psychiatric symptom or temperament (bio-behavioural) trait is associated with a team of neurochemical systems (Trofimova 2016a, 2018, 2019, 2021a,b; Trofimova and Gaykalova 2021; Trofimova and Robbins 2016). These teams partially overlap because they deal with the regulation of the transition from one stage of construction of action to another. There are subtypes of receptors in different locations and heteroreceptor complexes indicative of lower-level loops of regulation within neurochemical systems. Space does not permit going into details of this complexity, which calls for an international analytic project to summarize the details of these loops and their interaction with chemical environmental factors, such as diets, climates and the use of common stimulants. The discussion of a possible “Hippocrates” project that would map the interaction between neurochemical and

environmental-chemical systems in inducing consistent behavioural patterns was already proposed (Trofimova 2022, 2023; Trofimova et al. 2022).

It is important to note that all 12 functional aspects of behavioural regulation that constitute the FET framework are present in each task or action but to a different degree. For example, motor aspects and sustained attention lead to behavioural regulation in riding a bike. However, social-verbal aspects are also on standby mode, emerging as verbal reactions to an unexpected turn of events. Similarly, mental activities, such as learning quantum mechanics, also involve verbalization, impulse control, specific emotional dispositions and physical posture maintenance. Moreover, since the FET structure follows the universal architecture of action construction, it is applicable to any behaviour, no matter how dysfunctional this behaviour is. The FET, therefore, uses the idea of a health-clinical continuum (Trofimova and Sulis 2016a,b, 2018; Trofimova et al. 2022; Sulis 2018), unifying healthy neurochemical regulation (seen in temperament traits) and various degrees of dysregulation, including the clinical spectrum seen in psychopathology. Constructivism also allows avoiding the state-trait dichotomy in psychology. Since behaviour is generative, states are seen here as single compositions of an internal status of an individual without tasks’ parameters of behaviour, whereas temperament traits are seen as consistent features of an individual’s behaviour analysed in a 12-component matrix of task’s parameters and emotional dispositions.

### Back to learning: integrating neurodynamic and neurochemical perspectives

Coming back to neurodynamics described by Freeman, we suggest that the functionality of neurochemical systems highlighted in the FET (coloured rectangular logo in Figures 1 and 3) modulate the selection processes and induce the symmetry breaking in chaotic attractors and their transition to cycle and point attractors identified by Freeman. This modulation might be behind the finding of specific EEG patterns associated with temperament traits (Chernyshev et al. 2013; Rusalov et al. 2004). Freeman acknowledged the crucial contribution of neurochemical systems in the regulation of attractors; however, his main work was in electrodynamics and not in the neurochemistry of the brain. The differences in functionality of NT-modulators likely follow the differences in the stages of construction of behaviour and make a particular impact on the development of attractors in different areas of the brain. The non-Glu neurotransmitters highlighted in FET work as functional managers and modulate the “push” of an attractor from the point



**Figure 3:** Throw & Catch principle as contrasted against a common view on perception as processing all environmental stimuli (A). The Throw & Catch principle (B), suggests that the nervous system likely works on a much smaller set of DFs in behaviour and proactively self-generates a topical, biased excitation to contrast the perceiving spectrum against its expectations and needs.

of uncertainty into a certain trajectory, to a completely different attractor, or to extinction.

There are, indeed, studies showing the involvement of NE that can abruptly interrupt the chaotic activity of neural networks and re-organize them; this facilitates rapid behavioural adaptation to changing contexts (Bouret and Sara 2005). NE modulation of neuronal potential was found to be crucial in orientational aspects of behaviour (attention to novelty), *i.e.* in processing the features of immediately present reality (Aston-Jones and Cohen 2005; Espana and Berridge 2006; Robbins 1997). Involvement of another modifier, 5-HT, also trims excessive Glu excitation and partners with an inhibitory GABA influence when needed (Fink and Göthert 2007; Maejima et al. 2013). Multiple bifurcational contingent dynamics were described within cellular levels in the composition and release of neurotransmitters and opioid receptors (Furay and Neumaier 2011; Gupta et al. 2021; Waldhoer et al. 2014). There is a periodic recount of votes driving the trajectory of the summing waves within neurodynamics that makes behaviour flexible, changeable and adequate to situations. Otherwise, behavioural elements (perception, action, thoughts) would be stacked in one stereotypic pattern.

The neurochemistry of learning is a too extensive topic to attempt to cover here. Practically all neurotransmitter systems are involved and are sensitive in state-dependent memory retrieval (see, for example, Radulovic et al. 2017; Wideman et al. 2018; Zarrindast and Khakpai 2020), but space does not permit to cover the complex topic of the neurochemistry of learning process. What we know is:

- (1) There is not one but numerous, diverse neurochemical mechanisms and agents involved in learning, depending on a neurochemical system, type of receptors, types of mediators, types of transmission and also type of the tasks to learn (Bellfy and Kwapis 2020; Radulovic et al. 2017; Wideman et al. 2018).
- (2) These mechanisms and agents vary in the brain regions regulating specific functional aspects of behavioural construction. Out of all possible ways to divide these aspects into types, we find the FET framework the most beneficial, especially in the division between physical, socio-verbal and probabilistic aspects of behaviour (three top rows, Figure 2). This division is relative, as noted above, because all aspects are closely integrated.
- (3) In the context of learning, it is important to note that the FET differentiates between neurochemical and neuroanatomic systems regulating “deterministic” (automatic, habitual) actions (two middle rows, Figure 2) and actions generated in complex or novel settings (“probabilistic”, top row, Figure 2). Figure 4 summarizes the involvement of the FET components in three main scripts of integration of actions: impulsive (as a rough selection of DFs that was not supervised by cortical impulse control or careful information processing), plasticity-type (when cortical-ventral striatal systems are involved) and automatic, *i.e.* habits and skills-based. Cortical, especially frontal systems, are classically linked to the first stages of learning (Barlow et al. 2015), whereas dorsal striatum – to habit formation (Blazquez et al. 2002; Everitt and Robbins 2013; Graybiel 2005; Ikemoto 2007; Jog et al. 1999; Smith and Graybiel 2016). As can be seen in Figure 4, these three scripts have common components, and this allows an easy switch between the scripts. For example, the activation and use of motor habits in humans is closely monitored by the cholinergic forebrain system at both, automatic and novel actions (Ballinger et al. 2016), however habit-forming striatum systems have additional cholinergic system on interneurons (Gonzales and Smith 2015), and employs dopaminergic, GABA and delta-opioid receptor systems in reducing DFs to specific actions. The details could be found in our earlier reviews (Trofimova 2016a, 2019, 2021a; Trofimova and Robbins 2016). These systems operate in neuroanatomically distinct areas of the brain (Figure 4, the row “Brain structures”), which differ in their interconnectivity, level of segregation within their networks and degree of “mass action” in neurodynamics. The principle of having these three different types of integration relates to the differential ability of the nervous system to generate an action depending of urgency (impulsivity vs plasticity scripts) and novelty-complexity of situations (habits-based tempo vs plasticity scripts).
- (4) Inflammation and substance use has an impact on learning, proving the idea that learning, as a generative process, depends on the state of the body (Dutcher et al. 2020; Giuliano and Dalley 2020; Jupp et al. 2020; Zarrindast and Khakpai 2020).

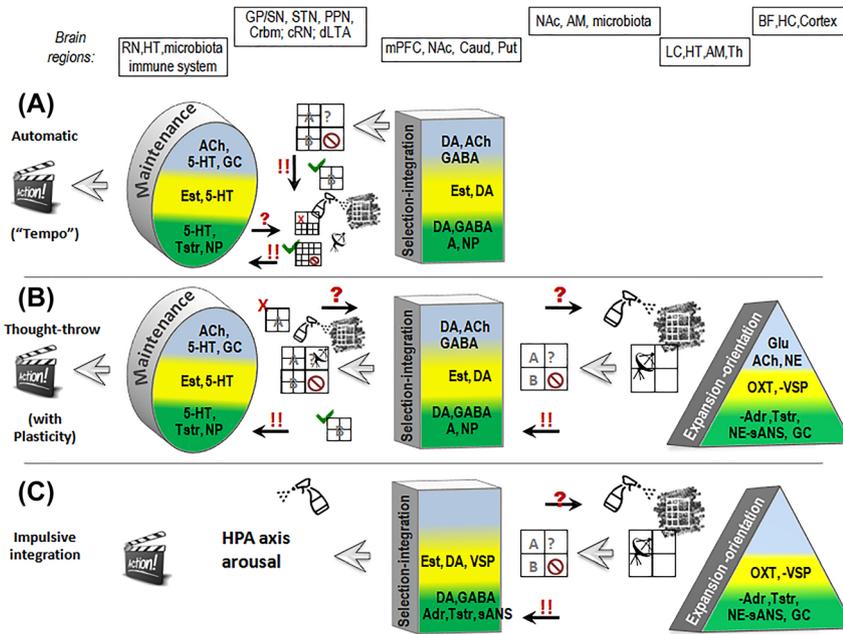
The progression from orientation to the selection of the first set of possible actions and then to the final action involves a massive reduction of degrees of freedom in targets of perception and trajectories of actions from thousands to single digits. Here we point out that, paradoxically, it appears that in order to reduce DFs in orientation and to make the final choices, it is beneficial to expand the DFs first. This brings us to our third example of constructivism, the Throw & Catch principle of neurodynamical regulation.

## The “Throw & Catch” principle

### The Throw & Catch principle in nature and evolution

The “Throw & Catch” (T&C) mechanism can be illustrated by the example of echolocation in some species of bats. Bats manage to find their way around their dark caves at night without smashing into the walls or their flying peers. They can do it by generating ultrasound waves that then bounce from the surfaces and get captured by bat’s sensors that process the returning wave pattern. In other words, they throw something out and then process the bouncing profile of the responding wave by sensors that are tuned in advance based on bat’s expectations (Moiseff and Haresign 2001; Parker et al. 2013). Moreover, the name of the T&C was chosen to also underline the organization of Catch processes in the form of relays progressing with the selection of DFs.

In the context of the nervous system, the “Throw & Catch” dual mechanism works like a flashlight on demand, generating a stream of potentials or excesses of elements that give a topical, internally controlled increase in their variance (“Throw” part). The second, “Catch”-type processes,



**Figure 4:** The graphic illustration of the role of the T&C mechanisms within neurochemical (coloured shapes) and neuroanatomic systems as summarized by the framework Functional Ensemble of Temperament (FET). The “Throw” processes proactively generate an additional variance to increase the visibility of details needed for the selection of degrees of freedom. The “Catch” processes (depicted as squares) have pre-organized matrices of receptors or anticipatory attractors assisting the selection of DFs in perception during orientation, a rough generation of programs of actions (plan A, B, etc. and a “no-action” plan), then a more detailed selection of specific actions to maintain selected patterns of behaviour. Blue (upper shade), yellow (middle) and green (lower shade) colour in the big shapes highlight neurochemical systems regulating (correspondingly) probabilistic, social and physical aspects of actions (see text for further details). Figure illustrates three scripts of integration of actions according to the FET: (A) habits and skills-based (automatic, or tempo) integration of actions; (B) plasticity-type; (C) impulsive type. Bigger light arrows show the progression of the selection of DFs; smaller black arrows show feedback processes. Red “?” and “!!” signs symbolize emotional amplifiers based on opioid receptor systems as described in our earlier reviews. When selected DFs do not work, a further search for alternatives is increased (“?”), and if it does – the chosen alternatives are approved (“!!”). The “?” system that generates the release of the catecholamines (DA in familiar elements of behaviour and NE in novelty) and the HPA axis arousal in rough emotional response is represented by KOR, some microbiota and cytokines systems. The “!!” system that generates the release of DA and suppresses the HPA axis activation is based on the action of MOR (in ventral striatum), DOR (in dorsal striatum) and some microbiota. Brain structures: (c) RN, (caudal)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 in ventral striatum; Put, putamen; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; Crbm, cerebellum; GP, globus pallidum; SN, substantia nigra.

are seen in much more structured, biased and strategic placement of reception sites, with a diversity of selective multi-filtering mechanisms. Figure 3 illustrates the contrast between the common model of informational flow and T&C principles. The common script of information processing implies that the nervous system processes all coming information and then sorts out the behavioural response of all DFs in behaviour, theoretically available to a phenotypic individual representing a given biological species (Figure 3A). This would limit perceptual and regulatory processes to primarily sorting DFs (“Catch”-type mechanisms), without an expansion of DFs. The T&C principle suggests that the nervous system likely works on a much smaller set of DFs in behaviour and proactively self-generates a topical, biased excitation to contrast the

perceiving spectrum against its expectations and needs (Figure 3B). Therefore, psychological processes are seen in constructivism as generative and proactive, having constant interactive feedback between what to look for (from Catch to Throw) and what is out there (from Throw to Catch). Moreover, both Throw and Catch mechanisms are tuned to the N–C of the individual and, therefore, have embodiment and experience-related biases.

Suppose behaviour is presented here as a constructive, generative process. In that case, it is natural to see the correspondence between principles of behavioural regulation and general principles of evolution, such as natural selection, the neutrality of evolution, multiplicity of configurations, multi-level selection and others (Cairns-Smith 1982; Gould 2002; Trofimova 2017). Indeed, the T&C principle is in

line with the idea that “nature proposes, evolution disposes”, and variations on “[something 1] proposes, [something 2] disposes”, known as natural selection. Cairns-Smith gave a wonderful and well-illustrated description of the generation of extremely complex configurations in evolution based on just two trends: “collectors” (generating the pools of configurations) and “selectors” (multiple factors of natural selection) (Cairns-Smith 1982). The T&C could also be seen in the proposed earlier explanation of sex differences in phenotypic distributions, including psychological abilities and disabilities (Trofimova 2012, 2013, 2015). In fact, the Evolutionary Theory of Sex highlights male variability as the core property of sex reproduction mechanisms that partition phenotypes on variable, exploratory and conservative-selective partitions (Trofimova 2015).

Moreover, several species use the “T&C” mechanism to detect relevant features of their environment. Echolocation, described above for bats, is also used by many species of dolphins and whales (Parker et al. 2013). Army ants also send (“spray”) their soldiers in a very organised symmetric manner to explore unknown environments and then collapse this flow to a more narrow direction once they find their target (Wilson 1978).

## T&C principle in the nervous and endocrine systems

The examples of the T&C principle within the nervous system include:

### Overproduction of neurons and synapses at birth and their subsequent significant pruning

By birth, the human brain has a well-documented overproduction of neurons, axons, dendrites, receptor sites and then, shortly after that – synapses, about half of which do not survive past two-three years of life (Abitz et al. 2007; Kolk and Rakic 2022; Lavezzi et al. 2006; Tau and Peterson 2010). Similar overproduction around the time of birth and then a significant pruning in early childhood is observed in animals’ brains (Ahern et al. 2013; Kolk and Rakic 2022). These processes are considered to be healthy if they follow a normative range and timing. Their time courses differ across brain regions, sex and age groups, however the production of synapses and their selective trimming is a common feature of brain connectivity. In fact, not only too much trimming but also insufficient trimming can cause developmental disorders. For example, both grey and white matter amounts were found to be higher in autism (Courchesne and Pierce 2005; Solso et al. 2016).

### Overproduction of sending neuronal pulses, in comparison to those that were passed through

As noted above, many more neurons send random, spontaneous, non-provoked pulses to their neighbours in comparison to the number of pulses accepted into further processing. Modern estimates indeed show that each of  $10^{10}$  neurons in the human brain has at least 10,000 inputs and sends out (on average) 100,000 outputs (Holt et al. 2019). Freeman and others point out that it takes more than a hundred inputs to one neuron to make it fire (Altman 1999; Arbib 2008; Arbib and Erdi 2000; Freeman 2000a; Liley et al. 2012; O’Reilly 1998). In other words, nine out of ten “knocks” from neurons to other neurons come unanswered and ignored. Just discussed example of anticipatory strange attractors in neurodynamics provides a selection mechanism, limiting future information processing to a few alternatives that the wings of strange attractors relate to.

The maximal amount of neurotransmission (just by the sheer volume of GG cells and their synapses) is happening in information-processing brain structures, *i.e.* cortex and hippocampus (HC), and this includes the maximal amount of both volume and synaptic neurotransmission. It seems paradoxical that whenever there is a need to sort through the diversity and multiplicity of DFs, the nervous system might increase the variance (*i.e.* the number of DFs): the higher is the challenge in the flow of DFs, the more excessive is the generation of (rather expensive) neurotransmission. The selection of relevant and suppression of unnecessary DFs in the construction of action transits from the cortex to the ventral striatum, then from the ventral to dorsal striatum, then from the striatum to the cerebellum, all under cortex–basal forebrain coordination (Blazquez et al. 2002; Everitt and Robbins 2013; Graybiel 2005; Ikemoto 2007; Jog et al. 1999; Smith and Graybiel 2016) (Figure 4). Interestingly, it was Bernstein’s experimental work on the construction of actions that was first to demonstrate the existence of “levels of control”, *i.e.* different neuronal complexes for novel and automatic behaviour. Bernstein, with the assistance of the famous neuropsychologist Luria, who shared some clinical material for Bernstein’s book, identified the cortical – ventral striatum networks as more conscious levels of control over the construction of actions, whereas more automatic levels were assigned to thalamic-globus pallidus and cerebellum networks (Bernstein 1947). In comparison, peripheral neurons do not have the interconnectivity of cortical or HC neurons; they seldom interact with other neurons via either volume or synaptic transmission and have individual paths from the peripheral receptor to the CNS. In other words, the higher the uncertainty, the more uncertainty the nervous system generates.

### The endocrine system uses the bloodstream for fast delivery of their hormones to target sites

Hormones also regulate brain activity, finding their way around the blood brain barrier (BBB), and this explains the presence of cortisol, estrogen, testosterone and progesterone receptors in the brain. For example, cortisol can penetrate BBB and diffuse through the cell membranes being highly lipophilic (Thomas et al. 2010); neurons and glial cells produce their own estradiol using aromatase localized at synaptic and non-synaptic locations in the brain (Brann et al. 2022). Growth hormone is produced within the hippocampus and depends on the amount of estrogen in this brain structure (Donahue et al. 2006). Hormones can, therefore, influence every part of the somatic and nervous regulatory system and, as in chronic stress, negatively affect cognition and even motor behaviour (Lucassen et al. 2006; Nieuwenhuys and Oudejans 2011; Sinclair et al. 2014). The hormone driven exploration of behavioural alternatives in stressful or sexually motivated situations cannot only suppress the “voice of reason” coming from memory and probabilistic processing, but can also induce biases stemming from the action of hormones. In this sense, not only adrenalin and cortisol, but also gonadal, social and Growth Hormones – can affect the normal course of behaviour, pushing it to unplanned DFs (Bartz et al. 2011; Bird et al. 2019; Carrillo-Garcia et al. 2014; Crespi 2016; Declerck et al. 2010; Maattanen et al. 2013; Meyer-Lindenberg et al. 2011; Montoya et al. 2012; Op De Macks et al. 2011; Ponzi et al. 2016; Procyshyn et al. 2020; Purves-Tyson et al. 2014; Unsicker and Strelau 2000). The “Catch”, *i.e.* position of hormonal receptors in the brain, is precise in favoring the cells that regulate the most “thoughtful” (information-based) aspects of behaviour. Thus, there is a well-developed “Catch” system of cortisol receptors on hypothalamic and hippocampal cells (Kim et al. 2015; Paul et al. 2015) and estrogen receptors in the cortex and hippocampus (Rudick et al. 2003; Russell et al. 2019).

### Different functionality of two parts of the autonomic nervous system (ANS)

As is well-known, the NE-based sympathetic autonomic nervous system (sANS) provides a fast non-specific massive arousal for immediate behavioural “readiness” in situations of urgency (Ondicova and Mravec 2010). This readiness is slowly trimmed by the ACh-based parasympathetic autonomic nervous system (pANS), allowing only relevant arousal potentials for specific actions and suppressing the rest. Therefore, the pANS and cholinergic regulation is more than just the inhibition of arousal by the sANS but the

construction of action by selecting DFs. Thus, the action of pANS on muscles allows the body to contract muscles selectively, change posture, focus perception and attention, and produce behavioural acts relevant to the context (Ondicova and Mravec 2010). It is important to underline that these overproductions – of cells, synapses, potentials, hormones and neurotransmitters, the majority of which are decomposed and forgotten soon after being produced – is the internally driven, decoupled from stimulation, “voluntary”, often unprovoked trend of the nervous and endocrine systems. For this reason this “Throw of resources” can be considered proactive, and not reactive, in nature.

### Volume transmission mechanism

All neurotransmitter systems use vesicle-based synapses even though it is not the only method of neurotransmission. There is increasing evidence that many NT systems use extra-cellular, volume (*i.e.* non-synaptic) transmission by releasing NT into the space outside the cell and having other neurochemical systems interact with them (Agnati et al. 2006; Guidolin et al. 2007). Evidently, all cortical monoamines (Agnati et al. 2010; Fuxe and Borroto-Escuela 2016; Fuxe et al. 2010), acetylcholine (Descarries and Mechawar 2000; Sarter et al. 2009) and likely other NT systems such as glutamate and GABA (Descarries and Mechawar 2000; Hampe et al. 2019) use volume transmission. Similarly, volume transmission was found within opioid receptor systems (Veening et al. 2012). In fact, some researchers suggest that not just some but most of the intracortical ACh is not released at synaptic contacts proper but rather diffusely into the extracellular space via volume transmission (Descarries and Mechawar 2000; Sarter et al. 2009). Glu volume transmission is common in the cortex, and this is especially surprising considering that, in terms of a number of synaptic transmissions, Glu already has an overwhelming dominance (Descarries and Mechawar 2000; Hampe et al. 2019). It looks like glutamate systems use both neurochemical interactions via volume transmission and electrodynamic potentials via wave-pulses transfers as described above.

In other words, most of the “talk” between the members of neurochemical ensembles happens not in the form of neurons firing in response to current stimuli but outside of those structures (*i.e.* outside of neurons and not bounded to specific brain areas) that neuroscientists commonly focus on. This means that brain cells and synaptic structures visible in common neuroimaging methods such as grey and white brain matter density or volume show only part of the “story” of CBP biomarkers within the brain’s functional systems. Another part hidden from neuroimaging involves

volume transmission, complex combinatorics and diversity of receptor systems providing negotiations between neurochemical systems that largely affect what DFs in behaviour will be chosen. That is why it is essential to develop an international project looking into this extreme neurochemical complexity, as not a single organization in the world could afford to study it to a full extent. Volume transmission, therefore, might be a supplement “Throw” mechanism for the more structured “Catch” system seen in the massive synaptic interconnectivity. This strategically localized “Throw” expansion of DFs in neurotransmission can be used not only for an orientation function but for any process requiring a review of DFs. Synaptic interconnectivity might be an infrastructure resulting from “channeling” and structuring this potential, as a part of two partitions of Catch processes described above.

### Where is the “Catch”?

The T&C in neurophysiology differs from the baseball analogy of “Throw” and “Catch”. If the throw in baseball involves a single item that other players have to catch, in neurophysiology it refers to multiple “balls” sprayed to the receiver. In this multiplicity, there should be a sorting mechanism to do a relevance check examining the compatibility between the thrown and preferred items based on an individual’s needs and capacities (N–C). When there are too many items to choose from, it makes sense to select a smaller list of “candidates” and continue selecting with more scrutiny, similar to the selection of candidates for a job. To facilitate this, there also should be additional systems to protect (maintain) the first stage rough selection from interference with the subsequent tighter selection. This maintenance system is not discussed here.

Potentially, it is a lot of work for the nervous system to check the whole Throw’s content, *i.e.* every single incoming stimuli and every option (DF) in actions every single second. Evolution provided a brilliant solution to this DF problem that could be summarized as “just ignore everything unless you need something”. Similarly to a customer coming to a hardware store to find one specific bolt that matches the customer’s household needs, the customer can ignore the huge collection of store items and inspect only their collection of bolts. This is consistent with the anticipatory and biased nature of perception discussed above when perception proactively generates hypotheses about the “bolts” ignoring the presence of other aspects of reality. We prefer the concept of T&C over other expressions (for example, “Spray & Sort” or Sow & Prune) for the relays between Catch systems at several levels of neuronal organization. At every

stage of the selection of DFs, the Catch’s sorting systems are influenced by the features of the T&C at the next stage of their selecting relay and not only by the items that are currently thrown onto them for selection. The “relevance check” in the Catch system can be, therefore, proactive, stemming from the compatibility between offered DFs and the features of the follow-up T&C stage eventually reflecting the individual’s needs and capacities (N–C).

To accommodate the selection processes, the “Catch” should be much more organized and complex in comparison to the “Throw” processes, having multiple mechanisms of selection and filtering of DFs up to the final choice of actions. Indeed, neuroanatomically, the “relevance check” of the information coming from thalamic-cortical networks is seen in the interaction between at least four “sorting hubs”, *i.e.* brain structures, which are unique for having the projections from all neurotransmitter systems and mutual projections between each other. These hubs are: HT-Pit complex lobbying the body’s needs and capacities; HC and cortical systems presenting information about the past and future probabilities and amygdala (AM), assessing the salience of the current events. Catching the priorities within these hubs and in their associations with other structures is facilitated by the modular connectivity in some of their parts, when projections between two brain structures go in a segregated manner. For example, areas that process sensory information (modality-related receptive areas → thalamus → cortex) tend to have “parallel” connectivity, and similar vertical segregations (“lateral to lateral, dorsal to dorsal, ventral to ventral”) are noted in hypothalamus-amygdala (Ledoux 1998; Zeng et al. 2021) and basal ganglia projections (Blazquez et al. 2002; Everitt and Robbins 2013; Graybiel 2005; Ikemoto 2007; Jog et al. 1999; Smith and Graybiel 2016).

There are also several types of connectivity: top cortical areas are known for their layers of associative interconnectivity and amplification-suppression connectivity between layers; other brain structures use “vertical” segregations specialized by modalities. This connectivity, of course, is relative and very plastic and depends on an individual’s activities even in the most vertically segregated associations. Moreover, practically every brain structure has additional internal functional partitioning. The most commonly known examples are substructures of the cortex, nuclei of the hypothalamus, and serotonergic raphe nuclei. However, the striatum (the main structure filtering degrees of freedom in actions and learned habits) also became a focus of attention in the past 20 years because of its fractal structure (Brimblecombe and Cragg 2017; Graybiel and Matsushima 2020; Khrenov et al. 2006). This structure includes a functional and structural division

between the ventral and dorsal striatum, each of which has several substructures. Furthermore, the nucleus accumbens (NAc) (the part of the ventral striatum) has functional and anatomic division into a core (dorsal and central NAc) and a shell (the rostral, medial, lateral, and ventral NAc) structures (Brimblecombe and Cragg 2017; Graybiel and Matsushima 2020; Khrenov et al. 2006). Moreover, the caudate nucleus, anterior putamen (both parts of dorsal striatum), and the NAc core each have compartmentalization into the system of striosomes and matrix, which differ in terms of the presence of opioid and neurotransmitter receptors plus connectivity with other brain structures (Brimblecombe and Cragg 2017; Gonzales and Smith 2015; Graybiel and Matsushima 2020).

It appears that the nervous system continues to keep its options open even at the final stages of selection, having multiple NTs in play at every neurotransmission. A co-release of different NTs and neuromodulators from the same cells is common (Devoto and Flore 2007; Devoto et al. 2020; Fink and Göthert 2007; Freeman et al. 2000; Granger et al. 2017; Maejima et al. 2013; Siegel et al. 2006), including their reciprocal suppression as between Glu and GABA (Gandal et al. 2012; Vargas et al. 2008), opioid receptors (Bodnar 2021), or hypothalamic neuropeptides (see Mains and Eipper 2006). The Catch (selection) mechanism also employs a more structural approach: an ensemble-like co-processing of neuronal signalling by receptors representing different neurotransmitters (heteromers). An exciting mechanism of such co-regulation was proposed by Altman (Altman and Bayer 1990) and Fuxe in the concept of “*receptor mosaic*” (Agnati et al. 2010; Fuxe and Borroto-Escuela 2016; Fuxe et al. 2010) and by Kenakin (2002) in his “conformational cafeteria theory of receptors” (Fuxe and Borroto-Escuela 2016; Fuxe et al. 2010). They described two types of receptor mosaic seen in heterometric complexes composed of receptors related to different neurotransmitters: with and without possible cooperation between receptors in generating a wave of a similar impact on other systems. These two opposite modes of cooperation are capable of generating contrasting patches, each represented by contrasting receptors that suppress each other. Fuxe and colleagues give examples of mosaic interactions between dopaminergic D2 and adenosine A2A receptors on ventral and dorsal striatal-pallidal GABA neurons and cortico-striatal glutamate terminals, as well as A2A *versus* D3 and D2 heteromers in the NAc. The dopaminergic receptors take the lead, as a neuromodulator over Glu, GABA and adenosine receptors shaping the precision of the formed action. Similarly, other neuromodulator systems (noradrenaline [NE], serotonin [5-HT] and acetylcholine [ACh]) use a supplementary mosaic with specific neuropeptides (such as Neuropeptide Y, Substance P,

prolactin, somatostatin, opioid peptides) (Nieuwenhuys 1985) as well as histamine and GG neurotransmitters (Fink and Göthert 2007). Therefore, heteromers and the receptor mosaic are composed of specific antagonistic pairs or trios of receptors belonging to different NTs. These pairs create local loops and patches of inhibition and excitation, allowing additional graining within the processes of selection of alternatives (Agnati et al. 2010; Altman and Bayer 1990; Fuxe and Borroto-Escuela 2016; Fuxe et al. 2010).

Importantly, selection and maintenance of selected DFs in behaviour occurs not only in the brain but also within and outside the body. First, embodiment phenomena emerge as a pro-body bias of cognition and decision making (Aranyosi 2019; Canino et al. 2022; Ostarek and Bottini 2021; Trofimova 2014). There are several neurophysiological correlates for these phenomena. Liver enzymes and some microbiota are needed to manufacture NT transponders and components for NT synthesis by brain cells (De Weerth 2017; Dinan and Cryan 2012; Farzi et al. 2018; Fung et al. 2017; Galland 2014; Lach et al. 2017) microbiota, liver and blood content, therefore, affect brain functioning (Dinan and Cryan 2012; Lach et al. 2017). Moreover, HT, *i.e.* the brain structure integrating activity of the endocrine and nervous systems, has projections from all key brain structures. Thus, hunger, thirst, food poisoning or sexual desire are examples of how the outside-the-brain factors coming from the state of the body can take over the selection of DFs. Another set of factors relate to the fact that any action should follow the configuration of objects around, highlighting the constructive, generative nature of behaviour. Properties of objects and events work as selective factors. The environment also provides the storage and “protection of selected DFs” by giving a chance to individuals to create specific functional “bubbles” of their favourite reinforcers, sources of tools and other resources (“Specialized Extended Phenotypes” – see more in Trofimova 2021b).

## Neurochemical T&C relays

### Distribution of NTs and their receptors suggests underlying functional “relays”

Nervous systems use the T&C principle in many settings, and neurochemistry gives the clearest illustration. As noted above, neurotransmission is a non-trivial contingent neurochemical process involving multiple chemical systems. Most neurotransmitter systems have a “Throw” process, manufacturing this NT and spreading it. Every NT system also has excitatory and inhibitory receptors enabling its

participation in selection of the DFs processes. Mapping of the receptors binding various NTs in the brain is challenging and more work should be done, but several remarkable studies have shown already that NT receptors are not evenly distributed in the brain (Delay-Goyet et al. 1987; Goulas et al. 2021; Hamel and Beaudet 1984; Lena et al. 1999; Mansour et al. 1987; Peckys and Landwehrmeyer 1999; Ren et al. 2019; Sharif and Hughes 1989). Instead, specific receptors have higher density in only a few areas, and this specificity is observed not only for the receptors representing different NT but also for different types of receptors within the same NT system. Similarly, the presence of NTs and neuropeptides within cells/synapses and in extracellular space (“Throw” distribution) is known to have specificity within the brain regions (Nieuwenhuys 1985).

Moreover, there is a consistent mismatch between the amount of neurotransmitters released into specific brain structures and the number of receptors for these NTs in these areas (Agnati et al. 2006, 2010; Fuxe and Borroto-Escuela 2016; Fuxe et al. 2010; Guidolin et al. 2007; Nieuwenhuys 1985). This mismatch could be interpreted as the “relays”, in which strategic positioning of the receptors follows the gradient of self-regulatory selection of DFs. Indeed, the generation of receptor density appeared to be a plastic process adapting to the amount of binding to agents and the presence of mediators needed for their synthesis. For example, studies in serotonin (Frey et al. 2008) and opioid receptors (Furay and Neumaier 2011; Gupta et al. 2021; Waldhoer et al. 2014) showed a decrease in binding potential and density of receptors with an increase in the binding of neurotransmitters.

Figure 4 borrows the idea of the FET about tentative neurochemical relays between the three main functional aspects of action construction: expansion of DFs (orientation, depicted as a triangle), selection of DFs (integration, depicted as a big rectangle) and energetic maintenance of chosen programs suppressing unwanted DFs (depicted as an oval shape). For the purpose of conceptual illustration, Figure 4 shows two transitions in action construction with two Throws and Catches (depicted as dented small squares with an increased density as the choice of actions becomes more detailed). There are many T&C processes in the brain, but the more uncertainty that brain structures have to deal with (such as sensory-orientation-processing by the cortex, thalamus and limbic system), the more Throw processes are present. With the decrease of uncertainty in actions, there is a clear gradient of increase of structural and neurochemical complexity in the processing areas. The FET underlines that the degrees to which NT

systems participate in T&C processes are very different and so are not limited just to excitation and inhibition functions. Here are a few examples.

## T&C contrasts among NT systems

### Glutamate-GABA (GG)

The most obvious example of a massively present neurotransmitter in the brain is glutamate (Glu). Nine out of 10 neurons and synapses in the brain use Glu as their NT (Braitenberg 2001; Hampe et al. 2019; Hassel 2006). After Glu, GABA is the second largest “working horse” in neurochemical transmission in the brain, having about 40% neurons that release it and, if we do the math, obviously having a co-localization with its rival Glu (let’s notate this pair as GG) (Bryson et al. 2020; Granger et al. 2017; Hassel 2006). Glu action is associated mainly (but not always) with excitation action in cortical pyramidal neurons, whereas inhibitory action is associated mainly (but not always) with GABA. The brain has more than twice excitatory Glu than inhibitory GABA, and this imbalance also is in line with the “Throw & Catch” principle. In line with the T&C relay concept, there is a gradient in the distribution of Glu and GABA neurons, with more Glu-excitatory neurons in cortical layers and more GABA neurons in brain areas that use the results of cortical processing and trim the action to more precise elements of actions (*i.e.* basal ganglia).

### GG versus MA and ACh

There is a second, less massive but more managerial trend for the T&C mechanism that emerges within the first, GG-associated T&C. It can be seen in the actions of monoamines (MA, *i.e.* 5-HT, NE, DA) and acetylcholine (ACh) systems on the potential generated by the GG neurons. In contrast to the massive presence of GG neurons and their numerous synapses in the cortex, MA and ACh systems are significantly less present. For example, there are 1000 times fewer MA and ACh neurons than GABA-releasing neurons, and the ratio of MA-to-Glu neurons is even more minuscule (Bryson et al. 2020; Granger et al. 2017). MA and ACh systems are, therefore, almost structurally and electrically invisible for neuroimaging and EEG measurements. However, they are more sneaky than locally bounded GG axons: the long and wide-spread branching of the MA and ACh systems allows them to regulate the activity of distant brain areas and often use GG as mediators. MA and ACh systems co-release their neurotransmitters with GG within synaptic

transmission and often release their NTs into the extracellular space to act on all neurochemical ensembles without making classic synapses (Agnati et al. 2010; Descarries and Mechawar 2000; Fuxe et al. 2010; Fuxe and Borroto-Escuela 2016; Hampe et al. 2019). In this way GG can influence their managers during neurotransmission whereas MA and ACh systems can influence the GG potentials by the choice of their projections on GG neurons.

For a remarkably clear example of a Catch-like process, ACh systems consistently use a biphasic action of GG systems and a combinatorics of excitatory cholinergic nicotinic (nAChRs), muscarinic M1/M5 (mAChRs) receptors and presynaptic inhibitory autoreceptors M2/M4 mAChRs to secure the relays between sensory thalamic-cortical networks and then between cortex and striatum. The locations, densities and interactions with other NTs in activity of these receptors differ and follow the T&C gradient. At the orientation stage, the activation of nAChRs on thalamo-cortical terminals increases Glu release in both sensory and association cortex (Disney et al. 2007; Gil et al. 1997; Picciotto et al. 2012). In addition to the fast-acting nAChRs, slow-acting M2 mAChRs suppress GABA release on the terminals of parvalbumin-expressing interneurons, enhancing Glu thalamocortical inputs to pyramidal neurons (Gil et al. 1997; Kruglikov and Rudy 2008; Picciotto et al. 2012). In this way there is a calibrated and regulated increase of the Throw process related to specific aspects of perception coming from the Catching ACh systems. The cholinergic nucleus basalis of Meynert in the basal forebrain (BF) that releases ACh, in turn, receives projections from both the noradrenergic LC (Sarter et al. 2005) and the dopaminergic VTA (Ballinger et al. 2016), *i.e.* from the Throw-systems, influencing the sorting performed by the ACh systems in the thalamus and the cortex.

The enhancement of perception would be improved if the background information and perceptual interpretation were suppressed. This, indeed is provided by the suppression of massive Glu activity of pyramidal cortical neurons via presynaptic M2/M4 mAChRs autoreceptors on their cholinergic terminals (Brown 2019; Gil et al. 1997; Hasselmo and Sarter 2011; Picciotto et al. 2012). There is also additional calibration of the sorting process: a fast inhibition of cortical neurons partially mediated by nAChRs and mAChRs acting on inhibitory GABAergic interneurons and a slow depolarization via M1/M5 mAChRs increasing cortical Glu neuron's excitability (see a detailed review by Picciotto and colleagues (2012)). Importantly, most of the intracortical ACh acts rather diffusely by its release into the extracellular space via volume transmission and not through synapses (Descarries and Mechawar 2000; Sarter et al. 2009). The interaction between GG, ACh and catecholamine systems represent additional examples of T&C processes.

## The brain NE and ACh systems

In contrasting these two systems, NE system certainly has more Throw features whereas ACh system has more Catching features. The mostly excitatory NE projections are rather homogenous, massively originating from the nucleus locus coeruleus (LC) (Aston-Jones and Cohen 2005; Beane and Marrocco 2004). In contrast, the brain's ACh systems have more distinct and relatively independent nuclei than any other NTs (Ballinger et al. 2016), having more sophisticated structure and diversity of mechanisms. Recent studies investigating the input-output relations of cholinergic neurons in the BF and noradrenergic neurons in the LC have shown that BF cholinergic cells receive selective inputs depending on their projection regions, whereas LC noradrenergic cells receive converging inputs that are not segregated to the neurons projecting to different areas (reviewed in (Rho et al. 2018)). Functionally, the central ACh is involved in many aspects of the trimming of DF in behaviour: sustained attention to probabilistic aspects of situations via cortical-basal forebrain systems; memory-driven bias in the selection of DFs via hippocampal systems, the selection of learned elements via cholinergic interneurons that regulate striatal DA-GABA networks and monitoring of execution of automatic actions via cholinergic forebrain and cerebellum systems (Ballinger et al. 2016; Gonzales and Smith 2015). Meanwhile, the arousal provided by the NE systems is linked to the screening of the environment for novelty (*i.e.* attention to novelty) and HPA axis arousal in stressful events, *i.e.* the expansion of DFs in behaviour (Aston-Jones and Cohen 2005; Beane and Marrocco 2004). In other words, NE, similarly to the cortical Glu systems, "sprays" the excitatory potentials to the brain areas and complex, multi-level, much better structured ACh systems "sort" and trim those potentials with, of course, the assistance of other mediators.

Salient stimuli were found to induce both NE and ACh release (Aston-Jones and Cohen 2005; Hasselmo 2006), so it is tricky to differentiate the function of NE and ACh in attention and learning. The NE-gic LC has two modes in modulating attention: a tonic-background arousal and phasic activation in response to novel or very relevant stimuli (Aston-Jones and Cohen 2005). The phasic NE release is useful in detecting outliers-stimuli that otherwise would be filtered out by the ACh system. This explains why NE release is coupled more with highly accurate responses than the ACh (Aston-Jones and Cohen 2005). In order to bring attention to outliers, the NE should override the sorting influence of the ACh system, and, perhaps that is what the projections of the LC to the BF do (Sarter et al. 2005). Thus, a simultaneous measurement of cortical ACh and NA efflux in the rat PFC during sustained visuospatial attentional performance (the

five-choice serial reaction time task) by Dalley and colleagues illustrated the ACh-NE interplay (Dalley et al. 2001). In their study, ACh influx increased significantly while NE influx during the regular task but it was an opposite pattern when contingencies changed, with the NE influx significant and ACh mild increase. In light of the relevant evidence, some authors proposed a “network reset” concept viewing the NE interference and widespread manner of phasic activation as a function of network reorganization and adaptation to environmental change (Bouret and Sara 2005; Sara 2009). As the authors pointed out, this helps to discard prior expectations when these expectations are violated (as in the case of novelty or surprise – IT).

Meanwhile, the ACh system, due to its remarkable ability for its NT’s double-storage and cortical-HC bidirectional communication (not discussed here due to the space limitations) has a unique capacity for drawing a time line of events using their comparison in different points of time. 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 (Hasselmo and Sarter 2011). 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 (Hasselmo and Sarter 2011). The ACh system, therefore, is well-equipped to derive the expectations of events (crucial for sustained attention) and adjust its Catch processes accordingly. Within this system, fast-acting nAChRs play the key role in sensory gain modulation related to fast-changing stimuli (Rho et al. 2018), whereas slow-acting excitatory M1, M3 and M5 mAChRs enhance (except the cortical layer V), and M2 and M4 mAChRs trim-suppress Glu-based neurodynamics, highlighting the most consistent or special features (Brown 2019; Groleau et al. 2015).

Here we could highlight what happens in regular learning, ambivalent stimuli and during a surprise and integrate it with Freeman’s neurodynamic discussed above. During regular learning tonic NE activation provides general arousal in attention; phasic NE activation via alpha1 receptors acting on Glu in the thalamus and the PFC screens for a wide range of features, including exceptional details; nAChRs in the thalamus, M1 mAChRs in cortex induce expectations-based selection enhancing some thalamic signals while cortical M2, M4 mAChRs suppress irrelevant activations. The ACh system’s features facilitate sustained attention and the NE system’s features facilitate accuracy and attention to specific details. When ambivalent stimuli are present, the encoding cortical systems use both ACh-based contrasting and encoding and NE-Glu-based additional spray within the PFC to add extra “light”

(variance from additional Glu-gic synapses) to the subject of perception (Dalley et al. 2001). In a situation of surprise, *i.e.* an outlier event, the expectations should be quickly removed (sometimes life can depend on it) so universally, the NE system takes over, likely significantly suppressing the ACh system via its alpha2 receptors in the cholinergic hippocampus, BF and LTA, and also suppressing the motivational influence of the DA-gic VTA (Brown 2019). At the same time, a surprise likely activates excitatory NE-gic alpha1 receptors that are strategically positioned in multiple brain areas, especially AM and the thalamus. The LC also has a high density of receptors for corticotropin releasing factor (Hauger et al. 2006), which HT paraventricular nucleus and several other brain structures release into the LC during stressful events. Several other brain structures and neurochemical systems are involved in the stress-response, which is not a topic of the current review.

#### DA and ACh systems

The T&C functional relay between ACh and catecholamine (CA) passes from thalamo-cortical NE-ACh interplay to the DA-ACh interplay in the striatum, especially in striatal interneurons and using corticostriatal synapses (Gil et al. 1997; Gonzales and Smith 2015). Importantly, LC does not project into striatum suggestive of a CA relay in line with the constructivism as progression in sorting of DF in actions. M1/M5 mAChRs stimulate the DA release from striatal synaptosomes, which, in turn, have additional heteromers and internal substructures (Brimblecombe and Cragg 2017; Gonzales and Smith 2015; Graybiel and Matsushima 2020; Khrenov et al. 2006). Moreover, as an illustration of a smaller-scale Throw mechanism, there is volume transmission of DA (*i.e.* neurotransmitter linked to the integration of actions) acting on the NE system (linked to orientation) in the PFC (*i.e.* information gathering and processing area) (Agnati et al. 2006; Devoto and Flore 2007; Devoto et al. 2020) – likely indicative of the pass of regulation from orientation to integration stages of action construction. Moreover, nigro-striatal and meso-limbic DA neurons likely use mainly volume transmission for their communication, differentially modulating D1 and D2 DA receptors of GABA pathways of the dorsal striatum and Glu synapses on striatal-entopeduncular/nigral and dorsal striatal-pallidal pathways (Borroto-Escuela et al. 2018). There is also an interaction between cholinergic interneurons and DA systems in this area using both volume and synaptic transmission (Descarries and Mechawar 2000; Sarter et al. 2009).

The list of T&C examples could continue with the Throw by subthalamic nucleus, the only portion of the basal ganglia

that produces a significant amount of Glu, or multi-stage Throws by HT-Pit in the form of released hormones and neuropeptides.

Our earlier reviews summarizing the FET framework pointed to several scripts in action construction and contingent relationships between neurochemical systems listed in the FET (Trofimova 2021a; Trofimova and Robbins 2016). Most commonly, an individual has a habits-based (automatic) integration of actions, with more involvement of dorsal-striatal DA-ACh systems (Figure 4A, and Physical or Social Tempo components in the FET, Figure 2). With an increase in the novelty and complexity of situations, a plasticity-type integration of action requiring cortical NE-ACh and ventral-striatum systems (Figure 4B) (Everitt and Robbins 2013; Graybiel 2016; Ikemoto 2007; Trofimova 2021a). An impulsive type of integration (Figure 4A) occurs when a rough selection of DFs is not supervised by impulse control and careful information processing by cortical and hippocampal systems (depicted by blue, *i.e.* top level of the shapes). In this case, an action can be maladaptive, involving the HPA axis activation but doesn't last long. Here we describe only the processes of a choice of DFs in actions but not motivational and emotionality regulation of behaviour (see the other FET reviews on those topics: Trofimova 2018; Trofimova and Gaykalova 2021).

### Mutual regulation between the T&C systems

Glu and GABA are known for their reciprocal regulation as they are generated by the same glial-neuronal mechanisms (Braitenberg 2001; Hampe et al. 2019; Hassel 2006). This reciprocity ensures multi-structured feedback between the process of selection of the final DFs in behaviour (“to Catch”) and requests for more information (to “Throw”) (Gandal et al. 2012; Vargas et al. 2008). Insufficient certainty in the selection processes within the GABA-dominant structures (such as striatum-based sorting of specific elements of actions) gives way to the expansion of the incoming Glu-based excitatory potentials in the sensory thalamic and cortical areas (Graybiel 2005; Smith and Graybiel 2016). Interestingly, within neurons having both GABA and Glu receptors, it is Glu, and not GABA systems, that decide how much GABA a neuron should have and, therefore, how much inhibition from GABA the Glu receptors should receive (Gandal et al. 2012; Vargas et al. 2008). This is like giving criminals the right to decide how many police should be in the area. Yet, GABA still wins in the end, trimming most of the Glu-based potential down via the structured Catch systems described above.

There is also a robust NE-ACh entanglement in attention processes, in which alertness to novelty and exceptionality is provided by NE modulation, whereas sustained attention is regulated by the ACh activity in the brain (Aston-Jones and Cohen 2005; Dalley et al. 2001; Robbins and Everitt 1996). This entanglement supports the idea that the Throw and Catch processes work together and have close feedback mechanisms. NE-ACh cooperation starts from the strong NE-ACh connectivity at the autonomic level of regulation; this cooperation then progresses to the mutual projections between NE-gic LC and ACh-gic dorso-lateral tegmental area (dLTA) in the brainstem and ACh neurons in the pedunculopontine nucleus (PPN), which send excitatory projections to the LC (España and Berridge 2006; Szabadi 2013). The cholinergic neurons in the dLTA have inhibitory  $\alpha 2$  receptors, and, vice versa, there are excitatory nACh receptors on the NE-gic LC neurons (Lena et al. 1999; Lindh and Hokfelt 1990). At the higher levels of the brain, the LC projections to cholinergic HC and BF use mostly inhibitory GABA release and  $\alpha 2$  receptors, even though excitatory  $\alpha 1D$  receptors were also found in the HC (España and Berridge 2006; Szabadi 2013). The NE-gic  $\alpha 1$  receptors on ACh neurons in the BF stimulate ACh release; however, the same receptors in the PFC can interfere with PFC function, whereas the adrenergic inhibitory  $\alpha 2$  receptors on the PFC neurons improve PFC functioning (España and Berridge 2006; Szabadi 2013). Moreover, both NE and ACh use volume transmission in the cortex, and there is likely a subtler level for their mutual regulation in extracellular space. Also, there are shared peptides in NE and ACh cells that control a co-release of NE and ACh or even the neurotransmitter profile of neurons (Lena et al. 1999; Lindh and Hokfelt 1990; Nieuwenhuys 1985). Still, similarly to Glu-GABA example in the previous paragraph, NE has a priority over ACh in novel or complex situations, as described above.

These examples of functional differences in NT systems and their mutual regulation suggest that the “Catch” ensemble directs the “Throw” ensemble where to spray next, whereas the Throw generates a local, controlled expansion of the variance in transmission potentials via the release of excitatory neurotransmitters.

The three mechanisms in neuronal regulation (Throw, Catch and Maintain) resemble three major stages of behaviour as outlined in the FET and, considering its similarity with evolutionary theories, these mechanisms might be universal for generative natural systems (Cairns-Smith 1982; Gould 2002; Trofimova 2015, 2017). It is also possible that the benefits of a local, targeted increase of variance (Throw) are associated not just with the generation of anticipatory biases that are compatible with the state of an individual

but also with other aspects of neuronal regulation. One such aspect might be a need not to let the electric or neurochemical transmission be too organized and too synchronized as it potentially can lead to high-amplitude electric or neurochemical events within the nervous system, pushing it off the healthy balance. Indeed, even Freeman, in his writing, noted that it would be too simplistic to consider mass action only as a “majority voting” coming from multiple synapses on one neuron to sum the wave. It would be non-adaptive if a significant portion of brain cells simultaneously send inputs to one location, “frying” the receiving neuron. As seen in epilepsy research, synchronization between excitatory (for example, glutamate) neurons can go over the board even with a relatively moderate number of additional inputs, causing seizures. Several mechanisms prevent it from happening (“recovery” time after firing, inhibitory inputs, glia’s monitoring, etc.), and a moderate amount of “Throw” dynamics preventing variance reduction to a clinical level might be one of these principles.

On the final note, the “Throw” mechanism, therefore, violates the advice of specialists in sampling theory to reduce variance in the reception of information, and the “Catch” mechanism violates the advice of this theory to avoid biases in receiving devices. Instead, the nervous system does exactly the opposite: it has specialized neurochemical mechanisms increasing the variance by “throwing” testing matter into the area that should be sampling reality and then generating multiple biases based on individual differences in neurochemical systems.

## Conclusions

A hungry kitten is not attentive to tails or other features of the toys that his perception should be evolutionarily tuned to in order to catch food: a hungry kitten’s perception is blind to the majority of stimuli around except the owner’s actions indicative of food provision. After meals, the same kitten plays with tailed toys for no reasons related to nutrition: these actions are generated by internal N–C to play and exercise the kitten’s perceptual and physical systems. This contrast between two behavioural patterns suggests a constructive, body’s based and not-reactive generation of behaviour at all levels of neuronal regulation, as illustrated in the three reviewed examples in this paper.

First, we highlighted Walter Freeman’s experiments and mathematical analysis that uncovered the existence of anticipatory attractors, *i.e.* non-random dynamical patterns in neurodynamics. Freeman’s work is in line with the constructivism principle as it has demonstrated that

breaking the symmetry in these attractors does not depend on stimulation. Instead, it depends on biases within the nervous system and the states of the N–C of the body.

The illustration of the functional neurochemical trends of these biases brought us to our second example, the neurochemical framework, Functional Ensemble of Temperament. Neurochemistry is a discipline that struggles with multiplicity, diversity, complexity and contingency in the action of neurochemical systems of behavioural regulation. To attempt a classification of functional neurochemical teams, the FET uses the principle of Functional Constructivism and summarises the most consistent findings in neurochemistry in a  $3 \times 4$  matrix of 12 universal aspects of action construction. These 12 neurochemical teams play managerial roles among neurochemical systems and, therefore, could “push” Freeman’s attractors from steady-state uncertainty to more certain trajectories needed for selecting DFs in behaviour.

Our third example related to the “Throw & Catch” principle that could be seen at many levels of neuronal regulation, including two levels described in another two examples: neurodynamics and functional differentiation between neurotransmitter systems. Other examples, such as volume transmission or molecular neuroscience, are yet to be explored. It appears that viewing neural regulation as gradual information processing involving only the selection of needed and suppression of unneeded DFs (*i.e.* pro-behaviourist view) misses a pro-active and constructive nature of this regulation. Indeed, neuroanatomic and neurochemical systems regulating integration and energetic maintenance of behaviour use a well-structured “Catch” mechanism at many levels of neurophysiological complexity. This mechanism allows multi-stage filtering of DFs in behaviour for the optimal selection of the final actions by gradual selective suppression (“trimming”) of generated potentials. There is, however, a pro-active, neurochemically expensive, massive but topical increase of potentials (“Throw”) in the brain (as discussed using examples of within electrodynamics and diversity of neurotransmitters) whenever there is an uncertainty in the selection of degrees of freedom. The “Throw” works as an internally generated “flashlight” that, contrarily to the expectations of entropy reduction, increases entropy and variance in affected areas – observed in orientation and action-formation processes.

As examples of T&C, Freeman’s work in electrodynamics showed that the nervous system generates non-random dynamical patterns reflecting biases in information processing associated with previous history and current N–C. Examples of functional differentiation between neurotransmitter systems show the distinct features of Glu

and NE systems in the brain aligned with the Throw mechanism that dominates by the amount of transmission. In contrast, GABA, monoamines, ACh and neuropeptides systems have much higher structural complexity and managerial capacities to modulate the generated variance (as “Catch” mechanisms). Moreover, there is likely a feedback regulation between the “Throw” and “Catch” processes. While generating and choosing the direction of the “Throw”, the nervous system also generates the “Catch relays”, in the form of anticipatory attractors described by Freeman, or in the form of heteromer receptor complexes or by the strategic positioning of receptors in the brain structures along the progression of DFs selection. Thus, whenever uncertainty occurs, the nervous system can turn its own T&C “flashlight” in both perception and selection of actions, generating mild and more targeted “play” within neuronal regulatory systems to improve its comparison of available options.

The benefits over the high neurochemical cost of the “Throw” mechanisms seen in neuronal mass action in some brain areas, synaptic overproduction and volume transmission might be associated with the ability of the nervous system to have its own “flashlight” that could be turned on locally to facilitate comparison of similar-looking elements in perception or actions. The benefits of mass action in neurodynamics could also be seen in the generation of anticipatory attractors related to the dispositions within the nervous system for future choices. These mechanisms facilitate the assessment of compatibility between current N–C, expected and actually coming events.

A mismatch between the locations of high NT presence and their receptors density, as well as their specificity in distribution in the brain requires hundreds comparison points for analysis. As per future directions, there could be benefits in a global international project mapping neurochemical T&C relays while taking into consideration regional environmental factors that might affect these distributions (sunlight, immune challenges, diets, exposure to toxins and common psychostimulants). Earlier we suggested to call this project “Hippocrates” (Trofimova 2022; Trofimova et al. 2022). The FET framework summarizing most consensual points in functional neurochemistry can be a good start for outlining possible variables of this project.

The discussed examples illustrate the constructivism principle that the nervous system’s activity is generative, very selective and biased towards the needs and capacities of individuals but mostly blind to the majority of environmental information. The generative nature of regulatory processes is seen in multiple areas of neuroscience, but its complexity slows down the progress in moving away from

old excitation-inhibition concepts toward new concepts. Much more work should be done in this direction, and an international project summarising functional differentiation within neurochemical systems is essential in verifying neuroscience principles.

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## Bionote



### Irina Trofimova

Laboratory of Collective Intelligence, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton L8S 2T6, ON, Canada  
 iratrofimov@gmail.com  
<https://orcid.org/0000-0001-6758-1389>

Prof. Irina Trofimova, PhD works as a Clinical Assistant Professor (Adjunct) within the CILab, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Canada since 1997. She is also a licensed Clinical Psychologist since 1999, Co-Directing a private practice Psychological Services (Toronto-Hamilton) and Co-Directing the Late Life Memory Clinic under Dunnville Hospital, Ontario. She has published 7 books, 70+ articles in the field of neuroscience, clinical, differential, personality, cognitive, evolutionary and mathematical psychology, nonlinear dynamics and classifications (taxonomies) of individual differences. Her main current interests are neurochemical biomarkers of consistent behavioural patterns (temperament in healthy people and symptoms of psychopathology in psychiatric disorders). Her detailed CV can be found at: <http://www.fhs.mcmaster.ca/cilab/ira/ira.html>.