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Review article

Temperament and arousal systems: A new synthesis of differential psychology and functional neurochemistry

Irina Trofimova[a,*], Trevor W. Robbins[b,1]

[a] CILab, Department of Psychiatry and Behavioral Neurosciences, McMaster University, 92 Bowman St., Hamilton L8S2T6, Canada
[b] Department of Psychology and the Behavioural and Clinical Neuroscience Institute, Downing St., Cambridge CB23EB, UK

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ABSTRACT

This paper critically reviews the unidimensional construct of General Arousal as utilised by models of temperament in differential psychology for example, to underlie 'Extraversion'. Evidence suggests that specialization within monoamine neurotransmitter systems contrasts with the attribution of a "general arousal" of the Ascending Reticular Activating System. Experimental findings show specialized roles of noradrenaline, dopamine, and serotonin systems in hypothetically mediating three complementary forms of arousal that are similar to three functional blocks described in classical models of behaviour within kinesiology, clinical neuropsychology, psychophysiology and temperament research. In spite of functional diversity of monoamine receptors, we suggest that their functionality can be classified using three universal aspects of actions related to expansion, to selection-integration and to maintenance of chosen behavioural alternatives. Monoamine systems also differentially regulate analytic vs. routine aspects of activities at cortical and striatal neural levels. A convergence between main temperament models in terms of traits related to described functional aspects of behavioural arousal also supports the idea of differentiation between these aspects analysed here in a functional perspective.

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* Corresponding author.
E-mail addresses: iratrofimov@gmail.com (I. Trofimova), twr2@cam.ac.uk (T.W. Robbins).
[1] Fax: +44 1223 33356.

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1. The concept of general arousal in psychophysiology and temperament research

1.1. The concept of temperament in differential psychology

This paper reviews the convergence of findings in behavioral neurochemistry and in temperament research on how arousal can be partitioned, and furthermore the relevance of this convergence for differential psychology.

In this paper the concept of temperament refers to neurochemically based individual differences in behavioral regulation. The original concept of Hippocrates and later, of Galen, was of four types of "temperamentums", or mixtures of bodily chemical components. In their theories a balanced mixture creates normality, whereas imbalance causes identifiable patterns of behavior. The characteristics described in the original "temperamentums" – impulsivity, aggressive tendencies, depressive tendencies, social detachment or sociability – appeared to exhibit a peculiar consistency once identified in someone's behavior, suggestive of underlying biological factors.

Two different approaches have been taken to the methodology and the conceptual framework in studying temperament. The European tradition in theory and studies of temperament (following upon the work of Hippocrates and Galen) was developed further by Wundt (see Robinson and Rieber 2001), Stern (1900, cited from Lamiell 2003), Lazursky (1921), Jung (1923), Pavlov (1928,1941), Heymans (1929), Adler (1925, cited from Lundin 1989), Kretschmer (1925), Spränger (1914), Teplov and Nebylitsyn (1963), Eysenck (1967), Thayer (1978), Gray (1991), Tellegen (1985), Rusalov (1989), Watson and Tellegen (1985), Strelau and Zawadski (1993), Strelau (1998), Trofimova (Rusalov and Trofimova 2007; Trofimova 2010a,b, 2016a). This European tradition started, as noted, within medicine and primarily used experimental methods within neuropsychology, neurophysiology and psychiatric research involving both adult human subjects and experimental animals.

The North American tradition of temperament research was scattered within three different disciplines: developmental psychology (Buss and Plomin, 1984; Kagan and Snidman, 2009, 1966; Rothbart et al., 2000; Thomas and Chess, 1977; Windle and Lerner, 1986), clinical psychology/psychiatry (Akiskal, 1998; Cloninger, 2000; Mehrabian, 1996; Panksepp et al., 1987; Zuckerman, 1994) and the lexical/psychometric approach in personality theory (Borgatta, 1964; Digman and Takemoto-Chock, 1981; Goldberg, 1993; McCrae and Costa, 1997; Norman, 1963; Thurstone, 1951).

Historically, therefore, there have been differences in terminology and methodology in studies of these consistent, biologically based individual differences. The European tradition and developmental psychology in North America called these differences "temperament", while most North-American psychologists called them "second-order personality traits". Despite these differences in terminology there has been consensus concerning the main properties characterizing temperamental traits (Kagan and Snidman, 2009; Derryberry and Rothbart, 1988; Rusalov and Trofimova, 2007; Strelau, 1998; Zentner and Shiner, 2012). These properties relate to independence from the content of activities (i.e. from values, motivation and attitudes which comprise personality): temperament manifests in dynamic aspects of behavior (e.g. the duration for which a person can sustain behavior, or the speed with which a new action can be generated or shifted from a previous action). These properties are relatively stable during the lifetime of an individual; they emerge without the awareness of the individual concerning these forms of behavior, and they have an early behavioral expression in childhood.

1.2. What this article is not about

This article analyses convergent points between two large but distant disciplines – behavioral neurochemistry and differential psychology (namely – temperament research) and therefore, for the sake of space, it must be very selective as to the topics covered in the cited references. Here are the main aspects of what this article is not about.

The literature on the functional roles of neurotransmitters and their receptors is vast, and each of these systems deserves a special review article. This inter-disciplinary review, however, focuses on evidence not from one science, but on points of convergence between several sciences in regards to the functional differentiation of behavioral activation, even though special attention is given to findings in neurochemistry. The reviews and references to experimental studies are given here therefore only as an illustration of objections to the general arousal concept, with an offer of a new framework for the analysis of neurotransmitters' functionality.

This article limits its scope only to neurochemically based individual differences, i.e. temperament and does not include references to studies in personality theory. Personality refers to a wide range of individual differences interacting with socio-cultural factors, including attitudes, systems of values, personal experience, etc. Sex, age and mental illness, however, are based on biochemical factors (for example, hormones, neurotransmitter imbalances) and are not considered as personality, even though they interact with socio-cultural factors. Similarly to sex, age and mental illness, temperament (based on neurotransmitter imbalances) is viewed here as a concept contributing to personality but having its own nature. All four of these biochemically-based characteristics (sex, age, mental illness and temperament) should not be conflated with the concept of personality, even though they interact with socio-cultural factors.

Topics including the unfolding temperament traits in childhood, their interactions with social and genetic factors, the epigenetics

of such interactions, their contribution to personality or to psychopathology.and evolutionary perspectives on temperament will not be covered here. This paper focuses on the dimensions (and functional roles) of temperament, primarily on findings related to differential structure, i.e. the separation between systems of temperament.

This paper concerns adult temperament, and references to temperament models within developmental psychology are only used for comparing dimensions.

It will also not discuss temperament models and findings using mainly the emotionality-related traits of temperament, and the role of neurotransmitters and the HPA axis in emotionality. This paper focuses primarily on the traits and neurochemical systems underlying the energetic aspects of behavioral activation.

1.3. Adoption of a concept of "general arousal" by differential psychology

The original idea of Hippocrates and Galen that chemical imbalances can form the bases of behavioral differences is echoed by several modern disciplines of science. For many decades a number of relatively independent disciplines – differential psychology, i.e. the psychology of individual differences, neurochemistry, as well as psychopharmacology and psychiatry, were attracted to each other's research in this regard. Early on, psychologists and psychiatrists developed theories linking single monoamine neurotransmitters to specific temperament traits, and *vice versa*, neuroscientists were extending their views on behavioral regulatory systems to psychology, offering their models of such temperament traits as "arousal", mobility, impulsivity, compulsivity, sociability, and sensation seeking.

One of the main concepts unifying these theories is that of arousal. The idea of the existence of a general arousal system emerged in the mid-20th century with the discovery of the Ascending Reticular Activating System (ARAS) in the so-called isodendritic core of the brain. At first it was thought that the ARAS provides *global, non-specific arousal* and wakefulness that fuels all aspects of behavioral activation, subjective consciousness (Lindsley, 1951; Moruzzi and Magoun, 1949), and learning (Hebb, 1961; Anderson, 1990; Grossberg, 1987).

Attribution of the activating properties to the ARAS and the discovery of emotional regulation by the limbic system together gave a strong boost to two-dimensional theories of temperament. Even before then, several researchers had suggested that the four classic Hippocrates-Galen temperament types could be explained by two dimensions: "energetic" and "emotional". This idea was first proposed by Kant (1798) and then developed in empirical studies by 20th century psychologists – Wundt (1893), as described by Robinson and Rieber, 2001), Stern (1900), cited from Lamiell, 2003), Heymans (1929), Pavlov (1928) – presented as "strength" and "balance"), Kretschmer (as constitutional energetic capacities characterizing schizothymic and cyclothymic types and "gay vs. sad" subtypes). Cholerics were described as emotional and energetic; Phlegmatics – as balanced and weak; Sanguines – as balanced and energetic, and Melancholics as emotional and weak.

The idea of general arousal was immediately adopted in differential psychology by Eysenck (1967) and Nebylitsyn (1972), who suggested that the reticular-cortical projections provided the energetic component ("Extraversion", in Eysenck's terms), and the limbic-cortical projections provided the emotionality component of temperament (or "Neuroticism"). This idea was echoed in the work of Thayer (1978), Watson and Tellegen (1985) followed by Carver and White (1994). In the other temperament models (that moved away from the four Hippocrates-Galen "temperamentums") a general "energetic" trait was described by psychologists as "vigilance" (Cattell, 1965), "strength of excitation" (Nebylitsyn, 1972; Strelau, 1998), "extraversion", "arousal" (Derryberry and Rothbart, 1988), "activity" (Buss and Plomin, 1984; Windle and Lerner, 1986), the Behavioral Activation (Approach) System (BAS; Gray, 1991), "drive persistence" (Carver and White, 1994; Cloninger, 2000) or simply "arousal" (Mehrabian, 1996). Following the appearance of the Big Five model, Eysenck (1992) noted that the two basic temperament dimensions were similar to two of its largest factors (i.e. Extraversion and Neuroticism).

2. Problems with the concept of general arousal

2.1. Problems in empirical temperament research

In temperament research early claims from the 1960's linking extraversion to physiological parameters of general arousal were contradicted by subsequent reports that failed to find such correlations. In early experiments administration to introverts of the classical arousing agent caffeine led to a worsening of their performance whereas for extraverts it improved performance (Eysenck, 1983; Revelle et al., 1980). However, the impact of caffeine on the performance of introverts and extraverts reverses throughout the day (Revelle et al., 1980), or might have only a weak effect on mood, slightly increasing happiness and vigor, more so among extraverts than introverts (Liguori et al., 1999). Kerkhof (1985) pointed out in his review that among 12 studies of relationships between the time of waking and extraversion-introversion, the 4 earlier studies had found such relationships while the later 8 studies had not. Body temperature was found to be consistently higher for people who awaken earlier, but there were no consistent differences between extraverts and introverts on this variable of "morningness": 5 earlier studies were for, 3 later studies against. A similar inconsistency was found for differences between extraverts and introverts in performing various tasks (3 studies for, 3 against) (Kerkhof 1985).

The idea of a "general arousal trait" was challenged in temperament research by suggestions that too many distinct traits were being assigned to the unidimensional concept of general arousal (or "extraversion", or "approach") (Corr, 1999; Fahrenberg, 1991; Hough, 1992; Guilford, 1975; Kerkhof 1985; Matthews and Gilliland, 1999; Rusalov and Trofimova, 2007; Trofimova, 2009, 2010a, 2014). For example, it has been shown that this category conflated the high sociability of extraverts with traits of impulsivity and/or psychopathy, and the low sociability of introverts with their high perceptual sensitivity. Sociability, impulsivity and perceptual sensitivity all require behavioral arousal, however the arousal systems underlying these traits appeared to be different.

Thus, Eysenck (1967) explained Jung's observations of sociability in extraverts by an insufficiency of their ARAS-cortical arousal that hypothetically leads them to orient their behavior to external (socially provided) stimuli expressed as distractibility, sensation seeking, social dependency and learning difficulties. Participants classified as "extraverts" in experimental studies had difficulty following the instruction to lie quietly on a couch (Eysenck, 1967), or inhibiting their behavior when either reward or punishment were possible outcomes, and in situations of approach-avoidance conflict were more likely to approach (Dienstbier, 1984; Newman et al., 1985; Patterson et al., 1987; Zuckerman, 1994). At the same time, critical assessment of Eysenck's studies pointed out that his inventory measured impulsivity (premature responding in the social context) rather than sociability (Gray, 1991; Eysenck, 1995; Rocklin and Revelle, 1981; Raine, 1989; Smillie et al., 2006). O'Gorman and Lloyd (1987), who recorded EEGs in extraverts and introverts, found low cortical arousal in individuals with high psychoticism but not in extraverts. Matthews and Amelang (1993) used EEG measures during performance tasks such as tracking, visual probe RT during short-term memory tasks, concentration and verbal comprehen-

sion tasks. They concluded that "the present study provides little support for the usefulness of traditional arousal theory as a unifying principle. . ." (p. 361)

Reports showing that impulsivity, sociability, perceptual sensitivity and learning abilities are regulated by different physiological systems raised concerns about the validity of the concept of Extraversion based on general arousal. After all, high sociability, i.e. the ability to sustain prolonged communications in extraverts, also required attention and behavioral arousal, and therefore both introverts and extraverts rely on arousal, though in different ways. This meant that arousal systems have multiple components, which sometimes regulate behavior in opposite directions, but should not be aligned into one dimension. For example, Pivik et al. (1988) showed that extraverts differ from introverts in motor excitability, but not in sensory sensitivity—contradicting the opposite placement of extraverts and introverts on a sensitivity scale.

In the 1980's Gray (1982) proposed a Reinforcement Sensitivity Theory (RST) that described two regulatory systems, the Behavioral Activation System (BAS) and the Behavioral Inhibition System (BIS), underlying temperament types. According to this model, impulsivity occurs whenever there is an excess of BAS activation over BIS, while high sensitivity (including anxiety) occurs whenever there is an excess of BIS over BAS. In experiments using negative reinforcement (as a strong arousing condition) introverts, according to Eysenck's theory, should learn worse because of excessive cortical arousal, whereas in Gray's model introverts should learn better (Gray, 1991). Several studies have shown that participants labeled as introverts reproduce (recall) learned material better under this strong arousing condition, and that they are more resistant to habituation of the orienting response (Corr, 1999, 2002; Eysenck, 1983; Stelmack and Michaud-Achorn, 1985; Wigglesworth and Smith, 1976). Gray's idea that behavioral arousal is a product of two systems, and not one general arousal system, appeared therefore to be supported. However, recent studies have suggested that the RST is insufficient to explain the complexity of arousal systems. High impulsivity was reported in patients with Generalized Anxiety Disoder (GAD) (Trofimova and Sulis, 2010; Trofimova and Christiansen, 2016), especially comorbid GAD and depression (Trofimova and Sulis, 2016a) contradicting Gray's model, since in this model impulsivity cannot be a symptom of anxiety because anxiety and impulsivity arise in mutually exclusive states of BAS-BIS balance (Gray, 1982, 1991).

These results of early empirical studies in temperament research showed evidence that various traits unified under the umbrella of Extraversion are regulated by different psychophysiological systems, and not by one, "general arousal" system.

2.2. Problems in studies of arousal and performance efficiency

Since the beginning of the 20th century studies on discrimination learning had discovered that arousal had an inverted U-shaped function later known as the Yerkes-Dodson effect. This curvilinear relation between arousal and efficiency of performance suggested an underlying complexity in arousal systems emphasized in the writings of Broadbent (1971) and others (e.g. Robbins, 1984) on "the two arousal systems". Humphreys and Revelle (1984) in their studies of memorization also proposed that the inverted U-shape of this function is not due to the action of one arousal system but is likely a product of combination of two arousal components: arousal as an ability to sustain information transfer (SIT) over extended periods and arousal that facilitates the speed of information transfer from inputs to outputs and therefore hinders the immediate availability of information held in working memory. Low arousal led to a lack of SIT resources and suboptimal performance whereas excessive arousal led to a slower speed of information transfer within working memory due to memory interference. We will see below that this idea from cognitive psychological studies about two components of arousal – sustaining and related to transfer/shifts processes – echoes with models in differential psychology and neurophysiology distinguishing two components.

2.3. Neurochemical perspective

2.3.1. The orexin system: evidence of functional heterogeneity

Recent discoveries have revealed a substantial role of hypothalamic neuropeptides such as orexins (also known as hypocretins) in behavioral arousal. Orexins appeared to be mediators of energy metabolism and regulators of endurance, adenosine-based arousal and appetite (Taheri, 2005). The effects of behavioral arousal linked to ARAS function could be mediated by projections to monoaminergic ARAS neurons from orexin-containing cells located exclusively in the lateral hypothalamus, with widespread projections to a variety of other brain structures (de Lecea et al., 1998; Sutcliffe and De Lecea, 2002; Sakurai et al., 1998; Tsujino and Sakurai, 2009). In other words, if there is a "general arousal" system, it should include these hypothalamic neuropeptides, and not simply ARAS monoamine (MA) networks (Fig. 1A).

However, complexity and functional differentiation within the orexin system dampens the idea of attributing general arousal to the orexin system and therefore questions the notion of whether a neural system inducing non-specific general arousal even exists:

1) Orexins apparently have at least two types of receptors with a differential distribution and specialization within the brain (Marcus et al., 2001) and different functionality (Harris and Aston-Jones, 2006; Gozzi et al., 2011; Gotter et al., 2012). For example, the noradrenergic locus coeruleus is densely packed with orexin-1 (Hpct1) receptors but does not contain orexin-2 (Hpct2) while the histaminergic tuberomammillary nucleus contains Hpct2 but not Hpct1 receptors (Mignot, 2001). Moreover, the orexin system is not the only system in the lateral hypothalamus that regulates wakefulness state. Burdakov et al. (2013) reviewed the role of three systems regulating basic-needs arousal in this brain region (neurons that produce orexin, melanin-concentrating hormone and leptin receptors) and their contrasting functionality.
2) Orexin regulation of ARAS monoamines appeared not to be a unidimensional, linear, "fuelling behavior" system, but rather a complex, contingent and nonlinear system (Phillips and Robinson, 2008; Saper et al., 2001; Tamakawa et al., 2006). Even when applied to transitions between sleep and awake states, the very arousal systems that are inhibited by sleep-promoting neurons also serve to disrupt these same sleep processes in order to return the body to a wakeful state (Saper et al., 2005). This dynamic suggests a highly specific and coordinated arousal system. In this sense "general arousal" mediated by orexins appears to be calibrated according to the amount of arousal needed within the context of the situation, rather than to the general requirements of the task.
3) The orexin regulation of MA neurons appeared to be selective and specialized. Tsujino et al. (2013) reported, for example, high responsiveness of noradrenalin (NA)-containing neurons in the locus coeruleus (LC) but low responsiveness of serotonin (5-HT) cells in the dorsal raphé during orexin release. In contrast to the other monoamines, the regulation of 5-HT neurons in the dorsal raphé nucleus by orexins was state-dependent (Takahashi et al., 2005) and acted in opposite directions, in the form of a direct excitatory action and an indirect inhibitory one (Liu et al., 2002).
4) The activity 5-HT, NA and histaminergic neurons was reported to respond to a decrease in orexin release during the NREM stage of sleep, whereas dopamine (DA) neuronal activity did not change significantly across the sleep cycle (McCarley and Massaquoi,

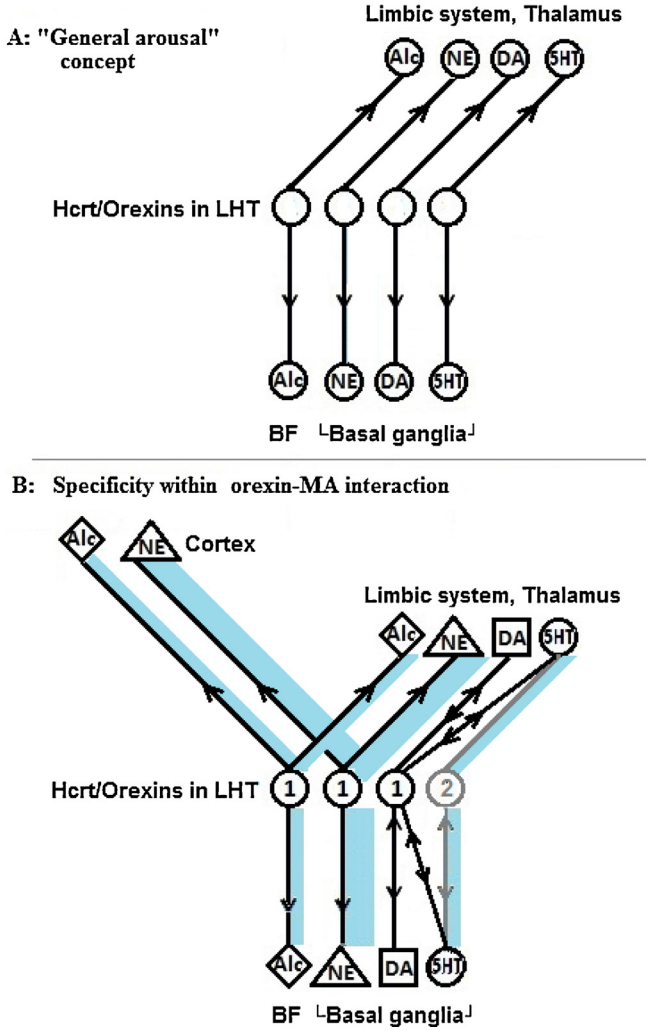

Fig. 1. Comparison of "general arousal" concept with specificity found within orexin-MA arousal systems. Two types of orexin receptors were found to be specialized in innervating different brain structures and also differential and mutual regulation of MA systems. *Note:* 1) only orexin-MA projections, and not all MA projections are shown; 2) grey-blue shadows indicate differential impact of orexin-MA interaction during the sleep cycle; 3) MA: monoamines, LHT: lateral hypothalamus, BF: basal forebrain.

1992). Such differential contributions by monoamines, including low DA activity in sleep regulation is surprising, considering that periodic leg movements (regulated by DA system of motor control), decreased prolactin and Growth Hormone release (also regulated by DA system) are symptoms of narcolepsy (Hungs and Mignot, 2001). At the same time, classically "arousing" function of NA appeared to be not always the case in the NA-ergic regulation of the orexin system and melatonin in sleep disorders: an increase of NA release under certain condition could facilitate sleep and not a waking state (Mitchell and Weinshenker, 2010).

5) Orexin neuron activity in the LH is not the same for all types of behaviour: it is high in heightened attentional states, in exploration and has tight interactions with cholinergic networks involved in sustained attention, but it is lower in grooming and eating (Alexandre et al., 2013; Mileykovskiy et al., 2005). Moreover, orexin neurons in another section (posterior) of hypothalamus were linked to arousal related rather to maintenance, and not initiation of activities, in contrast to the orexin neurons in the LH that show maximum activity in situations requiring attention and processing novely (Alexandre et al., 2013).
6) A degree of orexin acitivity is different for arousal related to a different emotional valence. Situations of negative emotional valence, even in such arousing conditions as foot-shocks or expectation of foot shocks induce significantly less orexin activity in comparison to situations that elicit positive emotions, such as the expectation of palatable food or drug reward (see Alexandre et al., 2013 for review). From a general arousal perspective it is hard to explain why negative emotional arousal (commonly considered as a behavioural mobilization needed for survival) has less of a response from the orexin system than positive emotional arousal.
7) Orexins do not merely regulate other neurotransmitters in a unidirectional manner. Dopamine has been found to be a modulator of orexin action, suggestive of mutual DA-orexin regulation in such behavior as orexin-induced hyperlocomotion, stereotypy and grooming (Alberto et al., 2006 Nakamura et al., 2000). A similar regulation of orexin effects was reported through the 5-HT_{1A} receptor by serotonin (Muraki et al., 2004), suggestive of a two-way regulation between 5-HT and orexin systems.

The contrast between theories attributing general arousal to orexin systems and recent reports on the specificity and complexity within orexin-MA interactions is summarized in Fig. 1B. Behavior requires arousal that is more than just an awake state, and functional specificity within orexin-MA systems likely relates to more than simple regulation of the sleep-wake cycle. Functional differ-

entiation within orexin systems suggests that even these systems cannot be viewed as the basis of general arousal, and with this the concept of general arousal is not supported by findings in neurochemistry.

2.3.2. Monoamine networks in ARAS: their diversity speaks against uni-functional concepts of arousal

Our views on the functionality of the ARAS changed considerably with the discovery of specific chemical neurotransmitter systems, with acetylcholine (ACh) and the monoamines (i.e. NA, DA and 5-hydroxytryptamine, 5-HT) systems originating in the brainstem, mesencephalon and basal forebrain regions (2003). Moreover, monoaminergic networks projecting to and from the ARAS have a diversity of neurotransmitters and receptors that imply multiple functionality within these networks. Each of these neurotransmitters has several types of receptors: there are (so far discovered) 5 types of dopamine receptor, 9 types of adrenergic receptor, 17 types of serotonin receptor, and more than 100 neuropeptides many of which co-exist with the monoamines as co-transmitters (Cooper et al., 2003; Siegel et al., 2006). A similar diversity of receptors has been found for acetylcholine, histamine, Gamma-Amino-Butyric Acid (GABA), glutamate (GLU) and the endogenous opioids. In addition to this diversity, brain structures with neurons containing the same type of neurotransmitters differ in terms of types of receptors, and apparently there are differences between mammalian species (for example, see Azmitia, 2010).

Concerns about the validity of the general arousal concept emerged several decades ago (Venables, 1984; Matthews and Amelang, 1993), however these concerns did not prevent a flood of studies over the past 30 years using Extraversion as a temperament/personality trait. In their analysis of the functionality of the main monoaminergic and cholinergic neurotransmitter systems, Robbins and Everitt (1996) noted: "The arousal construct is subject to enormous embarrassment from a number of empirical sources. Various indices of arousal do not intercorrelate to a high degree, as would be expected of a unitary construct (Eysenck, 1992), and putative manipulations of arousal, whether pharmacological or psychological, do not interact in a manner suggestive of an underlying unidimensional continuum" (p. 703).

3. If there is no one arousal system, how many partitions of arousal do exist?

The diversity and complexity of neurochemical systems related to behavioral arousal clearly should be reinforced in evolution by their importance in behavioral regulation. It is unlikely that we possess this diversity merely to provide redundancy for the protection of general arousal levels. More probably, humans possess this neurochemical diversity and complexity to manage unpredictable, novel and complex situations which entail several different psychological processes that are recruited according to prevailing contexts or states. A question arises: how to classify and partition this diversity, or various aspects of arousal?

3.1. Specific regulatory arousal systems related to basic needs

The latest versions of the "general arousal" theory suggest distinctions between two major classes of arousal: general versus localized, which co-exist and interact. Actions of localized arousal elements are described as being limited to basic needs behavior (food, sex, danger-related), whereas general arousal elements, according to this view, influence multiple classes of behavior, and mediate both specific and nonspecific effects of arousal (Jing et al., 2009; Pfaff, 2006; Pfaff et al., 2008). It has been proposed that basic needs systems are maintained relatively independently from each other and have specific arousal systems (Jing et al., 2009; Pfaff et al., 2008). Pfaff (2006) further argued that a primitive core of master cells in the brainstem represents the substrate of generalized arousal since a relatively small number of long-axoned connections of these monoaminergic neurons can fine-tune local modules of neurons (p. 50–51). These basic needs systems, however, likely co-exist with a very different architecture of arousal mechanisms regulating the complexities of most human behavior.

3.2. Facets of extraversion in factor-analytic models based on verbal descriptors (lexical approach)

Another (lexical) approach in differential psychology derives the structure of biologically-based traits related to arousal by applying factor analysis to estimations of verbal descriptors related to individual differences. Universally all models have a large Extraversion factor, as a main trait energizing the behavior (Digman and Takemoto-Chock, 1981; Eysenck, 1995; Goldberg, 1993; Guilford and Zimmerman, 1956; McCrae and Costa, 1997; Norman, 1963; Thurstone, 1951). Trofimova (2014) pointed out that the concept of Extraversion might be an artifact of the sociability bias of lexical material used to derive Big Five and other personality models that include the scale of Extraversion. Her experiments demonstrated that the use of lexical material skews the resulting dimensionality of models based on a factor analysis of such material due to a sociability bias of language and a negativity bias of emotionality.

Attempts had been made, however, to partition the Extraversion into more specific facets, and the results show high inconsistency between models and conceptual overlaps between these facets. For example, the Extraversion factor in the Eysenck Personality Profiler (1995) separates the facets of Sociability and Expressiveness, Aggression and Assertiveness, and Ambition and Dogmatism, in spite of the overlap between these facets within each pair. The structure of the Extraversion factor within the Big Five model has components termed Warmth, Gregariousness, Assertiveness, Activity, Excitement-Seeking, which are difficult to operationalize for investigation of their neurophysiological correlates. None of the models included the facet of Plasticity, which, as we discuss below, is based on a distinct neurophysiological system.

3.3. Proposed focus on functional features of behavior which are universal across situations

Here we suggest a different approach to taxonomy and to the functional partitioning of arousal systems. Our approach suggests a need to relate this partitioning to the functional architecture of human activities. When we examine the differentiation of neurochemical systems regulating behavior (which temperament research describes as "traits") it is useful to bear in mind that this differentiation has been reinforced throughout human evolution by the pressures of everyday functioning (Trofimova, 2016b). Humans and other animals regularly respond to diverse situations of variable complexity, unpredictability and instability. Therefore, it is impossible to have special arousal systems that have evolved to cope with every single situation or need, like the systems associated with thirst, hunger, sex or fear. Neither would it be economical in terms of resources since most situations are encountered only once or twice in life. In this sense it is unlikely that the biological systems underlying human behavioral regulation arose from the development of multiple "specific arousal" systems corresponding to particular needs.

More likely is that regulatory systems developed in tune with those functional properties of behavior that are general across tasks and situations rather than for specific tasks such as eating, drinking and sex. A description of such universal properties, or components involved in the construction of behavioral actions and routines was offered in early (Anokhin, 1964, 1975; Bernstein, 1947, 1996;

Table 1
Mapping of neurochemical systems and temperament factors within neurophysiology and developmental psychology models in the framework of the Functional Ensemble of Temperament (FET). Emotionality dimensions of temperament and models with primarily emotionality traits are excluded. Traits related to social-verbal and physical types of endurance and tempo are not separated in this Table (and grouped under deterministic aspects of behavior), however they are differentiated in the FET model (Fig. 4, Table 2). Note: *- an opposite pole of the trait is compared here to a similar FET trait; 5-HT: serotonin; DA: dopamine; NA: noradrenalin; ACh: acetylcholine; OX: orexins; OXY: oxytocin, PRL: prolactin; AdrR: adrenergic receptors.

Functional aspects	Maintenance		Speed of integration		Orientation	
Cortical vs basal ganglia regulation	analytic	determined	analytic	determined	analytic	determined
Traits in FET model	Attention/mental endurance	Endurance	Plasticity, re-programming	Tempo	Sensitivity to Probabilities	Sensation Seeking
Main neuro-transmitter systems	Ach, $NA_{5\text{-}HT}$	5-HT, GH, OX	DA_{GABA}, 5-HT	DA, PRL	NA, DA	NA, AdrR1
		Neuropsychology,	**psychophysiology**	**models:**		
Pavlov,1928,1941	Balance	CNS strength	Mobility	Mobility		
Anokhin, 1975	Executive	block	Program of	action	Afferent	Synthesis
Luria, 1948-70	Energetic	block	Programming	block	Information-	sensory
Teplov, 1947-61	Stren. of inhibition	Stren. of excitat-n	Mobility of	various types		
Teplov and Nebylitsyn, 1963	Strength of inhibition	Strength of excitation	Mobility	Lability, Dynamism		
Gray, 1982		BAS			BIS	BAS
Rusalov, 1989; Rusalov and Trofimova, 2007	Intellectual ergonicity	Motor and social ergonicity	Plasticity in 3 areas	Motor and social tempo		
	NA, DA	NA, DA	DA, GABA	DA,5HT,ACh		
Posner and Peterson, 1990	Executive	network	Orienting	network	Alerting	Network
Halgren and Marinkovic, 1995	Sustained	behaviour system	Event integration	Response choice sys	Orienting	Complex
Robbins and Everitt, 1996	NA-Ach	5-HT and ACh	DA	DA	NA, DA	NA
Jacobs and Azmitia, 1992	5-HT	5-HT			NA	NA
		Developmental	**psychology**	**models:**		
Kagan and Snidman 2009		Repression				Sexuality
Thomas & Chess, 1977	Persistence/Att	Activity level	Adaptability	Rhythmicity		Distractibility
Buss and Plomin, 1984		Activity, Sociability				
Rothbart et al., 2000	Effortful control	Activity, arousal			Orienting	Sensitivity
		Differential	**psychology**	**models:**		
Stern, 1900	Attention	Psychic energy	Combinatorial ability	Reaction, psychic tempo	Association	Sense receptivity
Wundt, 1902 (see Robinson and Rieber 2001)		Excitability				
Heymans, 1929		Activity/drive			Reasoning	
Spränger, 1914	Economic				Theoretical	
Lazursky, 1921					Combinator.abil	Sensitivity
Jung, 1923	Thinking				Introversion	Sensing
Kretschmer, 1925		Cyclothymia	Psychomotility	Psychic tempo	Schizothymic	
Adler, 1925		Energy	Creative Self	Func.finalism		
Cattell, 1965	Perfectionism*	Vigilance Liveliness	Openness to Change		Apprehension	
Eysenck, 1967		Extraversion		Extraversion		
Thayer, 1978		Energetic arousal				
Strelau, 1998	Stren. of inhib	Stren. of excit-n	Mobility			
Eysenck et al., 1985		Drive				Venturesoms
Tellegen, 1985						
Big Five, 1949-93		Extraversion			Conscientiousness	Openness to Experience
Hough, 1992	Locus of control	Potency	Intellectance		Dependability*	
Taylor and Morrison, 1992		Depression* Social activity			Objectivity	
Strelau and Zawadzki, 1993		Endurance Activity	Perseve-rance*	Briskness		Sensory sensitivity
Carver et al., 94		Drive				Fun seeking
Cloninger, 2000			Self-Directedness			Novelty seeking
Eysenck, 1995 (EPP)		Obsessiveness	Activity, Hypochondria* Manipulativeness	Dogmatism*, Non-conformity*	Irresponsibility* Practicality	Risk-taking
Mehrabian, 1996		Arousal				
Akiskal, 1998		Depression* Cyclothymia				
Zuckerman, 02		Activity Sociability				Sensastion Seeking

*- an opposite pole of the trait is compared here to a similar FET trait; 5-HT: serotonin; DA: dopamine; NA: noradrenaline; ACh: acetylcholine; PRL: prolactin; AdrR: adrenergic receptors.

Luria, 1966; Pribram and Luria, 1973) and more modern (Joel and Weiner, 2000; Halgren and Marinkovic, 1995; Posner and Petersen, 1990; Schall, 2001) studies and models of behavioural regulation within kinesiology, neurophysiology and clinical neuroscience. In spite of the diversity of these models and differences in methodology between these sciences, they converged upon at least three general components of any action (See Table 1)

- components variously named “afferent synthesis”, “orientation”, “orienting”, “sensory-information block”, or “exploration”;

- components variously named “programming”, “decision block” or “event integration”;
- components variously named “execution”, “exploitation”, “sustained behavior”, “energetic block”.

Regulation of the orienting, plasticity and energetic aspects of behavior has been linked to specific brain structures or systems but since the late 1980s it has been recognized that functional differentiation between three particular MA systems might have a similar specificity (Bloom, 1985; Jacobs, 1987, 1992; Robbins, 1997; Robbins and Arnsten, 2009; Robbins and Everitt, 1996).

4. Three points of consensus in regard to the functional specialization of MA arousal systems

4.1. Mutual regulation and diversity within MA systems create challenges for assessing their functionality

The diversity of MA receptors and their specificity in various brain structures should not be underestimated, and we do not suggest that it can be reduced to just three functions. Moreover, behavioural neurochemistry is a relatively young science trying to investigate the functionality of these diverse neurochemical systems and is still at the early stages of gathering a complete picture of this functionality. Yet, attempts should be made to offer solutions to the puzzle of the diversity and complexity of these systems, and we believe that a behavioral constructivism perspective provides a first important approximation into the classification of arousal systems.

The following sections briefly review the experimental evidence in regard to the functional roles of the classical monoamine neurotransmitter systems, but let us first comment on the challenges encountered in studies of neurotransmitter functionality.

First, there is likely no single neurotransmitter the release of which is independent of the action of other neurochemical systems, including other neurotransmitters. MA systems regulate one another’s release in a contingent manner via several mechanisms with different release patterns depending on the intensity of stimulation and the location and density of receptors (see Section 4.5.) In this complexity, as Fink and Göthert (2008) noted, none of the 5-HT receptor types modulating the release of DA and NA showed an exclusive control over the release of just one of these neurotransmitters. When we examine evidence related to the functionality of MA systems, therefore, we often see changes in all three MA systems in response to experimental manipulations. For this reason the model presented at the end of this article is called a neurochemical *Ensemble*, and it criticizes the dimensionality approach employing the concept of independent dimensions.

Second, whenever the functionality of MA systems is discussed we have to keep in mind that MA release does not happen in one continuous stage. There are several stages in this process that involves a cascade of GABA/GLU, enzymes and metabolites, G-protein coupled receptors, BDNF, CREB, calcium and other chemical systems, including partner monoamines (Holz and Fisher, 2006). In this sense the outcomes of pharmacological studies of the functionality of neurotransmitters that use agonists or antagonists of specific neurotransmitters often have limited value for conclusions on their functionality, as it is very hard to match and/or control all of the complexity of natural lower-level neurochemical mediations. Moreover, chronic exposure to agonists often results in diminished responsiveness and chronic exposure to antagonists often results in increased responsiveness of MA receptors (Kuhar et al., 2006).

Third, as noted above, the diversity of MA receptors and their different actions in different brain structures create another serious challenge for understanding the functionality of MA systems (e.g. Eisenegger et al., 2014; Seamans and Robbins 2009). Increased (for D1 and D5 receptors) vs. decreased synaptic excitability (for D2, D3 and D4) as different functions of these dopaminergic receptors suggests that common functionalities of DA receptors cannot be understood in terms of arousal (excitation) vs. inhibition functions, and alternative functional perspectives must be advanced.

Taking into account this functional diversity, the multi-stage nature of release and contingency of this release on the state of multiple chemical systems, the task of understanding neurotransmitter functionality appears to be enormous and cannot be accomplished just at one level of analysis. However, attempts to the question of classification of the functionality of MA systems should be made, and we are sure that other researchers will offer different perspectives. The next sections compare most commonly reported functionality of MA systems to the three formal aspects of behavior as noted in the previous section.

4.2. The role of the coeruleo-cortical NA systems in orienting to novelty and alerting behaviour

As noted above, NA systems, as well as other neurotransmitter systems do not modulate one homogenous psychological process. Instead all these systems may act differently depending on the level of arousal, type of receptors and their precise location within those neural systems controlling behavior (Berridge and Waterhouse, 2003; Robbins and Arnsten, 2009). Just to illustrate that an attribution of general arousal to NA systems (indeed implicated in attention processes) is not appropriate, it has been shown that under conditions of hyperarousal, NA release in the prefrontal cortex (PFC) impairs working memory but enhances long term memory consolidation in the amygdala – therefore the same level of NA arousal has differential effects on different psychological functions (Robbins and Arnsten, 2009).

Of the diversity of roles attributed to the noradrenergic coeruleo-cortical projections, their functioning in regulating *attention to novelty and orientation* is prominent. Other neurotransmitters, especially acetylcholine, have also been implicated in a spectrum of attentional processes (Everitt and Robbins, 1997), however NA appeared to be a key neurotransmitter specifically in attention dealing with novelty and/or uncertainty, whereas the ACh system was linked mostly to sustained forms of attention (Chamberlain and Robbins, 2013; Everitt and Robbins, 1997; Hasselmo and Sarter, 2011; Robbins, 1984; Robbins and Roberts, 2007). A body of evidence shows that the response of NA neurons rapidly habituates to repetitive sensory stimuli (Aston-Jones et al., 2000; Chamberlain and Robbins, 2013; Gibbs et al., 1997; Jacobs, 1987, 1992). The brain’s NA system is most active in an awake state, in stress, in darkness (for rodents), and in tasks requiring focused attention and orientation, especially upon the occurrence of unexpected sensory events. Jacobs (1987, 1992) described the activation of NA release with sympathetic response to novelty or danger in cats (heated environment, drug-induced increases or decreases in blood pressure, insulin-induced hypoglycemia, painful stimuli, systemic injections of morphine, loud noise, physical restraint, or a dog). These conditions invariably led to a doubling or tripling of NA activity in the LC above an active waking baseline (Jacobs 1987, 1992; Jacobs and Azmitia, 1992, p. 214). The NA response to novelty is so specific that even novel stimuli, which are presented repeatedly, gradually evoke less and less NA neuronal firing (Aston-Jones et al., 2000; Everitt et al., 1983; Jacobs 1987, 1992).

Moreover, for the past 3 decades it has been well established (since Levitt et al., 1984) that NA projections were especially dense in the somatosensory, parietal and visual cortex. This is in line with the “orientation” function defined as an expansion of behavioral alternatives, especially noted under conditions of novel or unpredictable events. A deficit of NA has been linked to compromised

attentional functioning (Robbins and Arnsten, 2009) and to new learning which both imply a modulation of orienting responses to novelty (Beane and Marrocco, 2004; Gibbs et al., 1997; see reviews by Berridge and Waterhouse, 2003; Chamberlain and Robbins, 2013). The NA system has also been implicated in shifting attention from one perceptual dimension to another (Kehagia et al., 2010; Robbins and Roberts, 2007; Tait et al., 2007), in provision of attention in its phasic mode and in distractibility in its tonic mode in nonhuman primates performing a go/no-go visual attentional task (Aston-Jones and Cohen, 2005). An excess in NA can also compromise performance as it increases distractibility by novel stimuli. An interaction between DA and NA appears to regulate the optimal level of NA-induced arousal, in modulating the strength of the signal and its interference from distracting events (Arnsten, 1997; Durstewitz and Seamans, 2006). Kehagia, Murray and Robbins (2010) reviewed evidence of differential impacts of cortical 5-HT and NA suggesting that PFC NA likely mediates a higher order flexibility during attentional set-shifting, consistent with its role in orientation whereas 5-HT in the orbitofrontal cortex (OFC) mediates the low level flexibility required of reversal learning.

A review of experimental evidence and dynamical modeling of the functionality of NA and DA neurons in LC using a target detection task suggested their different role in exploration and exploitation of behavioural alternatives (Aston-Jones and Cohen, 2005; McClure et al., 2005; Rey et al., 2007). Using this functional distinction these authors came to a consensus that while DA is correlated with response exploitation, NA release is correlated with exploration processes. The "exploration" concept is in line with the "orientation" component of actions described in models of kinesiology and psychophysiology (see Table 1). Both concepts deal with an expansion of behavioral alternatives, especially noted under conditions of novel or unpredictable events.

4.3. The role of dopamine release in prioritizing stimulus salience and action production

Striatal DA is well-known to have important roles in incentive-motivation and reinforcement learning, as well as behavioral activation and cognitive and motor output, whilst being modulated by the reciprocal influence of prefrontal DA (see e.g review by Robbins 2010). There is consensus concerning the role of DA systems in behavioral plasticity and motor performance (Seamans and Robbins, 2009; Seamans and Yang, 2004; Yin and Knowlton, 2006). Plasticity involves the simultaneous activation and suppression of several scripts of actions, the integration of a new program of actions (including effects of reward and incentive motivation) and the sequencing of instrumental behavior, including pre-learned habits. Striatal DA systems are key players in behavioral plasticity: DA projections to the PFC as well as the striatum have been shown to provide not only bottom-up activation, but also top-down regulation, i.e. sequencing and goal-directionality, of behavior (Costa et al., 2006; Grace et al., 2007; Seamans and Yang, 2004; Yin and Knowlton, 2006). The PFC receives more DA innervation compared with other cortical regions, especially in rodents, and such heterogeneity is characteristic only of DA projections as all other ascending monoaminergic projections are more evenly distributed among cortical regions. Such predominance of DA projections in the PFC, the "programming area of the brain" (Stuss and Knight, 2002) suggests its key role in the modulation of important cognitive and executive processes involved in planning, organization and reasoning. It is also noteworthy that the striatum,has very little NA input suggesting again quite specific roles of its DA innervation. This has led many neuroscientists to believe that the ascending DA system provides a spectrum of functions helping to prioritize and prepare a program of actions: from marking the significance of stimuli to making choices, to preparing motor actions and cognitive outputs (Siegel et al., 2006; Seamans and Robbins, 2009; Seamans and Yang, 2004; Yin and Knowlton, 2006).

DA release is also associated with the process of attaching significance to stimuli (saliency) regardless of emotional valence, rather than contributing specifically to positive emotionality or approach behavior (Oades, 1985; Berridge, 2007; Salamone et al., 1997). In fact, contrary to the notion of DA as a "neurotransmitter of pleasure", appetitive stimuli enhance activity in the mesocortical DA system to a lesser degree and more transiently than do aversive stimuli (see Seamans and Robbins, 2009 for a review). Multiple reports have described DA increase during reactions to the circumstance of defeat (Puglisi-Allegra and Cabib, 1990), aversive stimuli (Horvitz, 2000), stress (Anisman et al., 1993; Puglisi-Allegra et al., 1990; Tidey and Miczek 1996), foot shock (Salamone et al., 1997; Thierry et al., 1976), highly salient visual stimuli (Redgrave et al., 1999), motor readiness (Brown and Robbins, 1991), and paranoia, repetitive or stereotyped behavior (Tucker and Williamson, 1984). An excess of DA combined with a deficit in 5-HT has been hypothesized to cause obsessive-compulsive disorder (Denys et al., 2004; Koo et al., 2010; Szechtman et al., 1998). Investigators have found similar results for a variety of stressors, including handling, forced swimming, tail pinch, social defeat, conditioned aversive stimuli, and pharmacological anxiogenesis (Seamans and Robbins, 2009).

A role of DA D2 receptor stimulation in "salience-labelling" can be seen in its association with schizophrenia (Coyle, 2006; Gray, 1998; Kapur, 2003) and psychoticism (Corr and Kumari, 2000), both linked to an excess of dopamine. People with these conditions over-attribute significance to common details and objects in the environment, and show a poor ability to suppress non-important information. Studies of conditioned blocking, prepulse inhibition (PPI) and latent inhibition (LI) (as an ability to suppress a response to irrelevant stimuli) have indicated that both PPI and (sometimes) LI are reduced in schizophrenia (Gray 1998; Helmsley 1987; Swerdlow et al., 1992; Weiner 1990) and in normal individuals who scored high on psychoticism or schizotypy scales (Baruch et al., 1988; Kumari et al., 1997). Helmsley (1987), Oades et al. (1996) observed that an experimental increase of DA may compromise latent inhibition (which results in attention not being paid to irrelevant stimuli) and conditioned blocking, (which prevents redundant information being processed), and therefore causes an individual to pay attention to and assign significance to even irrelevant stimuli. When DA is released during a pleasurable experience it may amplify the significance of events and objects associated with pleasurable effects. Such amplifying effects of DA release have been described as incentive sensitization (Berridge, 2007) or alternatively as enhanced conditioned reinforcement (Robbins, 2010).

In addition to altering priorities in perception that contribute to a final programming of actions, DA release affects motor output, mediating "motor readiness" during response preparation by the striatum (Brown and Robbins, 1991; Seamans and Yang, 2004; Yin and Knowlton, 2006). In the caudate nucleus it amplifies the significance of actions, helping both to sequence and to switch between them (Seamans and Robbins, 2009). In studies on non-human primates a contribution of 5-HT was consistent with a tonic component of behavior to enable reversal learning, whereas the deficient contribution of PFC DA was consistent with compromised ability for prioritization of actions resulting in inappropriate perseveration during extinction of learned programs of action (Walker et al., 2009). These results suggest that DA plays a key role in integration (including prioritization, sequencing and programming) of actions.

Such diverse roles for DA release in behavioral regulation have one feature in common: all of them prioritize and therefore facilitate the choice of behavioral alternatives necessary for the integration of subsequent actions (whether perceptual-cognitive or motor). In fact, a recent study on the role of DA D2 receptors in

reinforcement learning reported that a D2 receptor antagonist did not disrupt learning, but rather induced profound impairments in choice performance (Eisenegger et al., 2014). It has been also shown that D1 and D2 receptors may be stimulated optimally at different levels of DA presynaptic activity, which may improve some aspects of cognition and hinder others (Floresco and Magyar 2006; Seamans and Robbins 2009).

4.4. Neurotransmitter systems for maintenance of behavioural arousal

When we use the term "maintenance of actions" we acknowledge the fluid nature of actions, and Bernstein's (1947/1996) idea that every action is being constructed anew, based on previously tried and constructed units. Maintenance of actions therefore is understood here as maintenance of that construction process, with all necessary variations required by changing situations or by decreasing executive capacities in repetitive activities. There are at least three ancient and distinct neurotransmitter systems that provide for maintenance of behavior:

- neuropeptides, that act slowly but with great plasticity and in tune with the metabolic state of the body (Mains and Eipper, 2006). Out of 100+ known neuropeptides we just point here to the abovementioned role of orexins, and also to Growth Hormone that was implicated in the maintenance of physical endurance;
- acetylcholine, that in addition to its fast transmission mechanisms in muscle control, has a slow-acting G-protein coupled receptor system employed in its key role in the parasympathetic system, vigilance of behavior and sustained attention (Everitt and Robbins, 1997; Sarter et al., 2001)
- serotonin system, that appeared to have a key role in repetitive aspects of behavior such as basic movement, caloric intake, sleep-wake circadian rhythms, tonic motor activity, modulation of neuroendocrine function, appetite, and trophic functions – contributions being noted in almost all organisms, from plants to vertebrates (Azmitia, 2010; Hensler, 2006).

The arousal of the 5-HT system differs from general awake-arousal provided by the hypothalamic neuropeptides, from the reactive physiological arousal provided by the hypothalamic-pituitary axis (HPA) and from the tonic-vigilance arousal provided by the ACh system. 5-HT-controlled arousal is more plastic and selective in nature and supports the repetition of behavioral units that were proven to be beneficial. Azmitia (2010) described that uninvolved 5HT neurons are generally either silent or highly rhythmically active and at first make indiscriminate connections. Their activity is gradually synchronized with neurons that are synchronous and is eliminated for neurons whose activity is asynchronous. In this sense the tonic arousal of the 5-HT neurons works like a glue binding the most synchronous elements. During this integration process 5-HT fibres also grow out to the periphery of a particular CNS target site and then await some signal before the final infiltration takes place. Once a functional group is established, 5-HT maintains their specific arousal. Jacobs and Azmitia (1992) pointed out that 5-HT neurons spontaneously discharge with an extraordinary tonic regularity and are strongly activated during rhythmic activities, such as feeding, licking, grooming, postural control, swimming, but inhibited during alert states requiring orientation.

Yet, as Jacobs and Fornal (2010) concluded, 5-HT neuronal activity supervises a process of integration and maintenance of actions rather than solely building particular motor acts or activating muscle groups. In this sense 5-HT provides a differential and plastic type of maintenance of established behavioral units. Several authors summarized the primary function of the 5-HT system as facilitation of behavioral output by coordinating autonomic and neuro-endocrine function and by a concomitant general suppression of afferent input from sensory channels (Hensler, 2006; Jacobs and Fornal, 2010). A supervisory role of 5-HT in the regulation of physical endurance can be seen from the anatomical location of 5-HT cells in all internal organs: in fact, the brain has only 1–2% of the serotonin of the body (Azmitia, 2010; Hensler, 2006). Despite this, the 5-HT system is widely represented in many well-defined brain structures, and the main source of 5-HT neurons, the dorsal and median raphé nuclei (RN), have the largest and the most complex efferent system in comparison to any other structure in the brain (Azmitia, 2010). Such a wide and structured 5-HT neuron organization might well reflect its diverse functions.

4.5. Functional interactions between neurotransmitter systems

Links between MA and ACh release and specific forms of arousal have been described here to illustrate the idea that neurotransmitters do not simply mediate or inhibit behavioral arousal. Instead, they likely have functional differentiations that provide various aspects of arousal. Moreover, ensemble-like mutual regulation of MA systems occurs through co-localization of their projections on the same neurons within various limbic structures and in their mutual interactions.

Thus, under the conditions of significance (which might be associated with high DA release) an orientational component (likely associated with NA release) should be activated. This is indeed observed as a co-release of DA and NA (Devoto and Flore, 2007). NA-DA interactions appear to be complex, as DA is present in NA neurons, being the biochemical precursor of NA and likely acting as a physiological ligand of NA receptors (Zhang et al., 2004). It has been suggested that in the cerebral cortex a consistent fraction of extracellular DA is recaptured into NA terminals by NA transporter, and a competition for the same transporter can be a mechanism regulating reciprocal suppression or mutual activation of DA and NA release (Devoto and Flore, 2007; Moron et al., 2002; Pozzi et al., 1994; Yamamoto and Novotney, 1998). If NA release is associated with orientation and DA release with selection and prioritization (i.e. with reduction) of these alternatives, then we would predict that DA systems may lead to a suppression of NA release, in order to enable behavioral output. This indeed what was observed in experimental studies showing that an imbalance, i.e. either insufficient or excessive DA D1 receptor stimulation, leads to an increase in NA synthesis that compromises attention and working memory through effects on stress (Arnsten, 1997; Brokaw and Hansen, 1987; Oades, 2002). Complementarily, the central NA system appears to have mechanisms for suppressing DA release, in line with the idea that the orientational component of behavioural regulation should have a way to suppress existing programs of actions (see Rey et al., 2007 for review) – the process that is important in shifting between actions and stopping already initiated actions (Bari and Robbins, 2013). In acute brain slices from the midbrain Paladini and Williams (2004) have observed an inhibitory effect of NA on DA neuron activity through activation of α1-NA receptors. In the Grenhoff et al. (1993) *in vivo* study of anesthetized rats, stimulation of the LC produced a long-lasting depression of DA cell activity in the ventral tegmental area (VTA) and substantia nigra (SN). Studies with the catecholamine stimulant d-amphetamine (Darracq et al., 1998) and NA receptor antagonists (Shi et al., 2000; Linner et al., 2001) have also shown that NA alpha2- adrenergic receptors likely have an indirect control over the DA outflow. Behavioral experiments showed that NA plays an important role in alerting responses (in line with the hypothesis about its role in attention to novelty), but this role is associated with inhibition of previously learned responses and stopping action for which execution was already initiated (Bari and Robbins, 2013).

The analysis of NA-5HT interactions suggests that exploration of novel behavioral alternatives, here termed *orientation,* is coupled with the selective suppression of previously learned and well-established units of behavior (even though with activation of a few well-learned units necessary for the specific processing of novel stimuli). In the classic sense, orienting towards a stimulus implies the interruption of ongoing activity (i.e. the inhibition of the maintenance and performance aspect of actions) and the concentration of attentional resources towards the stimulus that caused the orienting response (i.e. the expansion of information relevant for the adjustment/change of a program of future actions). At the same time, increasing tonic arousal for specific targets of attention (that is important in hunting or accounting tasks) requires a co-release of 5-HT and NA. Such dynamics are indeed observed in the location and in the action of 5-HT and NA receptors regulating each other's release (Adell et al., 2010; Fink and Göthert, 2008).

Activation of 5-HT1A and 5-HT3 receptors has been reported to be differentially mediated by GABA interneurons to increase the NA release in several brain areas, and the action of the 5-HT1A receptor on VTA DA function exhibited a biphasic dynamics dependent on the dose of the agonist (see Adell et al., 2010 for review). The activation of 5-HT2 receptors appeared to mediate an indirect inhibition of NA release in the hippocampus and spinal cord, but the 5-HT3 receptors appeared to act differently in different brain locations and in different species, via GABA/GLU neurons and also 5-HT2 receptors (see Fink and Göthert, 2008 for review). In turn, NA exerts a tonic facilitation of 5-HT transmission through α1-adrenoceptors and has inhibitory action through the α2-adrenoceptor (Adell et al., 2010). Moreover, the action of the 5-HT1A receptor on VTA DA release could not be described in classical terms of activation or inhibition as it demonstrated a biphasic dynamics: initial increase and then a decrease of DA release that is dependent on the dose of the agonist (Adell et al., 2010). In turn, NA appeared to have dual-regulation mechanisms of 5-HT release, facilitating 5-HT transmission through α1-adrenoceptors and inhibiting such transmission through the α2 -adrenoceptor (Adell et al., 2010).

Jacobs (1992), Azmitia (1992, p. 214), Jacobs and Fornal (2010) described an opposite pattern of response of NA and 5-HT neurones in cats under novel or stressful conditions that required orientation, such as heated environment, drug-induced increases or decreases in blood pressure, insulin-induced hypoglycemia, painful stimuli, systemic injections of morphine, loud noise, physical restraint, or a dog. None of these conditions evoke 5-HT neuronal activity in the RN (in the nucleus centralis superior or the nucleus raphe magnus) beyond the level typically seen during an undisturbed active waking state whereas the activity of NA neurons was almost tripled. This reciprocal regulation between NA and 5-HT systems might explain improved accuracy of stimulus detection with depletion of 5-HT (Carli and Samanin, 2000).

In terms of 5-HT-DA interactions, at least four types of 5-HT receptors have been found to facilitate DA release and one type – to inhibit it (Di Matteo et al., 2008). Activation of 5-HT2A and 5-HT3 receptors, via mediation by GABA neurons, inhibits the release of prefrontal neocortical DA, however activation of 5-HT3 receptors also increases DA release in the nucleus accumbens and the medial prefrontal cortex (mPFC) (Di Matteo et al., 2008; Fink and Göthert, 2008). DA also regulates 5-HT through projections from DA nuclei to the dorsal raphé nucleus (DR), by DA neurones within the DR or more indirectly, via action of D2 receptors on NA neurons (Matsumoto et al., 1996; Adell et al., 2010).

A functional dichotomy has also been reported for orexin (hypocretin) receptors, which, as mentioned above, were considered to be perhaps the best neurotransmitter candidates for a system of general arousal. Thus, orexin OX-1 receptors were found to modulate reward seeking (i.e. prioritization of actions), and multiple sets of NA and ACh (including cortical) projections with no regulation of cortical 5-HT systems (Fig. 1). At the same time OX-2 receptors were implicated in arousal maintenance (Gotter et al., 2012; Gozzi et al., 2011) regulating 5-HT but not ACh and NA systems. Orexin neurons in lateral (LHT) vs. posterior hypothalamus (PHT) appeared to have functional differentiation, with the LHT regulating initiation of actions, attention and exploration, in tight interaction with NA and Ach systems, and the PHT regulating maintenance of routine activities (Alexandre et al., 2013). Such specialization of orexin receptors, which, in turn stimulate MA and ACh neurons, corresponds to differentiation between functions of orientation vs. plastic maintenance (or informational vs. executive, or exploration vs. exploitation—in proposed dichotomies within various theories).

4.6. *Summarising functional differences and co-operation amongst the main neurotransmitter systems*

Above we briefly reviewed the evidence for differential contributions of MA and ACh systems to behavioral regulation. In summary, the following hypothetical partition between functional aspects regulated by these systems (though interacting with other neurotransmitter and hormone systems) has emerged, and these aspects deal with behavioral alternatives in different ways (Fig. 2).

- NA release was implicated in orientation necessary to address novelty and complexity of events, to modulate *inter alia,* pro-

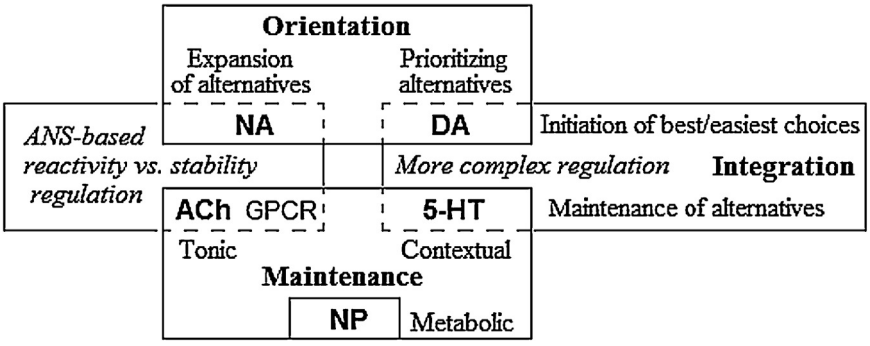

Fig. 2. Differences in functionality of main neurotransmitter systems in the perspective of functional aspects of behavioral regulation described in kinesiology models. Note that it is proposed that functional aspects are the result of relationships between several neurotransmitters rather than an action of a single system.

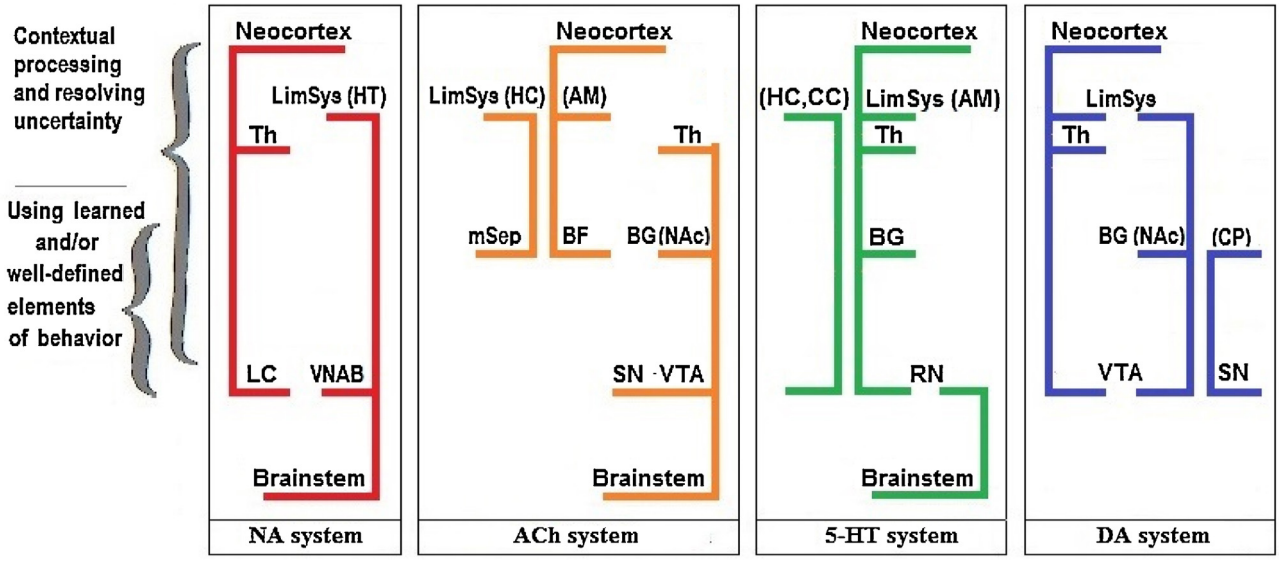

Fig. 3. Partitions within three monoamine systems dealing with two levels of contextual complexity or automaticity. Networks within the *lower bracket* level deal with well-defined (explicit or previously learned) features of situations; *upper bracket* networks deal with adjustment of behavior to situational context and probabilistic processing, including implicit (abstract) features of events.Th: thalamus; LimSys: limbic system including hypothalamus (HT), hypocampus (HC), amygdala (AM), cingulate cortex (CC) and PAG; BF: basal forebrain; mSep: medial septum, BG: basal ganglia; NAc: nucleus accumbens; VNAB: ventral ascending NA bundle; VTA: ventral tegmental area; NA: noradrenalin, DA: dopamine, 5-HT: serotonin, ACh: acetylcholine.

cesses of attention to stimuli. Such functionality relates to dealing with the exploration of behavioral alternatives.

- DA release was linked to multiple and diverse functions, however the common feature of these functions is the prioritization and integration activation of behavioral elements (i.e. plasticity, attribution of salience to stimuli, development of motivation and plans, and initiation of specific actions from a repertoire with multiple degrees of freedom). Such functionality also relates to a narrowing of the range of behavioral alternatives to those sets that are most relevant for the situation and for future actions and plans.
- Serotonergic and cholinergic systems appear to be crucial for maintaining the tonic arousal that energizes selected behavioral alternatives whilst also maintaining behavioral inhibition over irrelevant inputs and outputs.

5. Possible functional differentiation between cortical and basal ganglia MA systems

5.1. Between different levels of processing (analytic and automatic)

As noted above, having multiple orientational and executive alternatives would overload our arousal systems very quickly. We would constantly miss even the most important information, and our choice of action would be barely adequate if every time the programming system was required to consider all the existing alternatives anew in order to select relevant stimuli or actions. Passing control over previously learned behavioral elements to an automatic level of sensory processing or actions helped animals (including humans) to optimize, by easing and simplifying programming choices. As a result, a new program can use a complex combination of pre-packaged elements from previous actions and still have sufficient resources for optimal orientation and selection of actions (Bernstein, 1996; Kahneman, 1973; Logan, 1988; Treisman, 1979).

These two modes of behavior – analytic, contextual processing (required in probabilistic, uncertain situations) and automatic (using either pre-made habits and/or explicit, well-defined reinforcers) – complement each other in many ways and represent two sets of regulatory systems. It should be noted that the well-defined elements include not only well-learned executive routines but also stimuli and programs of actions offered by the environment. For the purpose of this review it is convenient to consider two levels of processing: cortical (Levin et al., 1991; Stuss and Knight, 2002) and basal ganglia/forebrain level (Robbins, 2010; Stocco et al., 2010; Yin and Knowlton, 2006).

Obviously, this grossly simplifies many other aspects of cortical (including hippocampal) and limbic processing, as well as subcortical mechanisms. Sometimes, there is no clear separation between the involvement of cortical vs. striatal areas or prefrontal vs. sensori-motor areas in any action: it is more accurate to talk about the degree of involvement, and not the absolute control by these structures. Thus the PFC participates not merely in conscious aspects of action control, but also during unconscious stimulus processing or action, and decision-making (Logan, 1988; van Gaal et al., 2008). PFC participation, however, is more profound during those tasks specifically involving conscious attention or probabilistic learning in uncertain or ambiguous contexts. Implicit processing also occurs, especially in sub-cortical structures; cortical vs. striatal levels differ in their degree of analytic processing, splitting behavioral regulation into 'mental' (analytic) and sensori-motor (related to more immediately present objects) aspects. This distinction may subsume for example the concept of goal-directed behavior and habit learning (Yin and Knowlton, 2006), as well as 'model-based' versus 'model free' behaviour, which denotes a distinction between a system that can plan ahead and respond to complex, probabilistic contingencies versus one dependent more or less directly on immediate contingencies of reinforcement learning '(including e.g. 'win-stay vs "lose-shift" behaviour) (Doll et al., 2015).

An analogous separation occurs in behavioural orientation, for conditioning of specific stimuli and exemplars versus the slower acquisition of category learning involving the same exemplars-processes associated respectively with the basal ganglia and the prefrontal cortex (Antzoulatos and Miller, 2011). In general, the two-level dichotomy is therefore relevant to many aspects of cognitive and behavioral function and, though a simplification, is helpful in terms of temperament research. However, although this two tier functional separation appears to be a fundamental principle

of cortical versus striatal functioning, its neurochemical underpinnings are less clear, particularly as the MAs tend to innervate both cortical and subcortical regions and hence influence both levels of processing.

5.2. Specialization of the MA systems for levels of processing e.g. cortical vs. basal ganglia functions

5.2.1. Functional differences between cortical vs. subcortical NA networks

From a neuroanatomical perspective it is significant that each of the central MA and ACh systems has at least two major sources of neurons that innervate different levels of telencephalic and diencephalic function (Fig. 3). Prominent among these are the central NA systems which, descending spinal cord projections aside, mainly consist of a coeruleo-cortical innervation (including the hippocampus) as well as a more ventral ascending system from a lateral tegmental group of NA-containing neurons, projecting to the hypothalamus and limbic system, with some overlap between these systems, for example, in the paraventricular nucleus of the hypothalamus (Berridge and Waterhouse, 2003; Levitt et al., 1984; Sawchenko and Swanson, 1982). This system contributes greatly to the regulation of autonomic, endocrinal and arousal processes, including HPA arousal. It is striking however, that despite its widely ramifying ascending projections, the coeruleo-cortical system has little if any innervation of the striatum; what sparse innervation occurs (in the shell region of the nucleus accumbens) originates from the more ventrally system caudal to the LC (Delfs et al., 1998).

There are also differences between cortical and mid-brain areas in the distribution and mutual regulation of NA and DA systems, which are described in special reviews (Devoto and Flore, 2007; Devoto et al., 2003; Rey et al., 2007). Arnsten (1997), in her description of differences in functionality of cortical vs. subcortical catecholamine systems, suggested that “high levels of catecholamine release during stress may serve to take the PFC ‘off-line’ to allow faster, more habitual responses mediated by the posterior and/or subcortical structures to regulate behaviour” (p. 151). The level of NA function optimal for attention and other cognitive processes appeared to be lower than the optimal level for behavioural element related to aversive situations (Chamberlain and Robbins, 2013). Moreover, even for aversive situations, it appears that behavioral and endocrine elements are subserved separately by LC and ventral ascending NA systems (Selden et al., 1990).

5.2.2. Functional differences between cortical vs. striatal DA networks

Neuroanatomical projections of the mesenecephalic DA systems, apart from their discrete innervation of the hypothalamus, ramify to innervate the dorsal (i.e. caudate-putamen) and ventral striatum (including the nucleus accumbens) (NAc) as well as limbic and neocortical structures, especially the PFC in rodents. There are differences in the functional neuroanatomy and neurochemistry of DA systems regulating the ease (speed) of integration of actions of three types: (1) goal-directed and adapted to a situational context (i.e. *Plasticity* of behaviour), (2) automatic, habit-based integration (termed here *Tempo*) and (3) premature integration lacking cortical control (*Impulsivity*). There are distinct separations between the pathways projecting from the VTA to the nucleus accumbens (as well as amygdala and a sparse projection to the hippocampus), implicated in incentive-motivational processes, and the PFC (regulating executive and behavioral plasticity processes). Pathways projecting from the more lateral substantia nigra to the dorsal striatum are implicated in regulating learned motor elements and habits (Faure et al., 2005; Robbins, 2010). Overall the speed and vigor of behavioral readiness (as an automatic integration of previously learned elements, whether cognitive or physical), i.e. tempo, as well as time keeping, temporal perception and rhythmicity were linked to the basal ganglia including the putamen, dentate nucleus of the lateral cerebellum, and to thalamic projections to the sensorimotor cortex, superior temporal gyrus and inferior frontal gyrus (see Fuster, 2002; Harrington et al., 1998; Coull et al., 2011 for reviews).

Yin and Knowlton (2006) also described two DA cortical-striatal ‘loops’ that supervise different degrees of contextual complexity of an action: the dorsal-medial striatum aligned with the parietal and prefrontal cortex (processing general action-outcome, goal-directed learning aspects) and the dorsal-lateral striatum/putamen linked to sensorimotor cortex (regulating more sensori-motor aspects of actions, including learned stimulus-response habits). These circuits may also utilise different types of DA receptors coupled to different types of glutamate receptors in the striatum (Yin and Knowlton, 2006). In the context of addiction, Voorn et al. (2004), Everitt and Robbins (2013) described a transition of control over behavioral acts from ventral to dorsal striatum with a concomitant process of habit learning that leads to automatic behavior, that becomes dysregulated still further into compulsive behavior by additional loss of top-down PFC control. These differences in functional neuroanatomy within DA system of arousal suggest that an aspect of arousal related to a speed of integration of behavioural elements likely has several sub-types that are regulated by different brain systems.

Moreover, neurochemically speaking, cerebral cortex and striatum have significant differences in DA reuptake: extracellular DA concentrations are dominated by release in cortical DA networks and by reuptake in the striatum (Garris and Wightman, 1994). These two levels also differ in the types of DA receptors, as D1 receptors dominate prefrontal and limbic cortices, and D2 receptors are most abundant in striatum (Sealfon and Olanow, 2000). The pattern of mutual regulation between DA and NA systems and the action of dopaminergic D1 and D2 receptors in NA release also appears to differ under different intensities of stimulation and also in cortical vs. basal ganglia brain structures (see Devoto and Flore, 2007 for review), which is in line with the (suggested below) different functionality of MA systems at least two levels of behavioural regulation.

5.2.3. The role of ACh-NA networks in mental forms of endurance (sustained attention)

There are two main sources of ACh neurons: the basal forebrain/medial septal system: a basal nucleus of Meynert innervates all parts of neocortex, basolateral amygdala, the basal ganglia and the reticular nucleus of the thalamus; medial septum innervates the hippocampus; the dorsal tegmental tract in the midbrain/brain stem which mainly innervates the thalamus and has inputs to the substantia nigra/VTA (Mesulam, 2010; Woolf, 1991)

ACh is known as a key neurotransmitter in sustained attention that can be viewed as “mental endurance”. In contrast to physical endurance mentioned earlier, mental endurance relies to a high degree on the function of neocortical-forebrain networks (Everitt and Robbins, 1997; Sarter et al., 2001). Earlier suggestions of a primarily cortical control of attention were confronted with findings that ACh networks in the forebrain have no less importance in sustained attention than cortical networks (Sarter et al., 2001; Hasselmo and Sarter, 2011). At the same time sustained attention during mental activities (such as reading or proof-editing) likely requires more active involvement of neocortex than attention during physical activities, considering the unique ability of the neocotex to process abstractions.

Sustained attention differs from attention to novelty, described as a functionality of the NA system, even though both types of attention involve NA release at the cortical level (Beane and Marrocco, 2004; Everitt and Robbins, 1997; Robbins and Roberts, 2007). Sustained attention or mental endurance is required in monitoring

well-learned actions, suppression of these actions and/or waiting for special but expected events to occur in a tonic state regulated by a parasympathetic (also ACh-supervised) system.

5.2.4. Functional differences between cortical vs. subcortical 5-HT systems

The 5-HT systems also have differential projections between cortical and subcortical structures. The dorsal and median raphé ascending systems innervate distinct regions of the telencephalon; for example the dorsal system projects mainly to the neocortex (including the PFC), striatum and amygdala, whereas the median raphé system innervates preferentially the hippocampus and cingulate cortex (Azmitia, 2010; Hensler, 2006; Hornung, 2010). There are also neurochemical differences in the 5-HT system between the PFC and one of the main midbrain structures: the 5-HT regulation of the NA release in the PFC is affected by a predominance of α1A and α1D adrenoceptors, whereas the α1B receptor subtype prevails in the DR (Adell et al., 2010). 5-HT regulation of DA release is also different for the PFC (where no direct regulation of such type was found, with indirect inhibitory regulation from 5-HT2C receptors in the VTA) (Pozzi et al., 1994) and striatum and nucleus accumbens (where DA release was found to be controlled by 5-HT_{2C} receptors) (see Adell et al., 2010 for review).

Comparison of the effects of cortical and striatal 5-HT and DA depletion in non-human primates revealed differential effects in cortical and striatal regions. OFC 5-HT loss impaired reversal learning whereas OFC DA depletion mainly prolonged extinction (both being indicative of compromised behavioral plasticity) (Clarke et al., 2007; Walker et al., 2009). 5-HT depletion also impaired the choice of previously non-rewarded alternatives in extinction (Walker et al., 2009). In contrast, in the striatum, DA depletion impaired reversal learning whereas 5-HT loss had no significant effect.

Forebrain depletion of 5-HT has also been linked to premature initiation of actions, i.e. impulsivity (Dalley et al., 2011; Harrison et al., 1997; Oades, 2002; Miyazaki et al., 2012; Winstanley et al., 2005) and it is possible that this modulation occurs both at the level of the ventral striatum (Robinson et al., 2008) and in the prefrontal cortex (Winstanley et al., 2003). Thus it is likely that 5-HT, like the other MAs contributes to processing in different ways according to its neuroanatomical ramifications.

5.3. Convergence with temperament models on differentiation between traits

In previous sections we reviewed findings that MA behavioural arousal systems are specialised for at least three functional (orientational, integrative and maintenance) aspects of behaviour. We borrowed from functional models of behavior within kinesiology, clinical neuropsychology and neurophysiology. Moreover, the cortical and subcortical specificity of MA systems suggests that these three functional aspects are regulated differently in situations where there is a considerable uncertainty and in more predictable scenarios (Fig. 4A).

As noted above, the concept of temperament in differential psychology relates to neurochemically based individual differences, and therefore "comparing notes" between this line of research and neurochemistry of MA systems might be mutually beneficial, for the taxonomy of arousal systems, and for the taxonomy of consistent individual differences. After all, the concept of Extraversion was described originally as a temperament trait (Jung, 1923). A subsequent attribution of Extraversion to an action of cortical-ARAS networks described as a general arousal system was an early attempt to integrate findings within neurophysiology with taxonomy of biologically based individual differences. Therefore we now examine overlaps between main temperament/personality models proposed over the course of the past century. Due to space limitations, this comparison is summarized in Table 1 which is structured around functional aspects of behavioural arousal described in the previous sections. As seen in Table 1, several temperament models moved beyond the concept of Extraversion and differentiated between more specific consistent individual differences, in line with the structure of functional aspects of arousal independently described in other disciplines.

The convergence between main temperament models, models in kinesiology and insights into functional specialisation of MA systems within neurochemistry is best described by the neurochemical model "Functional Ensemble of Temperament" (FET) (Fig. 4B, Table 2). The FET model is based on the Structure of Temperament model based on neurophysiological studies of individual differences in the properties of nervous systems (Rusalov, 1989; Rusalov and Trofimova, 2007; Trofimova, 2010a). These models suggest that each temperament trait contributes to certain aspects of performance but nonetheless these dimensions are interdependent, reflecting an interdependence of neurochemical systems regulating human behavior.

Moreover, there is further complexity within regulatory systems that was not discussed here, but is included in FET. The explicit, routine behavioral elements appear to be regulated differently for physical vs. social-verbal activities, and such differentiation is reflected in the Structure of Temperament Questionnaire, a predecessor of the FET model (Bishop et al., 1993; Bishop and Hertenstein, 2004; Dumenci, 1995, 1996; Rusalov, 1989; Rusalov and Trofimova, 2007; Stough et al., 1991; Trofimova, 2009, 2010c). This differentiation brings three more traits: Social-Verbal Endurance (as a capacity to sustain prolonged communication), Social-Verbal Tempo (as a speed of speech and reading), and Empathy (as an orientation/reinforcement of own behavior by other people's needs, feelings and motivation) (Table 2). Social-Verbal endurance has been termed also as traits of Sociability (Buss and Plomin, 1984; Eysenck, 1995; Zuckerman and Cloninger, 1996), Extraversion (Eysenck, 1967; McCrae and Costa, 1992), Social Ergonicity (Rusalov, 1989), Affiliativeness (Derryberry and Rothbart, 1988), Affiliation (Hough, 1992), Social Activity (Taylor and Morrison, 1992) and Social-verbal Endurance (Rusalov and Trofimova, 2007; Trofimova, 2010a,b; Trofimova and Sulis, 2011).

Such differentiation could be yet another example of functional specificity in neurotransmitter systems, in the light of reports of links between oxytocin and affiliative behavior (Bielsky and Young, 2004; Depue and Collins, 1999; Depue and Morrone-Strupinsky, 2005; Donaldson and Young, 2008), and of mutual regulation between 5-HT and oxytocin systems (Keverne and Curley, 2004; Vacher et al., 2002). Links between empathy and mirror neurons (Rizzolatti et al., 1999; Grezes et al., 2003) and also the role of oxytocin in affiliative behavior provide a promising perspective for this trait. Due to the space limitations this article has not discussed neurotransmitters linked to social- verbal aspects of activities, and included only the orientational trait of Empathy in Table 1. The FET model also integrated Jung's (1923) original concept of introversion-extraversion that was not related to general arousal. Instead, Jung described differences between introverts and extraverts as contrasting types of orientation to internal vs. extrinsic, readily-available reinforcers. Findings of the role of cortical 5-HT systems in stimuli-dependent behaviour and sensitivity to event probabilities described in Section 5.2.4. converge with this theory. Subsequently two traits relating to behavioral orientation towards immediately present external reinforcers (sensational objects or other people) were described as sensation seeking (Zuckerman, 1994) and empathy (Eysenck et al., 1985). Several theories have linked sensation seeking to specific neurotransmitter systems (Gerra et al., 1999; Netter et al., 1996; Shabani

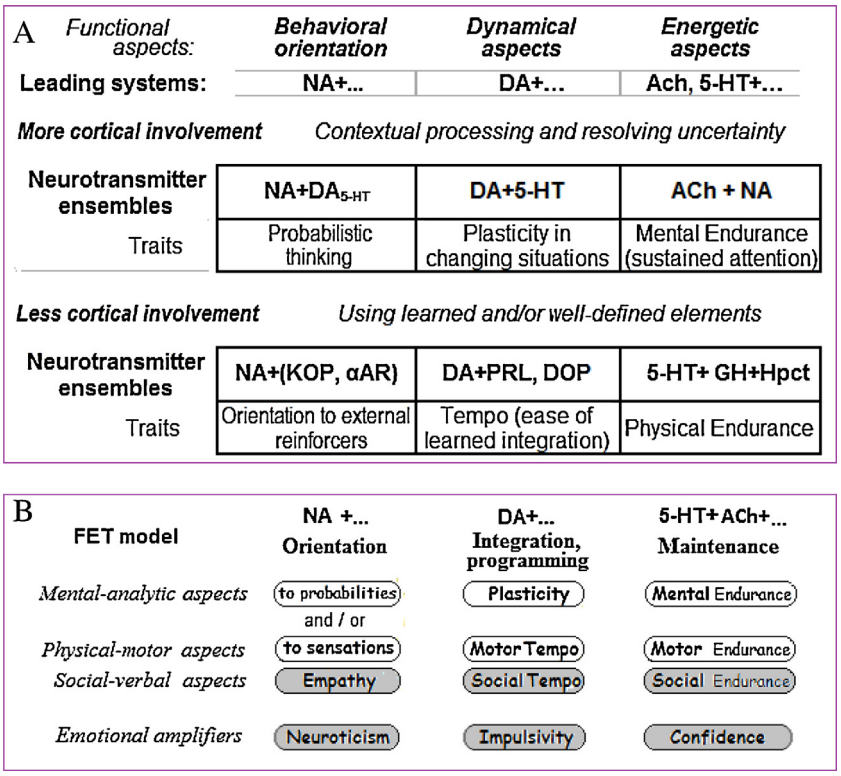

Fig. 4. **A**: Proposed differential regulation of MA and ACh systems at cortical and subcortical levels for six aspects of behavioral arousal. **B**: Convergence of specific systems regulating six differentiated aspects of arousal with six temperament traits of the FET model. The other six (shadowed) traits of the FET model are not discussed in the article (see Rusalov and Trofimova, 2007; Trofimova, 2016a).
Note: 5-HT: serotonin; DA: dopamine; NA: noradrenaline; ACh: acetylcholine; PRL: prolactin; GH: Growth Hormone; Hpct: hypocretins (orexins), DOP: delta-opioid receptors; αAR – alpha-adrenoceptors; the contribution of opioid and adrenoceptors in given traits is not discussed in this paper but is included in FET model and therefore is acknowledged in this Figure.

Table 2
Definitions of some temperament traits within Functional Ensemble of Temperament model and their hypothesized links to neurotransmitter systems. Note: 5-HT: serotonin; DA: dopamine; NA: noradrenalin; ACh: acetylcholine; PRL: prolactin; DOP: delta-opioid protein receptors.

Tempera-ment trait	Description	Hypothesized links to neurochemical systems
	Behavioral orientation traits	**NA +...**
Sensation Seeking	behavioral orientation to well-defined and existing sensational objects and events, underestimation of outcomes of risky behaviour	+ cortisol, AdrR, DA, PRL-NPY interactions
Empathy	behavioral orientation to the emotional states/needs of others (ranging from empathic deafness in autism and schizophrenia disorders to social dependency)	Possible action of OXY, MOPr interacting with the NA system
Sensitivity to Probabilities	the drive to gather information about commonality, frequency and values of events, to differentiate their specific features, to project these features in future actions	Interaction between neocortical NA, DA, 5-HT and ACh systems
	Action-integration traits	**DA +...**
Physical Tempo	speed of integration of an action in physical manipulations with objects with well-defined scripts of actions	DA-PRL, DA-GABA /Glu interaction in basal ganglia, DOPr
Social-verbal Tempo	the preferred speed of speech and ability to understand fast speech on well-known topics, reading and sorting of known verbal material	OXY and PRL under DA control, especially in dorsal striatum
Plasticity	the ability to adapt quickly to changes in situations, to change the program of action, and to shift between different tasks	DA-5-HT interaction in the cortical-basal ganglia networks
	Maintenance of activity traits	**5-HT, ACh +...**
Physical Endurance	the ability of an individual to sustain prolonged physical activity using well-defined behavioral elements	5-HT, ACh, GH-SOM, orexins
Social-verbal Endurance	sociability; the ability of an individual to sustain prolonged social-verbal activities using well-defined behavioral elements	5-HT, OXY, GH-PRL, oxerins
Mental Endurance, or Attention	the ability to stay focused on selected features of objects with suppression of behavioral reactivity to other features	Neocortical NA-ACh systems (with the lead of the NA)
	Emotional amplifier traits	**OR systems +** . . .
Neuroticism	A tendency to avoid novelty, unpredictable situations and uncertainty.	KOPr > MOPr imbalance → NA-HPA
Impulsivity	Initiation of actions based on immediate emotional reactivity	DOPr → (DA, MOPr, BDNF, CREB)
Self-Confidence	A sense of security, dominance, in high values – overconfidence with negligence to details	KOPr < MOPr → (5-HT, DA), SOM

Note: 5-HT: serotonin; DA: dopamine; NE: noradrenalin; ACh: acetylcholine; Glu: glutamate; GH: Growth Hormone; SOM: Somatostatin; PRL: prolactin; OXY: oxytocin; SubP: Substance P; NPY: Neuropeptide Y; KOPr, MOPr, DOPr: kappa-, mu- and delta-opioid receptors (OR) correspondingly; AdrR - adrenergic receptors.

et al., 2011; Zuckerman, 1994), but so far no consensus has been established.

The FET model also contains three emotionality related traits attributed to dysregulation within three opioid receptor systems: mu- (MOPr), kappa- (KOPr) and delta-opioid receptors (DOPr) (Trofimova, 2016a,). In the context of functional specialization between neurotransmitter systems discussed above it is important to note a key role of activation of opioid receptors in the release of monoamines (Bodnar, 2011; Schwarzer, 2009).

In this article we do not cover the functionality of other neurotransmitters suggested by the FET model (summarized in row 4 of Tables 1 and 2), due to limitations of space. It is important to underline, however, that MA do not solely regulate all aspects of behaviour. For example, neuropeptides play a much more crucial role than MA in deterministic aspects of behaviour such as physical endurance (Growth Hormone, orexins) or behavioral shifts (prolactin-dopamine interaction, see Freeman et al. (2000) for review). The amino-acid neurotransmitters glutamate and GABA, provide fast excitatory or inhibitory transmission in local network circuits, as well as distal communication between nodes in distributed neural networks, including top-down regulation of the MAs (Amat et al., 2005; Kaneko et al., 1990; Sulzer et al., 1998).

6. Generalized effect of arousal related to basic needs likely reflects their priorities for behavioral regulation

We described several functional aspects of arousal that are regulated by specific neurochemical systems. Behavioral arousal associated with basic needs (i.e. hunger, sex or safety) has a generalized nature and modifies a wide spectrum of behavior (from perception, cognition to physical state). Such generalized effects of a basic-needs system were for a long time an argument in favour of the concept of general arousal (Jing et al., 2009; Pfaff, 2006; Pfaff et al., 2008).

Indeed, it is easy to be confused about the generality of basic-needs arousing systems when individuals feel that these needs overwhelm their cognitive functions and dominate their behavior. Such generalized effects of hunger or other biological urges might, however, reflect a priority of basic-needs systems over fine-tuning of behavior in animals' life but not an existence of non-specific general arousal system. Behavioral priorities usually determine how much cognitive and physical resources should be recruited to attain these priorities, and such resource allocation is universal across tasks—whether we are referring to foraging for food, sex, safety or giving an important talk at a large gathering. Since humans can control hunger, fear and sex urges and perform complex activities, with assistance from their cortical capacities, such control suggests that arousal systems related to basic needs do not differ from control over other tasks. In fact, even basic-needs activation requires regulation in terms of orientation, prioritization-initiation of actions and their tonic energizing, i.e. those specific functional aspects of arousal described above.

7. Concluding summary

Common sense assumes that in order to conduct voluntary behavior an individual should be at least awake. This reasonable assumption does not mean, however, that behavior can be regulated in such general awake state without specific mechanisms helping to reduce and select behavioral alternatives. After all, even the most elementary action can be performed in many ways, and behavioral regulatory systems determine which way it will be performed on future occasions. Initially the Ascending Reticular Activating System was viewed as the neural basis of general arousal. Recent research has also discovered a hypothalamic orexin system that regulates wakefulness/sleep states as well as metabolism, and projects to many brain structures, including monoaminergic components of the ARAS. The "general arousal" concept was quickly adopted in differential psychology as a neural system a temperament/personality trait of Extraversion. In summary, for this review:

- We briefly reviewed evidence contradicting the idea that there is one general arousal system. Functional heterogeneity has been found even within the orexin system regulating basic wakefulness, and therefore even this system cannot be viewed as a uni-dimensional system that "energises" or drives behavior. If, however, there were many, and not one system of arousal, a question arose how we can classify functionality of these specific arousal systems.
- Attempts to classify arousal systems are confronted with the enormous functional diversity and complexity of neurotransmitter systems contributing to behavioural arousal. We suggested applying a multi-disciplinary framework in the theoretical partitioning of arousal, borrowing knowledge from boundary disciplines which study a functional structure of behaviour.
- The proposed framework is based on the conjecture that arousal systems developed in evolution in correspondence with the structure of human tasks and activities, and that our reasoning about functionality of neurochemical and temperament systems should include considerations of contingencies, dynamical and probabilistic properties of human behaviour that were missing in traditional behaviouristic accounts. We therefore looked next at the most convergent and well-known points in kinesiology, neurophysiology and clinical neuropsychology distinguishing main functional aspects of activities. Despite differences in models and in methodology, we found that these models converged on a differentiation between three aspects of behavioural regulation related to expansion (often called 'orientation'), integration (often called "programming") and maintenance of behavioural alternatives (often viewed as an energetic component of behaviour).
- We briefly reviewed the most commonly described functionality of monoamine systems, finding similar functional differentiation within these systems. We saw that a consistent functionality of the NA system relates to attention to novelty, i.e. to the expansion of behavioral alternatives (defined in early models as the "orientation" component of behavior). The functionality of the mesenecephalic-cortical DA systems relates to the prioritization of behavioral alternatives necessary for the integration of an act. Finally, there is an aspect of arousal related to plastic maintenance of repertoire of beneficial behavioral alternatives – the function that is hypothetically regulated by 5-HT systems.
- Moreover, in line with models from kinesiology and findings in neurophysiology, MA and ACh systems appeared to have different arousal systems regulating automatic, well-learned, and probabilistic and/or novel aspects of actions at different levels of processing, e.g. at cortical vs sub-cortical sites. As these aspects are present simultaneously in each action, they are co-regulated by the MA systems in an ensemble-like dynamics using co-localization of receptors, common mediators and other mechanisms making them contingent upon one another's release.
- In the context of the focus of this paper primarily on the role of neurotransmitter systems, the most relevant concept in differential psychology related to neurochemically based individual differences is "temperament", originally conceived as the regulation of human behavior by imbalances within chemical systems of the body. Differentiation between traits offered within temperament research have arrived at similar partitions of aspects of arousal and regulatory systems of behavior that was described in functional neurochemistry.

We therefore reveal a mismatch between the findings in neuroscience in regards to functional specialization of neurochemical regulatory systems and idea of existence of a general arousal system upon which a widely used concept of Extraversion is based. The complexities of the systems regulating specific forms of arousal emphasise the view that a general theory of arousal is no longer suitable for trait psychology. What is needed is an integrative theory that maps the complexities of arousal systems onto a comparable complexity of functional aspects of behavior that are subject to individual variation.

This article did not cover specific functions of all brain neurotransmitters, but focused on MA systems. We also did not review a massive body of research related to emotional regulation and impulsivity, and differentiation between social-verbal and physical aspects of behavioral regulation, reflected in a number of temperament models. These are the topics for future reviews. The present review is also merely a beginning in terms of providing a new platform for analysing temperament and traits in a neurobiologically informed manner. Other than considering some of the additional systems including opioids and neuropeptides, the next steps will be to (i) clarify the relevant dimensions in the light of likely new complexities in understanding the dynamics and interactions of relevant neurotransmitter systems (ii) begin a detailed study of individual differences, including genetic associations in the context of an integrated model of temperament such as FET and (iii) consider possible clinical implications.

Hypotheses and predictions of the position expressed in this article can be used in studies of relationships between neurochemical imbalances within MA systems and temperament traits described within the FET model (depicted in Fig. 4B and Table 2). In order to test this hypothesis, studies of the functional specificity of MA systems could employ the Structure of Temperament Questionnaire-Compact (STQ-77) that is based on the FET model and validated with multiple measures (Rusalov and Trofimova, 2007; Trofimova, 2010a,b; Trofimova and Sulis, 2011). The STQ can be used to form experimental groups contrasted by temperament profiles of participants who have (either induced or natural) differences in their MA release, measured potentially using PET. Examples of potential applications of these predictions to human psychological research and psychopathology relate to: (1) the new classification of psychiatric disorders based on functional aspects of arousal described within the FET model, as a contribution to the NIH initiative on Research Domain Criteria (Insel, 2014; Trofimova and Sulis,2016a,b); (2) new insights for research in psychopharmacology, and (3) mapping temperamental profiles associated with dispositions to specific psychiatric disorders.

References

Adell, A., Bortolozzi, A., Díaz-Mataix, L., Santana, N., Celada, P., Artigas, F., 2010. Serotonin interaction with other transmitter systems. In: Muller, C., Jacobs, B. (Eds.), Handbook of Behavioral Neurobiology of Serotonin. Elsevier Academic Press, NY.

Akiskal, H.S., 1998. Toward a definition of generalized anxiety disorder as an anxious temperament type. Acta Psychiatrica Scand. 98, 393.

Alexandre, C., Andermann, M.L., Scammell, T.E., 2013. Control of arousal by the orexin neurons. Curr. Opin. Neurobiol. 23, 1–8, http://dx.doi.org/10.1016/j.conb.2013.04.008.

Alberto, C.O., Trask, R.B., Quinlan, M.E., Hirasawa, M., 2006. Bidirectional dopaminergic modulation of excitatory synaptic transmission in orexin neurons. J. Neurosci. 26, 10043–10050.

Amat, J., Baratta, M.V., Paul, E., Bland, S.T., Watkins, L.R., Maier, S.F., 2005. Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. Nat. Neurosci. 8, 365–371, http://dx.doi.org/10.1038/nn1399.

Anderson, K.J., 1990. Arousal and the inverted-U hypothesis: a critique of Neiss' Reconceptualizing arousal. Psychol. Bull. 107, 96–100.

Anisman, H., Zalcman, S., Zacharko, R., 1993. The impact of stressors on immune and central neurotransmitter activity: bidirectional communication. Rev. Neurosci. 4, 147–180.

Anokhin, P.K., 1964. Systemogenesis as a general regulator of brain development. In: Himwich, W.A., Himwich, H.E. (Eds.), The Developing Brain. Elsevier, Amsterdam, pp. 54–86.

Anokhin, P., 1975. Biology and Neurology of the Conditioned Reflex. University Press, Oxford, UK.

Antzoulatos, E.G., Miller, E.K., 2011. Differences between neural activity in prefrontal cortex and striatum during learning of novel abstract categories. Neuron 71 (2), 243–249.

Arnsten, A.F., 1997. Catecholamine regulation of the prefrontal cortex. J. Psychopharmacol. 11 (2), 151–162.

Aston-Jones, G., Cohen, J.D., 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu. Rev. Neurosci. 28, 403–450.

Aston-Jones, G., Rajkowski, J., Cohen, J., 2000. Locus coeruleus and regulation of behavioral flexibility and attention. Prog. Brain Res. 126, 165–182.

Azmitia, E., 2010. Evolution of seroton: sunlight to suicide. In: Muller, C., Jacobs, B. (Eds.), Handbook of Behavioral Neurobiology of Serotonin. Elsevier Academic Press, NY.

Bari, A., Robbins, T.W., 2013. Inhibition and impulsivity: behavioral and neural basis of response control. Prog. Neurobiol. 108, 44–79.

Baruch, I., Hemsley, D.R., Gray, J.A., 1988. Latent inhibition and psychotic proneness in normal subjects. Person. Indiv. Diff. 9, 777–783.

Beane, M., Marrocco, R.T., 2004. Norepinephrine and acetylcholine mediation of the components of reflexive attention: implications for attention deficit disorders. Prog. Neurobiol. 74 (3), 167–181.

Bernstein, N.A., 1947. O postroenii dvijeniy [On the Construction of Motions]. Gosizdat, Medic-State Publish. House, Moscow.

Bernstein, N.A., 1996. Dexterity and its development. In: Latash, M.L., Turvey, M.T. (Eds.), Dexterity and Its Development. LEA, Hillsdale, New Jersey, pp. 3–244.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84.

Berridge, K.C., 2007. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacol. (Berl.) 191, 391–431.

Bielsky, I.F., Young, L.J., 2004. Oxytocin, vasopressin, and social recognition in mammals. Peptides 25, 1565–1574.

Bishop, D., Jacks, H., Tandy, S.B., 1993. Structure of temperament questionnaire (STQ): results from a U.S. sample. Person. Indiv. Diff. 14 (3), 485–487.

Bishop, D.I., Hertenstein, M.J., 2004. A confirmatory factor analysis of the structure of the temperament questionnaire. Educ. Psychol. Measure. 64 (6), 1019–1029.

Bloom, F.E., 1985. Neurotransmitter diversity and its functional significance. J. R. Soc. Med. 78, 189–192.

Bodnar, R.J., 2011. Endogenous opiates and behavior: 2010. Peptides 32, 2522–2552.

Borgatta, E.F., 1964. The structure of personality characteristics. Behav. Sci. 12, 8–17.

Broadbent, D.E., 1971. Decision and Stress. Academic Press.

Brokaw, J.J., Hansen, J.T., 1987. Evidence that dopamine regulates norepinephrine synthesis in the rat superior cervical ganglion during hypoxic stress. J. Autonom. Nerv. Syst. 18 (3), 185–193.

Brown, V.J., Robbins, T.W., 1991. Simple and choice reaction time performance following unilateratal striatal dopamine depletion in the rat: impaired motor readiness but preserved response preparation. Brain 114, 513–525.

Burdakov, D., Karnani, M.M., Gonzalez, A., 2013. Lateral hypothalamus as a sensor-regulator in respiratory and metabolic control. Psychol. Behav. 121, 117–124.

Buss, A., Plomin, R., 1984. Temperament: Early Developing Personality Trait. Erlbaum, Hillsdale.

Carver, C.S., White, T.L., 1994. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. J. Pers. Soc. Psychol. 67, 319–333.

Cattell, R.B., 1965. The Scientific Analysis of Personality. Penguin, London.

Chamberlain, S., Robbins, T.W., 2013. Noradrenergic modulation of cognition: therapeutic implications. J. Psychopharmacol. 27 (8), 694–718.

Clarke, H.F., Walker, S.C., Dalley, J.W., Robbins, T.W., Roberts, A.C., 2007. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cereb. Cortex 17 (1), 18–27.

Cloninger, C.R., 2000. Biology of personality dimensions. Curr. Opin. Psychiatry 13, 611–616.

Cooper, J.R., Bloom, F.E., Roth, R., 2003. The Biochemical Basis of Neuropharmacology. OUP, New York.

Corr, P.J., 1999. Does extraversion predict positive incentive motivation? Behav. Brain Sci. 22, 520–521.

Corr, P.J., 2002. J. A. Gray's reinforcement sensitivity theory and frustrative nonreward: a theoretical note on expectancies in reactions to rewarding stimuli. Person. Indiv. Diff. 32, 1247–1253.

Corr, P.J., Kumari, V., 2000. Individual differences in mood reactions to d-amphetamine: a test of three personality factors? J. Psychopharmacol. 14 (4), 371–376.

Costa, R.M., Lin, S.C., Sotnikova, T.D., et al., 2006. Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction. Neuron 52, 359–369.

Coull, J.T., Cheng, R.K., Mack, W., 2011. Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacology 36, 3–25.

Coyle, J.T., 2006. The neurochemistry of schizophrenia. In: Siegel, G.J., Albers, R.W., Brady, S.T., Price, D.L. (Eds.), Basic Neurochemistry. Elsevier, USA, pp. 875–885.

Dalley, J.W., Everitt, B.J., Robbins, T.W., 2011. Impulsivity, compulsivity, and top-down cognitive control. Neuron 69, 680–694.
Darracq, L., Blanc, G., Glowinski, J., Tassin, J.P., 1998. Importance of the noradrenaline-dopamine coupling in the locomotor activating effects of D-amphetamine. J. Neurosci. 18, 2729–2739.
de Lecea, L., Kildu, T.S., Peyron, C., Gao, X., Foye, P.E., Danielson, PE, et al., 1998. The Hypocretins: Hypothalamus-specific Peptides with Neuroexcitatory Activity, 95. PNAS, USA, pp. 322–327.
Delfs, J.M., Zhu, Y., Druhan, J.P., Aston-Jones, G.S., 1998. Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res. 806, 127–140.
Denys, D., Zohar, J., Westenberg, H.G., 2004. The role of dopamine in obsessive–compulsive disorder:preclinical and clinical evidence. J. Clin. Psychiatry 65 (Suppl. 14), 11–17.
Depue, R.A., Collins, P.F., 1999. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav. Brain Sci. 22, 491–517.
Depue, R., Morrone-Strupinsky, J., 2005. Neurobehavioral foundation of affiliative bonding:Implications for a human trait of affiliation? Behav. Brain Sci. 28 (3), 313–350.
Derryberry, D., Rothbart, M.K., 1988. Arousal, affect, and attention as components of temperament. J. Pers. Soc. Psychol. 55, 958–966.
Devoto, P., Flore, G., 2007. Dopamine and noradrenaline coupling in the cerebral cortex. In: Tseng, K.Y., Atzori, M. (Eds.), Monoaminergic Modulation of Cortical Excitability. Springer Science & Business Media, pp. 189–197.
Devoto, P., Flore, G., Longu, G., Pira, L., Gessa, G.L., 2003. Origin of extracellular dopamine from dopamine and noradrenaline neurons in the medial prefrontal and occipital cortex. Synapse 50, 200–205.
Di Matteo, V., Di Giovanni, G., Pierucci, M., Esposito, E., 2008. Serotonin control of central dopaminergic function:focus on in vivo microdialysis studies. Prog. Brain Res. 172, 7–44.
Dienstbier, R.A., 1984. The role of emotion in moral socialization. In: Izard, C., Kagan, J., Zajonc, R.B. (Eds.), Emotions, Cognitions, and Behaviour. Cambridge University Press, MA, pp. 484–514.
Digman, J.M., Takemoto-Chock, N.K., 1981. Factors in a natural language of personality: reanalysis, comparison and interpretation of six major studies. Multivar. Behav. Res. 16, 149–170.
Doll, B.B., Duncan, K.D., Simon, D.A., Shohamy, D., Daw, N.D., 2015. Model-based choices involve prospective neural activity. Nat. Neurosci. 18, 767–772.
Donaldson, Z.R., Young, L.J., 2008. Oxytocin, vasopressin, and the neurogenetics of sociality. Science 322, 900–904.
Dumenci, L., 1995. The relation between the structure of temperament questionnaire and other personality domains. Educ. Psychol. Measure. 55 (5), 850–857.
Dumenci, L., 1996. Factorial validity of scores on the structure of temperament questionnaire. Educ. Psychol. Measur. 56, 487–493.
Durstewitz, D., Seamans, J.K., 2006. Beyond bistability: biophysics and temporal dynamics of working memory. Neuroscience 139 (1), 119–133.
Eisenegger, C., Naef, M., Linssen, A., Clark, L., Gandamaneni, P.K., Müller, U., Robbins, T.W., 2014. Role of dopamine D2 receptors in human reinforcement learning. Neuropsychopharmacology 39 (10), 2366–2375.
Everitt, B.J., Robbins, T.W., 1997. Central cholinergic systems and cognition. Annu. Rev. Psychol. 48, 649–684.
Everitt, B.J., Robbins, T.W., 2013. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci. Biobehav. Rev. 37 (9A), 1946–1954.
Everitt, B.J., Robbins, T.W., Gaskin, M., Fray, P.J., 1983. The effects of lesions to ascending noradrenergic neurons on discrimination learning and performance in the rat. Neuroscience 10, 397–410.
Eysenck, H.J., 1967. The Biological Basis of Personality. Springfield, III.
Eysenck, H.J., 1983. Psychophysiology and personality: extraversion, neuroticism, and psychoticism. In: Gale, A., Edwards, J.A. (Eds.), Physiological Correlates of Human Behaviour: Individual Differences and Psychopathology. Academic Press, London, pp. 13–30.
Eysenck, H.J., 1992. Four ways five factors are not basic. Person. Indiv. Differ. 13, 667–673.
Eysenck, H.J., 1995. The Eysenck Personality Profiler (EPP) and Eysenck's Theory of Personality. Corporate Assessment Network, London.
Eysenck, S.B.G., Pearson, P.R., Easting, G., Allsopp, J.F., 1985. Age norms for impulsiveness, venturesomeness and empathy in adults. Person. Indiv. Differ. 6, 613–619.
Fahrenberg, J., 1991. Differential psychophysiology and the diagnosis of temperament. In: Strelau, J., Angleitner, A. (Eds.), Explorations in Temperament: International Perspectives on Theory and Measurement. Plenum, London, pp. 317–333.
Faure, A., Haberland, U., Condé, F., Massioui, N.E., 2005. Lesion to the nigrostriatal dopamine system disrupts stimulus-response habit formation. J. Neurosci. 25 (11), 2771–2780, http://dx.doi.org/10.1523/JNEUROSCI.3894-04.2005.
Fink, K.B., Göthert, M., 2008. 5-HT receptor regulation of neurotransmitter release. Pharmacol. Rev. 60 (1), 142–170.
Floresco, S.B., Magyar, O., 2006. Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology (Berl.) 188, 567–585, http://dx.doi.org/10.1007/s00213-006-0404-5.
Freeman, M.E., Kanyicska, B., Lerant, A., Nagy, G., 2000. Prolactin: structure, function, and regulation of secretion. Physiol. Rev. 80 (4), 1523–1631.
Fuster, J.M., 2002. Prefrontal cortex in temporal organization of action. In: Arbib, M.A. (Ed.), The Handbook of Brain Theory and Neural Networks. , 2nd ed. The MIT Press, pp. 905–910.
Garris, P.A., Wightman, R.M., 1994. Different kinetics governs dopaminergic transmission in the amygdale, prefrontal cortex, and striatum: an in vivo voltammetric study. J. Neurosci. 14, 442–450.
Gerra, G., Avanzini, P., Zaimovic, et al., 1999. Neurotransmitters, neuroendocrine correlates of sensation-seeking temperament in normal humans. Neuropsychobiology 39, 207–213.
Gibbs, S.E., D'Esposito, M., Coull, J.T., Frith, C.D., Dolan, R.J., Frackowiak, R.S., Grasby, P.M., 1997. The neural correlates of the noradrenergic modulation of human attention, arousal and learning. Eur. J. Neurosci. 9, 589–598.
Goldberg, L.R., 1993. The structure of phenotypic personality traits. Am. Psychol. 48, 26–34.
Gotter, A.L., Webber, A.L., Coleman, P.J., Renger, J.J., Winrow, C.J., 2012. International union of basic and clinical pharmacology LXXXVI. Orexin receptor function, nomenclature and pharmacology. Pharmacol. Rev. 64, 389–420, http://dx.doi.org/10.1124/pr.111.005546.
Gozzi, A., Turrini, G., Piccoli, L., Massagrande, M., Amantini, D., Antolini, M., et al., 2011. Functional magnetic resonance imaging reveals different neural substrates for the effects of orexin-1 and orexin-2 receptor antagonists. PLoS One 6, e16406, http://dx.doi.org/10.1371/journal.pone.0016406.
Grace, A.A., Floresco, S.B., Goto, Y., Lodge, D.J., 2007. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci. 30, 220–227.
Gray, J.A., 1982. The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System. Oxford University Press, Oxford.
Gray, J.A., 1991. Neurophysiology of temperament. In: Strelau, J., Angleitner, A. (Eds.), Explorations in Temperament. Plenum, New York, pp. 105–128.
Gray, J.A., 1998. Integrating schizophrenia. Schizophr. Bull. 24, 249–266.
Grenhoff, J., Nisell, M., Ferre, S., Aston-Jones, G., Svensson, T.H., 1993. Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat. J. Neural Trans. Gen. Sect. 93 (1), 11–25.
Grezes, J., Armony, J.L., Rowe, J., Passingham, R.E., 2003. Activations related to mirror and canonical neurones in the human brain:an fMRI study. Neuroimage 18, 928–937.
Grossberg, S., 1987. The Adaptive Brain, 1: Cognition, Learning, Reinforcement, Rhyrhm. Elsevier, Amsterdam.
Guilford, J.P., 1975. Factors and factors of personality. Psychol. Bull. 82, 802–814.
Halgren, E., Marinkovic, K., 1995. Neurophysiological networks integrating human emotions. In: Gazzaniga, M. (Ed.), The Cognitive Neurosciences. MIT Press, Cambridge, MA, pp. 1137–1152.
Harrington, D.L., Haaland, K.Y., Hermanowicz, N., 1998. Temporal processing in the basal ganglia. Neuropsychology 12, 3–12.
Harris, G.C., Aston-Jones, G., 2006. Arousal and reward: a dichotomy in orexin function. Trends Neurosci. 29, 571–577, http://dx.doi.org/10.1016/j.tins.2006.08.002.
Harrison, A.A., Everitt, B.J., Robbins, T.W., 1997. Central 5-HT depletion enhances impulsive responding without affecting the accuracy of attentional performance: interactions with dopaminergic mechanisms. Psychopharmacology (Berl.) 133, 329–342.
Hasselmo, M., Sarter, M., 2011. Modes and models of forebrain cholinergic neuromodualtion of cognition. Neuropsychopharmacol. Rev. 36, 52–73.
Hebb, D.O., 1961. The Organization of Behavior, a Neuro-psychological Theory. Wiley & Sons, NY.
Helmsley, D.R., 1987. An experimental psychological model for schizophrenia. In: Häffner, H., Fattaz, W.F., Janzavik, W.V.S. (Eds.), Search for the Causes of Schizophrenia. Springer-Verlag, Stuttgart, Germany, pp. 179–188.
Hensler, J.G., 2006. Serotonin. In: Siegel, G.J., Albers, R.W., Brady, S.T., Price, D.L. (Eds.), Basic Neurochemistry. USA, Elsevier, pp. 227–248.
Heymans, G., 1929. Inleiding tot de speciale psychologie. De Erven F. Bohn, Haarlem.
Holz, R.W. & Fisher S.K. (2006) Synaptic transmission and cellular signalling: an overview. In: Siegel, G.J., Albers, R.W., Brady, S.T., & Price, D.L. (eds.) Basic Neurochemistry, 7th edition, pp. 167–183.
Hornung, J.P., 2010. The Neuroanatomy of the Serotonergic System. In: Muller, C., Jacobs, B. (Eds.), Handbook of Behavioral Neurobiology of Serotonin. Elsevier Academic Press, NY.
Horvitz, J.C., 2000. Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience 96, 651–656.
Hough, L., 1992. The Big Five Personality variables—Construct Confusion: Description Versus Prediction. Human Performance 5 (1 & 2), 139–155.
Humphreys, M.S., Revelle, W., 1984. Personality, motivation, and performance: a theory of the relationship between individual differences and information processing. Psychol. Rev. 91, 153–184.
Hungs, M., Mignot, E., 2001. Hypocretin/orexin, sleep and narcolepsy. Bioessays 23, 394–397.
Insel, T.R., 2014. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. Am. J. Psychiatry 171 (4), 395–397, http://dx.doi.org/10.1176/appi.ajp.2014.14020138.
Jacobs, B.L., 1987. Brain monoaminergic activity in behaving animals. Progress in Psychobiological and Physiological Psychology 12, 171–206.
Jacobs, B.L., 1992. Physiological analyses of the afferents controlling brain neurochemical systems. Princeton University, NJ.
Jacobs, B.L., Fornal, C.A., 2010. Activity of brain serotonergic neurons in relation to physiology and behavior. In: Muller, C., Jacobs, B. (Eds.), Handbook of

Behavioral Neurobiology of Serotonin. Elsevier Academic Press, NY, pp. 153–162.
Jing, J., Gillette, R., Weiss, K.R., 2009. Evolving concepts of arousal: insights from simple model systems. Rev. Neurosci. 20 (5–6), 405–427.
Joel, D., Weiner, I., 2000. Striatal contention scheduling and the split circuit scheme of basalganglia-thalamocortical circuitry:From anatomy to behavior. In: Miller, R., Wickens, J.R. (Eds.), Conceptual advances in brain research:Brain dynamics and the striatal complex. Harwood Academic Publishers.
Jung, C.G., 1923. Psychological Types. Harcourt Brace, New York.
Kagan, J., Snidman, N., 2009. The Long Shadow of Temperament. Harward University Press, MA.
Kahneman, D., 1973. Attention and effort. Prentice-Hall, Englewood Cliffs, New Jersey.
Kaneko, T., Akiyama, H., Nagatsu, I., Mizuno, N., 1990. Immunohistochemical demonstration of glutaminase in catecholaminergic and serotoninergic neurons of rat brain. Brain Res. 507, 151–154.
Kant, I. (1798) Anthropology from a pragmatic point of view (trans. Mary Gregor). The Hague: Martinus Nijhoff, 1974 (Ak. VII).
Kapur, S., 2003. Psychosis as a state of aberrant salience: a framework linking biology, phneonmenology and pharmacology in schizophrnia. Am. J. Psychiatry 160, 13–23.
Kehagia, A.A., Murray, G.K., Robbins, T.W., 2010. Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. Curr. Opin. Neurobiol. 20 (2), 199–204.
Kerkhof, G.A., 1985. Inter-individual differences in the human circadian system:a review. Biol. Psychol. 20 (2), 83–112.
Keverne, E.B., Curley, J.P., 2004. Vasopressin, oxytocin, and social behaviour. Curr. Opin. Neurobiol. 14, 777–783.
Koo, M.S., Kim, E.J., Roh, D., Kim, C.H., 2010. Role of dopamine in the pathophysiology and treatment of obsessive-compulsive disorder. Expert Review in Neurotherapeutics 10 (2), 275–290.
Kretschmer, E., 1925. Physique and Character: an investigation of the nature of constitution and of the theory of temperament. Trans. W.J.H. Sprott. New York: Harcourt Brace.
Kuhar, M.J., Minneman, K., Muly, E.C. (2006) Catecholamines, In: Siegel, G.J., Albers, R.W., Brady, S.T., & Price, D.L. (eds.) Basic Neurochemistry, 7th edition. pp. 211-226.
Kumari, V., Toone, B., Gray, J.A., 1997. Habituation and prepulse inhibition of the acoustic startle reflex: Effects of smoking status and psychosis-proneness. Personality and Individual Differences 23, 183–191.
Lamiell, J.T., 2003. Beyond individual and group differences:human individuality, scientific psychology, and William Stern's critical personalism. Sage, Thousand Oaks, CA.
Lazursky, A., 1921. Classifikacia lichnostey (Classification of personalities). Peterburg, Russia.
Levin, H.S., Eisenberg, H.M., Benton, A.L. (Eds.), 1991. Oxford University Press, New York.
Levitt, P., Rakic, P., Goldman-Rakic, P., 1984. Region-specific distribution of catecholamine afferents in primate cerebral cortex: a fluorescence histochemical analysis. J. Comp. Neurol. 227 (1), 23–36.
Liguori, A., Grass, J.A., Hughes, J.R., 1999. Subjective effects of caffeine among introverts and extraverts in the morning and evening. Experimental Clinical Psychopharmacology 7 (3), 244–249.
Lindsley, D.B. Emotion. In: S.S. Stevens, 1951. Handbook of Experimental Psychology. John Wiley and Sons, NY.
Linner, L., Endersz, H., Ohman, D., Bengtsson, F., Schalling, M., Svensson, T.H., 2001. Reboxetine modulates the firing pattern of dopamine cells in the ventral tegmental area and selectively increases dopamine availability in the prefrontal cortex. J. Pharmacol. Exp. Ther. 297, 540–546.
Liu, R.J., van den Pol, A.N., Aghajanian, G.K., 2002. Hypocretins (orexins) regulate serotonin neurons in the dorsal raphe nucleus by excitatory direct and inhibitory indirect actions. J. Neurosci 22, 9453–9464.
Logan, G.D., 1988. Toward an Instance Theory of Automatization. Psychol. Rev. 95 (4), 492–527.
Lundin, R.W., 1989. Alfred-Adler's basic concepts and implications. Taylor and Francis.
Luria, A.R., 1966. Higher cortical functions in man. Basic Books, New York.
Mains, R.E. & Eipper, B.E., 2006. Peptides. In: Siegel, G.J., Albers, R.W., Brady, S.T., & Price, D.L. (eds.) Basic Neurochemistry, 7th edition, pp. 317-332.
Marcus, J.N., Aschkenasi, C.J., Lee, C.E., Chemelli, R.M., Saper, C.B., Yanagisawa, M., Elmquist, J.K., 2001. Differential expression of orexin receptors 1 and 2 in the rat brain. J. Comp. Neurol. 435, 6–25.
Matsumoto, M., Yoshioka, M., Togashi, H., Ikeda, T., Saito, H., 1996. Functional regulation by dopamine receptors of serotonin release from the rat hippocampus: in vivo microdialysis study. Naunyn Schmiedebergs Archives in Pharmacology. 353 (6), 621–629.
Matthews, G., Amelang, M., 1993. Extraversion, arousal theory and performance: A study of individual differences in the EEG. Pers. Individ. Diff. 14 (2), 347–363.
Matthews, G., Gilliland, K., 1999. The personality theories of H.J. Eysenck & J.A. Gray:a comparative review. Pers. Individ. Diff. 26 (4), 583–626.
McCarley, R.W., Massaquoi, S.G., 1992. Neurobiological structure of the revised limit cycle reciprocal interaction model of REM sleep cycle control. J. Sleep Res. 1, 132–137.
McClure, S.M., Gilzenrat, M.S., Cohen, J.D., 2005. An exploration-exploitation model based on norepinephrine and dopamine activity. Advances in Neural Information Processing Systems 18, 867–874.
McCrae, R.R., Costa Jr., P.T., 1997. Personality trait structure as a human universal. Am. Psychol. 52, 509–516.
Mehrabian, A., 1996. Pleasure-arousal-dominance:A general framework for describing and measuring individual differences in temperament. Curr. Psychol. 14, 261–292.
Mesulam, M.M., 2010. Acetylcholine Neurotransmission in CNS. Encycl. Neurosci., 1–4.
Mignot, E., 2001. A commentary on the neurobiology of the hypocretin/orexin system. Neuropsychopharmacology 25, S5–S13, http://dx.doi.org/10.1016/S0893-133X(01)00316-5.
Mileykovskiy, B.Y., Kiyashchenko, L.I., Siegel, J.M., 2005. Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 46, 787–798, http://dx.doi.org/10.1016/j.neuron.2005.04.035.
Mitchell, H.A., Weinshenker, D., 2010. Good night and good luck: norepinephrine in sleep pharmacology. Biochem. Pharmacol. 79 (6), 801–809.
Jacobs, B.L., Azmitia, E.C., 1992. Structure and functions of the brain serotonin system. Physiol. Rev. 72, 165–229.
Miyazaki, K., Miyazaki, K.W., Doya, K., 2012. The role of serotonin in the regulation of patience and impulsivity. Mol. Neurobiol. 45 (2), 213–224.
Moron, J.A., Brockington, A., Wise, R.A., Rocha, B.A., Hope, B.T., 2002. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J. Neurosci 22, 389–395.
Moruzzi, G., Magoun, H.W., 1949. Brain stem reticular formation and activation of the EEG. Electroencephalogr. Clin. Neurophysiol. 1, 455–473.
Muraki, Y., Yamanaka, A., Tsujino, N., Kilduff, T.S., Goto, K., Sakurai, T., 2004. Serotonergic regulation of the orexin/hypocretin neurons through the 5-HT1A receptor. J. Neurosci. 24 (32), 7159–7166.
Nakamura, T., Uramura, K., Nambu, T., Yada, T., Goto, K., Yanagisawa, M., Sakurai, T., 2000. Orexin-induced hyperlocomotion and stereotypy are mediated by the dopaminergic system. Brain Res. 873, 181–187.
Nebylitsyn, V.D., 1972. Fundamental Properties of the Human Nervous System. Plenum, New York.
Newman, J.P., Widom, C.S., Nathan, S., 1985. Passive avoidance in syndromes of disinhibition: psychopathy and extraversion. J. Pers. Soc. Psychol. 48, 1316–1327.
Netter, P., Hennig, J., Roed, I., 1996. Serotonin and dopamine as mediators of sensation seeking behavior. Neuropsychobiology 34, 155–165.
Norman, W.T., 1963. Toward an adequate taxonomy of personality attributes; Replicated factor structure in peer nomination personality ratings. J. Abnorm. Soc. Psychol. 66, 574–583.
Oades, R.D., 1985. The role of noradrenaine in tuning and dopamine in switching between signals in the CNS. Neurosci. Biobehav. Rev. 9, 261–282.
Oades, R.D., 2002. Dopamine may be 'hyper' with respect to noradrenaline metabolism, but 'hypo' with respect to serotonin metabolism in children with ADHD. Behav. Brain Res. 130, 97–102.
Oades, R.D., Zimmermann, B., Eggers, C., 1996. Conditioned blocking in patients with paranoid, nonparanoid psychosis or obsessive compulsive disorder: Association with symptoms, personality and monoamine metabolism. J. Psychiatr. Res. 30, 369–390.
O'Gorman, J.G., Lloyd, J.E.M., 1987. Extraversion, impulsiveness and EEG alpha activity. Pers. Individ. Diff. 8, 169–174.
Paladini, C.A., Williams, J.T., 2004. Noradrenergic inhibition of midbrain dopamine neurons. J. Neurosci 24 (19), 4568–4575.
Panksepp, J., Normansell, L.A., Cox, J.F., Crepeau, L., Sacks, D.S., 1987. Psychopharmacology of social play. In: Olivier, B., Mos, J., Brain, P.F. (Eds.), Ethnopharmacology of social behaviour. Martinus Nijhoff.
Patterson, C.M., Kosson, D.S., Newman, J.P., 1987. Reaction to punishment, reflectivity, and passive avoidance learning in extraverts. J. Pers. Soc. Psychol. 52, 565–575.
Pavlov, I.P., 1928. Lectures on conditioned reflexes, II. Types of the higher nervous activity, their interdependence with neuroses and psychoses and the physiological mechanism of neurotic and psychotic symptoms. Translated by W.H. Gantt. New York: International Publishers.
Pavlov, I.P., 1941. Lectures on conditioned reflexes, II. Types of the higher nervous activity, their interdependence with neuroses and psychoses and the physiological mechanism of neurotic and psychotic symptoms. Translated by W.H. Gantt. New York: International Publishers.
Pfaff, D.W., 2006. Brain Arousal and Information Theory. Harvard University Press, MA.
Pfaff, D.W., Ribeiro, A., Matthews, J., Kow, L.M., 2008. Concepts and mechanisms of generalized central nervous system arousal. Ann. N.Y. Acad. Sci. 1129, 11–25.
Phillips, A.J., Robinson, P.A., 2008. Sleep deprivation in a quantitative physiologically based model of the ascending arousal system. J. Theor. Biol. 225 (4), 413–423.
Pivik, R., Stelmack, R., Bylsma, F., 1988. Personality and individual differences in spinal motoneuronal excitability. Psychophysiology 25 (1), 16–24, http://dx.doi.org/10.1111/j.1469-8986.1988.tb00951.x.
Posner, M.I., Petersen, S.E., 1990. The attention system of the human brain. Annual Review of Neurosciences 13, 25–42.
Pozzi, L., Invernizzi, R., Cervo, L., Vallebuona, F., Samanin, R., 1994. Evidence that extracellular concentrations of dopamine are regulated by noradrenergic neurons in the frontal cortex of rats. J. Neurochem. 63, 195–200.
Pribram, K.H., Luria, A.R. (Eds.), 1973. Academic Press, New York.
Puglisi-Allegra, S., Cabib, S., 1990. Effects of defeat on dopamine metabolism in different brain areas of the mouse. Aggression and Behavior 16, 271–284.

Puglisi-Allegra, S., Kempf, E., Cabib, S., 1990. Role of genotype in the adaptation of the brain dopamine system to stress. Neurosci. Biobehav. Rev. 14, 523–528.
Raine, A., 1989. Evoked potential models of psychopathy: a critical evaluation. Int. J. Psychophysiol. 8, 29–34.
Redgrave, P., Prescott, T.J., Gurney, K., 1999. Is the short-latency dopamine response too short to signal reward error? Trends Neurosci. 22, 6–151.
Revelle, W., Humphreys, M.S., Simon, L., Gilliland, K., 1980. The interactive effect of personality, time of day, and caffeine: a test of the arousal model. J. Exp. Psychol. Gen. 109, 1–31.
Rey, H.G., Lew, S.E., Zanutto, B.S., 2007. Dopamine and norepinephrine modulation of cortical and subcortical dynamics during visuomotor learning. In: Tseng, K.Y., Atzori, M. (Eds.), Monoaminergic modulation of cortical excitability. Springer Science & Business Media, NY, pp. 251–264.
Rizzolatti, G., Fadiga, L., Fogassi, L., Gallese, V., 1999. Resonance behaviors and mirror neurons. Arch. Italian Biol. 137, 85–100.
Robbins, T.W., 1984. Cortical noradrenaline, attention and arousal. Psychol. Med. 14, 13–21.
Robbins, T.W., 1997. Arousal systems and attentional processes. Biol. Psycho. 45 (1-3), 57–71.
Robbins, T.W., 2010. From behaviour to cognition: functions of mesostriatal, mesolimbic and mesocortical dopamine systems. In: Iversen, L.L., Iversen, S.D., Dunnett, S.B., Bjorklund, A. (Eds.), Dopamine Handbook. Oxford University Press, pp. 203–214.
Robbins, T.W., Arnsten, A.F., 2009. The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Ann. Rev. Neurosci. 32, 267–287.
Robbins, T.W., Everitt, B.J., 1996. Arousal Systems and Attention. In: Gazzaniga, M. (Ed.), The Cognitive Neurosciences. MIT Press, Cambridge, MA, pp. 703–720.
Robbins, T.W., Roberts, A.C., 2007. Differential regulation of fronto-executive function by the monoamines and acetylcholine. Cereb. Cortex 17 (Suppl 1), 151–160.
Robinson, D.K., Rieber, R.W. (Eds.), 2001. Kluwer Academic Publishers, Dordrecht.
Robinson, E.S., Dalley, J.W., Theobald, D.E., Glennon, J.C., Pezze, M.A., Murphy, E.R., et al., 2008. Opposing roles for 5-HT2A and 5-HT2C receptors in the nucleus accumbens on inhibitory response control in the 5-choice serial reaction time task. Neuropsychopharmacology 33, 2398–2406.
Rocklin, T., Revelle, W., 1981. The measurement of extraversion: A comparison of the Eysenck Personality Inventory and the Eysenck Personality Questionnaire. Br. J. Soc. Psychol. 20, 279–284.
Rothbart, M.K., Ahadi, S.A., Evans, D.E., 2000. Temperament and personality: origins and outcomes. J. Pers. Soc. Psychol. 78, 122–135.
Rusalov, V.M., 1989. Motor and communicative aspects of human temperament:a new questionnaire of the structure of temperament. Pers. Individ. Diff. 10, 817–827.
Rusalov, V.M., Trofimova, I.N., 2007. Structure of Temperament and Its Measurement. PSP: Psychological Services Press, Toronto.
Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R.M., Tanaka, H., et al., 1998. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G-protein-coupled receptors that regulate feeding behavior. Cell 92, 573–585.
Salamone, J.D., Cousins, M.S., Snyder, B.J., 1997. Behavioral functions of nucleus accumbens dopamine: Empirical and conceptual problems with the anhedonia hypothesis. Neurosci. Biobehav. Rev. 21, 341–359.
Saper, C.B., Chou, T.C., Scammell, T.E., 2001. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci. 24 (12), 726–731.
Saper, C.B., Scammell, T.E., Lu, J., 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature 437, 1257–1263.
Sarter, M., Givens, B., Bruno, J.P., 2001. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. Brain Res. Rev. 35, 146–160.
Sawchenko, P.E., Swanson, L.W., 1982. Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. J. Comp. Neurol. 205 (3), 260–272.
Schall, J.D., 2001. Neural basis of deciding, choosing and acting. Nat. Rev. Neurosci. 2, 33–42.
Schwarzer, C., 2009. 30 Years of Dynorphins—New insights on their functions in neuropsychiatric diseases. Pharmacol. Therap. 123 (3), 353–370.
Sealfon, S.C., Olanow, C.W., 2000. Dopamine receptors: from structure to behavior. Trends Neurosci. 23, S34–S40.
Seamans, J.K., Robbins, T.W., 2009. Dopamine modulation of the prefrontal cortex and cognitive function. In: Neve, K. (Ed.), Dopamine Receptors. Humana, Totowa, NJ.
Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74, 1–57.
Selden, N.R., Robbins, T.W., Everitt, B.J., 1990. Enhanced behavioral conditioning to context and impaired behavioral and neuroendocrine responses to conditioned stimuli following ceruleocortical noradrenergic lesions: support for an attentional hypothesis of central noradrenergic function. J. Neurosci 10, 531–539.
Shabani, S., Dehghani, M., Hedayati, M., Rezaei, O., 2011. Relationship of serum serotonin and salivary cortisol with sensation seeking. Int. J. Psychophysiol. 81 (3), 225–229.
Shi, W.X., Pun, C.L., Zhang, X.X., Jones, M.D., Bunney, B.S., 2000. Dual effects of D-amphetamine on dopamine neurons mediated by dopamine and nondopamine receptors. J. Neurosci 20, 3504–3511.
Siegel, G.J., Albers, R.W., Brady, S.T., Price, D.L. (Eds.), 2006. Elsevier, USA.
Smillie, L.D., Pickering, A.D., Jackson, C.J., 2006. The new Reinforcement Sensitivity Theory: Implications for personality measurement. Pers. Soc. Psychol. Rev. 10, 320–335.
Spränger, E., 1914. Types of Men (Lebensformen; Halle (Saale): Niemeyer; translation by P.J.W. Pigors; New York : Stechert Company (1928).
Stelmack, R.M., Michaud-Achorn, A., 1985. Extraversion, attention, and habituation of the auditory evoked response. J. Res. Pers. 19, 416–428.
Stocco, A., Lebiere, C., Anderson, J.R., 2010. Conditional routing of information to the cortex: A model of the basal ganglia's role in cognitive coordination? Psychol. Rev. 117 (2), 540–574.
Stough, C., Brebner, J., Cooper, C., 1991. The Rusalov Structure of Temperament Questionnaire (STQ): results from an Australian sample. Pers. Individ. Diff. 12, 1355–1357.
Strelau, J., Zawadzki, B., 1993. The Formal Characteristics of 'Behaviour-Temperament Inventory (FCB-TI): theoretical assumptions and scale construction. Euro. J. Pers. 7, 313–336.
Strelau, J., 1998. Temperament: a psychological perspective. Plenum, New York.
Stuss, D.T., Knight, R.T., 2002. Principles of frontal lobe function. Oxford Univestity Press, New York.
Sulzer, D., Joyce, M.P., Lin, L., Geldwert, D., Haber, S.N., Hattori, T., Rayport, S., 1998. Dopamine neurons make glutamatergic synapses in vitro. J. Neurosci 18 (12), 4588–4602.
Sutcliffe, J.G., De Lecea, L., 2002. The hypocretins: setting the arousal threshold. Nat. Rev. Neurosci. 3, 339–349, http://dx.doi.org/10.1038/nrn808.
Swerdlow, N.R., Caine, S.B., Braff, D.L., Geyer, M.A., 1992. The neural substrates of sensorimotor gating deficits in schizophrenia. Pharmacol. Biochem.Behav. 44, 741–744.
Szechtman, H., Sulis, W., Eilam, D., 1998. Quinpirole induces compulsive checking behavior in rats:a potential animal model of Obsessive-Compulsive Disorder (OCD). Behav. Neurosci. 112 (6), 1475–1485.
Taheri, S. (2005) Neuroendocrine role of the orexins (hypocretins). In: S. Nishino, S.Takeshi (Eds) The Orexin/Hypocretin System: Physiol. Pathophysiol., 119-130.
Tait, D.S., Brown, V.J., Farovik, A., Theobald, D.E., Dalley, J.W., Robbins, T.W., 2007. Lesions of the dorsal noradrenergic bundle impair attentional set-shifting in the rat. Eur. J. Neurosci. 25 (12), 3719–3724, http://dx.doi.org/10.1111/j.1460-9568.2007.05612.x.
Takahashi, K., Wang, Q.P., Guan, J.L., Kayama, Y., Shioda, S., et al., 2005. State-dependent effects of orexins on the serotonergic dorsal raphe neurons in the rat. Regul. Pept. 126, 43–47, http://dx.doi.org/10.1016/j.regpep.2004.08.009.
Tamakawa, Y., Karashima, A., Koyama, Y., Katayama, N., Nakao, M., 2006. A quartet neural system model orchestrating sleep and wakefulness mechanisms. J. Neurophysiol. 95 (4), 2055–2069.
Taylor, R.M., Morrison, L.P., 1992. Taylor-Johnson Temperament Analysis Test. Psychological Publications, Inc: Los Angeles, California, US.
Tellegen, A., 1985. Structure of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In: Tuma, A.H., Maser, J.D. (Eds.), Anxiety and the Anxiety Disorders. Erlbaum, Hillsdale, New Jersey, pp. 681–706.
Teplov, B.M., Nebylitsyn, V.D., 1963. Experimental study of properties of the nervous system in man. J. Highest Nervous Activity 13, 789–797.
Thayer, R.E., 1978. Toward a psychological theory of multidimensional activation (arousal). Motivation and Emotion 2, 1–34.
Thierry, A.M., Tassin, J.P., Blanc, G., Glowinski, J., 1976. Selective activation of mesocortical DA system by stress. Nature 263, 242–244.
Thomas, A., Chess, S., 1977. Temperament and Development. Brunner/Mazel, New York.
Thurstone, L.L., 1951. The dimensions of temperament. Psychometrika 16/1, 11–20.
Tidey, J.W., Miczek, K.A., 1996. Social defeat selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. Brain Res. 721, 140–149.
Treisman, A., 1979. The psychological reality of levels of processing. In: Cermak, L.S., Craik, F. (Eds.), Levels of processing in human memory. Lawrence Erlbaum, Hillsdale, New Jersey, pp. 301–330.
Trofimova, I., 2009. Exploration of the benefits of an activity-specific test of temperament. Psychol. Rep. 105, 643–658.
Trofimova, I., 2010a. Questioning the general arousal models. Open Behav. Scie. Psychol. 4, 1–8.
Trofimova, I., 2010b. An investigation into differences between the structure of temperament and the structure of personality. Am. J. Psychol. 123 (4), 467–480.
Trofimova, I., 2010c. Exploration of the activity-specific model of temperament in four cultures. Int. J. Psychol. Psychol. Ther. 10 (1), 79–95.
Trofimova, I., 2014. Observer bias: how temperament matters in semantic perception of lexical material. PLoS One 9 (1), e85677, http://dx.doi.org/10.1371/journal.pone.0085677.
Trofimova, I., 2016. The interlocking between functional aspects of activities and a neurochemical model of adult temperament. In: Arnold, M.C. (Ed.), Temperaments: Individual Differences, Social and Environmental Influences and Impact on Quality of Life. Nova Science Publishers, Inc., NY, pp. 77–147.
Trofimova, I., 2016b. Phenomena of functional differentiation (FD) and fractal functionality (FF). In: Rzevski, G., Brebbia, C.A. (Eds.), Complex Systems. Wessex Institute of Technology Press, UK.
Trofimova, I., Christiansen, J., 2016. Comparison of tests on temperament and mental illness in four adult age groups. Psychol. Rep. 118 (2), http://dx.doi.org/10.1177/0033294116639430.

Trofimova, I., Sulis, W., 2010. An investigation of temperament in adults with comorbid depression and anxiety. Adv. Biosci. Biotechnol. 1 (3), 190–199, http://dx.doi.org/10.4236/abb.2010.13027.
Trofimova, I., Sulis, W., 2011. Is temperament activity-specific?: Validation of the Structure of Temperament Questionnaire—Compact (STQ-77). Int. J. Psychol. Psychol. Ther. 11 (3), 389–400.
Trofimova, I., Sulis, W., 2016a. There is more to mental illness than just negative affect: comprehensive temperament profiles in depression and anxiety. Clin. Psychol. Sci., Submitted.
Trofimova, I., Sulis, W., 2016b. Benefits of distinguishing between physical and social-verbal aspects of behaviour: an example of generalized anxiety. Front. Psychol., http://dx.doi.org/10.3389/fpsyg.2016.00338.
Tsujino, N., Tsunematsu, T., Uchigashima, M., Konno, K., Yamanaka, A., et al., 2013. Chronic alterations in monoaminergic cells in the locus coeruleus in orexin neuron-ablated narcoleptic mice. PLoS One 8 (7), e70012, http://dx.doi.org/10.1371/journal.pone.0070012.
Tsujino, N., Sakurai, T., 2009. Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. Pharmacol. Rev. 61, 162–176, http://dx.doi.org/10.1124/pr.109.001321.
Tucker, D.M., Williamson, P.A., 1984. Asymmetric neural control systems in human self-regulation. Psychol. Rev. 91, 185–215.
Vacher, C.M., Fretier, P., Creminon, C., Calas, A., Hardin-Pouzet, H., 2002. Activation by serotonin and noradrenaline of vasopressin and oxytocin expression in the mouse paraventricular and supraoptic nuclei. J. Neurosci. 22 (5), 1513–1522.
van Gaal, S., Ridderinkhof, K.R., Fahrenfort, J.J., Scholte, H.S., Lamme, V.A., 2008. Frontal cortex mediates unconsciously triggered inhibitory control. J. Neurosci. 28 (32), 8053–8062.
Venables, P.H., 1984. Arousal: an examination of its status as a concept. In: Coles, M.G.H., Jennings, J.R., Stern, J.P. (Eds.), Psychophysiological perspectives. Van Nostrand, New York.
Voorn, P., Vanderschuren, L.J., Groenewegen, H.J., Robbins, T.W., Pennartz, C.M., 2004. Putting a spin on the dorsal-ventral divide of the striatum. Trends Neurosci. 27 (8), 468–474.
Walker, S.C., Robbins, T.W., Roberts, A.C., 2009. Differential contributions of dopamine and serotonin to orbitofrontal cortex function in the marmoset. Cereb. Cortex 19 (4), 889–898.
Watson, D., Tellegen, A., 1985. Toward a consensual structure of mood. Psychol. Bull. 98, 219–235.
Weiner, I., 1990. Neural substrates of latent inhibition:The switching model. Psychol. Bull. 108, 442–461.
Wigglesworth, M.J., Smith, B.D., 1976. Habituation and dishabituation of the electrodermal orienting reflex in relation to extraversion and neuroticism. J. Res. Pers. 10, 437–445.
Windle, M., Lerner, R.M., 1986. Reassessing the dimensions of temperament individually across life time span: the Revised Dimensions of Temperament Survey (DOTS-R). J. Adolesc. Res. 1, 213–230.
Winstanley, C.A., Chudasama, Y., Dalley, J.W., Theobold, D.E., Glennon, J.C., Robbins, T.W., 2003. Intra-prefrontal 8-OH-DPAT and M100907 improve visuospatial attention and decrease impulsivity on the five-choice serial reaction time task in rats. Psychopharmacology (Berl) 167, 304–314.
Winstanley, C.A., Theobald, D.E., Dalley, J.W., Robbins, T.W., 2005. Interactions between serotonin and dopamine in the control of impulsive choice in rats: therapeutic implications for impulse control disorders. Neuropsychopharmacology 30, 669–682.
Woolf, N.J., 1991. Cholinergic systems in mammalian brain and spinal cord. Prog. Neurobiol. 37, 475–524.
Yamamoto, B.K., Novotney, S., 1998. Regulation of extracellular dopamine by the norepinephrine transporter. J. Neurochem. 71, 274–280.
Yin, H.Y., Knowlton, B.J., 2006. The role of the basal ganglia in habit formation. Nat. Neurosci. 7, 464–476.
Zentner, M., Shiner, R. (Eds.), 2012. Guilford Publications, NY.
Zhang, W.P., Ouyang, M., Thomas, S.A., 2004. Potency of catecholamines and other Ltyrosine derivatives at the cloned mouse adrenergic receptors. Neuropharmacology 47, 438–449.
Zuckerman, M., 1994. Behavioural expressions and biosocial bases of Sensation Seeking. Cambridge University Press.
Zuckerman, M., Cloninger, C.R., 1996. Relationships between Cloninger's, Zuckerman's and Eysenck's dimensions of personality. Pers. Individ. Differ. 21 (2), 283–285.