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ORIGINAL PAPER

Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance

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Abstract A certain level of arousal is required for an individual to perform optimally, and the locus coeruleus norepinephrine (LC-NE) system plays a central role in optimizing arousal. Tonic firing of LC-NE neurons needs to be held within a narrow range of 1–3 Hz to facilitate phasic firing of the LC-NE neurons; these two modes of activity act synergistically, to allow the individual to perform attentional tasks optimally. How this information can be applied to further our understanding of psychiatric disorders has not been fully elucidated. Here we propose two models of altered LC-NE activity that result in attentional deficits characteristic of psychiatric disorders: 1) 'hypoaroused' individuals with e.g. attention-deficit/hyperactivity disorder (ADHD) have decreased tonic firing of the LC-NE system, resulting in decreased cortical arousal and poor attentional performance and 2) 'hyperaroused' individuals with e.g. anxiety disorders have increased tonic firing of the LC-NE system, resulting in increased cortical arousal and impaired attentional performance. We argue that hypoarousal (decreased tonic firing of LC-NE neurons) and hyperarousal (increased tonic firing of LC-NE neurons) are suboptimal states in which phasic activity of LC-NE neurons is impeded. To further understand the neurobiology of attentional dysfunction in psychiatric disorders a translational approach that integrates findings on the LC-NE arousal system from animal models and human imaging studies may be useful.

Keywords Hypoarousal · Hyperarousal · Attention-deficit hyperactivity disorder · Anxiety

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Background

It is commonly accepted that an individual who is 'hypoaroused' or 'hyperaroused' will not perform optimally in cognitive and behavioural tasks. This view stems from the empirical work of Yerkes and Dodson (1908) on a 'dancing mouse' model in which they determined the time it took for an animal to demonstrate avoidance behaviour by varying the intensity of an electrical pulse (Yerkes and Dodson 1908). These data were subsequently developed into what is commonly known as the Yerkes-Dodson theory (Winton 1987), in which performance is a function of the level of arousal. The Yerkes-Dodson theory states that for an individual to attain optimal performance on cognitive and behavioural tasks, the individual's level of arousal needs to be held within a narrow 'range' (Fig. 1a). There are several central arousal systems which arise from nuclei in the brainstem (Moruzzi and Magoun 1949), one of these being the locus coeruleus-norepinephrine (LC-NE) system.

The LC-NE system is the sole source of norepinephrine (NE) in the cortex (Aston-Jones et al. 1999; Bunsey and Strupp 1995; Foote et al. 1980; Jentsch 2005; Southwick et al. 1999). LC-NE neurons can be distinguished by their characteristic tonic and phasic modes of firing. Tonic firing of LC-NE neurons can in turn be identified by its diurnal variation of activity, which is related to the state of cortical arousal of the

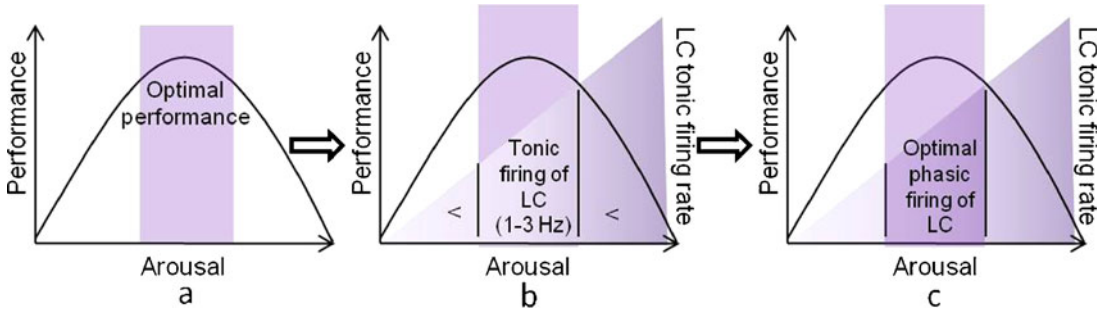

Fig. 1 Diagrammatic representation of the first hypothesis **a** Yerkes and Dodson theory that relates performance to the level of arousal, as an inverted-U. **b** Tonic firing of LC-NE neurons needs to be held within the 1–3 Hz range, which marks the range of arousal that will allow optimal performance. **c** Phasic firing of the LC-NE system occurs optimally when the tonic firing of the LC is within the 1–3 Hz range

individual (Aston-Jones et al. 2001). Thus during alert wakefulness the LC fires tonically in a range of 1–3 Hz and is associated with increased cortical arousal, while during deep sleep the LC does not fire tonically and there is decreased cortical arousal (Aston-Jones and Bloom 1981a, b; Berridge and Foote 1991; Foote et al. 1980; McCormick and Bal 1994).

Phasic firing of LC-NE neurons occurs during processes that involve attention, such as those required to perform voluntary behavior. Attention was early on elegantly described by William James as "taking possession by the mind in clear and vivid form, from one out of what seems several simultaneously possible objects or trains of thought" (James 1890). This description of active attention has been further developed to describe the individual processes that are required: (1) alerting, (2) orienting, and (3) executive control (Coull 1998; Posner et al. 2006). The LC-NE system plays a particularly important role in alerting and orienting; for example when a new stimulus is presented, the firing rate of LC-NE neurons changes from tonic firing to phasic bursts of activity, which enhance the 'signal' to 'noise' ratio. The tonic activity of the LC-NE system is then resumed after a refractory period (Aston-Jones and Bloom 1981a, b; Aston-Jones et al. 1991a, b; 1997; Bouret and Sara 2005; Grant et al. 1988; Rajkowski et al. 1994; Sara et al. 1995).

Attentional processes are reflected in electrophysiological recordings of electroencephalographic (EEG) event-related potentials (ERPs), specifically the P300 wave component. The production of the P300 is considered to reflect phasic activity of the LC-NE system (Nieuwenhuis et al. 2005). Lesions of the LC have been shown to decrease the amplitude of the P300 (Pineda and Westerfield 1993). The P300 is one of the distinct positive wave components, occurring approximately 300 msec post stimulus presentation, in the ERP waveform. The P300 is in turn comprised of fronto-central P3a and the parietal P3b components. The P3a has been strongly associated with 'orientating' responses, i.e. occurs predominantly in response to novelty and infrequent stimuli. The P3a then dissipates leaving the P3b component (Courchesne et al. 1975; Yamaguchi and Knight 1991), which has been strongly associated with 'cortical updating', i.e. the cortical representation of a task is updated continuously during each trial (Donchin and Coles 1988; Sokolov 1960; 1963).

Although the production of the P300 wave component reflects phasic activity of the LC-NE system, it is also affected by tonic activity of this system. Thus, the extent to which an individual updates the cortical representation of a task is dependent not only on changes in level of arousal over a time scale of seconds to minutes (phasic), but also on changes in arousal over a time scale from minutes to hours (tonic) (Hockey 1986; Hockey 1983; Polich and Kok 1995) The intensity of phasic LC firing has been related to cortical updating when valuable information and novelty are being processed (Aston-Jones et al. 1997; Foote et al. 1980). These data support the requirement for synergy between tonic and phasic modes of LC-NE firing for optimal performance, during tasks that require attention.

HYPOTHESIS 1: Balance between tonic and phasic firing of the LC-NE system permits optimal performance during tasks that require attention

From the above data we propose the following: (1) Optimal performance occurs when arousal is optimal, as per Yerkes and Dodson's theory (Winton 1987) (Fig. 1a). (2) Tonic firing of the LC-NE arousal system needs to be held within the range of 1–3 Hz to facilitate optimal arousal (Fig. 1b). (3) Phasic firing of the LC-NE neurons occurs when tonic firing of the LC is held within the 1–3 Hz range, this results in optimal attentional performance (Fig. 1c). The release of NE in the cortex, through phasic activity of LC-NE neurons has been shown to enhance the 'signal' to 'noise' ratio (Berridge and Foote 1994; Moxon et al. 2007; Waterhouse and Woodward 1980). Thus, orientation to a new stimulus requires suppression of non-informative information and enhancement of relevant information processing, which is achieved through synergistic tonic and phasic firing of LC-NE arousal system.

Despite the extensive empirical evidence relating the LC-NE system to arousal and attention in electrophysiological

experiments in animals and humans, the application of these data to models of psychiatric disorders that present with dysfunction in arousal and attention has not yet been fully undertaken. Here we develop the hypothesis that integration of tonic and phasic firing of the LC-NE system is needed for optimal performance, by considering empirical evidence on the activity of the LC-NE system in the context of dysfunctional arousal and attention.

HYPOTHESIS 2: Attention-deficit/hyperactivity disorder is a model of 'hypoarousal' resulting from decreased tonic activity of the LC-NE system

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood psychiatric disorders (Skounti et al. 2007). The main characteristics of ADHD include inability to sustain attention, impulsivity, and hyperactivity (Barkley 1997; Maedgen and Carlson 2000). ADHD has also been associated with conduct disorder and oppositional defiant disorder (Maedgen and Carlson 2000; Solanto et al. 2009). ADHD has been associated with decreased arousal, as measured peripherally by decreased skin conductance (Beauchaine et al. 2001; O'Connell et al. 2004). ADHD has also been associated with conduct disorder and oppositional defiant disorder (Maedgen and Carlson 2000; Solanto et al. 2009). There is much controversy regarding the diagnosis/subtyping of ADHD, including the under diagnosis of childhood post-traumatic stress disorder which presents with similar behavioural attributes, however the individual suffering from post-traumatic stress disorder is 'hyperaroused' and presents with avoidance behaviours, a key feature of anxiety disorders (Weinstein et al. 2000). Furthermore, cortical hypoarousal in ADHD is reflected in increased low frequency/decreased high frequency spontaneous cortical activity (i.e. increased cortical theta (θ, 4–7 Hz) band power and decreased cortical beta (β, 15–30 Hz) band power) (Clarke et al. 2001, 2002, 2007).

Indirect evidence of disrupted tonic and phasic activity of the LC-NE system in ADHD comes from ERP studies showing reduced amplitude of the P300 component of the EEG (Alexander et al. 2008), specifically over the parietal cortex (Johnstone and Barry 1996; Lazzaro et al. 2001) during performance of a cognitive (auditory odd-ball) task. In addition, individuals with ADHD showed increased fronto-central P300 amplitudes in response to a novel target (e.g. in response to no-go targets) (Wild-Wall et al. 2009). Similar findings have been reported for individuals with schizophrenia or individuals who are psychopathic (Kiehl et al. 2000). Both studies assigned the increased fronto-central P300 amplitude to decreased cortical inhibition of frontal attentional networks (Kiehl et al. 2000; Wild-Wall et al. 2009), which similarly suggests dysfunctional regulation of frontal neurons by the LC-NE system. This may account for the variability in performance by these individuals resulting from their increased fronto-central P3a amplitude (associated with 'orientating' responses) during experience of the novelty of the task to the decreased parietal P3b amplitude (associated with cortical updating) due to the monotony of the task and an inability to maintain a cortical representation required from the task.

Reduced tonic activity of the LC-NE system as measured by decreased cortical arousal may result in ineffectual phasic firing of the LC-NE system. Decreased synergy between tonic and phasic firing of LC-NE neurons may account for the impulsivity in individuals with ADHD, as measured by their inability to withhold or inhibit a response (Aron and Poldrack 2005). Individuals with ADHD appear to respond reflexively (Beauchaine et al. 2001; O'Connell et al. 2004) and are unable to expend sufficient effort or increase the level of cortical arousal necessary to reduce impulsivity and maintain attention through enhancement of their level of arousal (Beauchaine et al. 2001; Howells et al. 2010; O'Connell et al. 2004).

A widely used animal model of ADHD is the spontaneously hypertensive rat (SHR). SHR was initially developed from the Wistar-Kyoto rat (WKY) for the study of adult hypertension (Okamoto and Aoki 1963). This adult hypertension is a persistent characteristic of the strain (152±6 mmHg) in comparison to its 'standard' normotensive control, Wistar-Kyoto rat (WKY, 102±4 mmHg) (Kaehler et al. 2004; Singewald et al. 2000). In later years the SHR was found to exhibit characteristics of ADHD-C (Howells et al. 2009; Kaehler et al. 2004; Knardahl and Sagvolden 1979; Rogers et al. 1988; Wultz et al. 1990). These characteristics include poor sustained attention, as measured by errors in commission and omission, and high levels of impulsivity, as measured by increased exploratory behaviour and decreased anxiety-like behaviours. In addition, SHR have increased locomotor activity, particularly during pre-adolescence, comparative with the presentation of ADHD in children (Howells et al. 2009; Marti and Armario 1996; van den Bergh et al. 2006).

Empirical evidence supports dysfunctional regulation of tonic and phasic modes of firing of the LC-NE system in SHR. Attentional performance in SHR is improved by psychostimulant treatment, which increases the extracellular concentration of NE (Sagvolden et al. 1992; Wultz et al. 1990). Furthermore α_2-adrenoreceptor (presynaptic autoreceptors that attenuate the release of NE) function is reduced in SHR (Russell et al. 2000; Russell and Wiggins 2000; Tsuda et al. 1994), and expression of α_2-adrenoreceptors is reduced (Olmos et al. 1991). Drugs that are effective in improving attentional performance either primarily increase extracellular NE concentrations (Sagvolden et al. 1992) or improve autoreceptor function, such as was found after treatment with an α_2-adrenoreceptor agonist, guanfacine (Sagvolden 2006). Decreased autoreceptor function has been related to the behavioural characteristics of SHR (Howells et al. 2009; Leibowitz et al. 1989; Reyes et al. 2006; Valentino and Van Bockstaele 2008). These data indicate that

SHR have decreased extracellular concentrations of NE and suggest low tonic LC-NE firing. This may account for poor attentional performance as locally released glutamate-stimulated release of NE, through either direct infusion of glutamate or a behavioural stressor, is greater in SHR than in several control rat strains and for several brain areas (Howells and Russell 2008; Howells et al. 2009; Kaehler et al. 2004; Kawasaki et al. 1991; Leibowitz et al. 1989; Reyes et al. 2006; Russell et al. 2000; Russell and Wiggins 2000; Singewald et al. 2000; Valentino and Van Bockstaele 2008). This increased stimulated release of NE is possibly compensatory; we suggest that it is a result of low tonic firing of LC-NE neurons.

From the above data we propose: (1) Individuals who are 'hypoaroused' (i.e. individuals with ADHD and the SHR a widely accepted animal model of ADHD) will perform poorly in tasks that require attention. (2) Tonic firing of the LC-NE arousal system in such individuals is low or decreased, not held within the optimal range of 1–3 Hz, during wakefulness. This results in a low level of cortical arousal. (3) When phasic firing of the LC-NE neurons occurs, enhancement of the 'signal' is achieved with high levels of novelty and acute stressors; however maintenance of the 'signal' is not achieved. This results in poor attentional performance as well as related deficits in inhibitory processes and reflexive responding (Fig. 2).

HYPOTHESIS 3: Anxiety disorders as a model of 'hyperarousal' resulting from increased tonic activity of the LC-NE system

Anxiety disorders are the most prevalent psychiatric disorders in community studies (Kessler et al. 2007; Wittchen and Jacobi 2005). The anxiety disorders share a common clinical characteristic; they all present with excessive avoidance behaviours (Mineka and Zinbarg 2006). Excessive avoidance behaviours are in turn reflected in deficits in attention, as measured by increased arousal in response to target stimuli that overwhelms attentional networks and leads to errors of omission (Castaneda et al. 2008; Li et al. 2011; Waters et al. 2009). Cortical hyperarousal in individuals with anxiety disorders can be identified by decreased low frequency/increased high frequency spontaneous cortical activity (i.e. decreased cortical theta (θ, 4–7 Hz) band power and increased cortical beta (β, 15–30 Hz) band power) (Buchsbaum et al. 1985; Grin-Yatsenko et al. 2009, 2010; Matousek 1991).

Indirect evidence of altered tonic and phasic modes of LC-NE activity is derived from ERP studies of individuals with anxiety disorders which show reduced amplitude of the parietal P300 component (Bauer et al. 2001; Boudarene and Timsit-Berthier 1997). Individuals with anxiety disorders show deficits in the P300 wave component (decreased P300 amplitude) during presentation of target stimuli, but increased P300 amplitude during non-target information processing. The level of information processing is greater than the response to target stimuli (increased P300 amplitude) (Li et al. 2011). Peripheral information is given greater importance than the 'signal', with ineffectual suppression of the 'noise' and decreased attentional performance.

A range of findings points towards dysfunction of the LC-NE system in the anxiety disorders. Disrupted ultrastructure of the LC-NE nucleus, decreased neuron counts, increased α_2-adrenoreceptor expression and sensitivity, and down-regulation of NE re-uptake transporters have for example been reported in post-mortem studies of individuals with anxiety disorders (Arango et al. 1996; Baumann et al. 1999; Bracha et al. 2005; Issidorides 1990; Klimek et al. 1997;

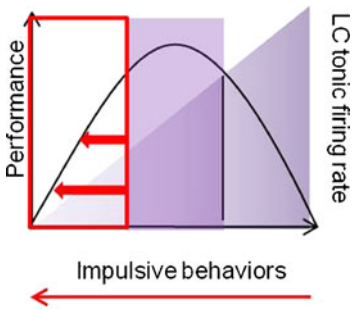

Fig. 2 Diagrammatic representation of the second hypothesis. Individuals that are 'hypoaroused' do not perform optimally (left side of inverted-U), tonic firing of the LC-NE system is low or decreased and not held within the 1–3 Hz range during wakefulness (*left pointing arrows*), when phasic firing of the LC occurs, optimal behavioural performance is not possible and the individuals appear inattentive and impulsive

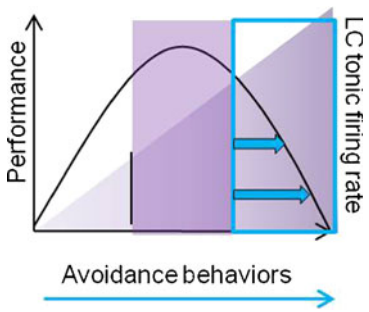

Fig. 3 Diagrammatic representation of the third hypothesis. Individuals that are 'hyperaroused' do not perform optimally (right side of inverted-U), tonic firing of the LC-NE system is higher or increased and not held within the 1–3 Hz range during wakefulness (*right pointing arrows*), when phasic firing of the LC occurs optimal behavioural performance is not possible and the individuals appear inattentive and display avoidant behaviours

Ordway et al. 2003; Southwick et al. 1999). These data suggest that the LC-NE system may have been down-regulated in an attempt to compensate for the lack of negative feedback required to re-establish synergy between the tonic and phasic modes of firing of LC-NE neurons by decreasing tonic activity.

The Wistar Kyoto rat (WKY/NCrl) has been proposed as a model of anxiety disorders (Jiao et al. 2011; McAuley et al. 2009). Indeed this strain has been used for several years as the comparator strain for SHR (Okamoto and Aoki 1963). However, when WKY animals were compared to other rat strains it became apparent that they also had deficits in attentional performance (Roessner et al. 2010; Sagvolden et al. 2009). Attentional performance deficits, or errors of omission, in WKY rats are, however, related to increased avoidance behaviours, as measured by decreased exploratory behaviour, increased anxiety-like behaviours, and decreased locomotor activity (Armario et al. 1995; Baum et al. 2006; Braw et al. 2006; Howells et al. 2009; Lahmame et al. 1997; Malkesman et al. 2005; Marti and Armario 1996; Pardon et al. 2002; Ramos et al. 1997; Sagvolden et al. 1993; Sukhanov et al. 2004; Tejani-Butt et al. 2003).

Empirical evidence supports dysfunctional regulation of tonic and phasic modes of firing of LC-NE neurons in WKY. Attentional performance of WKY is improved by enhancing extracellular concentrations of NE by blocking NE reuptake and stimulating α_2-adrenoreceptors (Tejani-Butt et al. 2003). NE release from LC-NE neurons stimulated by either direct infusion of glutamate or a behavioural stressor is decreased in WKY (Pardon et al. 2002).

From the above data we propose (1) individuals who are 'hyperaroused' (i.e. individuals with anxiety disorders and the WKY a promising model of anxiety disorders) perform poorly on tasks of attention. (2) Tonic firing of the LC-NE arousal system in such individuals is high or increased, not being held within the optimal 1–3 Hz range during wakefulness. This results in a high level of cortical arousal and perpetuation of hypothalamic pituitary axis activity. (3) When phasic firing of the LC-NE neurons occurs, enhancement of the 'signal' and suppression of 'noise' is not effectual, as high tonic levels of NE may have down-regulated postsynaptic β-adrenoceptors. Poor attentional performance is evidenced in part by avoidance behaviours, and there is an absence or attenuated response of the LC-NE system to novelty and stressors (Lukaszewska and Niewiadomska 1995) (Fig. 3).

Conclusions and implications

In the present paper, we propose a model of the LC-NE arousal system that explains deficits in attentional performance in individuals with different psychiatric disorders. The LC-NE system fires in two modes, tonic and phasic. These two modes of firing need to work synergistically. We propose that ADHD, a disorder of 'hypoarousal', presents with low tonic firing of the LC-NE system while anxiety disorders, conditions characterized by 'hyperarousal', present with high tonic firing of the LC-NE system. Either low or high tonic firing of the LC-NE system results in ineffectual phasic activity of the LC-NE system and results in attentional deficits and poor performance.

We would argue that these hypotheses allow an integration of data from multiple studies, including both human and animal research. The implications of the proposed hypotheses address several methodological aspects that have been negated in attempts to understand the attentional dysfunctions in the psychiatric disorders. (1) The neurophysiology of psychiatric disorders including the electrical signatures and neurochemical signatures should not be looked at in isolation. (2) We are now able to conceptualize the interactions between state (tonic) and trait (phasic) aspects of electrical and neurochemical properties of these systems, afforded by brain imaging techniques in humans and with the use of well characterized animal models of the disorder in study. We suggest that this integrative approach, albeit non-linear, is capable of providing greater insight to psychiatric disorders, and may serve as the next step in moving forward our understanding of the neurobiology of psychiatric disorders, including their attentional dysfunction. We hope that this paper provides some impetus for that work to succeed.

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