

# Orexin/Hypocretin System Dysfunction in ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations)

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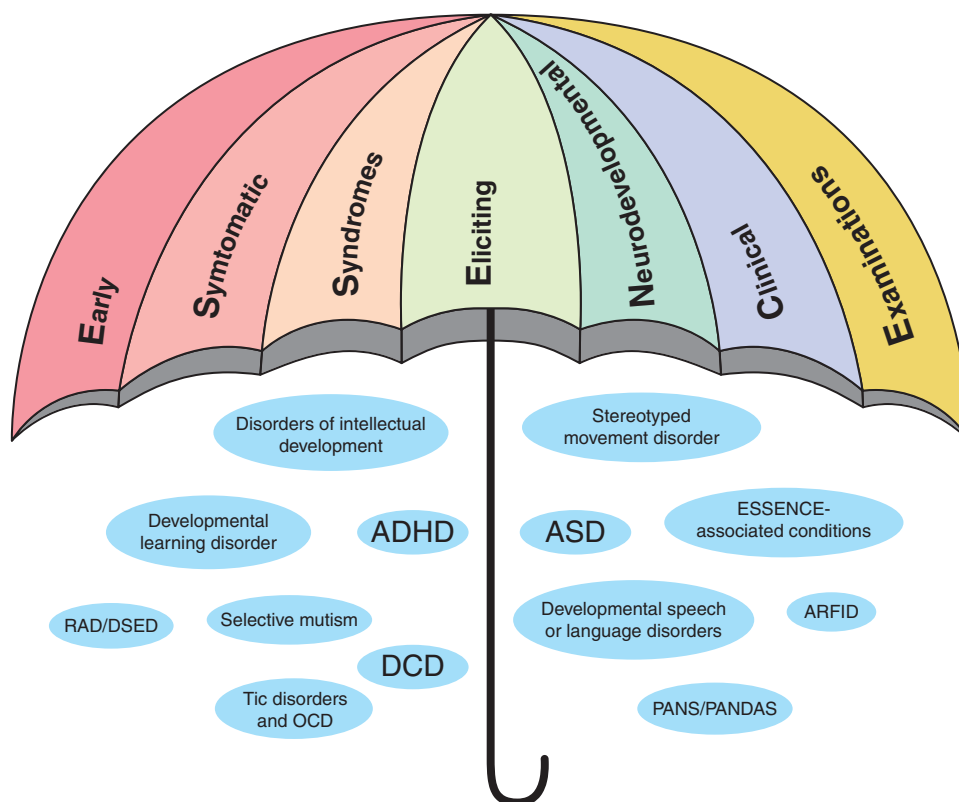
**Abstract:** Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) is an umbrella term covering a wide range of neurodevelopmental difficulties and disorders. Thus, ESSENCE includes attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and other neurodevelopmental disorders (NDDs) and difficulties, with a variety of symptoms in cognitive, motor, sensory, social, arousal, regulatory, emotional, and behavioral developmental domains, frequently co-occurring and likely having partly common neurobiological substrates. The ESSENCE concept is a clinical paradigm that promotes organizing NDDs in everyday clinical practice according to their coexistence, symptom dimensions overlapping, and treatment possibilities. Despite increased knowledge regarding NDDs, the neurobiological mechanisms that underlie them and other ESSENCE-related problems, are not well understood. With its wide range of neural circuits and interactions with numerous neurotransmitters, the orexin/hypocretin system (Orx-S) is possibly associated with a variety of neurocognitive, psychobiological, neuroendocrine, and physiological functions and behaviors. Dysfunction of Orx-S has been implicated in various psychiatric and neurological disorders. This article provides an overview of Orx-S dysfunctions' possible involvement in the development, presentation, and maintenance of ESSENCE. We provide a focused review of current research evidence linking orexin neuropeptides with specific clinical NDDs symptoms, mostly in ADHD and ASD, within the Research Domain Criteria (RDoC) framework. We propose that Orx-S dysfunction might have an important role in some of these neurodevelopmental symptom domains, such as arousal, wakefulness, sleep, motor and sensory processing, mood and emotional regulation, fear processing, reward, feeding, attention, executive functions, and sociability. Our perspective is presented from a clinical point of view. Further, more thorough systematic reviews are needed as well as planning of extensive new research into the Orx-S's role in ESSENCE, especially considering RDoC elements.

**Keywords:** attention-deficit/hyperactivity disorder, autism spectrum disorder, developmental coordination disorder, neurodevelopmental disorders, research domain criteria, orexin, hypocretin

## ESSENCE as a Clinical Paradigm

Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) is an umbrella term covering a wide range of neurodevelopmental difficulties and neurodevelopmental disorders (NDDs), such as attention-deficit/hyperactivity disorder (ADHD), developmental coordination disorder (DCD), and autism spectrum disorder (ASD), with a variety of symptoms in cognitive, motor, sensory, social, arousal, regulatory, emotional, and behavioral developmental domains, which frequently co-occur and likely have partly common neurobiological substrates.<sup>1</sup> There is a variety of disorders, syndromes, and disabilities under the ESSENCE umbrella, as schematically presented in Figure 1. ESSENCE disorders are highly prevalent, together affecting about 10% of school-age children and more frequently males, and in many cases persist into adulthood.<sup>2</sup>

On one hand, the concept behind ESSENCE could be viewed as a clinical paradigm as it promotes organizing diagnoses according to their coexistence seen in everyday clinical practice and their possible common underlying



**Figure 1** Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) diagnoses and conditions.

**Notes:** **Developmental learning disorder**, learning disorders with impairment in reading, written expression, or mathematics; **ESSENCE-associated conditions**, behavioural phenotype syndromes (eg Down's syndrome, fragile X syndrome and premutation FraX, sex chromosome anomalies, tuberous sclerosis complex, 22q11 deletion syndrome, Prader-Willi and Angelman syndrome, neurofibromatosis, foetal alcohol spectrum disorder/syndrome, valproate acid syndrome), neurological conditions and disorders (eg epilepsy or seizures, cerebral palsy, disorders of muscles), severe early-onset mental disorders (eg early-onset bipolar disorder, schizophrenia, disruptive mood dysregulation disorder).

**Abbreviations:** ADHD, attention-deficit/hyperactivity disorder; DCD, developmental (motor) coordination disorder; ASD, autism spectrum disorder; RAD, reactive attachment disorder; DSED, disinhibited social engagement disorder; ARFID, avoidant-restrictive food intake disorder; PANS, paediatric acute-onset neuropsychiatric syndrome; PANDAS, paediatric acute-onset neuropsychiatric disorder associated with streptococcal infection; OCD, obsessive-compulsive disorder.

neurobiology. The use of categorical diagnoses and classifications, thus far, has failed NDDs.<sup>3</sup> Instead, we should approach these disorders dimensionally. Applying a “spectral approach” to understand NDD symptoms, measure the impact that such symptoms have on an individual's functioning and quality of life, and suggest optimal intervention strategies requires that the paradigm used in clinical practice be both comprehensive and easy to understand. ESSENCE might also serve as a framework that helps researchers understand the need for a comprehensive approach to questions of possible common neurobiological substrates for the disorders under the ESSENCE umbrella. Rather than focusing on isolated or subspecialized parts that might provide only limited insight into research problems and partial answers, the ESSENCE conceptualization invites researchers to take a broader perspective.

On the other hand, the Research Domain Criteria (RDoC) represent a research paradigm with a possible clinical utility. The RDoC framework for psychopathology research relies on genetics and neuroscientific research tools to reveal biosignatures,<sup>4,5</sup> representing an alternative to the more classical categorical approach to the conceptualization of psychopathologies. The dimensional psychopathology measures that the RDoC framework uses include “indicators of functional brain disruption”.<sup>6</sup> The RDoC system is designed to develop a biologically oriented classification<sup>7</sup> of mental and behavioral disorders, and it is organized in a matrix of six domains: cognitive systems, negative and positive valence systems, systems for social processes, arousal/regulatory systems, and sensorimotor systems, each with several constructs/subconstructs.<sup>8</sup>

In clinical practice, deconstructing NDDs down into their “target symptoms” based on the ESSENCE and RDoC paradigms combined, may guide practitioners in choosing optimal therapeutic strategies. Deconstructing a psychiatric

disorder into its specific symptoms, which may involve unique neurobiological mechanisms, could lead to personalized psychopharmacological therapeutic strategies,<sup>9,10</sup> which could be relevant for NDDs conditions, too.

## Neurobiological Mechanisms That Underlie ESSENCE

There are several medical, neurological, and psychiatric disorders, conditions, and symptoms that coexist with ADHD and ASD, such as oppositional defiant disorder, conduct disorders, substance use disorder, anxiety, depression, DCD, tic disorders, obsessive-compulsive disorder (OCD), disorders of intellectual development and language, epilepsy, gastrointestinal problems, and sleep disorders.<sup>1,2,11</sup> Finding a shared biological substrate of ESSENCE that might account for the overlap of symptoms could guide clinicians in choosing optimal treatment strategies.

Despite increased awareness of NDDs, the neurobiological mechanisms underlying NDDs are not well understood. Recently, orexin/hypocretin system (Orx-S) dysfunction has been implicated in a variety of psychiatric and neurological disorders,<sup>12</sup> including ADHD and ASD.<sup>13–18</sup> Kohyama was likely the first to connect the Orx-S with both ASD and ADHD, suggesting that Orx-S hyperactivity might play a role in insomnia in these two classical NDDs.<sup>17</sup>

The current paper aims at providing a new perspective and an overview of possible involvements of Orx-S dysfunction in the development, presentation, and maintenance of NDDs and some other ESSENCE conditions, focusing on specific neuropsychiatric symptoms—mostly in ADHD and ASD—in the context of the RDoC framework. Currently, there is no consensus regarding what kinds of symptom dimensions best capture ADHD and at which levels these dimensions should be assessed.<sup>19</sup> Furthermore, ADHD is heterogenous in its presentation,<sup>20</sup> which motivates the use of the RDoC approach when aiming to close the gap in our understanding of symptoms and causes.<sup>6</sup> ADHD spans the entire RDoC matrix, and individuals with ADHD may differ in the extent to which their neurological processes are affected in the multiple brain systems involved.<sup>6,7</sup> Regarding ASD's phenotypic heterogeneity, the RDoC framework also offers an alternative way of characterizing ASD features, representing a continuum that extends into the “normative” span.<sup>4</sup> Furthermore, Ibrahim and Sukhodolsky pointed out that “current research using the RDoC framework in ASD has suggested conceptualizing ASD symptoms along positive, negative, and cognitive dimensions, similar to a dimensional approach traditionally used for schizophrenia”.<sup>4</sup>

Autism is officially conceptualized as a spectrum disorder,<sup>21,22</sup> whereas ADHD is still viewed categorically, although its symptomatology might also be better conceptualized as a spectrum than a discrete diagnostic entity.<sup>20,23</sup> Finally, considering ADHD and ASD as related spectra may help identify their partly common neurobiological substrates, and Orx-S dysfunction might be one such common pathway.

## Orexins/Hypocretins

The orexins, ie orexin-A/hypocretin-1 (Orx-A) and orexin-B/hypocretin-2 (Orx-B), are neuropeptides that originate in the lateral hypothalamus.<sup>24–27</sup> Orexins act on orexin type 1 receptor (Orx1R) and orexin type 2 receptor (Orx2R), which are “widely distributed across the brain”, but their mRNA has also been determined in peripheral tissues.<sup>26–29</sup> Outside of the central nervous system, the Orx-S could be linked to the peripheral nervous system and several peripheral tissue types (ie, the gastrointestinal tract, pituitary gland, pancreas, adrenal gland, adipose tissue, and male reproductive system).<sup>30–32</sup> Orx1R shows a higher affinity for Orx-A than Orx-B, while Orx2R binds both orexins with similar affinity.<sup>24</sup> The different distribution patterns of the two orexin receptor subtypes suggest different physiological roles<sup>33</sup> and likely non-overlapping and/or opposite functions, such as anxiolytic versus anxiogenic responses.<sup>25,34</sup>

Orexin-producing cell bodies reside in the hypothalamus, but their projections are widely spread through the brain and spinal cord with dense projections throughout the hypothalamus and the basal forebrain, specifically in cholinergic areas.<sup>25,35</sup> Orexins produced by cells in the hypothalamus are released in various brain areas.<sup>26</sup> These areas include monoamine neurotransmitter centers in 1) the tuberomammillary nucleus (for histamine), 2) in the ventral tegmental area (for dopamine), 3) the locus coeruleus (for noradrenalin), 4) pedunculopontine tegmental and laterodorsal tegmental nuclei (for acetylcholine), and 5) the raphe nucleus (for serotonin).<sup>26,28,36,37</sup> Orexin projections seem to also impart effects on 6) glutamate release from the thalamus and the prefrontal cortex and on 7) gamma-aminobutyric acid (GABA) release from the nucleus accumbens and the striatum.<sup>36</sup> Orexin neurons receive numerous input signals linked to environmental, physiological, and emotional stimuli and from regions related to sleep–wake states, circadian phase, motivation, and visceral

cues.<sup>24,38</sup> Thus, the Orx-S may interact with the noradrenergic, dopaminergic, serotonergic, histaminergic, cholinergic, glutamatergic, and GABAergic systems.<sup>24–28,36–39</sup> For example, manipulations of the Orx-S simultaneously modulate neurotransmitters associated with alertness and wakefulness (ie, dopamine, norepinephrine, acetylcholine, and histamine).<sup>27</sup>

GABA is the major inhibitory neurotransmitter in the brain.<sup>26,40</sup> “Glutamate is the major excitatory neurotransmitter in the central nervous system”, sometimes considered the “master switch” due to its potential ability to excite almost all neurons in the brain.<sup>26</sup> Interestingly, the effects of some neurotransmitters change during embryogenesis; for example GABA is excitatory in the embryo but inhibitory postnatal.<sup>41</sup> The GABA shift seems to be delayed or absent in some individuals with NDDs.<sup>40</sup> In addition to GABA, glutamate seems important in ASD and ADHD, as evidence has implicated relative loss of GABA inhibitory action with “corresponding glutamate-mediated hyper-excitation in the development” of these NDDs.<sup>42</sup> Orexin neurons may have capability of glutamate co-release and be “considered to have a glutamatergic phenotype”.<sup>43</sup> However, a subpopulation of orexin neurons seems to have the ability to synthesize GABA.<sup>43</sup> Thus, it is implied that the Orx-S may play a role in the complex interplay and balance of glutamatergic and GABAergic transmission.

Orexins' function in metabolic pathways is not yet fully understood,<sup>24</sup> although it is hypothesized that the central Orx-S could modulate whole-brain activity.<sup>33</sup> Orexin receptor signalling is more diversified than originally considered.<sup>30,31</sup> The Orx-S is associated with a variety of neurocognitive, psychobiological, neuroendocrine, physiological functions and behaviors. Suggested regulation/modulation roles of the Orx-S include arousal, vigilance states, sleep–wakefulness, somatic motor control, ventilation modulation, locomotion and spontaneous physical activity, stereotypical and obsessive-compulsive behaviors, enhanced hippocampal neurogenesis, various autonomic process, affect, mood and emotional regulation, fear and anxiety (anxious behaviors), motivation and reward (reward processing), reward-seeking/addictive behavior, stress processing (regulations of behavioral and neuroendocrine responses during stress) and stress resilience, appetite modulation (food intake) and feeding (feeding behaviors), gastrointestinal and reproductive functions, the micturition reflex, thermoregulation/thermogenesis, energy homeostasis and metabolism (metabolic regulation), cognitive function and cognitive flexibility, attention and decision making, memory, and (aversive) learning.<sup>12,24–28,31,33–36,38,39,44–53</sup> Orx-S dysfunctions have been suggested to underlie various neurological and neuropsychiatric disorders, and psychopathological conditions.<sup>12,24,46</sup> These include depressive and anxiety disorders, sleep and eating disorders, substance addictions, and post-traumatic stress disorder; whereas changes in orexin levels have been reported in depressive and bipolar disorders, narcolepsy, age-related cognitive decline, anorexia nervosa (AN), ADHD, schizophrenia, and neurodegenerative brain diseases, such as Parkinson's disease, Alzheimer's disease (AD), Huntington's disease, amyotrophic lateral sclerosis, and multiple sclerosis.<sup>12,13,24,25,27,32,38,46,54–56</sup> The Orx-S is also involved in metabolic syndrome, chronic inflammations, and cancers; moreover, orexin has a proposed role on “inverse comorbidity between cancer and neurodegenerative disorders”.<sup>32,56</sup>

The Orx-S is a potential therapeutic target for several disorders.<sup>27</sup> Orexin receptor antagonists (ie, suvorexant and lemborexant) have been approved for the treatment of insomnia, while daridorexant is currently close to registration for the same indication.<sup>27</sup> There are many registered clinical trials that explore suvorexant for the treatment of insomnia in different patient populations (ie, adolescents, those with fibromyalgia, and bipolar disorder).<sup>27</sup> Of special interest is the suggestion that orexin receptor antagonists might be promising for treatment of insomnia in adolescents,<sup>57</sup> and children with NDDs.<sup>58</sup> In addition to insomnia, the potential and effectiveness of orexin-based therapeutics in the treatment of other conditions and disorders (ie major depressive disorders, anxiety disorders, panic disorder, post-traumatic stress disorder, eating disorder, addiction/substance-use disorder, ADHD, narcolepsy, some type of excessive daytime sleepiness, chronic fatigue syndrome, and cognitive impairments related to ageing, neurodegenerative disease and sleep deprivation) have also been implicated.<sup>25,27,34,57–61</sup> Orexin antagonists may reduce motor impulsivity induced by psychostimulants and may diminish “sympathetic overactivity during withdrawal syndrome”.<sup>12,62</sup>

## The Orexin System and ESSENCE

Cortese et al proposed that orexin neurons in the perifornical and dorsomedial hypothalamus may be hypoactive in ADHD, while those in the lateral hypothalamus may be overactivated.<sup>14</sup> Recently, Baykal et al reported that children with ADHD had significantly lower Orx-A serum levels than neurotypical children.<sup>13</sup> In addition, orexin levels were found significantly lowered in inattentive than in hyperactive and combined ADHD.

Kohyama presumed an increase in orexinergic system activity to be involved in insomnia symptoms in ADHD and in ASD.<sup>17</sup> Messina et al, in a single-case, ASD study, showed that plasma Orx-A levels were higher than reference values,<sup>18</sup> while Kobylinska et al found the distributions of plasma levels of Orx-A to be variable in children with ASD but similar to those of neurotypical children.<sup>16</sup> The same study found that the lower the plasma levels of Orx-A, the greater the severity of ASD symptoms would be, and vice versa (moderate correlations). Thus, the role of orexin in ASD pathogenesis has also recently been implicated, although results are very preliminary.

## Orx-S Dysfunction and Main Symptom Domain of ESSENCE Within the RDoC Framework

At present, direct connections between orexin and certain RDoC elements have been established for the negative valence system and positive valence system domains, and domain arousal/regulatory system.<sup>8</sup> The Orx-S with its two peptides, two types of receptors, orexin neurons projections to many parts of the brain, and possible interactions with a range of neurotransmitters may affect many systems and behaviours in NDDs. Here, we focus on symptom domains that might be the most relevant for ADHD and ASD (Table 1). Some of these symptoms, such as fear, reward, and arousal already belong to RDoC domains connected with orexin.

**Table 1** ADHD and ASD Symptoms and Plausible Orexin/Hypocretin System (Orx-S) Involvement

Main Symptom Domain of ADHD/ASD	ADHD and ASD	Plausible Role of Orx-S
<b>Arousal</b>	<ul style="list-style-type: none"> <li>Deficient and/or excessive arousal pathways may be linked to ADHD<sup>10</sup></li> <li>Within RDoC matrix, deficit in arousal/regulatory system (eg, biological rhythm) in ADHD<sup>7</sup></li> <li>Altered HPA axis function in ADHD and ASD<sup>63,64</sup></li> <li>Constellation of symptoms described as “brain fog” among patients with ASD<sup>65</sup></li> <li>Children with hyperactive/impulsive symptoms of ADHD have higher pupil dilation in response to happy faces<sup>66</sup></li> <li>Children with ASD show “decreased pupil responses to human faces” and differ in tonic pupil size from age-matched controls<sup>67</sup></li> <li>Pupillometry may differ in individuals with and without ASD<sup>68</sup></li> </ul>	<ul style="list-style-type: none"> <li>“Orexin is a key component of the arousal system”<sup>36</sup></li> <li>Monoaminergic neurons in the brainstem are strongly excited by orexin neurons<sup>69</sup></li> <li>Orexin activates the HPA axis<sup>36</sup></li> <li>“Brain fog” may be linked to impairments in Orx-S<sup>70</sup></li> <li>Orx-A might modulate pupil size<sup>71</sup></li> </ul>
<b>Wakefulness and sleep</b>	<ul style="list-style-type: none"> <li>Shared neuronal mechanisms (with increased Orx-S activity) proposed to underlie insomnia in patients with ASD and ADHD<sup>17</sup></li> </ul>	<ul style="list-style-type: none"> <li>Orexin neurons “modulate sleep and wakefulness”<sup>35</sup></li> </ul>
<b>Sensorimotor system, sensory processing, and perception</b>	<ul style="list-style-type: none"> <li>Many children with ASD and ADHD show motor impairments<sup>72</sup></li> <li>Fine motor skill difficulties are common in pediatric ADHD<sup>73</sup></li> <li>Many children with NDDs may have DCD<sup>72</sup></li> <li>Sensorimotor deficits have an impact on the performance of daily living skills in preschool children with ASD, impacting their autonomy<sup>74</sup></li> <li>Atypical sensory-processing is a common feature of ADHD and ASD<sup>75</sup></li> <li>Sensory abnormalities: core ASD diagnostic criterion<sup>21,22,75</sup></li> <li>Altered perceptual functions in ADHD (ie, olfactory detection threshold)<sup>76</sup></li> <li>Children with ASD show altered olfactory function<sup>77</sup></li> <li>Volitional eye movement control is associated with ADHD traits<sup>78</sup></li> <li>Subtle language and social processing differences in eye movement studies in ASD found<sup>79</sup></li> </ul>	<ul style="list-style-type: none"> <li>Loss of orexin neurons likely involved in the pathophysiology of some movement disorders<sup>50</sup></li> <li>Orexin neurons are sensorimotor controllers<sup>80</sup></li> <li>Orx-S exerts excitatory effect on dopamine neurons in the ventral tegmental area<sup>81</sup></li> <li>Sensory-evoked and self-generated movements are regulated by the orexin neurons<sup>80</sup></li> <li>Orx-S relates to spontaneous physical activity<sup>24</sup></li> <li>Orx-S might orchestrate central motor control<sup>51</sup></li> <li>Orexin possibly modulate olfactory perception<sup>82</sup></li> <li>Orx-A might modulate eyelid position, and possibly convergence movements and eye alignment<sup>71</sup></li> </ul>

(Continued)



Table 1 (Continued).

Main Symptom Domain of ADHD/ASD	ADHD and ASD	Plausible Role of Orx-S
<b>Impulsivity and compulsivity</b>	<ul style="list-style-type: none"> <li>Impulsivity and compulsivity are present in ADHD and ASD<sup>26</sup></li> </ul>	<ul style="list-style-type: none"> <li>In narcolepsy with orexin deficiency, “selective impairment of alerting network” exists<sup>83</sup></li> <li>Orexins are associated with stereotypic behaviors<sup>12</sup></li> <li>Orx-S might be involved in compulsive and repetitive behaviors<sup>49,84</sup></li> <li>Potential therapeutic use of orexin antagonists to reduce motor impulsivity induced by psychostimulants<sup>62</sup></li> </ul>
<b>Reward, motivation, and feeding</b>	<ul style="list-style-type: none"> <li>Within RDoC matrix, deficit in positive valence systems (eg, sustained responsiveness to reward) in ADHD<sup>7</sup></li> <li>Dopamine reward pathway disruption is likely “associated with motivation deficits in ADHD”<sup>85</sup></li> <li>Within RDoC matrix, deficit in negative valence systems (eg, frustrative non-reward) in ADHD<sup>7</sup></li> <li>Deficiencies in the mesolimbic reward pathway might underlie impaired social skills in children with ASD<sup>86</sup></li> <li>Individuals with ASD exhibit atypical neural processing of “social, non-social, and potentially restricted interest rewards”<sup>87</sup></li> <li>Reward system dysfunction has been suggested to support the emergence and maintenance of ASD symptoms (social and non-social)<sup>88</sup></li> <li>Atypical eating behaviors are more common among children with ASD, than in children with other disorders or with typical development<sup>89</sup></li> <li>Association between eating disorders/eating pathology and ADHD in adolescents<sup>90</sup></li> <li>Positive association between body mass index and ADHD<sup>91</sup></li> </ul>	<ul style="list-style-type: none"> <li>Orexin neurons might modulate the reward system<sup>24</sup></li> <li>Orexins might have a role in translating motivational activation into adaptive behavior<sup>44</sup></li> <li>Orexin has a role in feeding behaviors<sup>92</sup></li> <li>Orx-S regulates dietary preferences and the anticipation of food rewards<sup>93</sup></li> <li>Presence of orexin cells in the lateral hypothalamus, a crucial site of food intake regulation<sup>48</sup></li> <li>Orexin-based therapeutics have been proposed to increase food intake in patients with anorexia nervosa<sup>25</sup></li> <li>Orexin signaling disruption leads to increased body mass index<sup>94</sup></li> <li>Orexin neurons may promote foraging behavior<sup>95</sup></li> <li>Orexin might be seen as promotor of homeostatic eating<sup>95</sup></li> </ul>
<b>Fear and social play</b>	<ul style="list-style-type: none"> <li>Social deficits may be affected by hypothalamic atrophy in ASD<sup>96</sup></li> <li>Morphofunctional alterations of the hypothalamus have been implicated in ASD's pathophysiology, particularly atypical socio-emotional behaviours<sup>97</sup></li> <li>Unusual fears common in ASD<sup>98</sup></li> <li>Fear circuits' abnormalities during extinction learning and recall have been reported in ADHD<sup>99</sup></li> <li>Within RDoC matrix, deficit in systems for social processes (eg, social communications) in ADHD<sup>7</sup></li> </ul>	<ul style="list-style-type: none"> <li>Orx-S might modulate expression of social play behavior and fear<sup>45,100</sup></li> <li>Activity of orexin neurons might promote “emotional arousal or fear-related responses” upon presentation of emotional stimuli<sup>24</sup></li> <li>Orx-S' regulatory role in social (fear) behavior is partly sex-dependent<sup>45</sup></li> <li>Orx-S dysregulation might have a contribution in the etiology of anxiety disorders and fear<sup>101</sup></li> <li>Orexin neurons might modulate behavioral fear expression<sup>60</sup></li> <li>Orx-S may modulate conditioned fear<sup>102</sup></li> <li>Orexin deficiency might probably affect social behaviour and emotional regulation<sup>103</sup></li> </ul>
<b>Executive functions and memory</b>	<ul style="list-style-type: none"> <li>Working memory is impaired in ASD<sup>104</sup></li> <li>Within RDoC matrix, deficit in cognitive systems (eg, working memory) in ADHD<sup>7</sup></li> <li>Using RDoC framework, common thinking patterns and behaviours in ASD (eg, rigidity of thinking, impaired attention) may represent cognitive features<sup>4</sup></li> </ul>	<ul style="list-style-type: none"> <li>Orexin transmission is possibly “involved in executive functions”<sup>62</sup> and other cognitive functions, such as cognitive flexibility, the activation of learning, and the acquisition and consolidation of memory<sup>12,27,94</sup></li> <li>Orexin deficiency modulates particular cognitive flexibility's phases<sup>105</sup></li> <li>Orexin has a sexually dimorphic role in regulating cognitive flexibility<sup>105</sup></li> <li>Orx-A may enhance some cognitive deficits<sup>13</sup></li> <li>Orexin agonists may hypothetically benefit individuals with “age-related cognitive decline, attention disruptions caused by sleep deprivation or circadian dysregulation, and ADHD”<sup>27</sup></li> </ul>

**Abbreviations:** ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; Orx-S, orexin/hypocretin system; NDDs, neurodevelopmental disorders; Orx-A, orexin-A/hypocretin-I; DCD, developmental coordination disorder; HPA, hypothalamus-pituitary-adrenal; RDoC, Research Domain Criteria.

## Arousal

Direct connection between orexin and the domain arousal/regulatory system (construct: arousal, and construct: sleep-wakefulness) is already established.<sup>8</sup> “Orexin is a key component of the arousal system”,<sup>36</sup> and Orx-S is a “key player in arousal stability”.<sup>27</sup> Monoaminergic neurons in the brainstem are strongly excited by orexin neurons,<sup>69</sup> and this might represent the main plausible explanation for orexin’s potential role in NDDs. On the other hand, the excitation of orexin neurons by external or internal stimuli leads to increased neurotransmission and activation of brain regions/circuits and peripheral responses, ie, including promotion of attention, cognition, and learning, as well as activation of the hypothalamus-pituitary-adrenal (HPA) axis.<sup>36</sup>

Deficient and/or excessive arousal pathways may be linked to ADHD,<sup>10</sup> ie, “reduced HPA axis responsiveness to stress”.<sup>64</sup> The intranasal administration of Orx-A may enhance arousal and, by consequence, alleviate cognitive impairments induced by hypoarousal (eg, attentional impairment due to sleep deprivation).<sup>25</sup> Theoretically, based on estimated orexin levels in patients with ADHD and resultant impairments, orexin replacement (ie, agonists) or orexin antagonist therapy may be needed to target the dysfunctionality of the Orx-S. Baykal et al found that Orx-A levels were significantly lower in the inattentive ADHD subtype, compared to the hyperactive and combined subtypes.<sup>13</sup> It seems reasonable to suggest that the choice of orexin-based therapeutic agents might be guided by the predominance of inattention or hyperactivity/impulsivity, but also by possible coexisting sleep problems, which might suggest whether or not imbalance in the arousal system is due to hypo- or hyperstimulation. Furthermore, pupil size reflects the arousal network's activity,<sup>106</sup> and might be used as an indirect indicator of arousal level. Thus, pupillometry belongs to the diagnostic procedure in the RDoC domain arousal/regulatory system.<sup>8</sup> Orx-A might modulate pupil size.<sup>71</sup> This may be important in the context of NDDs as children with hyperactive/impulsive symptoms in ADHD have increased pupil dilation in response to happy faces,<sup>66</sup> while children with ASD show “decreased pupil responses to human faces” and tonic pupil size differences compared to age-matched controls (ie, larger pupil size in ASD).<sup>67</sup> A recently published meta-analysis revealed that measuring pupil size and reactivity differs in individuals with and without ASD.<sup>68</sup>

According to Taylor and Corbett, the HPA axis is slow to respond to physical or physiological manipulations in ASD.<sup>63</sup> A key, common finding is hyper-responsiveness in otherwise benign social situations or in those involving unpleasant stimuli, and hypo-responsiveness to stressors involving social-evaluative threat.<sup>63</sup> Overall cognitive dysfunctions may result from an increase in arousal (ie, overstimulation), but diminished arousal (ie, understimulation) may lead to inattentiveness and cognitive dysfunction.<sup>10,26,36</sup> In summary, compounds that activate the Orx-S usually represent a treatment option for hypoarousal, while compounds that suppress this system are utilized in treatment of hypervigilance (ie, insomnia and addiction-related hyperarousal).<sup>28</sup>

The arousal spectrum of sleep and wakefulness<sup>26,36</sup> could represent a spectrum of a possible dysfunctionality of the Orx-S,<sup>70</sup> considering that both too much and too little stimulation may lead to different levels of arousal and, eventually, different levels of cognitive dysfunction. The constellation of various cognitive symptoms, including cognitive impairment, which can be described as “brain fog”,<sup>107</sup> found also among patients with ASD,<sup>65</sup> may be potentially linked to impairments in the Orx-S.<sup>70</sup>

## Wakefulness and Sleep

In addition to two key neurotransmitters (ie, histamine from the tuberomammillary nucleus and GABA from the ventrolateral preoptic [VLPO] nucleus), the lateral hypothalamus' orexin-containing neurons and the suprachiasmatic nucleus' melatonin-sensitive neurons are also responsible for the regulation of the sleep/wake switch.<sup>26,35,36</sup> Orexin neurons, as histamine neurons do, modulate wakefulness and sleep,<sup>35</sup> and antihistamine agents block orexin’s excitatory effect.<sup>12</sup> Benzodiazepines act by sensitizing GABA receptors,<sup>35</sup> while orexin antagonists do not act directly on them.<sup>36</sup> GABA<sub>B</sub> receptors on orexin-producing neurons are necessary to stabilize and consolidate sleep/wake states,<sup>108</sup> and paradoxical reactions to benzodiazepines<sup>109</sup> might reflect possible Orx-S abnormality in individuals with NDD. Suvorexant, used in treatment of insomnia, represents a novel mechanism of action, by “inhibiting the wakefulness-promoting orexin neurons”.<sup>35</sup> The orexin receptor antagonists have more favourable adverse effects than conventional hypnotics,<sup>27</sup> and may be treatment options if traditional hypnotics are contraindicated (ie, benzodiazepines).<sup>28</sup>

Kohyama proposed shared neuronal mechanisms underlying insomnia in ASD and ADHD, which possibly involve increased Orx-S activity, reduced serotonergic and melatonergic system activity, and rapid eye movement sleep reduction.<sup>17</sup> Narcolepsy and neuropsychiatric disorders may share some clinical features, with an orexin deficiency proposed as a pathophysiological mechanism.<sup>48</sup> Narcolepsy, one of hypersomnolence's central disorders, is classified into two types: narcolepsy type 1 (ie, NT1; narcolepsy with cataplexy [characterized by cataplexy and cerebrospinal fluid Orx-A deficiency], and narcolepsy type 2 (i.e., “narcolepsy without either cataplexy or orexin deficiency”).<sup>48,110</sup> The profound loss of orexin neurons in NT1 may result from exposure to antigens and, consequently, autoimmune reactions that result in the selective loss or dysfunction of orexin neurons in the lateral hypothalamus of genetically predisposed individuals.<sup>26,36,50,110</sup> NT1 may be considered as a hypothalamic disorder that affects “motor, psychiatric, emotional, cognitive, metabolic, and autonomic functions”; thus, it may not affect only sleep–wake regulation.<sup>110</sup>

Symptoms of ADHD frequently co-occur with narcolepsy, accounting for more than 30% of cases.<sup>111</sup> On the other hand, children with narcolepsy experience treatment-resistant ADHD symptoms at high levels.<sup>112</sup> Narcolepsy may be more common in ADHD than among the general population; however, it remains unclear what the proportion of undiagnosed narcolepsy is in patients with ADHD.<sup>113</sup> Furthermore, ADHD and narcolepsy may be genetically related.<sup>114</sup> Although based on a limited number of cases, a pathogenetic link between ASD and narcolepsy has been suggested.<sup>115</sup> It has also been argued that social functioning is commonly impaired in children with NT1, especially in girls, and it has been suggested that orexin deficiency affects emotional regulation and social behavior, in addition to causing cataplexy and hypersomnolence in children with narcolepsy.<sup>103</sup>

## Sensorimotor System, Sensory Processing, and Perception

The rapid loss of orexin neurons is likely “involved in the pathophysiology of the movement disorders”, frequently observed at disease onset in childhood NT1, while secondary dopaminergic abnormalities might also be involved.<sup>50</sup> The orexin exerts an excitatory effect on dopamine neurons in the ventral tegmental area.<sup>81</sup> According to Burdakov, sensory-evoked and self-generated movements are regulated by the orexin neurons.<sup>80</sup> Even more, the Orx-S is related to spontaneous physical activity.<sup>24</sup> Given that several motor deficits are associated with the loss of orexins and that Orx-S may orchestrate central motor control,<sup>51</sup> motor phenomena might also be conceptualized as a spectrum, with the Orx-S playing an important role.<sup>70</sup>

Atypical sensory processing is a common feature of many neurodevelopmental disabilities, including ADHD and ASD.<sup>2,75</sup> While sensory abnormalities have been included in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders in the core diagnostic criteria for ASD, this is not the case for ADHD.<sup>21,75</sup> Nevertheless, the similarity in sensory symptoms imply that there may be a common neuronal mechanism of sensory dysfunction across developmental disabilities.<sup>75</sup>

Altered touch and pain processing have been tentatively confirmed in several psychiatric conditions, with pain processing in ASD and ADHD being a focus of research interest.<sup>116</sup> While hypersensitivity to pain is reported in a single study on ADHD, the findings are inconsistent in several studies in ASD.<sup>116</sup> Psychiatric conditions' underlying pathophysiology could be elucidated by a better understanding of pain processing in them, particularly due to the psychobiological overlap between these pathways.<sup>116</sup> Pain regulation closely associates with the Orx-S.<sup>117,118</sup> Manipulation of orexin neurons influences pain-related behaviors; therefore, activation of the Orx-S has been proposed as a novel approach to analgesic treatment.<sup>28</sup> In addition, suvorexant has shown efficacy in improving sleep time and reducing next-day pain sensitivity, such as in patients with fibromyalgia and comorbid insomnia.<sup>119</sup>

All levels of rats' olfactory system include both orexins and orexin receptors, suggesting a possibility that these neuropeptides modulate olfactory perception.<sup>82</sup> People with ADHD have been shown to have altered perceptual functions such as increased olfactory detection threshold.<sup>76</sup> Relative to typically developing peers, children with ASD also demonstrate altered olfactory function.<sup>77</sup>

Orx-A might modulate eyelid position, and possibly convergence movement and eye alignment.<sup>71</sup> Volitional eye movement control is associated with ADHD traits—more specifically, inattentive traits with premature anticipatory eye movements—and this phenotypic association appears attributable to shared genetic etiology.<sup>78</sup> Several eye movement studies provide evidence of subtle processing differences in both language and social



processing with potential to impact everyday communication in ASD.<sup>79</sup> Attention levels during visual exploration might vary, and thus, “depending on intrinsic states”, eye movement may represent attentional load.<sup>120</sup>

## Impulsivity and Compulsivity

Impulsivity and compulsivity are “forms of cognitive inflexibility”.<sup>26</sup> Both impulsivity and compulsivity are symptoms of many NDDs, with an example of ADHD, ASD, Tourette’s syndrome/tic disorders, OCD, and stereotyped movement disorders to be possible categorized as impulsive–compulsive disorders, based on impulsivity and compulsivity endophenotypes present.<sup>26</sup> Filardi et al showed more severe ADHD hyperactive–impulsive symptoms present in patients with NT1 versus in narcolepsy type 2 and healthy controls, indicating orexin’s direct role in modulating impulsivity.<sup>83</sup> Furthermore, stereotypical behaviors are also associated with orexins.<sup>12</sup> The involvement of the Orx-S in compulsive and repetitive behavior is indicated by several preclinical findings,<sup>49,84</sup> and study in rats has suggested the potential therapeutic use of orexin antagonists to reduce motor impulsivity induced by psychostimulants.<sup>62</sup>

## Reward, Motivation, and Feeding

It has been indicated that orexin neurons modulate the reward system<sup>24,26</sup> and proposed orexin’s role in translating motivational activation into adaptive behaviors.<sup>44</sup> There is establish connection between orexin and RDoC positive valence system domains (construct: reward responsiveness; subconstruct: initial response to reward).<sup>8</sup> In ADHD, a deficit in sustained responsiveness to reward (RDoC - positive valence system) and frustrative non-reward (RDoC – negative valence system) are present<sup>7</sup> and dopamine reward pathway’s disruption is thought to be in relation with motivation deficits.<sup>85</sup> Regarding ASD, it has been shown that deficiencies in the mesolimbic reward pathway underlie impaired social skills in children with this disorder.<sup>86</sup> Individuals with ASD also exhibit atypical neural processing of “social, non-social, and potentially restricted interest rewards”.<sup>87</sup> Moreover, reward system dysfunctions have been suggested to support the emergence as well as the maintenance of ASD symptoms, both social and non-social.<sup>88</sup> The impaired motivational process, affecting both social and non-social rewards, has been shown to possibly characterize ASD.<sup>121</sup>

In the context of motivation and reward, it should be mentioned that orexin plays a role in feeding behaviors.<sup>27,36,92</sup> Orexin neurons may promote “phenomena involved in successful foraging, including food-anticipatory locomotor behavior, olfactory sensitivity, visual attention, spatial memory, and mastication”.<sup>95</sup> Orexin might stimulate food intake, motivation for food rewards and promote binge eating.<sup>27,28</sup> Taking the orexin as promotor of homeostatic eating<sup>95</sup> opens possibilities to consider the Orx-S involvement in the whole spectrum of eating disturbances observed in NDDs.

The Orx-S regulates both dietary preferences and the anticipation of food rewards.<sup>93</sup> This is of particular interest, as more than 70% of children with ASD have atypical eating behaviors, with limited food preferences being the most common feature.<sup>89</sup> In addition to ASD,<sup>89</sup> few studies have found an association between eating disorders/pathology and ADHD.<sup>90,122,123</sup> During childhood, individuals with ADHD could be at risk for disordered eating, while eating disorders - including AN, bulimia nervosa, and binge eating - may occur later on.<sup>122</sup> Changes in dopamine receptors have been connected with reward system insufficiency.<sup>123</sup> Reward deficiency syndrome might link genetic differences in the dopaminergic system to behavioral phenotypes and represent “a transdiagnostic feature between ADHD, eating disorders, obesity, and substance-abuse disorders”,<sup>122</sup> all of which are associated with the Orx-S. Cortese et al have been suggested the Orx-S role in feeding behaviors in ADHD.<sup>14</sup> Orexin-based therapeutics have been proposed to increase food intake in patients with AN.<sup>25</sup> Neither AN nor bulimia nervosa are currently grouped within ESSENCE. On the other hand, avoidant-restrictive food intake disorder (ARFID), highly comorbid with ASD,<sup>124</sup> is extremely common in ESSENCE,<sup>2</sup> and ADHD might be associated with restrictive eating, too.<sup>125</sup> Generally defined as restriction of food intake that leads to functional impairment,<sup>2</sup> ARFID could be considered a disorder related to impairment of the Orx-S.

Some studies have shown increased rates of neurodevelopmental problems among children with obesity,<sup>126</sup> and a higher prevalence of obesity in children and adolescents with ASD than in a neurotypical controls.<sup>127</sup> In addition, 43% of the children who are overweight or obese normalized weight when receiving stimulant treatment for their ADHD.<sup>128</sup>

As orexin modulates obesity and reward,<sup>129</sup> the findings of a recent study of a positive association between body mass index and ADHD,<sup>91</sup> might be of interest. The authors proposed that genetic factors related to body mass index—particularly reward system-related ones—might be involved in this association. Conceptualizing eating pathologies as spectra and the role of the Orx-S in motivation and reward, Orx-S dysfunction could be considered a “common pathway” for associations of feeding/eating disturbances/disorders with NDDs.

As we have already mentioned, the role of orexin has been recognized within positive valence system.<sup>8</sup> This is of special importance, as the complex neurobiology of anhedonia may involve dysfunction of the pathways regulating reward and motivation.<sup>26,130,131</sup> In the context of anhedonic phenotype<sup>132</sup> it might be of interest that the orexinergic innervation of the ventral pallidum seems to be of importance in hedonic valence, during which processing, the orexin's signaling might be amplified by the insula.<sup>28</sup> Reduced orexin-signaling might be implicated in anhedonia.<sup>27</sup> Several psychopathologies (ie, ADHD and major depressive disorder) have been associated with low hedonic tone,<sup>131</sup> with hedonic responsiveness being what depressive and ADHD's inattentive symptoms might have as a common endophenotype.<sup>133</sup> Hedonic deficits are also reported in the context of a broader autism phenotype, as autistic traits were associated with social hedonic capacity being reduced in a general population.<sup>134</sup> In addition, anhedonia is a component of depression and schizophrenia.<sup>135</sup> Considering that disorders of intellectual development, ASD, and ADHD, as childhood NDDs, and schizophrenia and bipolar disorder, as adult psychiatric disorders, could be conceptualized as lying on a same neurodevelopmental continuum,<sup>3</sup> a hedonic responsivity might be of interest for their etiology and differential diagnostic challenges. In summary, anhedonia or hedonic valence/tone and Orx-S function might represent an important research area, in this regard.

## Fear and Social Play

Another RDoC domain, the negative valence system domain (construct: acute threat “fear”) has also been connected to orexin.<sup>8</sup> In animal models, the Orx-S modulates the expression of social play behaviors and fear.<sup>45,100</sup> In addition, orexin neurons fire maximally during exploratory behavior.<sup>136</sup> Moreover, the activity of orexin neurons might promote responses related to fear or emotional arousal upon presentation of emotional stimuli.<sup>24</sup> Orx-S' regulatory role in social (fear) behavior is partly sex-dependent, with observed reduced sociability and decreased social novelty behavior in orexin-deficient female animal.<sup>45</sup> However, the same study shows that “prolonged expression of social avoidance after social fear conditioning” could be attributed to orexin deficiency in both sexes.

Wolfe et al suggested that numerous neurophysiological functions and phenotypes connected to social deficits may be affected by hypothalamic atrophy and may explain symptomatologic commonalities in ASD and several other psychiatric diagnoses.<sup>96</sup> The severe socioemotional dysfunctions following hypothalamic lesions, and morphofunctional alterations of the hypothalamus have been implicated in ASD's pathophysiology, particularly atypical socio-emotional behaviour.<sup>97</sup>

The Orx-S modulates fear (threat) learning by acting “upstream of the amygdala via the noradrenergic locus coeruleus”.<sup>60,101</sup> Thus, Orx-S dysregulation might have a contribution to the etiology of anxiety disorders and fear.<sup>101</sup> Orexin neurons in the hypothalamus, when activated by fearful stimuli, increase sympathetic nervous outflow,<sup>60</sup> while at the same time, the lack of orexin might inhibit sympathetic activity.<sup>137</sup> The Orx-S may modulate conditioned fear, and selective Orx1R antagonism might be a treatment option for disorders related to fear.<sup>102</sup> Unusual fears have long been identified as common among patients with ASD.<sup>98</sup> Recently, fear circuits' abnormalities during extinction learning and recall have been reported in medication-naïve, non-traumatized subjects with ADHD.<sup>99</sup>

## Executive Functions and Memory

A role of orexin in cognitive processes and executive functions has been suggested.<sup>27,62</sup> Its deficiency modulates particular cognitive flexibility's phases,<sup>105</sup> as orexin plays an important part in activation of learning, and acquisition and consolidation of memory.<sup>12,94</sup> Working memory and/or cognitive control—two RDoC subconstructs associated with cognitive system—are impaired in ADHD, ASD, mild intellectual disability, and borderline intellectual functioning.<sup>7,104,138,139</sup> Several studies have shown an increased risk of developing neurodegenerative disease during later life for patients with a history of ADHD,<sup>140</sup> including a large multi-generation cohort study in Sweden that associated ADHD with AD and any dementia across generations.<sup>141</sup> However, well-designed prospective longitudinal studies are necessary to reassure the validity of estimated

neurodegenerative risk for patients with ADHD.<sup>140</sup> Future studies would preferably also investigate the possible role of an underlying Orx-S dysfunction.

## The Orx-S Dysfunction in Some Conditions Within or Associated with ESSENCE

Other than ADHD and ASD, there are several other neurodevelopmental conditions under the ESSENCE umbrella—as well as ESSENCE associated conditions—in which Orx-S dysfunction may have a role (Figure 1; Table 2). This brings to mind the proposed diagnosis of deficit in attention, motor control, and perception that has been in clinical use in Scandinavia,<sup>142</sup> although it is not recognized as an official diagnostic category. Nowadays, clinicians usually use DCD (or Developmental motor coordination disorder<sup>22</sup>) with associated ADHD, instead. However, DCD is still one of the most neglected group of problems under the ESSENCE umbrella as many clinicians fail to recognize it, and this has an impact on providing effective interventions.<sup>2</sup> Other developmental abnormalities accompanying the sensorimotor disability of DCD<sup>143</sup> may be a clinical manifestation of dysfunctionality in the Orx-S. In addition, deficits in attention, motor control, and perception may be co-occurring with a variety of problems and overlapping conditions, including depression and anxiety,<sup>142</sup> diagnosis that already have been associated with Orx-S dysfunction. Altogether, this underlies the need to focus more attention on DCD in clinical practice and in research.<sup>2</sup> Evaluating the role of Orx-S in association across several symptom domains, viz, attention, motor control, and perception, might be of importance in understanding the basic neurobiology of DCD and associated ADHD.

**Table 2** Proposed Role of the Orx-S in Disorders and Conditions Associated with ESSENCE

Symptoms, Conditions, Disorders, or Diagnoses	Proven or Plausible role of Orx-S in the Context of Presented Symptoms, Generating Orx-S Dysfunction Hypotheses
<b>OCD</b>	<ul style="list-style-type: none"> <li>OCD symptoms may be linked to orexinergic system and its interactions with the dopaminergic systems (based on results from animal models)<sup>49</sup></li> </ul>
<b>Some types of epileptic seizures</b>	<ul style="list-style-type: none"> <li>The mean serum Orx-A levels in patients with some types of epileptic seizures were found to be significantly higher compared to those with non-epileptic seizures<sup>144</sup></li> </ul>
<b>RAD/DSED</b>	<ul style="list-style-type: none"> <li>Serum Orx-A levels seem to be attachment-related; positively associated with secure attachment scores and negatively with insecure (avoidant, anxious/ambivalent) attachment total scores in healthy individuals<sup>145</sup></li> </ul>
<b>BPS</b>	<ul style="list-style-type: none"> <li>Orx-A was found to be significantly decreased in individuals with Down's syndrome<sup>146</sup></li> <li>Orexin might have a role in sleep dysfunction in an animal model of tuberous sclerosis complex<sup>147</sup></li> <li>Lower levels of cerebrospinal fluid orexin in patients with Prader–Willy syndrome compared to control subjects<sup>148</sup></li> </ul>
<b>FAS/FASD</b>	<ul style="list-style-type: none"> <li>Orx-A neurons areas and volumes were significantly smaller in groups not exposed to prenatal alcohol than in the group with chronic alcohol exposure, while orexinergic boutons' density in the anterior cingulate cortex was lower in the chronic alcohol group than in the other groups (in an animal model)<sup>149</sup></li> <li>Embryonic ethanol exposure, although low-dose, had various, ongoing, and asymmetric effects on the early development of orexin neurons in the hypothalamus, which resulted in abnormalities of “their ultimate location that may contribute to behavioral disturbances”<sup>150</sup></li> <li>Excessive orexinergic neuron activity contributes to motor hyperactivity among animals after a perinatal alcohol exposure; however, the antagonism of Orx1R may alleviate these symptoms<sup>151</sup></li> </ul>
<b>PANS/PANDAS</b>	<ul style="list-style-type: none"> <li>Symptomatic overlap between sleep problems in PANS with other sleep disorders, such as narcolepsy and Kleine–Levin syndrome,<sup>152</sup> could also suggest an Orx-S dysfunction in the pathogenesis of sleep alterations in PANS,<sup>70</sup> as it has been suggested that orexin dysregulation also plays a role in the pathophysiology of Kleine–Levin syndrome<sup>153</sup></li> <li>Sleep, motor, and cognitive symptoms in PANS<sup>152</sup> imply that Orx-S dysfunction might plausibly have a role in the development of PANS<sup>70</sup></li> <li>Some children with NTI also have high ASLO titers<sup>50</sup> implying hypothetically that Orx-S dysfunction might play a role in the PANDAS, as well</li> </ul>

(Continued)

Table 2 (Continued).

Symptoms, Conditions, Disorders, or Diagnoses	Proven or Plausible role of Orx-S in the Context of Presented Symptoms, Generating Orx-S Dysfunction Hypotheses
<b>Catatonia and Stiff-Man Syndrome</b>	<ul style="list-style-type: none"> <li>• Catatonia, long considered a motor disorder, might be also understood as an evolutionary-based fear response ("Scared Stiff")<sup>154</sup> and thus potentially connected with orexin, as Orx-S has a role in the context of fear (ie, in fear memory and impaired freezing response)<sup>8,28,155</sup></li> <li>• Orexin reduction is associated with reduction in motor control<sup>153</sup></li> <li>• Akinetic catatonia may be associated with GAD65 antibodies<sup>156</sup></li> <li>• Most patients with Stiff-Man syndrome have serum GAD65 antibodies<sup>157</sup></li> <li>• Orexin neurons activate the GAD65 network of the LH submodule which governs physical activity and overactivation in GAD65<sub>LH</sub> cell leads to hyperlocomotion<sup>158</sup> thus, GAD65 may suggest a "common pathway" how Orx-S dysfunction is related to catatonia and Stiff-Man syndrome, and ESSENCE-related conditions with motor symptoms</li> </ul>
<b>ME/CFS</b>	<ul style="list-style-type: none"> <li>• Symptoms of ME/CFS such as chronic fatigue, post-exertional malaise, and "brain fog"<sup>107</sup> might be associated with Orx-S dysfunction</li> <li>• Post-COVID-19 syndrome, called as "long COVID" have features that might follow ME/CFS<sup>159</sup></li> <li>• Autoantibodies may contribute to both ME/CFS and post-COVID illness symptoms<sup>159</sup></li> <li>• Orexin receptor antibodies (of importance for sleep and fatigue)<sup>159</sup> were found in patients with COVID-19<sup>160</sup> showing that ME/CFS might potentially be connected with Orx-S dysfunction</li> <li>• Described clinical observation of several symptoms overlapping between CFS and ASD, including brain fog and fatigue, although not proven in one study<sup>161</sup></li> <li>• CFS is one of the indications that might be approached with orexinergic agents<sup>27</sup></li> </ul>
<b>Fibromyalgia</b>	<ul style="list-style-type: none"> <li>• Fibromyalgia is associated with a variety of symptoms, including non-refreshing sleep, debilitating fatigue, joint stiffness and irritable bowels;<sup>162</sup> symptoms that might be associated with Orx-S such as fatigue, sleep<sup>159</sup> and gastrointestinal functions<sup>163,164</sup></li> <li>• Higher incidence of NDDs has been observed in juvenile fibromyalgia<sup>162</sup></li> <li>• ADHD and certain fibromyalgia subtypes might have etiological pathways in common<sup>165</sup></li> <li>• The orexin antagonist, suvorexant, has shown efficacy in improving sleep time and reducing next-day pain sensitivity in patients with fibromyalgia and comorbid insomnia<sup>119</sup></li> </ul>
<b>Connective tissue disorders, HSD/hEDS</b>	<ul style="list-style-type: none"> <li>• Connective tissue disorder (ie, hEDS) may underlie ESSENCE-related problems during childhood<sup>166</sup></li> <li>• HSD/hEDS may be associated with anxiety disorders, chronic pain, fatigue, and ADHD/ASD,<sup>167,168</sup> all of this might be associated with Orx-S dysfunction</li> </ul>

**Abbreviations:** ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; OCD, obsessive-compulsive disorder; Orx-S, orexin/hypocretin system; Orx-A, orexin-A; Orx1R, orexin type 1 receptor; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; RAD, reactive attachment disorder; DSED, disinhibited social engagement disorder; BPS, behavioral phenotype syndromes; PANS, pediatric acute-onset neuropsychiatric syndrome; PANDAS, pediatric acute-onset neuropsychiatric disorder associated with streptococcal infection; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; ME, myalgic encephalomyelitis; CFS, chronic fatigue syndrome; HSD, hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos syndrome; GAD65, glutamic acid decarboxylase 65; ASLO, anti-streptolysin O; COVID-19, coronavirus disease 2019; LH, lateral hypothalamus; NT1, narcolepsy type 1 or narcolepsy with cataplexy.

## Plausible Explanation Models for Orx-S Dysfunction Pathways Within ESSENCE

Our understanding of Orx-S potential and implications in pathophysiology of ESSENCE is complicated by the several aspects. These include orexin receptor signaling's high level of diversity, the broad spread of orexin neurons projections within the brain, orexin's ability to trigger responses in many tissues in addition to the central nervous system, its sexual dimorphisms, and the orexin physiology significantly differing among species.<sup>25,29–31,45,105,169,170</sup> However, there are several hypothetical considerations for the Orx-S dysfunction pathways in ESSENCE, raised as research questions. In Table 3 are given a few areas that might be of interest, and were not mentioned previously in this paper.

**Table 3** Research Questions Regarding the Role of Orx-S Dysfunction in ESSENCE, that Require Further Studies

Research Questions Based on Proposed Explanation Model	ADHD and ASD in the Context of Research Question	Rationale for Proposed Orx-S Dysfunction Role in ESSENCE
<b><i>Orx-S dysfunction role in the field of Immunopsychiatry</i></b>	<ul style="list-style-type: none"> <li>Potential role of neuroinflammation in the pathophysiology of ADHD has been supported by a recent review<sup>171</sup></li> <li>Associations between parental autoimmune diseases and ASD or ADHD in offsprings<sup>172,173</sup></li> <li>Anti-sense transcript to the HLA-DQB1 locus on chromosome 6 is elevated roughly twofold in people with ADHD<sup>174</sup></li> <li>Recent study with a large dataset suggested the role of HLA genes in ASD and intellectual disability<sup>175</sup></li> <li>HLA polymorphisms can possibly distinguish regressive and non-regressive ASD<sup>176</sup></li> <li>HLA-DPA1*01-DPB1*04 sub-haplotype “may exert a protective effect against regression”<sup>176</sup></li> <li>Serum GAD65 autoantibodies were found in some children with ASD or ADHD<sup>177</sup></li> </ul>	<ul style="list-style-type: none"> <li>Orx-A may reduce the production of pro-inflammatory cytokines, suggesting its immunomodulatory role<sup>164</sup></li> <li>Connection between the Orx-S, “the HPA-axis, and associated glucocorticoid secretion and/or sympathetic tone” may point toward the influence of orexin signaling pathways on peripheral immune function<sup>27,178</sup></li> <li>Sleep, stress, and peripheral immune responses interact robustly, highlighting orexin's central role in this relationship<sup>27</sup></li> <li>HLA and the T-cell receptor variants have strong predisposing effects on the destruction of orexinergic cells, and this destruction may be considered an autoimmune event<sup>179</sup></li> <li>HLA-DPB1*04:02 shows the strongest protection from narcolepsy<sup>180</sup></li> <li>Orexin activates the GAD65 network of the LH sub-module which governs physical activity<sup>158</sup></li> </ul>
<b><i>Orx-S dysfunction may be associated with alterations of the microbiome-gut-brain axis</i></b>	<ul style="list-style-type: none"> <li>Microbiome-gut-brain axis alterations might be responsible for the appearance of NDDs in children (ie, in ADHD)<sup>181</sup></li> <li>Association between alteration of gut microbiota composition and ASD has been suggested by recent meta-analysis<sup>182</sup></li> </ul>	<ul style="list-style-type: none"> <li>During gastrointestinal inflammation, Orx-A has potential role as one of central mediators of the microbiota-gut-brain interactions<sup>183</sup></li> </ul>
<b><i>Interplay between vitamin D and steroids with Orx-S may explain their role in NDDs</i></b>	<ul style="list-style-type: none"> <li>Steroid abnormalities of various kinds (cortisol, testosterone, estrogens, progesterone, and vitamin D) have been linked with ASD, suggesting an underlying cholesterol-steroid hormone pathway<sup>184</sup></li> </ul>	<ul style="list-style-type: none"> <li>Several possible mechanisms proposed to explain association between vitamin D deficiency and high risk of sleep disorders, one of which pointed to vitamin D receptor expression in human brain areas that play important roles in sleep regulation, such as the hypothalamus<sup>185</sup></li> <li>Orexin stimulates adrenocorticotropin and the secretion of corticosteroids<sup>12</sup></li> <li>Orexin receptors have been detected in many peripheral tissues, such as adrenal glands and male reproductive tract<sup>29,170</sup></li> <li>Sexual dimorphism of the Orx-S<sup>29,105</sup></li> <li>“Orexin stimulation induces an increased steroidogenesis”<sup>170</sup></li> <li>Orx-S might “act in a steroid-sensitive manner” on activation of the mesolimbic dopaminergic system<sup>81</sup></li> <li>Orx-S relate to testosterone production<sup>186</sup></li> <li>Orexin receptor mRNA in the adrenal glands was four-fold higher than in the male animal brain<sup>29</sup></li> </ul>
<b><i>Potential of orexin for orchestrating heart rate variability</i></b>	<ul style="list-style-type: none"> <li>Children with ADHD may exhibit an autonomic dysfunction - HRV's overall reduction and sympatovagal imbalance<sup>187</sup></li> <li>Different HRV measures may give significant insights into sustained attention, as well as in the impairments of behavioral and emotional regulation in ADHD<sup>188</sup></li> <li>HRV as indicator of “flexible and adaptive autonomic response systems”, has become a crucial part of the pathogenetic triad in proposed unifying theory for ASD<sup>189</sup></li> </ul>	<ul style="list-style-type: none"> <li>HRV during periods of non-stress was associated with greater stress resilience<sup>190</sup></li> <li>HRV belongs to the RDoC arousal domain<sup>8</sup></li> <li>Chronic lack of orexin results in a “blunted circadian variation of heart rate”<sup>191</sup></li> <li>Orx-S “integrates diverse inputs modulating arousal”<sup>27</sup> and controls some key features of cardiovascular “homeostatic output”<sup>192,193</sup></li> </ul>

(Continued)



Table 3 (Continued).

Research Questions Based on Proposed Explanation Model	ADHD and ASD in the Context of Research Question	Rationale for Proposed Orx-S Dysfunction Role in ESSENCE
<b><i>CACNA1C, as a novel explanation model for pathogenesis of some psychiatric disorders, could associates with the Orx-S dysfunction</i></b>	<ul style="list-style-type: none"> <li>• <i>CACNA1C</i> gene is associated with various psychiatric conditions<sup>194</sup></li> <li>• Association between <i>CACNA1C</i> voltage-gated calcium channel gene, autism, ADHD, schizophrenia and bipolar disorder<sup>195</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Sleep disorders (eg, insomnia and narcolepsy) have been associated with polymorphisms in the <i>CACNA1C</i> gene<sup>194</sup></li> <li>• <i>CACNA1C</i> gene encodes the alpha-1 subunit of L-type <math>Ca^{2+}</math> channels (<math>Ca_v1.2</math>) and their depletion seems to attenuate Orx-A "mediated excitation of wake-related neurons", in animal models<sup>194</sup></li> </ul>

**Abbreviations:** ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; OCD, obsessive-compulsive disorder; Orx-S, orexin/hypocretin system; Orx-A, orexin-A; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; HPA, hypothalamus-pituitary-adrenal; HLA, human leukocyte antigen; HRV, heart rate variability; NTL, narcolepsy type 1; NDDs, neurodevelopmental disorders; GAD65, glutamic acid decarboxylase 65; LH, lateral hypothalamus.

## Conclusion and Implications

We propose that Orx-S dysfunction might account for many symptoms in a variety of ESSENCE, especially in ADHD and ASD. As one of the key homeostatic neuropeptides linked to arousal, wakefulness, sleep, motor and sensory processing, mood and emotional regulation, fear processing, reward, feeding, attention, executive functions, and sociability – orexin might represent a missing puzzle-piece in the etiology of several disorders under the ESSENCE umbrella. In addition to the already proposed role of Orx-S dysfunction in ADHD and ASD, which we have attempted to highlight here, we would also like to stress the need for broader conceptualization of Orx-S dysfunction as a possible pathophysiological pathway in several other ESSENCE-associated conditions, potentially contributing to a new perspective in the whole field of neuropsychiatry/neurodevelopmental research.

More research is now needed to systematically review the available literature, and confirm the explanation model that our perspective suggests. Our paper has clear limitations, the main of which lies in the fact that this article is not a systematic study of all the available literature, and it could be affected by our own understanding of the topic and our subjectivity in selecting relevant evidence from published studies. Furthermore, our perspective has here been presented from a clinical point of view by clinicians; child and adolescent psychiatrists and child neurologists, in the future, this type of review should involve preclinicians and neuroscientists in the context of a broader neurotranslational research.

The main implications of our perspective paper are that there is (1) a need for a deeper, more systematically driven review that will include basic neurochemistry, neurobiology, and symptoms expressions; (2) a need for empirical, clinical studies testing proposed models, and (3) a need for testing available orexin agents in treatment studies of individuals affected by ESSENCE.

We hope that our perspective might serve as a glance through the window of opportunity to point researchers in directions that might provide new explanations and therapeutic possibilities to clinicians and, most importantly, generate new possibilities to help our patients obtain their maximal capacity and functionality and live a life of the best possible quality, which is essential in ESSENCE.

## Abbreviations

AD, Alzheimer's Disease; ADHD, Attention-Deficit/Hyperactivity Disorder; AN, Anorexia Nervosa; ARFID, Avoidant Restrictive Food Intake Disorder; ASD, Autism Spectrum Disorder; ASLO, Anti-Streptolysin O; BPS, Behavioral Phenotype Syndromes; CFS, Chronic Fatigue Syndrome; COVID-19, Coronavirus Disease 2019; DCD, Developmental Coordination Disorder; DSED, Disinhibited Social Engagement Disorder; ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; FAS, Fetal Alcohol Syndrome; FASD, Fetal Alcohol Spectrum Disorder; GABA, Gamma-Aminobutyric Acid; GAD65, Glutamic Acid Decarboxylase 65; hEDS, Hypermobile Ehlers-Danlos Syndrome; HLA, Human Leukocyte Antigen; HPA, Hypothalamus-Pituitary-Adrenal; HRV, Heart rate variability; HSD, Hypermobility Spectrum Disorder; LH,

Lateral Hypothalamus; ME, Myalgic Encephalomyelitis; NDD, Neurodevelopmental Disorder; NT1, Narcolepsy Type 1; OCD, Obsessive-Compulsive Disorder; ODD, Oppositional-Defiant Disorder; Orx-A, Orexin-A/Hypocretin-1; Orx-B, Orexin-B/Hypocretin-2; Orx1R, Orexin/Hypocretin Type 1 Receptor; Orx2R, Orexin/Hypocretin Type 1 Receptor; Orx-S, Orexin/Hypocretin System; PANDAS, Paediatric Acute-Onset Neuropsychiatric Disorder Associated with Streptococcal Infection; PANS, Pediatric Acute-Onset Neuropsychiatric Syndrome; RAD, Reactive Attachment Disorder; RDoC, Research Domain Criteria; VLPO, Ventrolateral Preoptic.

## Disclosure

The authors report no conflicts of interest in this work.

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