Collicular dysfunction in attention deficit hyperactivity disorder

Paul G. Overton *

Department of Psychology, University of Sheffield, Sheffield, Western Bank, S10 2TP, UK

Received 30 October 2007; accepted 18 November 2007

Summary Attention deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder characterised by (inter alia) an increase in distractibility. The current front-line pharmacotherapies for the treatment of ADHD, namely the psychostimulants methylphenidate and amphetamines, have clear abuse potential, hence there is a strong need to develop new drug treatments for this disorder. Central to this process is the identification of the pathophysiological changes which underlie ADHD. Given the heterogeneity of the disorder, multiple loci are probably involved, providing multiple potential therapeutic targets. Here, we hypothesise (Hypothesis 1) that one such locus is the superior colliculus (SC), a sensory structure intimately linked with distractibility and the production of eye and head movements. It is proposed that in ADHD, the colliculus is hyper-responsive, leading to the core symptom of increased distractibility. Hypothesis 1 is supported by: 1. ADHD patients show increased distractibility in tasks which are sensitive to collicular function; 2. ADHD patients have a general problem inhibiting saccades, the generation of which involves the SC; 3. Saccadic deficits in ADHD include defects in the production of saccadic types (anti-saccades and express saccades) which are particularly associated with the colliculus; 4. Covert shifts in attention (which also have been argued to involve the SC) are also impaired in ADHD; 5. Reading disorders are frequently co-morbid with ADHD; dyslexia (which is associated with eye movement problems) is linked to a specific visual perceptual deficit in the M pathway, a major recipient of which is the colliculus. Whether or not the SC is indeed hyper-responsive in ADHD as Hypothesis 1 suggests, the SC may well represent an important therapeutic target for drugs. In fact current psychostimulant therapies, which reduce distractibility, may already work at that level (Hypothesis 2), a contention which is supported by: 1. The colliculus and structures immediately afferent to it contain the neurochemical machinery necessary to respond to these drugs; 2. d-Amphetamine depresses visually evoked activity in the rat colliculus in a dose-dependent manner. Fortunately, again, even if psychostimulants do not achieve their therapeutic effects on distractibility in ADHD by acting on the SC, then the development of drugs which dampen stimulus-related activity in the colliculus could still represent an important novel path for drug development to take. Pharmacological manipulations of this structure are able to decrease distractibility. As a consequence, sensory responsiveness in the SC may represent a new model system for use in the development of non-addictive pharmacotherapies for ADHD.

© 2007 Elsevier Ltd. All rights reserved.
Attention deficit hyperactivity disorder: general features

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder of childhood, the main clinical symptoms of which are overactivity, impulsiveness and inattentiveness [1]. Estimates of the prevalence of the disorder in various countries range from 1.7% to 16.1%, depending on where and how the studies were conducted, and the diagnostic criteria employed [2]. Although ADHD is primarily thought of as a childhood disorder, ADHD symptoms persist into adulthood in between 8% and 43% of sufferers [2].

At present, the most common treatment for ADHD is pharmacotherapy with psychostimulants — either methylphenidate (Ritalin) or amphetamines [3]. Evidence suggests that psychostimulants are particularly effective at ameliorating attentional problems in ADHD [4]. Therapeutic efficacy aside, methylphenidate, like amphetamines, has clear abuse potential (e.g. [5]), and hence these substances are far from ideal as long-term treatments. However, the development of non-addictive pharmacotherapies is hampered by two inter-related obstacles. Firstly, despite the proposal of several models of the pathophysiological changes underlying ADHD (reviewed for example by [6]), the neurobiology of ADHD is far from completely understood [7]. Secondly, possibly partly because of this pathophysiological uncertainty, the therapeutic mechanism of action of current psychostimulant medications in ADHD is also far from clear [2].

Attention deficit hyperactivity disorder is a heterogeneous disorder [8], and sub-types lie at the heart of the diagnostic criteria in the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM IV; [9]), a widely used diagnostic standard. As a consequence, it is possible, or even likely, that several pathological loci exist in this population. Arguably a better strategy therefore for the development of treatments would be to focus on a specific aspect of symptomatology and attempt to trace its underlying cause, rather than trying to develop more global and integrative theories. In terms of ADHD symptomatology, distractibility has been considered by many to be one of most common symptoms (along with overactivity) of the disorder in children [10], a position that goes back to the neuropsychiatrist A.A. Strauss in the 1940s and 50s (e.g. [11]). Clinical accounts often describe ADHD children as distractible. For example, Thorley [12] states that hyperkinetic children show significantly more 'distractibility on examination' than controls, and 'Is often easily distracted by extraneous stimuli' is one of the core symptoms for 'Predominantly Inattentive Type' (and 'Combined Type') ADHD children according to the DSM IV [9].

Superior colliculus and distractibility

A structure which is intimately linked with distractibility is the midbrain superior colliculus (SC). The SC constitutes the main subcortical visual system, and is highly conserved across species. It appears to play a particular role in detecting and organising responses to unexpected phasic stimuli in a range of modalities [13], and particular emphasis has been placed on the involvement of the SC in orienting the head and eyes toward such stimuli (e.g. [14]). This facility is enabled by the fact that the superficial layers, which are exclusively visual (receiving direct input from the retina [15]), contain a retinotopic map of the visual field. The deeper layers, which are multi-modal, also contain sensory maps which are in register with each other and the superficial layer visual map [16], and connect with brainstem effector systems [13]. Consistent with its role in detecting unexpected phasic stimuli, work in a range of species has shown that collicular lesions lead to a decrease in distractibility (rat [17]; cat [18]; monkey [19]). In humans, disconnecting the colliculus from the controlling influence of the prefrontal cortex leads to an increase in distractibility [20], suggesting that the structure’s function of detecting and responding to unexpected (distracting) stimuli is preserved in humans.

Hypothesis 1: Attention deficit hyperactivity disorder involves a collicular dysfunction

Given the presence of distractibility in ADHD and the link between the SC and distractibility, we hypothesise that ADHD is associated with a collicular dysfunction. The SC is widely acknowledged to be an important part of the circuitry which generates eye movements (saccades; reviewed by [21]). Research in the monkey suggests that superficial layer neurons respond more vigorously to a stimulus if the stimulus is the target for a saccadic eye movement [22]. In terms of recent conceptualisations of the manner in which bids for motor expression, by systems (like the colliculus) capable of specifying actions, are processed by the brain...
Collicular dysfunction in attention deficit

[23], enhanced activity can be seen as putting a stronger 'bid' into the central selection device (hypothesised to be the basal ganglia), which makes the bid more likely to win and generate a motor output, hence the eye movement. As a consequence, it might be suggested that in ADHD, sensory responsiveness in the colliculus is abnormally high, leading to an increased tendency to respond — make eye and head movements — to stimuli activating the structure (this is referred to below as 'collicular hyper-responsivity' for short). Such an increased tendency to respond would be manifested outwardly as an increase in distractibility. In this regard it is interesting that decreasing inhibitory GABAergic tone in the SC with bicuculline (a GABA<sub>A</sub> receptor antagonist), which increases sensory responsiveness in the SC [24], produces irrepressible saccades in the monkey to the area of visual space subtended by the disinhibited part of the colliculus [25].

Although distractibility links ADHD and the SC, making the case for the involvement of the SC in ADHD plausible, further evidence is required if the case is to be truly convincing. With that in mind, we now turn to consider more direct evidence for a collicular dysfunction in ADHD. This evidence comes from two major sources: 1. Studies of distractibility in ADHD patients, and 2. Studies of eye movements (and covert shifts in attention) in ADHD patients.

Collicular lesions in animals lead to a decrease in distractibility for distractors that are unpredictable (unexpected) and extrinsic to the task, for example light and sound stimuli presented as animals perform a brightness discrimination task (e.g. [17]). Increases in distractibility have been reported in ADHD patients using tasks that are similar to this. Unpredictable presentation of a very loud hooter during a key pressing task lengthened reaction times more in hyperactive children than in controls [26], and unpredictable sounds presented during a visual categorisation task enhanced the number of response omissions more in ADHD children than controls [27]. Although supportive of the basic hypothesis of collicular hyper-responsivity in ADHD, the foregoing studies both used an indirect measure of distraction, namely changes in general task performance. When responses to the distractors themselves have been examined, again deficits have been reported in ADHD. More hyperactive children were found to respond (move their eyes) to unpredictable visual and auditory stimuli than controls as they read stories, and more stimuli elicited a response in hyperactive children than in controls [28]. Indeed, hyperactive children are more likely to glance off task than controls when performing a range of tasks [29]. These studies are particularly significant in the current context because, as stated above, in primates the SC plays a key role in the generation of saccades.

Indeed, given the intimate link between the SC and saccades, the literature on eye movements in ADHD is a fruitful source of evidence relevant to the collicular hyper-responsivity hypothesis. There are numerous reports of eye movement abnormalities in ADHD: in particular, ADHD sufferers seem to have problems with inhibiting saccades to visual targets [30,31]. The inability to inhibit saccades to targets could arise because of the increased 'pull' of the target location as a result of collicular hyper-responsivity. However, a more compelling case for collicular dysfunction in ADHD could be made if sufferers had difficulties with aspects of saccades in which the SC was particularly implicated. Evidence at present suggests that this is does appear to be the case for two specific saccadic types: anti-saccades and express saccades. Anti-saccades are saccades performed (in an experimental setting) in the direction opposite to a suddenly presented visual target [32]. The SC appears to be involved in the generation of this saccadic type [33], and ADHD sufferers have problems making these saccades [31]. Presumably, making a saccade in the direction opposite to a target is more difficult for ADHD sufferers because of the increased pull of the target. Interestingly, disconnecting the colliculus from the inhibitory controlling influence of the prefrontal cortex in humans leads to an increased error rate in anti-saccade tasks [20], and methylphenidate, the most widely used pharmacotherapy for ADHD [34], decreases both the error rate and anti-saccade latencies in anti-saccade tasks [31].

As well as playing a role in the production of anti-saccades, the SC also plays a role in express saccades: short latency saccades elicited under experimental conditions in which a temporal gap exists between the extinguishing of a fixation point and the appearance of a saccadic target [35]. Children suffering from ADHD make fewer of these express saccades [30]. Although, as with the data on anti-saccades, this is suggestive of a collicular dysfunction in ADHD, it is unclear why ADHD patients (with putative collicular hyper-responsivity) might make fewer express saccades. However, ADHD patients in this study were found to make more saccades with latencies shorter than traditional express saccades. Hence, one intriguing possibility is that under conditions of collicular hyper-responsivity, express saccades could be speeded so that some of them now fall outside the accepted range of latencies for express saccades.

Please cite this article in press as: Overton PG, Collicular dysfunction in attention deficit ..., Med Hypotheses (2008), doi:10.1016/j.mehy.2007.11.016
Finally on the subject of eye movements in ADHD, reading difficulties and ADHD are frequently co-morbid [36], and poor saccadic control has been reported in dyslexics [37]. It is now widely acknowledged that developmental dyslexia is associated with visual perceptual deficits, in particular with a deficit in the magnocellular (M) pathway that carries visual information centrally from the Y-type ganglion cells in the retina [38]. Although the M pathway is normally considered in relation to the geniculostriate visual system, in the present context it is potentially significant that SC receives inputs from Y-type retinal ganglion cells (which give rise to the M pathway), but not from X-type cells (which give rise to the parvocellular or P pathway [39]). The possibility therefore exists that ADHD and dyslexia may both arise in part due to a collicular dysfunction.

As well as overt shifts of attention using eye movements, attention can also be shifted covertly in the absence of eye movements [40]. According to the ‘premotor theory’ of attention, saccades and spatial shifts of attention (covert orienting) share a common functional module with a distinct neuronal basis, and hence the colliculus is considered to be involved in such shifts [41]. Covert shifts in attention are usually examined using the Posner [40] paradigm. In this, a target is presented after a cue. The target may either agree in position, when it appears, with direction implied by the cue, or it may not – so the cue is valid or invalid. Responses (button presses) to targets preceded by valid cues are faster than those preceded by invalid cues (or no cue), arguably because of covert shifts in attention to the cue’s location [40]. ADHD patients have been found to respond more slowly than controls in the invalidly cued condition, when attention is explicitly drawn to a target location by a cue (‘exogenous cuing’) [42]. The increased reaction times to invalidly cued targets in ADHD may arise as a result of the increased pull of the cued location due to collicular hyper-responsivity.

Hypothesis 2: Psychostimulants act therapeutically at the level of the superior colliculus in attention deficit hyperactivity disorder

Psychostimulants have been found to be effective against distractibility in ADHD patients (e.g. [43]). Following on from Hypothesis 1 above – that the SC is hyper-responsive in ADHD – we hypothesise that these drugs act therapeutically at the level of the SC (or afferent regulatory structures) in ADHD to effect distractibility improvements, presumably by dampening collicular sensory responsivity. Evidence for such a possibility comes from two major sources; 1. Neuropharmacological studies of the SC; 2. Recent studies from our laboratory on the effects of d-amphetamine on visually evoked activity in the SC of the rat.

The proximal effects of amphetamines are mediated by increasing synaptic levels of the monoamines dopamine (DA) and noradrenaline (NA; [44]) and, at higher doses, serotonin (5-HT; [45]). Methylenidate has a similar profile of action ([44]). Evidence suggests that in a wide range of species, including rats and humans, structures immediately afferent to the SC receive monoaminergic innervation (e.g. visual cortex; rat [46]; human [47]). Evidence also suggests that the SC itself receives extensive noradrenergic [48] and serotonergic [49] innervation, as well as a limited dopaminergic input [50]. Noradrenergic and serotonergic afferents appear to preferentially (but not exclusively) target the superficial visual layers [49, 51]. Since the visual response properties of deep layer neurons are critically dependent on superficial layer inputs [52], disrupted superficial layer function will affect all visually-related efferent activity from the colliculus.

So, structures immediately afferent to the SC, and the colliculus itself (especially the superficial layers) contain the neurochemical substrate necessary for psychostimulant action. As a consequence, we recently performed an investigation into the effect of d-amphetamine on visual responses within the superficial layers of the SC in the rat [53]. To this end, two studies were performed. In the first, d-amphetamine was administered systemically to rats under urethane anaesthesia whilst local field potential (LFP) and multi-unit (MUA) responses were recorded from the superficial layers of the SC in response to whole-field light flashes. In the second, d-amphetamine was administered directly into the colliculus itself whilst animals underwent the same stimulation and recording protocol. As can be seen in Fig. 1, systemic d-amphetamine dose-dependently decreased the responsiveness of cells in the superficial layers of the SC to visual stimuli, measured both by LFPs and MUA. Similar results were obtained with intra-collicular administration, suggesting that the effects of systemic d-amphetamine on visual responses in the superficial layers of the SC appear to be produced, at least in part, by a local action in the colliculus.

The main effect of d-amphetamine in our study was to reduce visual responsiveness in the superficial layers of the SC [53], consistent with the
predominantly inhibitory actions of NA and 5-HT on superficial layer visual responses [54,55]. By depressing visual responses in the SC, it might be anticipated that the expression likelihood of eye and head movements to unexpected visual stimuli would be reduced by d-amphetamine, leading to a reduction in distractibility and a correlative improvement in sustained attention. In support of this, intra-collicular micro-injection of S-CM-GTNH2, a 5-HT 1B-1D receptor agonist has been found to reduce distractibility in behaving rats [56]. Similarly, intra-collicular injections of the GABA agonist muscimol in the monkey, which lead to localised inhibition of the SC, decrease the production of saccades to the area of visual space subserved by the inhibited region [25].

Conclusion, implications and future directions

The current front-line pharmacotherapies for the treatment of ADHD, namely methylphenidate and amphetamines, have clear abuse potential, hence there is a strong need to develop new drug treatments for this disorder. Central to this process is the identification of the pathophysiological changes which underlie ADHD. Given the heterogeneity of the disorder, multiple loci are probably involved, providing multiple potential therapeutic targets. Here, we hypothesise (Hypothesis 1) that one such locus is the SC. It is proposed that in ADHD, the colliculus is hyper-responsive, leading to the core symptom of increased distractibility. Hypothesis 1 is supported by: 1. ADHD patients show increased distractibility in tasks which are sensitive to collicular function; 2. ADHD patients have a general problem inhibiting saccades, the generation of which involves the SC; 3. Saccadic deficits in ADHD include defects in the production of saccadic types (anti-saccades and express saccades) which are particularly associated with the colliculus; 4. Covert shifts in attention (which also have been argued to involve the SC) are also impaired in ADHD; 5. Reading disorders are frequently co-morbid with ADHD; dyslexia (which is associated with eye movement problems) is linked to a specific visual perceptual deficit in the M pathway, a major recipient of which is the colliculus.

Whether or not the SC is indeed hyper-responsive in ADHD as Hypothesis 1 suggests, the SC may well represent an important therapeutic target for drugs. In fact current psychostimulant therapies may already work at that level (Hypothesis 2), a contention which is supported by 1. The colliculus and structures immediately afferent to it contain the neurochemical machinery necessary to respond to these drugs; 2. d-Amphetamine depresses visually evoked activity in the rat colliculus in a dose-dependent manner. Fortunately, again, even if psychostimulants do not achieve their therapeutic effects on distractibility in ADHD by an action at the level of the SC, then the development of drugs which dampen stimulus-related activity in the colliculus could still represent an important novel path for drug development to take. Pharmacological manipulations of this structure are able to decrease distractibility [56]. As a consequence, sensory responsiveness in the SC may represent a new model system for use in the development of non-addic-

**Figure 1** Visual responses in the superficial layers if the superior colliculus to whole-field light flashes. (A) Local field potential (LFP) and (B) Multi-unit (MUA) responses in a representative animal. In A and B, data were averaged over blocks of 240 stimulations, corresponding to epochs of 8.0 min. Responses are shown at Baseline, and after cumulative doses of 2 mg/kg (Dose 3), 4.0 mg/kg (Dose 4) and 8 mg/kg (Dose 5) d-amphetamine (i.v.). Stimulus onset was at time zero. Stimulus-related neuronal activity is clearly depressed by the drug.
tive pharmacotherapies for ADHD, and as such may be of interest to the pharmaceutical industry.

Clearly, the evidence for collicular hyper-responsivity in ADHD, and for psychostimulant-induced changes in responsivity, are at present indirect. To move these ideas forward it will be necessary to obtain more direct evidence. To achieve this, two approaches seem potentially fruitful. Firstly, neuroimaging: since activation of the colliculus has now been successfully imaged in humans using functional magnetic resonance imaging (fMRI) [57], the possibility that the SC is hyper-responsive to phasic sensory stimuli in ADHD could now be investigated, as could the possibility that psychostimulant pharmacotherapies decrease stimulus-related activity in the colliculus. Secondly, eye movements: collicular lesions in monkeys have been shown to lead to characteristic deficits in eye movement production, both to distractor stimuli and others (e.g. [58]). It should be possible to test ADHD patients in similar or identical tasks and compare outcomes. The effects of psychostimulant medication should qualitatively resemble those of collicular lesions, although this may appear against a background (drug-free) increase in responsivity (relative to controls) to the same kind of sensory stimuli negatively affected by the drugs.

References

Collicular dysfunction in attention deficit

[38] Stein J, Walsh V. To see but not to read: the magnocellular theory of dyslexia. Trends Neurosci 1998;20:147–52.