experiences related to injury in early life" (Merskey & Bogduk 1994). Over the years, this definition has propagated undue credibility for the verbal expression of pain, defined within the context of adult consciousness, engendering medical practices that regard verbal self-report as the "gold standard" for pain (K. D. Craig 1997; Cunningham 1998; 1999). Major flaws in this definition include its excessive reliance on verbal self-report, the criterion that some form of learning is required in order to experience pain, and its focus on use of this word rather than the experience of pain (Anand & Craig 1996; Anand et al. 1999; K. D. Craig 1997; Shapiro 1999; Wall 1997).

Confusion regarding pain perception in early life continues to hinge on various interpretations of this flawed definition (Benatar & Benatar 2001; Derbyshire 2006; Lee et al. 2005), generating a circular argument that "to experience pain, infants must first learn what is pain; to learn what pain is, they must first experience it." The experience of pain primarily informs conscious beings of bodily harm; its perception is vital to survival and cannot depend on putative memories of prior painful experiences (Anand et al. 1999; Cunningham 1999). Consistent with this rationale, even the first exposure to bodily injury demonstrates the clinical signs of pain, regardless of whether tissue damage occurs during fetal or neonatal life (Grunau & Craig 1987; Williams 2005). The experience of pain must precede any responses that ensue (verbal, behavioral, or physiological), whereas the relationships between feeling pain and reporting pain are highly context-dependent (Anand & Craig 1996; A. D. Craig 2003).

The entity of consciousness, as discussed in greater detail elsewhere (Anand et al. 1999; Benatar & Benatar 2001), is mistakenly equated with development of the human mind (Benatar & Benatar 2001; Cunningham 1998; Derbyshire 2006) and burdened with "*the expectation that living organisms must exhibit certain attributes or capabilities analogous to the adult human in order to fulfill the criteria for consciousness*" (Anand et al. 1999). Some authors argue that fetuses or neonates are not conscious, that they are complex automatons (Derbyshire & Furedi 1996; Lloyd-Thomas & Fitzgerald 1996; Zelazo 2004), simply manifesting various reflexes triggered by tissue injury, but incapable of experiencing pain because they lack consciousness or cortical maturity (Benatar & Benatar 2001; Derbyshire 2006; Lee et al. 2005; Mellor et al. 2005).

Closer examination reveals three major flaws in this scientific rationale. First, pain perception is portrayed as a 'hard-wired' system, passively transmitting pain impulses until "perception" occurs in the cortex (Derbyshire 2006; Lee et al. 2005; Mellor et al. 2005). Beginning from the Gate Control Theory of pain (Melzack & Wall 1965), accumulating evidence over the past 40 years should lead us to discard this view of pain.

Second, it assumes that fetal or neonatal pain perception must activate the same neural structures as in the adult; immaturity of these areas then supports the argument that fetuses or premature neonates cannot experience pain. However, multiple lines of evidence show that the structures used for pain processing in early development are unique and different from adults and that some of these structures/mechanisms are not maintained beyond specific developmental periods (Fitzgerald 2005; Narsinghani & Anand 2000). The immature pain system thus plays a crucial signaling role during each stage of development and therefore uses different neural elements available at specific times during development to fulfill this role (Glover & Fisk 1996).

Third, the immaturity of thalamocortical connections is proposed as an argument against fetal pain perception (Derbyshire 2006; Lee et al. 2005; Mellor et al. 2005). This reasoning, however, ignores clinical data showing that ablation or stimulation of somatosensory cortex does not alter pain perception in adults, whereas thalamic ablation or stimulation does (Brooks et al. 2005; A. D. Craig 2003; Nandi et al. 2003). The fetal thalamus develops much earlier than the cortex (Erzurumlu & Jhaveri

1990; O'Leary et al. 1992; Ulfig et al. 2000), supporting clinical observations of fetal behavior in response to tissue injury (Fisk et al. 2001; Williams 2005). Functionally specific cortical activity in response to tactile or painful stimuli in premature neonates (Bartocci et al. 2006; Slater et al. 2006) provides further evidence for the thalamocortical signaling of pain.

Functional development of the centrencephalic system very likely mediates the onset of consciousness in fetal life, defining the "being" in biological terms (Hepper & Shahidullah 1994 and Merker's target article), and enabling its responses to invasions of bodily integrity (Wall 1996, 1997).

Theoretical sequelae of a chronic neglect and unawareness of prefrontotectal pathways in the human brain

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Abstract: Attention research with prefrontal patients supports Merker's argument regarding the crucial role for the midbrain in higher cognition, through largely overlooked and misunderstood prefrontotectal connectivity. However, information theoretic analyses reveal that both exogenous (i.e., collicular) and endogenous (prefrontal) sources of information are responsible for large-scale context-sensitive brain dynamics, with prefrontal cortex being at the top of the hierarchy for cognitive control.

In his target article Merker reminds us of the critical role of midbrain structures for higher cognition in humans. This timely reminder should renew the interest for the study of cortical–subcortical interactions underlying human cognition. Our own research on the attentional disorders in neurological patients, although partly consistent with Merker's claims, calls for a revision of the theoretical implications of the centrencephalic hypothesis in light of the superordinate position of prefrontal cortex in the functional hierarchy of control in the human brain (Barceló & Knight 2000; in press; Barceló et al. 2000; Fuster 1997). In his otherwise very thorough review of brain anatomy and function, Merker does not consider the existence of direct prefrontotectal pathways in the human brain (Figs. 4 and 6 of the target article). In our view, this piece of anatomy carries crucial implications for computing and interpreting information processing within the central nervous system.

Direct prefrontotectal pathways have remained relatively unexplored since their discovery in primates by Goldman-Rakic and Nauta (1976). Failure to notice the relevance of prefrontotectal pathways abounds even in authoritative reviews of prefrontal anatomy (Petrides & Pandya 2002), and consequently, the putative functions of such connectivity have been overlooked or downplayed by recent models about the neural control of human cognition (Miller & Cohen 2001; Posner & Petersen 1990). This route was originally thought to aid the tracking of visual targets in spatial coordinates and was related to the cortical control of visually guided saccades and visuospatial distractibility (Gaymard et al. 2003; Pierrot-Deseilligny et al. 1991). Only recently has this route been related to the top-down control of voluntary and goal-directed behavior (Barceló & Knight 2000; in press; Friston 2005; Munoz & Everling 2004). The dorsolateral

prefrontal region involved, which corresponds to the middle third of the principal sulcus in the monkey, has been shown to subserve not only spatial, but also more general working memory functions closely tied in with awareness (Petrides & Pandya 2002). Hence, it seems justified to ponder the role of prefrontotectal pathways in target and action selection (sects 3.2 and 4 of the target article). In contrast to Merker's proposal of an "*anatomically subcortical but functionally supra-cortical*" system, we argue that prefrontotectal pathways evolved to allow the human prefrontal cortex to control the centrencephalic

system, in line with the evolution of control architectures in the nervous system (cf. Fuster 1997).

Our argument can be substantiated by the extensive research on the neural bases of selective attention (i.e., orienting) to spatial, target, and task-set information. Most evidence for a collicular implication in target selection revolves around the selection of *the spatial location* of relatively novel, salient, or distinct perceptual objects whose abrupt onset triggers sensory and motor adjustments collectively known as an *orienting response* (Sokolov 1963). A cortical marker of the orienting response can
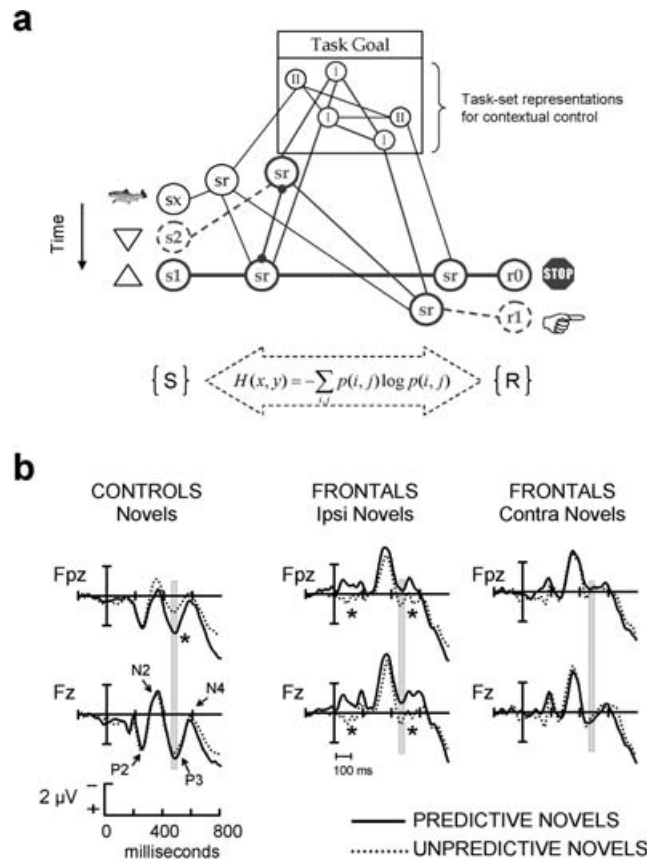

Figure 1 (Barceló & Knight).   Hypothetical prefronto-tectal interactions during visual orienting to familiar and novel task-set information. (**a**) Information theoretic model of prefrontal function (adapted from Miller & Cohen, 2001). The neural representation of pools of stimulus features {S} and motor responses {R} are connected through several hierarchical levels of intervening sensorimotor processes in the central nervous system (cf. Fuster 1997). Familiar and well-rehearsed visual discriminations between upright (distracters) and upside-down (target) triangles rapidly and randomly flashed to both visual hemifields require sustained maintenance of a superordinate task-set representation (*task-set I*). This higher task-set representation holds other subordinate sensorimotor units (*sr*) in an active state at subcortical and/or posterior cortical structures, thus providing intervening pathways between perceptual and motor units. Lateral prefrontal cortex has been proposed to hold superordinate contextual representations in working memory (Miller & Cohen 2001). The onset of a familiar event triggers the updating of its corresponding sensory (*s1, s2*) and sensorimotor units (*s1-r0, s2-r1*) at subcortical and/or posterior cortical structures, without modifying the superordinate representation of familiar information. On the contrary, task-irrelevant unexpected novel events (*sx*) trigger an orienting response that demands updating of the active superordinate representation of task-set information (to new *task-set II*). The novel task-set II competes for attentional resources with the familiar task-set I, thus causing behavioral conflict and distractibility. When the novel event predicts the appearance of a target event in a predictable context, then a momentary conflict between two superordinate task-sets rapidly turns into anticipatory activation of the familiar task-set I, resulting in an amelioration of behavioral distractibility. (**b**) The cortical marker of the orienting response to unpredictive and predictive novel events displayed at the ipsi- and contralesion visual hemifields of patients with unilateral lesions to their dorsolateral prefrontal cortex (middle and right columns) are compared with data collapsed across both visual hemifields in controls (left column). Novel events evoked frontally distributed "novelty P3" potentials in Controls that were severely reduced in the Frontal patients regardless of the predictive value of the novel events or its visual hemifield of display. Importantly, predictive novels elicited anomalous sustained early 50–200 ms negativities over the lesioned prefrontal cortex (Ipsi Novels). The early timing of these negativities suggested conflict signals from prefrontotectal pathways that could not be dealt with because of missing superordinate task-set representations at prefrontal cortex. Grey bars indicate the time window for novelty P3 measurement. Fpz: Mid-frontopolar region; Fz: Mid-frontocentral region (for a full explanation of the task design, see Barceló & Knight 2000; Barceló et al. 2000).

be measured as a stereotyped scalp-recorded event-related potential, the so-called "novelty P3," which indicates that a novel event has captured attention and, at that point in time, is most likely within the focus of mind (Friedman et al. 2001). The novelty P3 potential depends on the integrity of a distributed cortical network including dorsolateral prefrontal, temporo-parietal, and mesial temporal cortices (Knight & Scabini 1998). This cortical marker of the orienting response was originally described as an involuntary reaction to novel and salient stimulation reflecting modality nonspecific cortical-subcortical interactions (i.e., visual novelty P3 activations do not follow the retinotopy of the geniculostriate pathways; cf. Sokolov 1963; Friston 2005), that most likely involve faster prefrontotectal pathways (see Fig. 1b; Barceló & Knight, in press). These cortical modulations could be likened to the property of the centrencephalic system of being "symmetrically related to both cerebral hemispheres" (sect. 3.2 of the target article). New task designs and an information theoretic analytical approach have revealed more top-down cortical control in this brain's orienting response than was originally suspected (see Figs. 1a, 1b; Barceló & Knight 2000; in press; Barceló et al. 2002, 2006).

Target and action selection require integration of contextual information across the spatio-temporal dimensions of our physical world. We orient to those targets that are perceptually salient or behaviorally relevant. However, the information content of a target for perception or action depends on the learned associations between exogenous sensory signals and past short- and long-term memories and plans of action. These context-dependent associations between sets of stimuli and responses for the accomplishment of internal goals are putatively encoded at hierarchically ordered levels of representation in the nervous system (Fig. 1a). Even if the centrencephalic system has direct control over sensory (i.e., *s1, s2*), motor (i.e., *r0, r1*), and some sensorimotor (*sr*) representations needed to perform simple and familiar visuospatial discriminations, it does not seem as well equipped as prefrontal cortex for accessing the short- and long-term memories necessary for the temporal organization of human behavior (Fuster 1997). The neural decisions about whether a novel sensory signal should be selected as a target (i.e., sensorimotor pathway *s2-r1* in Fig. 1a), or inhibited as a distracter (i.e., *s1-r0* in Fig. 1a), and whether these associations are to be temporarily reversed in a different task context, demand activation of a frontoposterior cortical network for updating episodic task-set information (Barceló et al. 2002, 2006).

In a recent study (Barceló & Knight, in press), we observed that dorsolateral prefrontal cortex is necessary for establishing the contextual meaning of novel events either as irrelevant distracters in an unpredictable context (i.e., pathway *sx-r0* in Fig. 1a), or as anticipatory cues for target and action selection in a predictable context (i.e., pathway *sx-r1* in Fig. 1a; Barceló & Knight 2000; in press). Unilateral prefrontal lesions disrupted novelty P3 activity in both hemispheres regardless of the predictive value or the hemifield of novel display (Fig. 1b). Moreover, the temporal contingency between predictive novels and targets was learned *only* when novels were displayed at the ipsilesional (good) visual hemifield of patients. In this condition, predictive novels elicited anomalous sustained early 50–200 ms negativities over the lesioned cortex (Fig. 1b; Ipsi Novels). The early timing of this anomalous negativity, onsetting before visual information could reach prefrontal cortex through geniculostriate pathways, suggested incoming signals from a prefrontotectal route that could not be adequately dealt with because of missing prefrontal task-set representations. The inability to learn the novel-target contingency when predictive novels were flashed contralesionally concurs with these patients' target neglect and other superordinate deficits in cognitive control (i.e., anosognosia). From an information theoretic approach to brain function, both exogenous (i.e., collicular) and endogenous (i.e., prefrontal) sources of information are necessary to compute the informational content of sensory signals (Fig. 1a).

However, the meaning of human conscious experience seems to emerge from large-scale cortical dynamics, with the prefrontal cortex acting as the chief executive in the hierarchy of cognitive control (cf. Fuster 1997).

The hypthalamo-tectoperiaqueductal system: Unconscious underpinnings of conscious behaviour

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Abstract: The insight that, in terms of behaviour control, the meso-diencephalic system is superordinate to the cortex should have profound implications for behavioural sciences. Nevertheless, the thalamocortical system could still be deemed an "organ of consciousness" if we came to accept that consciousness is not central to purposeful behaviour, in accordance with instinct theory. Philosophically, Merker's concepts of basic consciousness and ego-centre warrant critical discussion.

I begin with a long quote from William James' *The Principles of Psychology*, which considers the nature of self-experience in relation to action and consciousness:

> If we divide all possible physiological acts into *adjustments* and *executions*, the nuclear self would be the adjustments collectively considered; and the less intimate, more shifting self, so far as it was active, would be the executions. But both adjustments and executions would obey the reflex type … The peculiarity of the adjustments would be that they are minimal reflexes … uninteresting except through their uses in furthering or inhibiting the presence of various things and actions before consciousness … These characters would naturally keep us from introspectively paying much attention to them in detail, whilst they would at the same time make us aware of them as a coherent group of processes strongly contrasted with all other things consciousness contained – even with the other constituents of the "Self," material, social, or spiritual, as might be the case … Everything arouses them; for objects which have no other effects will for a moment contract the brow and make the glottis close … These primary reactions … are the permanent core of turnings-towards and turnings-from, of yieldings and arrests, which naturally seem central and interior in comparison with the foreign matters, apropos to which they occur, … It would not be surprising, then, if we were to feel them as the birthplace of conclusions and the starting points of acts, or if they came to appear as … the "sanctuary within the citadel" of our personal life … it would follow that all that is experienced is, strictly considered, objective; that this Objective falls asunder into two contrasted parts, one realised as "Self," the other as "not-Self;" and that over and above these parts there is nothing save the fact that they are known, the fact of the stream of thought being there as the indispensable subjective condition of their being experienced at all. (James 1890, pp. 302–304)

Merker should be applauded for emphasising the evolutionary significance of the mesodiencephalic system – comprising hypothalamus, periaqueductal gray, and superior colliculus – and pointing out that the cerebral cortex is at the service of this system. The insight that more primitive upper-brainstem-based mechanisms occupy a superordinate position in the regulation of behaviour does not mean, however, that consciousness, too, is merely elaborated by the cortex. The superior colliculus implements a form of "analog reality simulation"; however, it seems unjustified to infer that such simulation in its interaction with action representations "constitutes a conscious mode of function" formed under the influence of "feelings reflecting momentary needs" (sect. 4.2, para. 5). Reality simulation biased by motivational variables and target selection may be crucially dependent upon mesodiencephalic structures indeed, but,