TO THE EDITOR: We are grateful to our colleagues in providing valuable commentary to our Viewpoint (3). We respond to the key points as we see them. Our aim was to present potential cerebral pathways involved in exercise tolerance, regulation and termination. As stated by Dr. Lutz (see Ref. 1), this model is by no means exclusive and we hope it serves further exploration. We appreciate Micklewright et al.’s (see Ref. 1) recognition that methodological limitations currently mean that we need to draw on neurocognitive evidence to begin the exploration of this area. We certainly agree with Professor Meeusen (see Ref. 1) that we do not have the tools available yet to fully investigate this area. Therefore as per the recommendations within the commentaries, it is important to continue with interdisciplinary research examining neurophysiological responses in conjunction with the measurement and manipulation of internal and external factors. As proposed by Micklewright et al. it is important to consider external factors altering motivational status (see Ref. 1) but also environmental factors altering perceived exertion (2).

Professor Meeusen (see Ref. 1) correctly interprets our discussion proposing that the brain integrates various signals and emotions but points out that the brain may not make decisions to avoid catastrophe. We would like to clarify that it was not our intention to prove nor refute the tenet of the Central Governor Model but rather provide potential pathways involved in the interpretation of physiological signals and other factors present in exercise environments, which might influence what decisions are made about exercise regulation. As stated by Drs. Rauch and Pires (see Ref. 1), these brain processes are likely to be different depending on the situation of the sporting event and exercise model in question. Dr. Pires (see Ref. 1) outlines how changes in metabolic costs measured at the PFC suggest a greater involvement of the PFC in more demanding exercise bouts. Professor Cheung (see Ref. 1) provides evidence that highly fit participants have a greater ability to tolerate physiological sensations and provide better performances in conjunction with attenuated insular activation. This adds weight to the concept that repeated tolerance of adverse sensations can aid in the ability to tolerate them (3, 4).

Dr. Perrey (see Ref. 1) confirms that the orbitofrontal cortex and anterior cingulate are involved in the cost benefit analysis of exerciser tolerance and adds that the PFC may become disengaged, leading to exercise cessation. Dr. Rauch (see Ref. 1) adds that the point of fatigue may be attributable to subcortical structures with reduced PFC processing, particularly at higher exercise intensities. We agree that there is likely a strong subcortical component to this regulatory process, e.g., dopamine release. However, if indeed the PFC is involved in motivational processes as discussed by Dr. Lutz (see Ref. 1), at which point does this motivation become redundant in the face of this alternate system? Future research needs to develop an understanding of both neural correlates of exercise regulation and fatigue but also the psychological elements that go with this. As it stands, our understanding of psychological processes affecting exercise are predominately limited to theoretical constructs rather than neurophysiological responses and it is difficult to connect the two.

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Commentaries on Viewpoint: A role for the prefrontal cortex in exercise tolerance and termination

IS IT THE BRAIN OR THE BODY?

TO THE EDITOR: Fatigue during exercise is a complex phenomenon and has historically been assigned to peripheral mechanisms. Recently more attention is paid to the “central” origin of fatigue, where failure of the motor cortex, changing neurotransmitter concentrations, decreased blood flow, etc., are put forward as underlying mechanisms (3). Both hypotheses (peripheral and central) contain the same “mistake” when isolating the head from the body and vice versa. In their Viewpoint, Robertson and Marino (4) link the prefrontal cortex (PFC) with exercise tolerance and possible fatigue. The PFC could play a role as switchboard during exhaustive exercise, taking part in “decision” making on exercise cessation (4). A declined EEG response to exercise was found in the PFC when exercise intensity increased (5), which confirms previous results with exhaustive exercise in the heat (2). This might indicate that electrocortical activity is diminished at exercise cessation or that other brain areas become more “active” (1). The important message of the recent paper (4) is that the authors clearly try to explain that the brain integrates several signals and emotions. However, the question remains if the brain really “thinks” and “makes decisions” to avoid catastrophe. It might also be that during exercise the disturbance of peripheral and central homeostasis are integrated and that several neurotransmitter systems influencing frontal and other brain regions overshoot or even become depleted at exhaustion (3). Also, temporary depletion of brain substrates (glucose, glycogen, lactate) could be involved. At this stage we probably don’t have the right tools (methods) available to confirm or reject this hypothesis.

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PREFrontAL CORTEX ACTIVATION AND AFFERENT FEEDBACK IN DIFFERENT EXERCISE MODES

TO THE EDITOR: The Viewpoint by Robertson and Marino (4) highlighted that the coordinative role of the PFC during exercise may depend on the exercise model under consideration. Although not exclusively, the ability to perform a particular exercise mode may be related to the capacity to tolerate unpleasant sensations triggered by afferents from peripheral organs and muscles (2). Previous study showed that the muscle recruitment for a given, submaximal power output was greater in controlled-pace exercise than in self-paced exercise (3). This suggests that the muscle recruitment-produced bioproducts accumulation was higher in this former exercise mode, thus probably triggering a greater III/IV muscle afferents and cardiorespiratory response (1) toward interoceptive regions of the PFC areas (2, 4, 5). The PFC is suggested to integrate afferents from periphery into messages with emotional relevance when processing homeostatic adjustments to guide the decision making (4), so that the increased peripheral afferents during a controlled-pace exercise may impose a greater metabolic cost to PFC when integrating these afferents. As a result, controlled-pace exercise would further require higher cerebral (de)oxygination, neurotransmitters depletion and temperature, with a concomitant higher effort sensation (3). Thus, a possible higher energy cost in PFC areas during controlled-pace exercise may implicate an unpleasant, less tolerable exercise mode, thereby limiting the capacity to maximally perform this exercise (when compared with self-paced exercise). Indeed, as reported to submaximal intensity, controlled-pace exercise is more psychologically and physiologically challenging than self-paced exercise (3). Future studies are required to confirm this hypothesis in maximal aerobic exercises performance.

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COMMENTARY ON “A ROLE FOR THE PREFrontAL CORTEX IN EXERCISE TOLERANCE AND TERMINATION”

TO THE EDITOR: The contribution of specific brain activities to (voluntarily or involuntarily) reduce muscle force/power (i.e., fatigue) or quit an exercise (task failure) is being more and more recognized. With the current paper (1), the authors present a model of how the brain forms the decision whether to terminate an exhaustive task. This model proposes one of several possible—and not mutually exclusive—mechanisms. Others include a change of serotonin concentration in the brain (2) or an insular processing loop proposed to regulate motor drive (3).
Eventually, these mechanisms may be combined into one model, as tentatively sketched in Fig. 1 of the present paper. However, we have to be clear about the concepts to be explained: motivation, effort, and pain should be understood as distinct factors influencing each other as well as supraspinal fatigue and task failure. It will be interesting to more specifically formulate hypotheses about how the proposed components of the system interact in different contexts. For example, many studies outside the field of exercise science link PFC to motivational processes. On the other hand, PFC modulates activity in regions like insula and thalamus known for sensory processing during placebo analgesia (4).

Thus, possibly, there are regulatory mechanisms of exercise tolerance on several hierarchical levels: more direct loops involving insular cortex analysis of interoceptive signals, and more indirect loops, involving PFC activities related to higher order cognition and motivation. The present paper provides an excellent starting point to investigate such possibilities.

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BEHAVIOR AND EXERCISE TOLERANCE IN EXTREME ENVIRONMENTS

TO THE EDITOR: Robertson and Marino (4) present an interesting neural architecture linking the prefrontal cortex and its role in executive function and motivation, its integration of external and internal afferents, and ultimately the control of motor regions and exercise behavior. This parallels work on the neurological origins underlying human behavioral thermoregulation. Both streams can inform investigations into the determinants of exercise capacity in extreme environments. Dopamine reuptake inhibitors increase exercise tolerance only in hot but not in temperate conditions, primarily from elevated brain dopamine levels raising voluntary core temperatures in the heat but not in temperate environments (5). Higher core temperatures are also found at voluntary termination during uncompensable heat stress in highly fit compared with moderately fit individuals regardless of hydration or heat acclimation status, despite no differences in the rate of heat storage (1). In contrast, physiological capacity does not become degraded to a greater extent in untrained populations. Although low aerobic fitness and activity level are associated with a generally decreased tolerance to passive hyperthermia, maximum force production and voluntary activation were impaired to an equal level regardless of training status in those able to attain 39.0°C core temperature (2). Paulus et al. (3) provide insight into brain activation during an aversive stimulus from increased breathing load, reporting that experienced adventure racers performed better on cognitive tasks and also had attenuated insular cortex activation compared with untrained controls. Future research should determine if manipulating the perceptual interpretation of homeostatic signals and motivation can influence exercise tolerance and cognition during environmental stress.

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EXERCISE TERMINATION IS A COGNITIVELY CONTROLLED DECISION

TO THE EDITOR: The possibility for the prefrontal cortex (PFC) to be involved in exercise tolerance and termination nicely postulated by Robertson and Marino (5) is timely. However, in the absence of compelling data, this hypothesis is currently based upon insufficient evidence from exercise studies. There remains uncertainty about how PFC accommodates to physical exertion by modulating cognitive control. Self-regulatory fatigue could occur due to either lack of increased PFC activity, heightened activity in subcortical structures, or both. Overcoming fatigue development likely requires the PFC to inhibit the anterior cingulate and insula activated in proportion to the degree of subjective fatigue (3). As suggested by the authors (5) the problem can be reduced to a trade-off between the costs and benefits of effort exertion, which has been extensively investigated in the decision-making literature (1). Fatigue as an increased accumulation signal (i.e., influence of afferent fibers’ feedback on central motor output as a sensed perceived exertion) during exercise leads to high cost estimates compared with expected benefits and task difficulty. In this approach the decision whether to continue the exercise task is refined dynamically depending on cost and benefits until reaching upper bounds of the accumulation process that underpins effort allocation (4). At a brain level, current evidence supports a network of brain regions that are functionally connected with both the anterior cingulate and orbitofrontal cortices during an ongoing cost-benefit analysis (2). When cost exceeds benefits, PFC regions involved in an inhibitory process underlying cognitive control are disengaged, which quickly leads to the cessation of exercise.
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COMMENTARY ON “A ROLE FOR THE PREFRONTAL CORTEX IN EXERCISE TOLERANCE AND TERMINATION”

TO THE EDITOR: I agree with the gist of the authors’ Viewpoint (5) but not that the PFC can “sustain exercise despite severe deficiencies in motor control.” PFC function is well described in the cognitive/emotional/behavioral literature (2), and we assigned a similar role to the PFC in our review, although focusing on feed-forward drive (3). Thus, although PFC pathways can be expected to “act in an integrated manner to choose a response” during cognitive tasks and more moderate exercise, it probably does not do so during peak sporting performance. For instance, crucial as PFC “task response selection” is for Stroop Task performance, it would be a liability when hitting a match winning serve at Wimbledon. Instead the PFC would be focused on singular goal (1)—an awareness of optimal ball placement—which would be disrupted by any attempt at “task response selection” during the execution of movement. Ditto for endurance exercise. Clayton’s famous “I’m going to smash you into the ground” statement at the start of the 1969 Antwerp Marathon helped him shatter the world record. Clayton’s success was largely due to his extraordinary ability to remain goal directed, allowing him to “extend exercise tolerance in the face of afferent feedback,” presumably via midbrain dopamine release and stress induced analgesia (3). Instead of “exerting top down effects,” a more apt description would be reduced PFC processing at high exercise intensities (4). The authors allude to same in their “reinforced neural pathways” (hardwired rather than “choosing a response”) to explain increased exercise tolerance in athletes.

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EXTEROCEPTION IS AN IMPORTANT FACTOR IN EXERCISE TOLERANCE

TO THE EDITOR: We congratulate Robertson and Marino (3) for their prefrontal cortex model of exercise tolerance and termination, which is a welcome contribution to our broader understanding of the limits of human performance. The authors have constructed their model by bringing together neurocognitive evidence derived from their own and others’ observations. Given the present methodological limitations of imaging whole brain activity during vigorous physical activity, particularly regarding functional interactions between various brain structures, their approach to model construction is warranted.

Nevertheless, we note that although their model is clear about interoceptive mechanisms of exercise tolerance, other than by the inclusion of the orbitofrontal cortex, exteroceptive pathways are understated. In this respect, we would like to stress the importance of incorporating human-environment interactions in models of human performance, especially given their relevance to real-life applications seen in sport, rehabilitation, or physical occupations. Recent work has found that situational and informational variations to the external environment influence exercise tolerance as measured through the perception of exertion (2, 5). In addition, the importance of natural, interactive behavior is demonstrated in a recent review on perception and action in pacing (4) and situational factors such as the presence of opponents appear to affect decision-based pacing and tactics in sports competition (1).

In summary, we think this is a very exciting paper explaining the interoceptive mechanisms of exercise tolerance and one that we hope will stimulate positive discussion and new research in this area. We would like to add that future research should also focus on including human-environment interactions.

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A role for the prefrontal cortex in exercise tolerance and termination

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IN Volvement of the brain in endurance exercise regulation is not a particularly new concept. Although exercise termination has been proposed to occur when generation of the required power output is no longer possible because of failure at sites within the musculature (1), there is growing evidence that there is a neural component to our ability to tolerate sensations of fatigue and that exercise termination includes a psychological element (23). This involves afferent feedback of the disturbances in homeostasis at the musculature and cardiopulmonary systems to the brain (23), where these signals are interpreted. That the motor cortex (MC) is not activated maximally at exercise termination suggests that regions upstream of the MC provide such input into how we interpret these signals and when we terminate exercise.

Several authors have now addressed areas of the cortex that are activated during the control of voluntary movement and postulated how areas of the brain may be involved in exercise termination (21, 30, 31). There is strong evidence that our tolerance of physiological sensations can be modulated by a variety of psychological factors such as motivation (35) and presence of competitors (34); however, the neural pathways for volitional control of movement and their interaction with these factors has yet to be established (31). The aim of this Viewpoint is to present potential cerebral pathways involved in the interpretation of physiological signals, which combine with internal and external factors present in exercise environments, to determine exercise tolerance (see Fig. 1). We propose the prefrontal cortex (PFC) may have a role in the integration of such information providing a relevant response to the exercise situation, exerting a top down effect and, thus, allowing for motor unit derecruitment, or in some situations, overriding of these signals and prolonging motor output (30) despite significant downregulation of motor control.

The PFC was previously proposed to be involved in terminating incremental exhaustive exercise due to declines in prefrontal cerebral oxygenation (COxy) preceding exhaustion (6). The maintenance of prefrontal COxy during self-paced exercise also suggests effective pacing involves COxy being at an appropriate level to avoid early exercise termination (7). Notably much of this research has been undertaken on the PFC due to accessibility of the site for NIRS rather than from a definitive hypothesis. As such, specifically how the PFC might be involved in exercise termination has rarely been proposed. Although there is not yet definitive evidence during exercise that a decline in COxy occurs in conjunction with a decrease in neural activity, it was recently shown that neural activity declines in the PFC at the respiratory compensation point (RCP) (25) where severe reductions in COxy are known to occur (6). Studies failing to show a decline in prefrontal COxy (16) or neural activity (2) before exhaustion during incremental exercise have not used individual thresholds that might account for this discrepancy. There is some debate as to whether these changes in the PFC reflect part of the cerebral regulation of exercise due to the lack of importance of the PFC in motor control (16). Alterations in the PFC may reflect a redistribution of blood and oxygenation to more important and active parts of the brain (16) or to exercising musculature (27) to ensure metabolism is secure in these areas and subservient in quiescent regions less required for the generation of motor output.

The PFC is well known for its executive function, where cognitive control coordinates thought and actions related to the achievement of internally derived goals (20). Although the PFC is not directly connected with major motor control regions, it is indirectly linked via the premotor area (PMA). It has been proposed to be able to supersede more direct regions of motor execution (12) that might be necessary in extending exercise tolerance in the face of afferent feedback. Main cortical areas shown to receive afferent feedback include the brain stem, lamina I spinothalamocortical system, somatosensory cortex (SSC), and insula cortex (IC) (9, 15). In contrast to the catastrophic model of exercise termination, whereby a specific system reaches failure (1, 28), an ability to tolerate homeostatic disturbances has been proposed to be dependent on the exercise model under consideration (18). In this latter situation, interpretation of afferent feedback in combination with the specific exercise environment and the cues involved in that environment are likely to help inform what response occurs (18): that is, whether to maintain intensity, moderate the pace, or stop altogether.

Pathways for the interpretation of afferent signals could be via the anterior cingulate cortex (ACC), premotor area (PMA), and regions of the PFC, such as the lateral PFC (LPFC) and orbitofrontal cortex (OFC). These regions of the brain have roles in motivation (14), reward (4), planning, and execution (22, 26): cognitive and emotional functions that may be involved in the ability to increase exercise tolerance (5, 13, 34). Because internal information is continuously updated during exercise, these regions may respond to this changing environment, as well as consolidate experiential learning required for optimal pacing (19). Afferent feedback from the spinothalamic system reaches the OFC (8) and allows processing of signals to provide emotional relevance (affect) (8). Affect (pleasure-displeasure) is known to play a role in exercise tolerance and may play a role in the specific response chosen to accommodate uncomfortable sensations (32). Such responses have been shown to represent different physiological changes at the PFC (32).
The OFC is also able to integrate multiple sources of information regarding the outcome of a task response and, in effect, calculate how rewarding an action is (11). To maintain exercise under intolerable conditions, external cues such as visual feedback of performance (35), other competitors (34), or internal cues like self-belief (13) may play a role in our interpretation of how rewarding tolerating disrupted physiological signals might be. The OFC processes both emotional and motivational responses to stimuli in an ongoing manner that would be required to make continuous decisions about motor output (30). This process is likely to be in conjunction with the ACC (4, 24) and other reward centers such as the amygdala, thus increasing the implication of dopamine and its role in exercise tolerance (33). The ACC is proposed to give motivational context to situations by providing incentive values from past events (14). This pathway may provide the experiential nature of exercise as previously reported (19) where interpretation of homeostatic signals is likely to play a role (19). During interpretation of afferent feedback there is coactivation of the ACC with the AIC, suggesting that both these are involved in perception of bodily states (10, 24).

Processing task response selection is suggested to involve the LPC in conjunction with information delivered by the ACC and OFC (3). Sustaining motor output under conditions of homeostatic perturbations is likely to trigger internal conflict (34), which is suggested to involve the ACC (3, 22). The LPFC integrates internal conflict about selecting a response in combination with the reward outcome, to guide selection of an appropriate response, which occurs in conjunction with PMA (17). Together these pathways are suggested to act in an integrated manner to choose a response that is likely then passed through the basal ganglia (BG) for motor execution (14) (see Fig. 1). The competitive nature of the brain means that expression of a certain behavior will be achieved by the pathways with the strongest sources of support (20). An athlete’s ability to sustain exercise, despite severe deficiencies in motor control, may be implemented in situations where psychological drive ensures that the task-relevant response chosen is to continue exercise (30). Attention paid to motivational and emotional cues from the environment and situation, rather than from the homeostatic signals, would facilitate this, which has been shown to be relevant for both incremental tests to exhaustion (35) and self-paced exercise (5). Persistent choice of specific task responses reinforces neural pathways (20) and may explain why athletes have a higher ability to tolerate such sensations (29). Although the PFC may not be considered to be involved directly in the execution of motor output (16), we posit it may be intimately involved in the capacity to tolerate high levels of physical exertion and possibly in the determination of exercise termination. As such, evaluating neurophysiological and psychological responses when high levels of physiological demand are present, during externally controlled and self-paced exercise, will assist in our understanding of cerebral alterations in exercise tolerance and how they impact our regulation of exercise performance.

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AUTHOR CONTRIBUTIONS

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