The brain's cingulo-opercular action-mode network

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The brain is always intrinsically active, utilizing energy at high rates, while moving between global functional modes. Awake brain modes are tied to corresponding behavioral states. During goal-directed behavior, the brain enters an action-mode of function. In the action-mode, arousal is heightened, attention is focused externally, and action plans are created, converted to movements, and continuously updated based on relevant feedback, such as pain. Here, we synthesize classical and recent human and animal evidence that the brain's action-mode is created and maintained by an action-mode network (AMN), which we had previously identified and named the cingulo-opercular network (CON) based on its anatomy. Controlling the brain's action-mode accounts for the large variety of functions previously associated with the cingulo-opercular AMN, such as increasing arousal, processing of instructional cues, task general initiation transients, sustained goal maintenance, action planning, sympathetic drive (e.g., connectivity to adrenal medulla) for controlling physiology and internal organs, as well as action-relevant bottom-up signals such as pain, errors and viscerosensation. In the brain's mode space, the AMN-generated action mode is the antipole to the default-mode for self-referential, emotional, and memory processing.

At rest, in the absence of externally oriented, purposeful behavior, the brain enters the default-mode [1,2], during which it engages in self-referential and emotional processing, and recollects prior experiences [3]. Default-mode processing is supported by a dedicated set of brain regions, the default-mode network (DMN) [4,5]. To engage with the environment through goal-directed behavior, the brain switches to an action-mode, which is characterized by attenuation of default processes [1,2,6,7], heightened alertness [8,9], extrinsic focus [7,10-13], voluntary purposeful movement [14], and processing of action-relevant feedback, such as pain [15] and errors [16]. Recent studies [17-19] have provided additional evidence that this action-mode is supported by a circuit we previously identified and originally named the cingulo-opercular network (CON), based on its anatomical pattern (Fig. 1) [7,12,13]. Here, we revisit our original, more limited framing of the CON as an executive control circuit characterized by task initiation and goal maintenance signals [7,20]. We review and synthesize a wide range of evidence for CON's involvement in supporting action-mode functions (Table 1), in counterbalance to the default-mode, and its push-pull relationship to the DMN (Fig. 2). We thus reconceptualize CON and rename it the action-mode network (AMN) (Box 1).
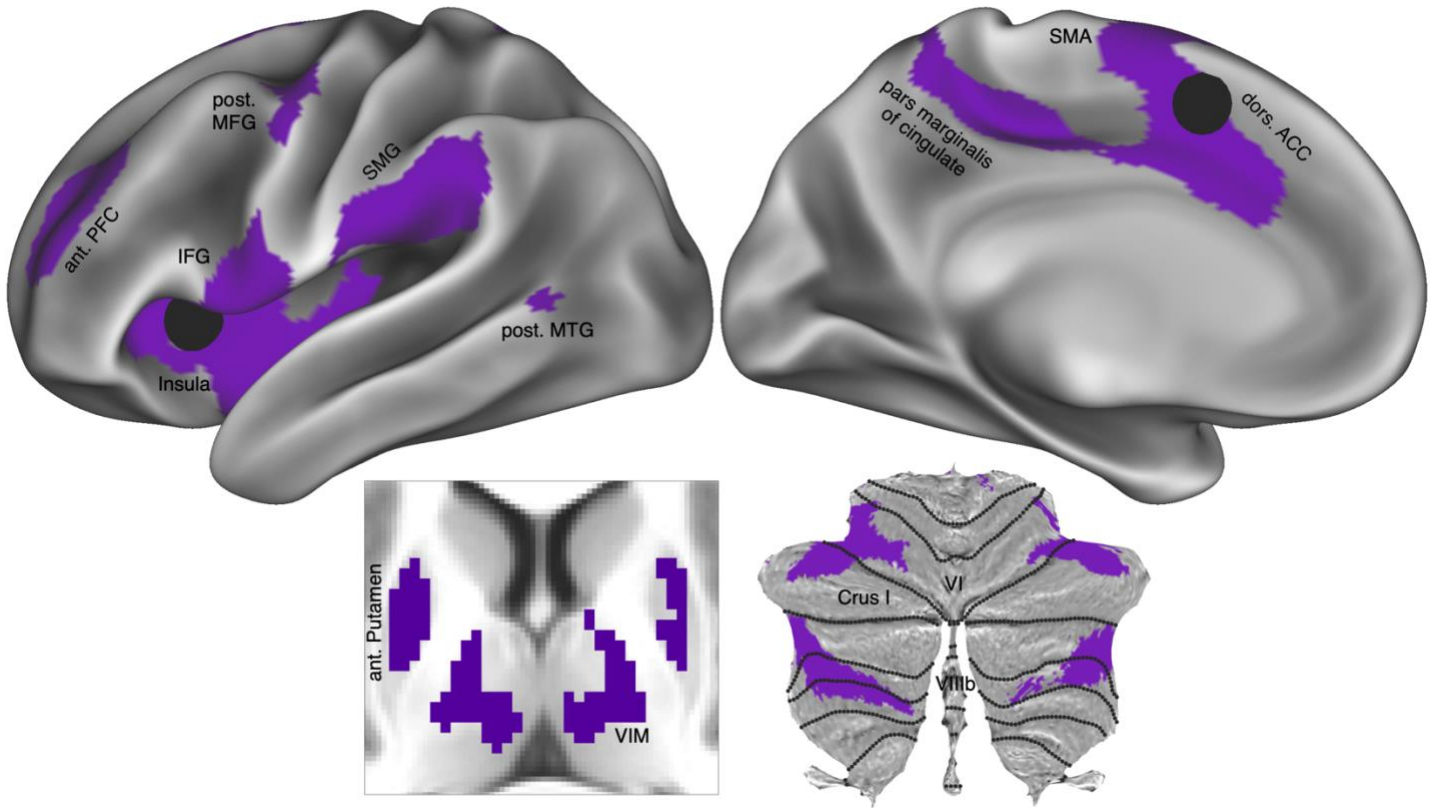
Figure 1. Cingulo-opercular action-mode network (AMN). The action-mode network (AMN; purple), which we had previously labeled the cingulo-opercular network (CON) because of the prominence of the dorsal anterior cingulate cortex (dACC) and frontal operculum(/anterior insula), is also represented in many other cortical and subcortical locations, including supplementary motor area (SMA), anterior prefrontal cortex (aPFC), supramarginal gyrus (SMG), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), pars marginalis of the cingulate gyrus, middle temporal gyrus (MTG), putamen, thalamus (anterior nucleus [AN], centromedian [CM], ventral intermediate [VIM]), cerebellum, and more. The AMN shown here is from the Adolescent Brain Cognitive Development (ABCD) Study [21,22] (group averaged; n = 11,874). Black circles indicate core AMN regions of interest, first described in 2006 [7].

Functional network origins

The default-mode network (DMN)

A 1997 meta-analysis of nine PET (positron emission tomography) studies [1] provided the data for a breakthrough realization: a set of brain regions, including the ventromedial prefrontal cortex (vmPFC) and precuneus (Fig. 2), were deactivated relative to the true resting-state (eyes open) metabolic baseline [2,23], during goal-directed, extrinsically oriented tasks. These data sparked the proposal of an organized default-mode of brain function, supported by these brain regions, that is temporarily attenuated during specific goal-

directed behaviors [2]. Subsequently, the same set of task-deactivated brain regions was identified as a coherent network in the earliest resting state functional connectivity (RSFC) studies [4,5], and fittingly named the default-mode network (DMN). Later studies revealed that the DMN also includes the anterior and middle hippocampus [24] and is more active during self-referential memory encoding and retrieval [3,25]. A defining feature of the DMN is its anticorrelation with brain regions commonly activated during extrinsically oriented, goal-directed tasks [5] (Fig. 2).
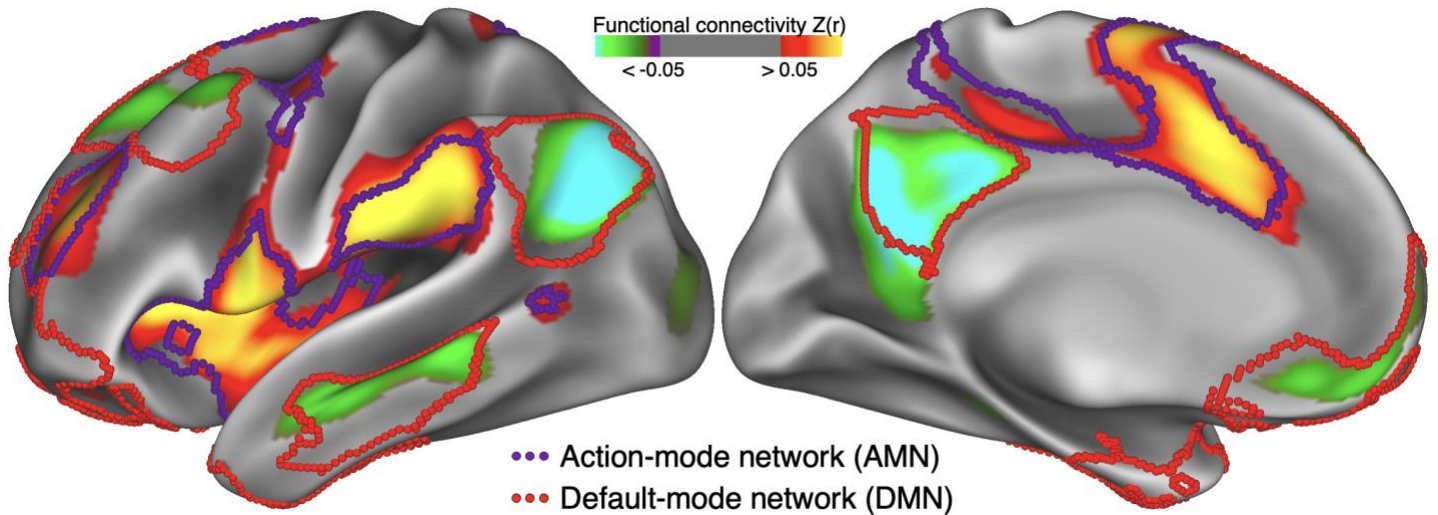
Figure 2. The action-mode network (AMN) and default-mode network (DMN) are anticorrelated. Functional connectivity seed mapping shows that the AMN (purple outlines) and the DMN (red outlines) are strongly anticorrelated with each other. Example shown here is from the Adolescent Brain Cognitive Development (ABCD) Study. Seeding the AMN regions reveals that the strongest negative correlations overlap almost perfectly with the DMN.

The cingulo-opercular network (CON)

Motivated by the PET meta-analyses [1,6] that identified the brain's default-mode and the network for implementing it, a 2006 meta-analysis of functional MRI (fMRI) studies [26] characterized a set of brain regions with the opposite activation pattern (Fig. 1) [7]. Across goal-directed tasks, the dorsal anterior cingulate cortex (dACC), anterior insula/frontal operculum (aI/fO), anterior prefrontal cortex (aPFC) and supramarginal gyrus (SMG) exhibited executive control signals, including transient action initiation [7,20], sustained goal maintenance [7,26], and error-feedback [7,13,16]. Initial RSFC analyses [12,13] showed that these regions also form a coherent functional network. Improved functional connectivity methodology later revealed that the CON also includes regions in the SMA and lateral premotor cortex; middle insula; pars marginalis of the cingulate sulcus, lateral cerebellum, central thalamus and anterior putamen [27-29] (Fig 1).

The original CON, based on task fMRI regions of interest (ROI), was limited to the dACC, frontal operculum [7], anterior PFC, and SMG [12,13], and thus partially overlapped with the RSFC defined task-positive network [5]. Despite strong evidence for the CON's importance in task execution, it initially seemed most appropriate to give it an anatomically descriptive name [12,13]. There was hesitancy to assign a functionally descriptive label such as "executive control network" because other studies had reported signals, including such as salience [30] (see Box 2), conflict monitoring [31], pain [32], and motor control (i.e., pre-supplementary motor area) [14,33]. It was unclear whether these various signals were in overlapping or spatially adjacent brain regions and networks because the available data had relatively low spatial specificity. At the time, pain and motor signals seemed difficult to square with the conceptualization of CON as a higher-order top-down control network. We hoped that future work would either reconcile seemingly disparate signals (i.e., action control, arousal, pain, motor) under a superseding functional category (see Box 1) or subdivide cingulo-opercular regions into distinct functional networks (see Box 2), or both.

Brain						Person		
Intrinsic Activity	**Energy Use**	**Global Mode**	**Controlling Network Functional Name**	**Anatomical Name**	**fMRI Activations**	**Behavioral State**	**Attentional Focus**	**Physiology & Body**
ongoing	high	action	**action-mode network AMN**	cingulo-opercular network CON	task-positive	goal-directed	allocentric	strive & survive
ongoing	high	default	default-mode network DMN	med. fronto-parietal network m-FPN	task-negative	rest	egocentric	rest & digest

Table 1. Action-mode (AMN) and default-mode (DMN) functional networks.

Confusion of association cortex network names

Following recognition of the DMN [2,4,5], multiple different research groups proposed various higher-order cognitive networks within the non-DMN parts of association cortex [12,30,38-41]. For largely methodological and data quality reasons, it was initially almost impossible to be confident about whether any given pair of separately named networks might be representing the same brain structure using different names, or whether a single network named by one group might converge with several separable networks named by another group. Finally, in 2011, back-to-back functional network parcellations were published by Yeo et al. [28] and Power et al. [27]. These studies used two different advanced network identification methods and two different datasets but converged onto a very similar set of networks. While these studies clarified that association cortex outside the DMN is divided into a series of distinct parallel functional networks, much of the confusion surrounding network names persists.

Here, we focus on the functional annotation of the specific network depicted in Fig. 1, which is identifiable in every individual, given sufficient fMRI data quality and quantity [19,24,42-52]. We previously labeled it the cingulo-opercular network (CON) [12,13] and are now renaming it to action-mode network (AMN). The salience network [30,37] is clearly a separate entity, but it has a similar cingulo-opercular spatial pattern and is frequently confused with the AMN (see Box 2). The new action-mode vs. salience functional annotation will help alleviate prior confusion fueled by their close spatial adjacency in the anterior cingulate and frontal operculum.

Several other previously named functional networks overlap strongly with the AMN, both anatomically and conceptually, but tend to extend well beyond AMN, usually into frontal and parietal regions. The cognitive control network (CCN) [41] is similar in proposed function to our original conceptualization of the AMN but extends into lateral frontal and parietal regions that are less action-oriented and

are clearly separable with RSFC. The multiple demand system (MDS) [35] was defined based on task fMRI contrasts and similarly combines the AMN with parts of other fronto-parietal networks. While the presence of multiple demands does increase activity in certain AMN nodes, multi-tasking is not required for entering the goal-directed mode. The extrinsic mode network (EMN) [53,54] is also more extensive than the AMN, encompassing both fronto-parietal and salience networks.

The publications by Yeo et al. [28] and Power et al. [27] both included networks that were spatially convergent to the present AMN, but were given different labels. Yeo et al. labeled the AMN/CON the ventral-attention network (VAN), positing that it was the same system for bottom-up attentional capture previously identified by [55]. Reflecting on the inherent difficulties with network annotation, Yeo et al. also discussed that this ventral attention network could also be the CON, salience network, or both [28]. Power et al. labeled Yeo's VAN as the CON [27]; but, contributing further confusion, Power's et al.'s networks also included a VAN that is a different network than Yeo's VAN. The network referred to as VAN by Power et al. overlaps with the language network [56,57].

Other higher-order networks with a more fronto-parietal distribution, referred to variably as ECN (executive control network) [30], CEN (central executive network) [40], DAN (dorsal attention network) [38], and FPN (fronto-parietal network) [12,58] are more obviously spatially distinct, but a detailed discussion of them is beyond the scope of this article.

Salience network (SAL) ■ Action-mode network (AMN) ■

Box 2: <u>Differentiating the cingulo-opercular action-mode and salience networks</u>
In 2007, coinciding with the CON/AMN, the salience network was described based on resting-state functional connectivity (RSFC) and task fMRI data [30]. Like the AMN, the salience network is most prominently represented in the frontal operculum/anterior insula and anterior cingulate. Thus, it was initially unclear if the AMN and salience networks are distinct or merely different labels for the same circuit. Improved methods for dividing the whole brain into non-overlapping functional networks using resting state fMRI data [27,28] made it clear that the AMN and salience are distinct, despite being spatially adjacent—a position upheld by all of the groups who first reported these networks [37]. Specifically, the AMN lies more posterior along the cingulate than the salience network and is more superior in the anterior insula. The AMN extends dorsally to be immediately adjacent to motor regions along the midline and central sulcus, while the salience network does not. A defining function of the salience network seems to be reward processing, thought to be mediated by dopamine signaling [37], and the salience network has a critical node in the nucleus accumbens [48] that is being evaluated as a deep brain stimulation (DBS) target in the treatment of various addictions [59,60]. Unfortunately, the AMN and salience networks are occasionally still confused, misnamed, or mistakenly treated as one entity [61].
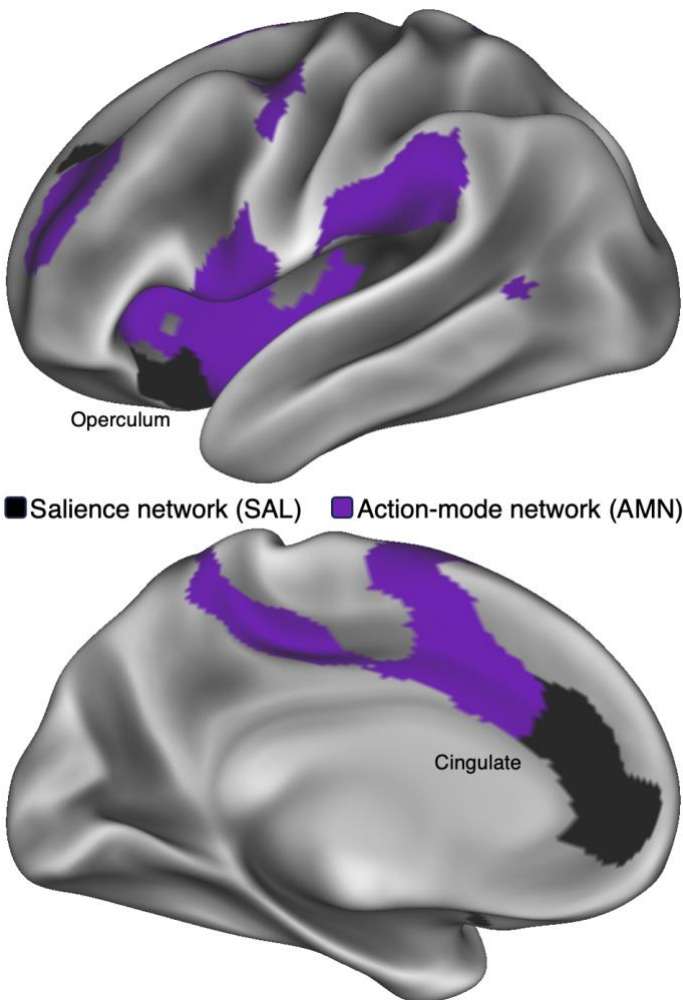
Recent evidence for cingulo-opercular AMN function

Cingulo-opercular AMN is important for motor plasticity

Precision functional mapping (PFM) for the first time enabled the accurate identification of the cingulo-opercular AMN in individuals [42,43], allowing for within-person longitudinal studies and experimental manipulations. Within-participant motor plasticity studies revealed that disuse of the dominant upper extremity due to casting (two weeks) induced large, replicable functional connectivity changes not only in primary motor cortex but also in the AMN [17,18,62,63], such that connectivity between disused upper extremity-specific motor cortex and AMN was strengthened. Other networks important for higher-order control were unaffected, suggesting a greater and more specific role of the AMN in motor behavior than previously thought.

Realizing that the cingulo-opercular AMN is central to rapid motor circuit plasticity must lead to a re-evaluation of the concept of executive control and its interdependence with goal-directed movement. In retrospect, there was always ample evidence for the AMN's involvement in pre-motor processes, but, beholden to a false dichotomy between movement and cognition, we had ignored this evidence in favor of more abstract functional ascriptions. In non-human primates, the cingulate motor areas (CMA) are critical for hierarchical motor planning, in which goals and intentions are translated to progressively more concrete action plans [14,33,64]. Their human homologues are likely located in the dACC portion of AMN, and their output projections are thought to primarily target the SMA, another AMN region [14,33,64]. The dorsal MFG (middle frontal gyrus) AMN regions are typically interspersed between eye movement controlling FEF (frontal eye fields) and SEF (supplementary eye fields) and overlap with classical lateral premotor cortex regions [65]. In subcortex, AMN includes the anterior putamen, which is known to receive projections from premotor areas in macaques [66]. Motor nuclei in the central thalamus [45] are also strongly functionally connected to the AMN (Figure 1). Regions of the vermis and the anterior and posterior cerebellum [44], with suspected motor control roles, are also part of the AMN.

AMN is interconnected with the somato-cognitive action network (SCAN)

A breakthrough in understanding the cingulo-opercular AMN's function came with the recent discovery of the somato-cognitive action network (SCAN), which integrates whole-body physiology, as well as smooth and skeletal muscle movement, with behavioral goals [19]. In the brain's motor circuits two parallel systems intertwine in an integrate–isolate pattern: effector-specific regions for isolating fine motor control of the foot, hand and mouth; and the SCAN for integrated action execution. The SCAN's inter-effector nodes not only alternate with effector specific foot/hand/mouth regions in primary motor cortex, but also are strongly connected with AMN regions in SMA and dACC. In addition, the SCAN includes the centromedian nucleus (CM) of the thalamus, the dorsal posterior putamen, and crus VI and VIIIa of the cerebellum (paravermian), all regions where SCAN and AMN are spatially adjacent. SCAN inter-effectors lack movement specificity [19,67,68] and co-activate during action planning (coordination of hands and feet) and axial body movement (such as of the abdomen or eyebrows) [19]. In macaques, direct cortical stimulation of SCAN is thought to evoke complex actions [69-73] and animal studies have demonstrated connectivity to internal organs such as the adrenal medulla [74,75], stomach [76], kidney [77] and heart [78]. Deep brain stimulation (DBS) targets for Parkinson's, namely the subthalamic nucleus (STN), globus pallidus pars interna (GPi) and ventral intermediate thalamus (VIM) are part of the SCAN [19,79]. The STN, GPi and VIM show hyperconnectivity to cortical SCAN nodes in Parkinson's, which is reduced by successful DBS [79].

A hallmark feature of the SCAN is its strong and specific connectivity to the AMN. The strongest SCAN-AMN inter-connectivity is found along the dorsal midline in the SMA and posterior dACC, which control voluntary action [14]. The special relationship to the SCAN prompted us to reassess the AMN's arousal [8,9,80], pain [15], viscerosensation [81,82] and viscerocontrol signals [78], which we had previously been unable to reconcile with its role in top-down executive control. The SCAN discovery suggests that the AMN's role in goal-directed behavior was not limited to executive and motor control but extended towards setting the proper conditions for successful activity, by affecting arousal, body physiology, and pain processing. In this action-centered framework [19,73,83], the SCAN functions as the AMN's actuator, implementing goal-directed actions via coordinated skeletal and smooth muscle movement

and hormone release (e.g., increased sympathetic tone).

Evidence synthesis: Action-mode is implemented by cingulo-opercular AMN

An action-mode of brain function
The human brain accounts for 20% of our energy expenditure at rest, even though it constitutes only 2% of our body weight [84-86]. Over 90% of this energy supports the brain's intrinsic activity, which is independent of specific behavioral demands [87,88]. The brain's energy usage only increases by ~ 5% over baseline in regions specifically associated with a task (e.g., hand movement and effector specific motor cortex) [88], in contrast to skeletal muscle which can increase its energy demands by up to 1,800% with exercise [89]. Therefore, the brain is always using energy at very high rates; intrinsic brain activity never ceases. What is the purpose of all of this energetically demanding intrinsic activity?

From an evolutionary perspective, the purpose of a nervous system is goal-directed behavior, typically expressed as safely moving to explore and exploit one's environment [90,91]. Organisms that cannot actively move, such as plants, corals, or polyps, do not have brains [92]. Cisek argues that: "all aspects of brain function, including thoughts and feelings, must ultimately serve overt action or they would not have been supported by natural selection [90]." However, in practice, awake animals are not always behaviorally striving, but often spend time resting and digesting [93]—a very distinct pattern of behavior that must be just as critical for survival. Thus, the awake behavioral state space divides into distinct goal-directed and resting states (Table 1).

In simpler, phylogenetically less refined animals, the moving/resting behavioral state spectrum maps closely onto the basic division into action and default brain modes [90,91,93]. In the behavioral resting state, the brain enters its default-mode, to maintain and update itself through intrinsic processes. When an animal is actively behaving, its brain transitions to the action-mode to achieve allostasis [89,94,95] through interaction with the extrinsic environment. The equilibrium between action- and default-modes balances current behavioral needs against future behavior readiness and quality. In higher animals, the default-mode also includes remembering and egocentric imagining, while the action-mode also includes decision making, planning, and action-

preparation/pre-motor processes. The brain's default-mode has been well substantiated, but what about evidence for the action-mode that it seems to alternate with?

In humans, physiological and neuroimaging work strongly supports the existence of an action-mode of function. Initiation of goal-directed behavior coincides with physiological alertness markers driven by greater sympathetic tone, such as pupillary constriction [80], brain-wide EEG (electroencephalogram) [96], and fMRI signal changes [7,20,26]. These neurophysiological markers of the action-mode also correlate with improved performance on cognitive and motor tasks [96-99]. Pain, perhaps the most salient feedback signal also increases arousal and can interrupt the default in favor of the action-mode [100].

Electrophysiology and imaging studies in rodents also support the existence of a task generic action-mode of brain function. In these studies, the action-mode is most clearly indexed by movement signals [93,101]. During mouse decision making, global cortical representation of task engagement is encoded in the activity dynamics of cells and superficial neuropil across the majority of dorsal cortex [101]. Recordings of the mouse brain during decision tasks showed neural responses to be correlated with motor action almost everywhere in the brain, in contrast to the more focal responses to sensory stimuli [102]. This suggests that the neural representations of movement may be linked to a brain-wide change in neural processing during action periods.

In addition to alternations between extended periods (minutes, hours) of goal-directed behavior and rest, there are also more rapid arousal fluctuations, on the timescale of seconds (infraslow: 0.01-0.2 Hz), along the brain mode continuum, cycling from action to default in both humans [103] and mice [104]. These fluctuations are related to variance in behavioral performance [105-107], as variability in EEG [107], event-related fMRI task activations [98] and performance [108] have been linked to intrinsic infra-slow fluctuations in brain mode. Such mode-related fluctuations in turn are related to spontaneous changes in arousal [103,104]. In mice, cortex-wide functional networks are embedded within a canonical arousal cycle indexed by increased pupil diameter and locomotion, and changes in hippocampal activity [104]. In humans, analyses of the coherence between arousal (i.e., pupillometry, vital signs) and

RSFC data revealed that global waves, which are part of the RSFC signal and contribute to the division of the brain into distinct functional networks, are time-locked to spontaneous arousal fluctuations [103]. These arousal-locked waves are phase shifted across functional networks, such that the AMN is maximally offset from the DMN, sitting at opposite ends of the action- to default- arousal space [103,109]. Infraslow (0.01-0.2 Hz) fluctuations have been shown to modulate the amplitude of higher frequency brain activity (1-40 Hz), via phase-amplitude coupling [107,110]. The yoked infraslow (0.01-0.2 Hz) fluctuations in arousal, performance and spontaneous brain activity may confer a memory/skill encoding benefit to offset any potential performance decrements. The infraslow rotating brain mode waves are themselves embedded within blocked, even lower frequency brain mode changes tied to behavioral changes humans are consciously aware of (e.g., "I am editing a manuscript").

The cingulo-opercular action-mode network (AMN)
Just as the brain's default-mode is controlled by the DMN, the action-mode is controlled by a specific set of brain regions. In mice, a region in anterolateral premotor cortex seems critical for entering the brain's action-mode, since optogenetic inhibition abolishes both the cortex-wide response to task-initiation cues and the voluntary behavior [101]. In macaques, neural activity consistent with the initiation and maintenance of the brain's action-mode has been recorded from prefrontal cortex (PFC) across a variety of different tasks [111].

In humans, the cingulo-opercular task-positive regions (see Box 1) control the action-mode. Hence, we have reconceptualized the CON, which we first proposed in 2007 [12], as the action-mode network (AMN) that combines functions for achieving behavioral goals through successfully interacting with the environment. The AMN initiates, maintains, and controls a generic action-mode of brain function. Many specific behaviors may be performed during the action-mode, from complex mental tasks to physical actions, but these actions all share common required processes that are implemented by AMN regions. These include planning, goal maintenance, alertness, sustained extrinsic attention, feedback processing (pain, physiological and body states, motor & cognitive errors) and often planning/initialization of some form of motor output [7-9,12-16,20,29,35,36].

The AMN is critical for initiating and maintaining higher-arousal states. The AMN shows very large activity onset and offset transients required for moving out of and into rest periods [7,20], with sustained goal maintenance signals throughout the task periods [7]. Activity in the central thalamic nuclei (centromedian (CM), ventroposterolateral (VPL)), which are part of the AMN and SCAN, leads all other brain regions when arousing from sleep [112]. Dorsal ACC regions of the AMN are the first cortical areas to become active in the brain's arousal cascade [112]. The AMN may extend even deeper into the brain's motor systems, to the substantia nigra (SN), subthalamic nucleus (STN), red nucleus (RN) [113], dentate nucleus, locus coeruleus (LC) and the vagus nerve nuclei, but better brainstem imaging methods are needed to know conclusively (see Box 3: Open questions).

Alteration of or damage to the AMN prevents or alters goal-directed behavior. For example, lesions within AMN cause apathy and abulia [114,115], decreasing spontaneous self-initiated activity. AMN lesion patients can perform activities when specifically instructed, but they do not become active voluntarily. Similarly, seizures in the pars marginalis of the cingulate have been shown to cause a loss of the sense of bodily agency [116-118], such that patients were consciously aware of their own self and they were aware that they were moving, but they did not feel that they were the agent or cause of their own activity. The apparent efficacy of centromedian (CM) DBS in reducing seizures [119,120] may also be attributable to the CM's place in the AMN/SCAN circuitry for regulating cortical arousal via changes in the cortical excitatory/inhibitory (E:I) ratio [121]. In contrast, human direct electrocortical stimulation of AMN regions in the anterior cingulate has been shown to reliably induce a sense of determination to persevere and continue despite adversity [122].

The AMN is the functional network most anticorrelated with the DMN (Fig. 2). Thus, the AMN counterbalances the DMN and is more activated during goal-directed extrinsic activity, when DMN activity is attenuated, independent of the specific task demands [7,13]. Importantly, the AMN also plays a key role in processing physically painful stimuli. The dACC and the anterior insula are the brain regions are activated during application of painful stimuli [15,123]. This pattern is generally consistent across both somatic and visceral pain [124] and is separate from negative affect or social pain [123].

Conclusion: The brain is also for action

The evolutionary origins of the AMN's basic circuitry are likely more distant than those of other association brain systems, since animals in the human lineage were behaving before they developed the rich inner life thought to be supported by the DMN [91]. The AMN's neuroanatomy, including its representation in SMA, striatum, and cerebellum, as well as its strong connection to SCAN in primary motor cortex, betrays its roots as a system for moving the body to achieve behavioral goals. The AMN seems to derive from simpler control systems for movement of the body (skeletal muscles) and movement within the body (smooth muscles).

Through phylogenetic refinement, the human AMN, like the rest of our brain, has become capable of extremely abstract processing. It no longer only produces physical movement, but also complex cognition. However, the AMN's principal differentiator from all other higher-order functional brain networks is that it remains closest to the original biological reason for using a brain: goal-directed movement, also known as action. Thus, even the most complex AMN processing is best conceptualized as cognition for action, which complements the self-referential thought supported by the DMN.

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Declaration of Competing Interest

N.U.F.D. has a financial interest in Turing Medical Inc. and may benefit financially if the company is successful in marketing FIRMM motion monitoring software products. N.U.F.D. may receive royalty income based on FIRMM technology developed at