Prova n.2

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Action-mode subnetworks for decision-making, action control, and feedback

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The action-mode network (AMN) is a canonical functional brain network first identified using resting-state functional connectivity (RSFC). Based on animal and human data, we have proposed that AMN supports the brain's action mode by controlling functions required for successful goal-directed behavior. However, task fMRI averaged across groups has associated AMN regions with a variety of behaviors, contributing to uncertainty about AMN function. Here, we investigated the AMN using an inside-out approach, in which the network architecture of the AMN is first precisely mapped within individuals and then associated with behavioral functions. Individual-specific precision functional mapping with >5 h of RSFC and task functional magnetic resonance imaging (fMRI) data revealed a replicable AMN subnetwork structure. AMN subnetworks were characterized and annotated by combining a meta-analytic network association method with RSFC, intrinsic timing, and task activation profiling. We demonstrate the existence of AMN-Decision, -Action, and -Feedback subnetworks that are distributed across lobes, forming a temporally sequential within-network processing stream by which the brain adjudicates between possible goals, sets action plans, and modifies those plans in response to feedback such as pain. A subnetwork in the pars marginalis of the cingulate was distinct from the Decision, Action, and Feedback subnetworks and may be important for the construction of the bodily self.

action-mode network | cognitive control | functional connectivity | action control | precision functional mapping

Significance

The human brain is organized into large networks. One important brain network is the Action Mode Network, which controls functions related to goal-directed behavior. In group-averaged data, this network emerges as a unitary whole, despite its involvement in a variety of behaviors. Here, we tested whether Action Mode networks found in individual humans, rather than group-average networks, might contain organized substructure that helps explain its functional heterogeneity. In individuals, we identified four subnetworks within the Action Mode Network related to decisions, action implementation, feedback, and the bodily self. Together, these subnetworks form a processing stream by which the brain decides goals, sets action plans, and modifies those plans in response to feedback such as pain.

The human brain is organized into about a dozen canonical functional networks that have been repeatedly verified across populations, datasets, and analyses (1–7). One of the first functional networks discovered was the action-mode network (AMN) (8), which was originally referred to as the cingulo-opercular network (9–11) based on its neuroanatomy. AMN is composed of functionally coupled regions in the dorsal anterior cingulate cortex (dACC), supplementary motor area (SMA), anterior and middle insula, supramarginal gyrus (SMG), pars marginalis of the cingulate gyrus, anterior prefrontal cortex (aPFC), anterior putamen, the central portion of the thalamus (in or near the ventral intermediate nucleus), and lateral cerebellum (5, 6, 9–13). The AMN has often been confused with the Salience network (14), though these two networks are anatomically and functionally distinct. Relative to AMN, Salience is localized more anteriorly in dACC and inferiorly in anterior insula and exhibits subcortical connectivity [to nucleus accumbens rather than anterior putamen (15, 16)] and function [reward and motivation (17, 18)] inconsistent with the AMN. Animal and human studies suggest that the AMN initiates and maintains the brain's action mode, a state in which arousal is heightened, attention is externally focused, and action plans are created and converted to movements (8, 9, 19–23). Lesions to AMN regions impoverish voluntary behavior while preserving other functions (24, 25). Thus, AMN appears to control and enable behavior expressed as physical actions—the most important outcome of any set of complex brain processes.

Task fMRI research has associated AMN regions with a wide variety of behaviors, leading to significant uncertainly about AMN function. The AMN coactivates (along with several other brain networks) across a wide variety of cognitive tasks, leading to high-level characterizations of task-positive activity as reflecting a broad extrinsic-mode network (26, 27). The more restricted set of AMN regions was initially characterized as a network critical for exerting top–down control over other cognitive functions. Large signals are observed in the AMN when complex cognitive tasks are initiated (9, 28, 29), and it exhibits sustained signals related to task goal maintenance (9–11). AMN regions also respond strongly to feedback, enabling more effective control in the future. The AMN exhibits large error responses; its activity is modulated by trial difficulty (i.e., time on task); and

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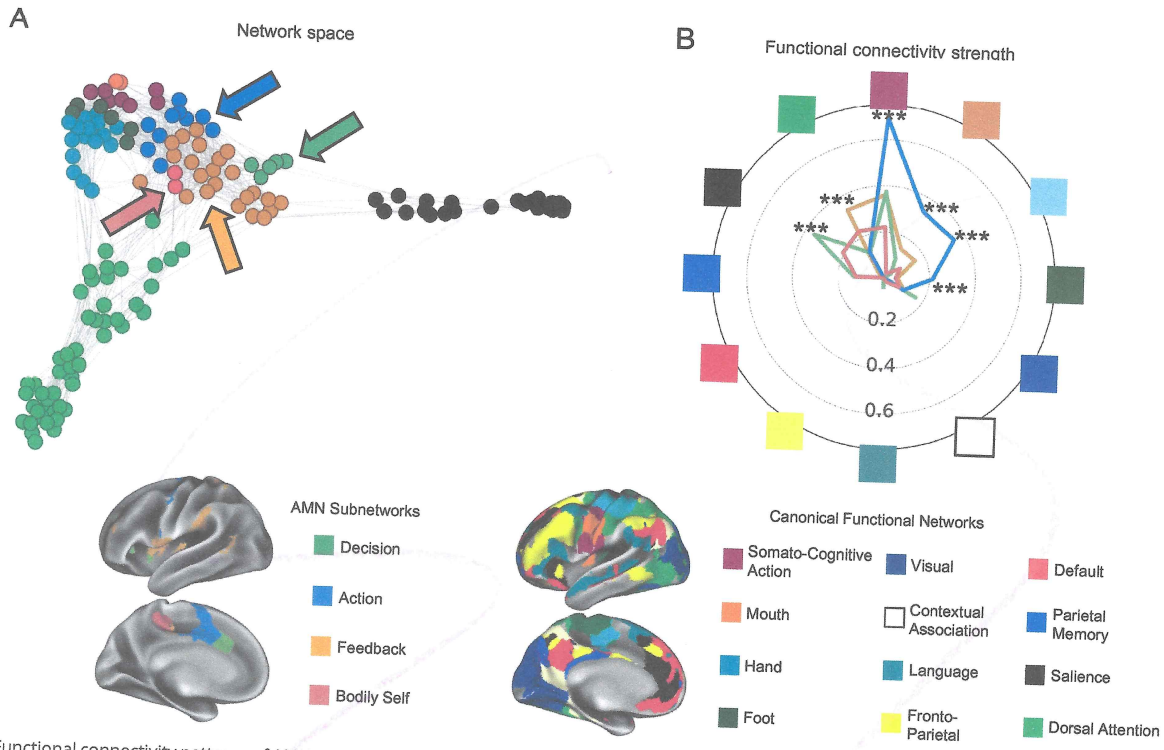

Fig. 4. Functional connectivity patterns of AMN subnetworks. (*A*) A spring-embedded plot in an exemplar participant (P01) illustrates the preferential connectivity of Action Mode subnetworks to large-scale functional networks. For clarity of visualization, only networks most closely associated with the subnetworks are shown. See *SI Appendix*, Fig. S4 for all individual participants. (*B*) Across participants, individual-specific action-mode subnetworks demonstrate preferential connectivity to other individual-specific functional networks. The radial axis indicates the strength of functional connectivity Z(r) between each AMN subnetwork and each canonical functional network. Negative connectivity values are not represented. Significant differences among subnetwork connectivities to each network, determined via ANOVA, are indicated as ***P(corr.) < 0.001. Colors and spatial locations of AMN subnetworks (*Left*) and other canonical networks (*Right*) are shown in the exemplar participant at the *Bottom*.

significant vs. the Bodily Self subnetwork [Feedback vs. Action, vs. Decision: ts(12) > 4.2, Ps < 0.001; Feedback vs. Bodily Self: t(12) = 2.0, P = 0.07]. Similarly, the Decision subnetwork exhibited stronger connectivity than any other subnetwork to the Salience network, though this difference was not significant vs. the Bodily Self subnetwork [Decision vs. Feedback, vs. Action: ts(12) = 6.5, Ps < 0.001; Decision vs. Bodily Self: t(12) = 1.6, P = 0.14]. All post hoc paired t tests can be found in *SI Appendix*, Table S2.

Some of the strong subnetwork-to-network connectivity preferences (e.g., AMN-Decision to Salience) were between physically adjacent portions of the cortex. To ensure that the strong FC values were not driven by local autocorrelations of the fMRI signal, the above analyses were replicated after excluding all functional connections between cortical vertices within 20 mm of each other. Connectivity profiles did not change (*SI Appendix*, Fig. S5); all network-level ANOVAs remained significant (all Ps < 0.005); and all post hoc t tests reported significant above remained significant (all Ps < 0.005).

Spontaneous fMRI Signals in AMN Subnetworks Are Temporally Ordered. Differential timing of infraslow rs-fMRI signals (0.08 to 0.1 Hz) among network structures suggests a temporally ordered processing stream, as has been identified among different subnetworks of the default-mode network and among networks in the precentral gyrus (45, 73). Here, lag analyses demonstrate the temporal order of infraslow rs-fMRI signals within networks of the putative action output processing stream, including Salience, AMN subnetworks, SCAN, and effector-specific motor networks (Fig. 5). A one-way ANOVA found a significant main effect of subnetwork/network identity [F(6, 94) = 9.92, P < 0.0001]. Post hoc t tests indicated that signals in the Salience network occurred later than those in all AMN subnetworks, SCAN, or motor Hand [all ts(14) > 3.1, all Ps < 0.009]. Further, spontaneous activity in Feedback, Decision, and Bodily Self subnetworks occurred later than Action, SCAN, or Hand activity [ts(14) > 2.3, all Ps < 0.04]. All temporal lag t tests can be found in *SI Appendix*, Table S3. Previous reports have associated interregional lags in infraslow (<0.1 Hz) signals with temporally ordered delta activity (0.5 to 4 Hz) lags in the opposite direction (94). Thus, these results suggest a temporal ordering of delta-frequency activity from Salience to the AMN-Feedback, Decision, and Bodily Self subnetworks, and then to the Action subnetworks, SCAN, and effector-specific motor networks, consistent with the expected relative ordering of a feedback–decision–action cycle.

Discussion

A Functional Processing Stream of the AMN. Traditional outside-in approaches for identifying brain regions associated with a priori cognitive functions have described a surprisingly varied range of functionality for AMN regions. Here, we employ an alternative, inside-out network annotation approach (59) to first identify the organization of the AMN and to subsequently probe function within this organization.

The brain-first, inside-out approach describes the AMN as a functionally integrated system with networked substructures that each have specific inputs and outputs, and which contain circuits spanning many cortical lobes and subcortical structures. These AMN subnetworks exhibit different task responses and sequential lagged timing of signals, suggesting that together they enable serial processing of information cutting across specific a priori