Open Review of “Open Review of ‘A somato-cognitive action network alternates with effector regions in motor cortex’ (Gordon et al., 2023)” (Muret et al., 2023)

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Muret et al. are expert in and have previously conducted group-averaged motor task fMRI studies in humans$^1$. Their review of our work on the somato-cognitive action network (SCAN) focused on the human task fMRI results, largely sidestepping the resting state functional connectivity and structural MRI findings. They also did not discuss the recently published human BCI and sEEG or the non-human primate tracer work consistent with our results.

The realization that effector specific and SCAN regions alternate down the central sulcus was driven by our synthesis of multimodal MRI (task, functional connectivity, structural; humans and macaques) data with extant electrophysiology results (BCI, sEEG, stimulations) and retrograde tracer studies. Human motor task fMRI data alone would likely have been insufficient to make confident claims about the SCAN. Task fMRI is well suited for characterizing brain systems related to isolated effector movements (e.g. finger tapping), but not for realistic whole-body actions (e.g. throwing an object to hit a target). This fundamental limitation of task fMRI may well have contributed to the delays in recognizing the SCAN. Technical factors, such as insufficient data quantity and quality and the use of group-averaging and winner-take-all mapping, may also have played a role.

Despite these caveats, the individual-specific task fMRI findings are more consistent with the SCAN than a strict homunculus. Individual-specific motor task fMRI data, even when analyzed with a winner-take-all approach (strongest activation for a given movement) show that foot, hand, and face regions are organized as concentric functional zones, consistent with a wealth of macaque electrophysiology data. When we move beyond winner-take-all analyses (Fig. 3b, Ext. Data Fig. 7), it becomes clear that task fMRI responses within the foot, hand and mouth regions are strongly selective for specific body parts, but the SCAN nodes are not (Fig. 3c,d, Ext. Data
Fig. 7), consistent with human sEEG work. While the action planning contrast shown in Fig. 3e should not be considered an effective SCAN localizer, because it still relies on isolated movements performed while lying flat, it nonetheless shows greater SCAN activation during the planning than the execution phase, a classical ‘premotor’ signal.

Below we discuss Muret et al.’s specific arguments against the SCAN. We do not discuss the beginning of their review, which mostly highlights evidence against the homunculus theory, because we agree with these points. As highlighted in our original article, prior human and non-human primate electrophysiology, functional MRI, and structural MRI have suggested organization within M1 that is inconsistent with the homunculus. We apologize that citation count restrictions made it impossible to cite all of the important studies highlighted by Muret et al.

1. The key conceptual contribution of the study is the introduction of these body-part (or parcel) boundaries as so-called inter-effector regions that, as the authors argue, form a somato-cognitive action network for mind-body integration. But as clearly demonstrated in the activity maps of the two participants, these regions are housed by representations of the abdomen (dorsal spot), upper-face (middle spot), and throat/inner-mouth (ventral spot). It is therefore unclear to us why the hegemony of these body parts over these cortical territories is dismissed. Instead, we believe it is important to consider the alternative hypothesis that the increased correlation between these sub-regions is caused by their functions. For example, these body parts may be co-engaged during breathing (i.e., involving both abdominal and inner-mouth/throat motion for air inflow/outflow) and blinking, which are some of the main muscular activities taking place during resting-state data collection. Such synchronized activity during rest could contribute to the increased inter-regional correlation that the authors interpret as increased functional connectivity (as demonstrated in Duff et al. (2018)). Conceptually, instead of classifying these areas as inter-effector regions, they could, in our view, also be classified as representing the abdomen, upper-face and throat.

The individual-specific precision task fMRI data show the opposite of ‘hegemony’ of a specific body part over each of the SCAN nodes. Fig. 3 and Ext. Data Fig. 7 were included in the manuscript to specifically highlight the lack of effector specificity in the SCAN nodes. Fig. 3d demonstrates that while the foot/hand/mouth regions are strongly effector specific, the inter-effector regions are not. Fig. 3c is an example selected to show that in two independent participants, isometric tensing of the abdomen results in activity within all three SCAN nodes, a clear violation of the homunculus theory. Fig 3a (classical winner-take-all) already reveals concentric functional zones, which violate the homunculus theory. Most critically, Ext. Data Fig. 7 shows that the winner-take-all approach obscures the fact that there is minimal activation
peak separation between body parts in the SCAN nodes, and that that the effector specific regions are deactivated when moving other effectors, which is not the case for the SCAN. Note that this distributed, nonspecific representation has already been validated in intraoperative sEEG recordings of SCAN regions$^2$.

When trying to understand the strong inter-node connectivity in SCAN, one of our earliest thoughts was also whether it could have something to do with correlated body part movements in every-day behavior. But this idea was inconsistent with many of the results, novel and published. For example, we routinely coordinate our arms and legs for walking, and we routinely coordinate hand and mouth movements for eating, yet these effector-specific regions are not strongly functionally connected to each other. In addition, the correlated movement hypothesis cannot account for the strong selective connectivity to the cingulo-opercular network (CON), including the dorsal anterior cingulate cortex (dACC), and anterior prefrontal cortex (aPFC; lateral area 10) (Fig 2; Fig S1).

Muret et al. more specifically propose that co-occurrence of breathing and blinking could drive the strong functional connectivity amongst SCAN regions, as these are physical activities that do occur in the resting state. Here, it is important to note that, in order to artifactually drive functional connectivity of this magnitude, blinking and breathing would have to not just occur during the scan, but in fact would have to be temporally correlated. We are unaware of any physiological reason why breathing and blinking would be temporally correlated, or any prior research that suggests they are.

The Muret et al. hypothesis is that co-occurrence of blinking and breathing activities drives SCAN connectivity. This implies that the SCAN should be absent when blinking and breathing do not co-occur. To empirically test this hypothesis, we examined the Poldrack MyConnectome data$^{3,4}$ (https://openneuro.org/datasets/ds000031/versions/2.0.2), which to our knowledge is the highest quality extant PFM dataset in which resting-state data was collected in the eyes-closed condition (absence of blinking). A seed placed in precentral gyrus clearly demonstrates a SCAN connectivity pattern in this data, demonstrating that SCAN connectivity is not driven by the co-occurrence of blinking and breathing.

Fig. 1. SCAN identified in eyes-closed resting-state data from the MyConnectome dataset.
In principle, the SCAN is unlikely to drive simple breathing in the same way that the motor hand area controls fine finger movements, because the brainstem alone reflexively supports breathing even when cortex is incapacitated, and MCA stroke patients do not tend to have prominent central apnea. Instead, as mentioned in the original article, the SCAN’s role may be to coordinate breathing with actions such as speech or singing, or adjusting for other physiological demands while speaking. Fascinating work has shown that the depth of a breath anticipates and matches the length of an upcoming speech segment—a clear integration of a simple motion with a planned action that might be enabled by SCAN connectivity with CON.

2. The authors use connectivity ‘network sub-divisions’ in their resting-state datasets to identify the so-called “inter-effector” regions. However, rather than providing a systematic approach based on independent measures (anatomical and/or task-related activity markers), it seems that these regions (black outlines in Fig 1b) were defined based on their resting-state functional connectivity differences. Taking the fact that these regions (after defining them thus) have different functional connectivity profiles as a basis for the argument of a new organisation scheme in M1 seems circular to us.

Network subdivisions were not used to initially identify the SCAN, as Muret et al. seem to suggest. Much to our delight, the functional connectivity differences between the SCAN and effector-specific regions are so powerful and readily apparent in every data set (except human newborns) that the SCAN was clearly identifiable with simple seed maps, and by running a series of seeds down precentral gyrus (as described in our Methods). Each separate individual-specific map (n = 7; Ext. Data Fig. 1a) and each of the separate group-averaged data sets (ns = 120 – 4000; Ext. Data Fig. 1c), represent a successful replication of the original finding. In addition, we also conducted split-half replications within participant (n = 3; Ext. Data Fig. 1b) for additional validation.

After identifying the SCAN and replicating the finding in all available data sets (other than newborns), we aimed to characterize it. One of our primary questions was how SCAN structure and functional connectivity to the rest of the brain (including circuits known to be involved in motor functions) might differ from effector-specific regions. This required definition of a single set of ROIs for structural and functional analyses. Thus, we used our previously published subnetwork detection algorithm to define SCAN and effector-specific ROIs. The resting-state connectivity-derived divisions in M1 converged closely with the task localizers for the effector-specific regions (Ext. Data Fig. 1d), verifying that it produces very similar functional divisions as task fMRI.

To compare SCAN and effector functional connectivity, we first evaluated the spatial pattern of connectivity differences (Fig. 2b; left panel: difference image). No statistics were employed in this map. The significance testing in Fig 2b (right panel) is not of a difference between the effector-specific and SCAN nodes, but of the relative pattern across networks. The asterisks do not indicate a difference between SCAN and effectors, but rather indicate that amongst all the
networks, the CON is the relatively strongest differentiator, across participants. Thus, the statistics in Fig. 2b are not circular. Fig. 2d does not evaluate functional connectivity (zero lag correlations), but instead an independent metric of signal lags and is therefore also not circular. Fig. 2e evaluates a structural MRI metric and is therefore not circular.

The analyses in Ext. Data Fig. 4i,j,k are also of structural metrics and thus not circular. The analyses in Ext. Data Fig. 4b,c,d,e,f,g evaluate functional connectivity to subcortical structures and to the middle insula. These ROIs were all defined structurally, not using the functional data, so the statistics are not circular.

That leaves Ext. Data Fig. 4a, which visualizes the functional connectivity of the SCAN and effector regions to the CON (defined from functional connectivity), as possibly containing biased statistics. Ext. Data Fig. 4a is meant to serve as a quantification of Fig. 2b that shows the sign and magnitude of the pairwise, within-participant connectivity. As such, the p-values are superfluous.

However, encouraged by Muret et al.’s comment, we conducted an additional statistical analysis similar to Ext. Data Fig. 4a that was designed to avoid any concerns of circularity. We replaced the individual-specific SCAN, effector, and CON ROIs with ROIs defined from an independent dataset (HCP group average data).

Using these independent ROIs in PFM subjects, we replicated our original statistical results in Ext. Data Fig. 4a. SCAN-to-CON functional connectivity was larger than Foot-to-CON, Hand-to-CON, or Face-to-CON connectivity in every subject; and all paired t-tests were significant (SCAN vs Foot: paired t = 6.51, p=0.00063; SCAN vs Hand: paired t = 7.22, p = 0.00036; SCAN vs Face: paired t = 5.77, p = 0.0012).
Fig. 3. Differences in SCAN-to-CON vs effector-to-CON connectivity in PFM subjects using group-derived ROIs

3. Perhaps the most speculative claim of the study is that these so-called inter-effector regions function as somato-cognitive integrative regions. The authors used exploratory functional connectivity analysis with higher order areas to support their interpretation. However, the function of an area should not be inferred post-hoc and solely based on a thresholded resting-state connectivity map, especially considering that these higher order areas have been associated with a large range of functions. Labelling the primary function of the brain areas as a somato-cognitive interface for the whole-body action plans certainly doesn’t seem to provide a sufficiently precise hypothesis to critically test. A more detailed functional investigation of the inter-effector regions, for example using representational similarity analysis to identify task-relevant information content, and TMS to infer on consequences of stimulation of these regions, is required to test the hypothesis put forward here.

SCAN’s suggested functions were not solely based on its strong and selective functional connectivity to the cingulo-opercular network (CON). As described in the article, the discussion of SCAN’s function is based on a wealth of multimodal evidence, encompassing novel and previously published data, such as the observation that localized cortical stimulation can evoke
complex, multi-effector movements\textsuperscript{8-10}, or the existence of cortical projections to internal organs for preparatory, pre-action allostatic regulation\textsuperscript{11-13}.

Furthermore, the existence of the SCAN generates a long list of testable hypotheses related to apraxia, movement disorders, stroke recovery, lesion deficits, and more—work which has already been initiated with TMS, sEEG, direct electrocortical stimulation and other techniques.

To pick out an example, the SCAN provides a new explanation for one particularly puzzling phenomenon: the fact that direct stimulation of M1 ameliorates chronic pain\textsuperscript{14,15}. The mechanism for this treatment makes little sense if we think of M1 as only controlling movement. However, the expanded conceptualization of SCAN and CON as a circuit integrating body and action planning—necessarily including pain feedback signals—suggests a potential role for SCAN in pain processing, and suggests that SCAN neuromodulation could treat chronic pain.

A clear testable hypothesis deriving from this idea is that regions which process pain stimuli should include both CON and SCAN. Below, we show a publicly available map of pain processing (main effect of high-intensity heat stimulation, from\textsuperscript{16}, thresholded as in Figure 2 of that article; map available here: https://github.com/coghill-painlab/IDP_fMRI_activationMaps). Both CON and SCAN were activated by this pain stimulus.

We want to emphasize that we do not consider SCAN a “pain” network any more than we consider it a “breath coordination” network. As with all connectivity-derived networks, functional ascriptions are difficult and necessarily incomplete, constrained as they are by the limited set of tasks that can be performed in an fMRI scanner. We would love to continue the discussion about all of the functions the SCAN may be supporting, and how to test even more hypotheses.
4. Where the authors do evaluate the function of the hypothesized inter-effector regions, the statistical evaluation is often insufficient. For example, the authors claim that the inter-effector regions have a special role in the planning of whole-body movements. This claim relies on task-related fMRI data (Fig 3e) from n=2 participants, making an assessment of the inter-subject variability of the results impossible. The statistical argument appears to rely on the fact that the planning-related activity was higher than the execution related activity, but that in other regions this effect was not significant. Inspection of Fig 3e however clearly also reveals planning related activation in the mouth region, which, similarly to the “inter-effector” regions was less involved in the execution of the movement. Thus, it is likely that the reported regional differences were due to the high execution-related activity in hand and foot regions (and the results would not replicate if the authors were to study coordination of muscles controlling the trunk and upper-face). For example, in our recent work, we did not find elevated activity or movement encoding in the supposed inter-effector regions during movement planning (Ariani et al., 2022).

Each participant that completed the repeated precision task fMRI sampling represents an independent experiment (244 min of data per subject). The maps shown demonstrate significance in each participant independently. In our view, the question of “variation across individuals” should be a secondary question explored after establishing robust effects within each individual. We have previously shown that high-data within-individual testing can produce very large effect sizes in every individual subject (Cohen’s ds between 1.0 and 3.8)\(^1\); and the statistical effects observed in each subject in the present work are similarly very large. Indeed, this approach follows the more traditional approach employed in non-human primates, in which statistical significance is established first and most critically in each animal before expanding questions to variation across animals. Prior work has suggested that with large effects and highly reliable data, three participants/animals would guarantee statistical significance, but most studies are sufficiently powered with two animals\(^1\).

We also note that the conclusions in the discussion about the role of the SCAN do not hinge solely on the task fMRI data, but also take into account important macaque electrophysiology work\(^{10,12,19}\), as well as human BCI data which have shown ‘premotor’ planning signals in supposed M1\(^2\).

It is difficult to compare our results to Ariani et al.\(^1\) because they evaluated isolated finger movements, a specialization likely supported by effectors-specific circuitry for the hand, while our task required planning different combinations of foot and hand movements that sometimes conflicted with each other. We suspect that such planning signals would be even more robust if a study could be designed to involve more whole-body coordinated movements, either within an MRI scanner or using other, ideally mobile technology.
Muret et al. suggest that the second-peak activity we observe may be a result of indirect activation spreading from sensory cortex. This interpretation is inconsistent with decades of causal non-human primate research observing a nearly identical concentric distal-to-proximal organization, and showing that direct stimulation of sites on both sides of the concentric ring causes movement. For example, here are intracortical stimulation findings from Kwan et al., 1978\textsuperscript{21} demonstrating a concentric organization of the hand area:

5. During the task-related functional mapping, behaviour was not sufficiently rigorously monitored or in fact considered when interpreting the data. For example, would it be possible that some of the double-peaks observed using the Gaussian analysis could correspond to the representation of two body parts? For example, when moving the shoulder, the hand and wrist will receive sensory input through the induced movement, which would in turn impact MI activity. We also think that the interpretation that differences in connectivity profiles between the neonate and the other samples (where breathing and blinking are co-occurring), interpreted as ontogenetic development, could have been influenced by task execution. Specifically, there are multiple differences during the ‘resting’ state of the neonates, who were asleep. Beyond blinking that is obviously absent when sleeping, sleep patterns are known to change rapidly during the first months of life (Weerd & Bossche, 2003). In addition, even if restrained, neonates, while sleeping, are more likely to move in the scanner, something that was not monitored here, and which could have influenced the resulting ‘connectivity’ maps. This criticism (recording during sleep and motion more likely) also holds for the macaque dataset.
From Park et al., 2001.
From Dum and Strick, 2005:

And from Dancause et al., 2006:

This work demonstrates that activity in these second-peak regions causes movement, rather than being indirectly evoked by movement.

As a side note, in our view this convergence of individual-specific precision fMRI in humans with fine-grained electrophysiological mapping in non-human primates is thrilling. It suggests that the quality of human fMRI has improved sufficiently to allow us to make observations of detailed anatomical organization, more similar to non-human primate research, providing opportunities for cross-species comparisons.

Why are there two peaks at all? Muret et al. suggest spreading activity from sensory cortex. However, a view more consistent with existing data would be that the double peaks represent
the paired antagonistic muscles of a joint (i.e. flexors and extensors). This is consistent with both direct electrical stimulation studies in macaques\textsuperscript{25}:

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{macaque_joints.png}
\caption{Schematic of the paired antagonistic muscles of a joint in macaques.}
\end{figure}

as well as with fine-detail human fMRI data of finger movements\textsuperscript{26}:

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{human_fMRI_finger.png}
\caption{Schematic of human finger movements and associated brain activity.}
\end{figure}

Muret et al. also suggest that the absence of SCAN connectivity in neonates (Ext. Data Fig 2a,b) and/or macaques may be because they are sleeping and/or moving. However, the existence of the SCAN cannot be solely attributed to sleep, as the SCAN was successfully observed in the 11-month-old (Ext. Data Fig 2c), who was also asleep.

Movement is also not a concern. Infants have minimal movement during sleep (lower motion than awake adults), but start moving when they wake up\textsuperscript{27}. Neonatal fMRI scans are stopped when this happens. In sedated macaques, we observed a system apparently homologous to the SCAN (Ext. Data Fig 9). Motion was minimal in these data because the animals were anesthetized.

It is true that neonates exhibit differences in sleep patterns, but to our knowledge there is no evidence that such differences invalidate connectivity-based estimations of brain organization, nor any mechanistic rationale for how such an effect might occur. Indeed, there are many groups actively pursuing an improved understanding of infant brain organization using fMRI data obtained during sleep\textsuperscript{28,29}. 
The idea of an interspersed network that works qualitatively differently (and functionally on a hierarchically higher level) than the rest of M1 is an intriguing hypothesis. Given the lack of hard evidence for this claim, however, we believe it is premature to suggest that the new diagram of M1 (Fig 4b) provides a more adequate characterization.

Muret et al.’s first sentence in this paragraph reveals a misunderstanding. We are unaware of evidence that the SCAN regions are on a hierarchically higher level than the effector specific regions, and we do not claim so in the article. Rather, we have tried to highlight the striking degree of parallelism between the two. For example, the last sentence of our Abstract begins: “In M1, two parallel systems intertwine, forming an integrate–isolate pattern”. We apologize if this point was not sufficiently clear.

REFERENCES: