depressive-like behavior in mice with chronic pain. The observations demonstrate the existence of a circuit between the LHb, the DRN and the CeA, raising the possibility that reverberating activity between these structures may sustain depressive behavior.

Although these findings stem from preclinical models, which are not free from controversy and caveats[10,11], the study boosted its potential for clinical relevance by demonstrating in imaging analyses that the connectivity between the CeA and the DRN is indeed decreased in patients with chronic back pain. Thus, the study by Zhuo et al.[5] reveals exciting mechanistic insights into the highly prevalent comorbidity of depression and pain, which may well find their way into clinical application.

At the same time, the findings reported here are thought-provoking and open up several questions. The novel LHb–DRN–CeA–LHb circuit (Fig. 1) described here raises the question as to which of these regions and cell types ultimately constitutes the 'driver' and which constitutes the output 'effector' for depressive-like behaviors. Here it will be of critical importance to map the cellular identity of the LHb neurons receiving inputs from SOM^{CeA} cells and study how they feed into the LHb–DRN pathway described previously[6]. Moreover, mapping additional targets of projections from the LHb or DRN will be helpful, especially because it remains to be resolved how this circuit relates to other cortical areas that also play a key role in depressive-like behaviors in rodent models of chronic pain, such as the anterior cingulate cortex[12]. In human comorbidity of depression and chronic pain, the prefrontal cortex–nucleus accumbens connection has also been implicated.

Furthermore, this study is suggestive of specific mechanisms accounting for depression developing secondary to chronic pain as opposed to primary depressive disorders; how this highly intriguing specificity is generated remains to be elucidated. Similarly, because all of the regions described in this novel circuit are also implicated in anxiety and fear disorders, it will be interesting to delineate how the cellular circuits ascribed to depressive behavior in this study[5] differ from those mediating anxiety; the authors studied and clustered anxiety under 'anxio-depressive behavior', but did not consistently investigate it in all nodes of the described circuit.

Finally, particularly with a view toward treating therapy-resistant depression in patients with established chronic pain, it will be important to obtain a finer temporal map of the involvement of the novel circuit described here. It is known that time is a factor when analyzing emotional consequences in chronic pain models[10], which is also supported by Zhuo and colleagues' results[5]. Because longitudinal studies are typically not performed, there are inconsistencies across reports[10,11]. Moreover, like pain, anxio-depressive behaviors have been reported to evolve and spontaneously resolve and disappear over time in a different rodent model of neuropathic pain[12], raising the question of whether depression is temporally bound to periods of ongoing pain or whether it outlives pain. These and additional questions will spur new studies in this dynamic field at the interface of pain and mental disorders.

Taken together, the study by Zhuo et al.[5] has opened up an exciting new branch of research, and the basic mechanisms described here may pave the way for testing novel therapeutic approaches in comorbid depression and pain. ❐

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DECISION-MAKING & MOVEMENT

A new spin on fidgets

We express decisions through movements, but not all movements matter to the outcome. For example, fidgeting is a common yet 'nonessential' behavior we exhibit. New evidence suggests that this non-task-related movement profoundly shapes neural activity in expert mice performing tasks.

Mackenzie Weygandt Mathis

There may be moments in the day when you find yourself fidgeting: while waiting for the subway or sitting in a less-than-thrilling lecture, you may make nonessential movements or play with an object (perhaps an aptly named fidget spinner). Psychologists have ascribed these fidgets to boredom, a form of stress relief, or perhaps as a subconscious way to increase memory[1,2]. We sometimes do this even when we are seemingly actively engaged in a task. For example, you might glance around to find your lab-mates hard at work, yet flipping a pen or tapping their foot. How fidgets modulate their neural activity across the brain remains unclear. We know that certain brain regions drive actions (such as motor cortex) and many others receive this information (such as sensory areas), in part to distinguish self-generated from non-self-generated movements. But how are these

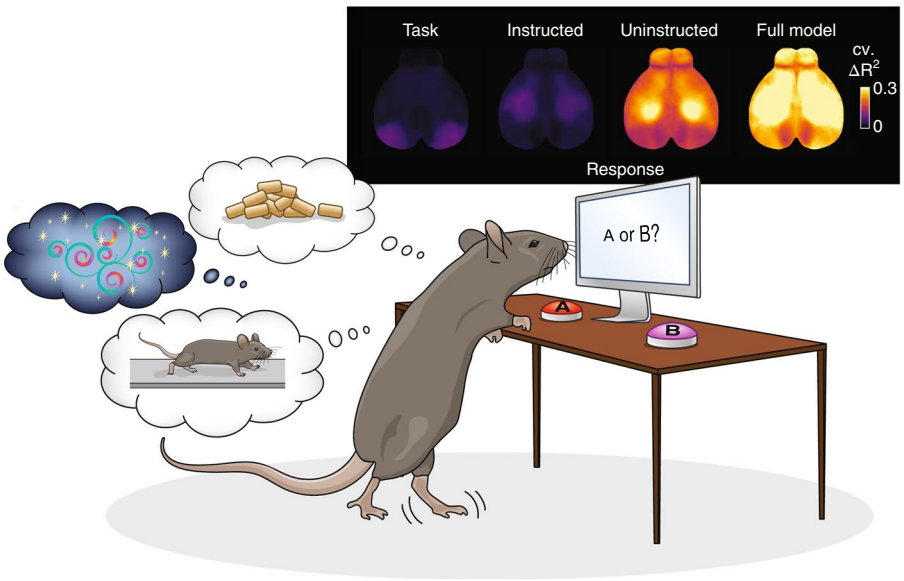

Fig. 1 | Movement signals dominate neural activity across the brain. This schema depicts an expert mouse making decisions while making essential and nonessential movements (i.e., foot tapping). Moreover, other internal states may modulate the neural activity, such as hunger and thirst state or other abstract internal thoughts that are hard for experimenters to currently measure. The image of neural activity is adapted from Musall, Kaufman et al.[3], Nature Publishing Group.

movements modulating brain-wide neural dynamics? Could this non-task-related foot tapping be enough to change how predominantly decisions are encoded in the brain?

In this issue of *Nature Neuroscience*, Musall, Kaufman, et al.[3] show that in expert mice performing a task, non-task-related movements dominate the single-trial neural activity (Fig. 1). This is an exciting finding that underlines why measuring behavior and other variables are key for exploring the neural code. While several recent studies have shown that many brain regions are dynamically regulated across both bouts of spontaneous activity and task-related movements[4,5], the resolution, in terms of both single-trial dynamics and cellular resolution, remained largely unexplored until recently[3,6]. This has now become possible due to several technological advances.

Specifically, the advances in large-scale recordings in recent years have allowed an unprecedented look into neural activity in awake, behaving animals[4–10]. Voltage-sensitive dyes were used to demonstrate that in sensory-guided decision-making tasks, whisker-deflections are rapidly transmitted across multiple areas of the dorsal cortex[4], and they were also used to explore how multimodal sensory-evoked responses shape spontaneous activity hemisphere-wide[5]. Multi-area electrophysiological studies have yielded important insights into the temporal order and flow of sensorimotor information in non-human primates[11] and in rodents[10]. Recently, genetically encoded calcium indicators were used to explore how brain activity in a multitude of areas was influenced by movement[3,6,8,9,12].

Conceptually, the notion that movement variables should be encoded across the brain is not new: in 1811, Steinbuch articulated the idea[13] that the motor system sends efference copies to other brain regions to allow it to compute self- vs. non-self-movement (i.e., is the sensory feedback caused by me turning my head or is the world moving?). Nonetheless, how motor signals may influence (or be multiplexed with) 'non-motor' variables, such as the presentation of a cue, is a challenging question to address. The reason is twofold: first, previous research has often collected data across hundreds of repeated trials to average across the measured neural activity and separate the signal from the noise, i.e., the variability of neural firing even in similar conditions[14]. Second, while signatures of movement-related activity were previously described in 'pure' primary sensory areas, such as visual cortex (V1)[12,15], the encoding of movement-related variables was often not measured in decision-making or pure visual system coding papers, for example. This was, in part, due to the fact that nuanced behavior was difficult to accurately measure, but now new machine learning tools are making this more feasible. Thus, historically many researchers explicitly looked for motor-related activity or modality-specific (i.e., pure visual) coding, which left a gap: what was the relationship between task-related decision-making variables and movements in brain-wide neural activity?

This past year, several groups have begun to leverage large-scale recordings with more sophisticated behavioral analysis to further explore whether an individual neuron's variation in activity was indeed noise or was related to non-task-locked activity. Stringer et al.[6] recorded thousands of neurons in V1 of naive mice that were headfixed and allowed to freely run while passively viewing natural images. They found that within individual neurons, the 'spontaneous' activity was actually highly linked to the facial movements of the mice. But do expert mice that are engaged in a task show the same level of movement-based modulation? One hypothesis could be that when recording spontaneous activity, the neural activity is dominated by movement signals, as they might have higher relative saliency. Thus, one open hypothesis was that task-irrelevant movement variables would be suppressed in the neural activity of expert mice performing a task—after all, they need to attend to task-relevant variables to carefully make decisions and collect rewards.

Musall, Kaufman, et al.[3] fill this gap and demonstrate that the observed task-irrelevant, movement-related neural activity was not just neural noise to the 'real' decision-making signal, nor did it contribute only a small part of the explanatory power of the recorded neurons: it was actually a dominant feature. Both Stringer et al. and Musall, Kaufman, et al. used similar behavioral variables from the face, or face plus body, respectively, as regressors in their computational analysis to test the hypothesis that task-irrelevant movement-related activity influences the neural dynamics. Musall, Kaufman, et al. found that even in expert animals that were performing a complicated decision-making task, individual neurons across multiple areas showed that the uninstructed movements were highly predictive of the measured neural activity. They also show that the dominance of the movement-related neural activity was stronger during training of the task vs. that seen in trained expert mice, which suggests the ratio between task variables and movement variables is not fixed.

How did they show this? The authors elegantly applied a technical tour-de-force, using three neural recording modalities during auditory- and visual-based decision-making tasks: they employed wide-field

one-photon calcium imaging to capture large populations of multi-unit activity, two-photon calcium imaging for single-cell resolution in the cortex, and Neuropixel probes for high temporal resolution in cortical and subcortical areas. They then used statistical models to study the effects on the task-related variables and the measured behavior. With every recording technique, the authors found that a linear encoding model could have some explanatory power if they only considered task-related variables (≈17% of the variance), but the animal's uninstructed movement (or 'fidgets') were a better predictor of the neural activity (nearly 40% of the variance). Adding in the task variables did little to improve the correlation. Only during the small time window when the cue (stimulus) was presented was there a clear task-related modulation, and likewise, instructed movements (i.e., for the required response) only mattered at those specific times in the task.

In summary, while self-generated movement signals (and sensory feedback) need to be broadcast across the brain, it was not clear that 'unnecessary' movements affected neural activity in a substantial way. Musall, Kaufman, et al. show that these movements (and all movements) actually dominate the neural activity during times when the mouse should be actively engaged in the decision-making task.

This study opens up several new and exciting questions. Why do the mice actually fidget? Are they doing so to help them focus on the task[2], releasing energy or making postural adjustments for comfort? These internal states are not as easy (or even possible) to explicitly measure. Perhaps as more tools become available to measure multi-cell-type activity paired with neuromodulators (i.e., dopamine at axon terminals), and as we better understand the relationship between neural activity and states such as 'mood', 'attention', 'boredom' and so forth, it will become possible to answer these questions.

How are movement variables used across the brain? Currently, it is not possible to simultaneously measure across the myriad different cell types that may be involved in decision-making or motor control. Here the authors recorded primarily from layer 2/3 excitatory neurons. Do inhibitory neurons, or projection-specific neurons, carry more nuanced 'movement' vs. 'decision' signals? While nearly every area might need various aspects of movement signals to perform relevant computations, it may be that distinct circuits comprising several cell types are involved in computing self vs. non-self in each sensory area. If so, examining only excitatory neurons could limit us to one part of the equation.

Hence, while the measured task and behavioral variables capture a high degree of the neural variance, there is still room to examine what information is encoded in individual neurons or at the population level. Historically, a lot of variance has been attributed to noise, but now these series of papers largely question this dogma. Therefore, if what was commonly attributed to noise is partly due to movement, what else can be explained by concrete phenomena? ❐

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Competing interests

The author declares no competing interests.