Review

Twitches, Blinks, and Fidgets: Important Generators of Ongoing Neural Activity

Patrick J. Drew[1,2] (iD), Aaron T. Winder[1], and Qingguang Zhang[1] (iD)

Abstract

Animals and humans continuously engage in small, spontaneous motor actions, such as blinking, whisking, and postural adjustments ("fidgeting"). These movements are accompanied by changes in neural activity in sensory and motor regions of the brain. The frequency of these motions varies in time, is affected by sensory stimuli, arousal levels, and pathology. These fidgeting behaviors can be entrained by sensory stimuli. Fidgeting behaviors will cause distributed, bilateral functional activation in the 0.01 to 0.1 Hz frequency range that will show up in functional magnetic resonance imaging and wide-field calcium neuroimaging studies, and will contribute to the observed functional connectivity among brain regions. However, despite the large potential of these behaviors to drive brain-wide activity, these fidget-like behaviors are rarely monitored. We argue that studies of spontaneous and evoked brain dynamics in awake animals and humans should closely monitor these fidgeting behaviors. Differences in these fidgeting behaviors due to arousal or pathology will "contaminate" ongoing neural activity, and lead to apparent differences in functional connectivity. Monitoring and accounting for the brain-wide activations by these behaviors is essential during experiments to differentiate fidget-driven activity from internally driven neural dynamics.

Introduction

> But when the audience is bored . . . they sway from side to side . . .
>
> —Francis Galton (1885)

Animals possess the ability to move, and the need to control these motions drove the evolution of the nervous system. Motor behaviors in animals can be in the form of stereotyped patterns of muscle contractions in support of physiological processes such as breathing (Feldman and others 2013), digestion (Marder 2012), or locomotion (Grillner 2006). Movements can also be learned actions with complex dynamics (Churchland and others 2012; Vallentin and others 2016). While these two extremes of motor behavior are well studied, there is a less well-studied range of spontaneous motor actions (such as blinking, twitching, sniffing, postural adjustments, and the movement of sensory organs such as eyes and vibrissae, which we collectively refer to as "fidgeting"), in which both awake animals and humans constantly engage (Galton 1885). Though these movements can be small, they have been linked with widespread alterations of neural activity and hemodynamic signals (Bristow and others 2005a; Ferezou and others 2007; Guipponi and others 2014; Winder and others 2017), and the impact of these changes

on ongoing brain dynamics have been greatly underappreciated. Moreover, the frequency and timing of these movements are influenced by sensory stimulation, tasks, and arousal. Because these movements are not typically monitored in awake animals or humans during neuroimaging experiments, they present a confound in interpreting brain-wide activity (Gonzalez-Castillo and others 2012) in the "resting-state" (Fox and Raichle 2007), in which spontaneous patterns of activity are attributed to internal rumination rather than external sensory signals.

Here, we review evidence from studies in humans and animals showing that these spontaneous behaviors drive neural activity and functional activations in a wide variety of brain regions. The frequency of these "fidgeting" behaviors vary over a wide range of time scales (Fig. 1), are affected by tasks and brain state, and will consequently

[1]Department of Engineering Science and Mechanics, Pennsylvania State University, University Park, PA, USA
[2]Department of Neurosurgery and Department of Biomedical Engineering, Pennsylvania State University, University Park, PA, USA

Corresponding Author:
Patrick J. Drew, Department of Engineering Science and Mechanics, Pennsylvania State University, W317 Millennium Science Complex, University Park, PA 16802, USA.
Email: pjd17@psu.edu
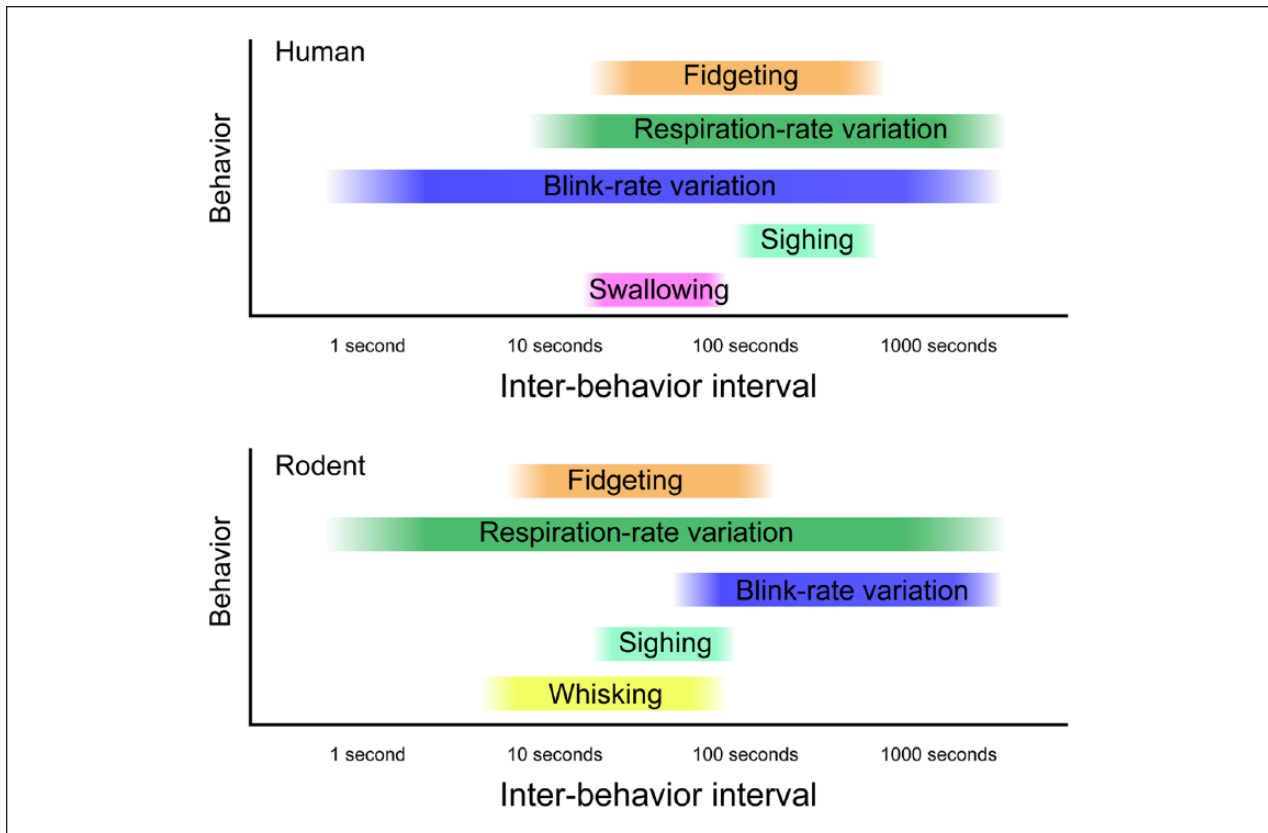
Figure 1. Spontaneous behaviors have characteristic time scales on the range from seconds to thousands of seconds. For each behavior, the interbehavior interval (typical time between behaviors or timescale on which the behavior varies) is plotted. Note that many behaviors vary on the 10- to 100-second time scale. Top shows humans, bottom rodents. The same range of timescales is used to assay functional connectivity in functional magnetic resonance imaging experiments (0.01 Hz to 0.1 Hz). See relevant sections for references.

impact brain activity in addition to any other changes. Though we refer to this neural activity as "fidget-driven", the relationship between neural activity and the movement could be of several (nonexclusive) origins. Neural activity associated with the fidgeting movement could be part of the motor commands that drive the movement, or somatosensory responses driven by touch receptors or proprioceptors. Fidget-related neural activity in a brain region could also result from common drive from a region that modulates the fidgets. As systems neuroscience moves toward whole-brain imaging using voltage-sensitive probes (Ferezou and others 2007; Mohajerani and others 2013), genetically encoded indicators in awake animals (Allen and others 2017; Chen and others 2017b; Murphy and others 2016; Xie and others 2016), and large-scale electrophysiological recordings from multiple brain regions (Dotson and others 2017; Harris and others 2016), we argue that careful behavioral observation should be done to avoid the confounds that "fidgeting"-induced activations will cause in these studies.

We focus on three easily detectable and quantifiable behaviors: blinking, spontaneous whisker motion, and postural adjustments. All these behaviors involve bilateral activation of distributed brain networks. We also touch upon other behaviors, and the potential physiological roles of spontaneous behaviors and fidgeting. We conclude by discussing the confounds introduced by these movements, and potential ways of monitoring and accounting for them.

Blinking Drives Brain-Wide Neural Signals and Blink Rate Is Affected by Mental State

Humans, other primates, and rodents constantly move and blink their eyes (Payne and Raymond 2017), changing the visual information reaching the retina. A great deal of progress has been made in understanding the neural control and perceptual effects of eye movements, which are beyond the scope of this review. The physiological

purpose of blinking is well understood, as blinking protects the cornea from damage and prevents drying of the eye. Blinks are also accompanied by a distinct type of eye movement (Khazali and others 2016). Humans blink their eyes every few seconds (Karson 1983; Stern and others 1984). Rats and mice also blink, though at lower rates than humans (Blount 1927; Kaminer and others 2011). During the blink, the eyelid occludes the visual field for a few tens of milliseconds, resulting in a transient period of darkness. Many endogenous and environmental factors can alter the blink rate, including mental state, fatigue, and the nature of the task at hand (Stern and others 1984). For example, both fatigue (Stern and others 1994) and prolonged video screen viewing increase blink rate (Nakamori and others 1997). The spontaneous blink rate is inversely correlated with mental load (Holland and Tarlow 1972; Van Orden and others 2001). Drugs that modulate the dopaminergic system also alter blink rate (Karson 1979, 1983). Blink rate is elevated in schizophrenics (Karson and others 1990). Blink rate is affected by tasks and visual stimuli. When viewing a video clip, blink events are synchronized across repeated viewing by the same subject and across subjects, indicating that they are reliably driven by certain patterns of sensory input (Nakano and others 2009). Thus, the rate of blinking depends on both internal state as well as the external stimulation.

Changes in neural activity and blood oxygen level–dependent (BOLD) signals caused by blinking are not only found in early visual areas but are also seen in higher areas throughout the brain (Fig. 2). Blinks cause decreases in the firing rates of neurons in early visual areas (Gawne and Martin 2000; Golan and others 2016), and the neural responses to blinking in the visual cortex are similar, but not identical, to those induced by a brief darkening of the visual scene. Blink-related modulations are visible in BOLD functional magnetic resonance imaging (fMRI) signals in the primary visual cortex (Bristow and others 2005b; Hupe and others 2012), as well as higher brain regions, such as the frontal eye field (FEF), and regions associated with the default network and somatosensory areas (Bristow and others 2005a; Guipponi and others 2014; Nakano and others 2013), though these signals are not always detectable in surface electrodes in epileptic patients (Golan and others 2016). Because of the bilateral nature of blinking movements, blink-related activation patterns are bilaterally symmetric (Bristow and others 2005a; Guipponi and others 2014; Hupe and others 2012; Nakano and others 2013), similar to the networks extracted from resting-state studies. Because blinks alter neural activity in many brain regions, they are not just a confound for visual perception studies.

If the rate of blinking were constant, ongoing blinks would not be an issue, and they would simply be averaged out. However, spontaneous eye blink rate dynamically varies on slow time scales (~0.001 Hz to 0.1 Hz), and these variations can drive correlated activity in multiple brain regions. The interblink interval in both humans and rats follows a power-law distribution (Kaminer and others 2011), similar to spontaneous hemodynamic signals in the cortex (He and others 2010), and blinking in humans and rodents are autocorrelated, producing low-frequency modulations in baseline rates. These changes in blink rate occur on the scale of tens to hundreds of seconds (Kaminer and others 2011) and will drive modulation of functional signals in the frequency bands used in functional connectivity studies (Chang and Glover 2010). Blink-driven neural activity could play a role in the generation of the ubiquitous slow, 1/f-like fluctuations seen in neural activity (Leopold and others 2003), brain oxygenation (Li and others 2015), and hemodynamic signals (Fox and Raichle 2007). Thus, the nonstationarity of blinking behavior precludes the neural and hemodynamic signals that are correlated with blinking from being removed by temporal averaging.

Any difference in blink rate across subjects will cause changes in the input to the visual system and will drive changes in the correlations in blink-related brain areas. These differences in blink rate will show up as changes in functional connectivity. Blinking can be thought of as a bilateral, slowly varying visual and somatosensory stimulus that is *not* under direct control of the experimenter.

Spontaneous and Stimulus-Evoked Vibrissae Movements Drive Neural and Hemodynamic Responses

Rodents have emerged as a preeminent model system for systems neuroscience research due to their genetic tractability and ability to perform relatively complex behavioral tasks (Hanks and Summerfield 2017; O'Connor and others 2009). Rats and mice use their vibrissae (whiskers) to sense the world around them by engaging in "bouts" of intermittent whisking that can last from hundreds of milliseconds to several seconds (Kleinfeld and Deschênes 2011). The whiskers are actively moved to generate contact forces on objects in order to form a sensory percept, analogous to the creation of visual images by eye movements (Kleinfeld and others 2006). The rodent vibrissae system has been an invaluable model for the investigation of cortical circuits (Petersen 2007) and active sensation (Kleinfeld and Deschênes 2011). Whisker movements can be tracked with high-speed video (Clack and others 2012; Ritt and others 2008). Whisker motion is controlled by a brainstem central pattern generator linked to the respiratory control nuclei (Moore and others 2013), and both protraction and retraction are under active control. Volitional whisker movement is associated with activation of multiple sensorimotor areas. Volitional whisking
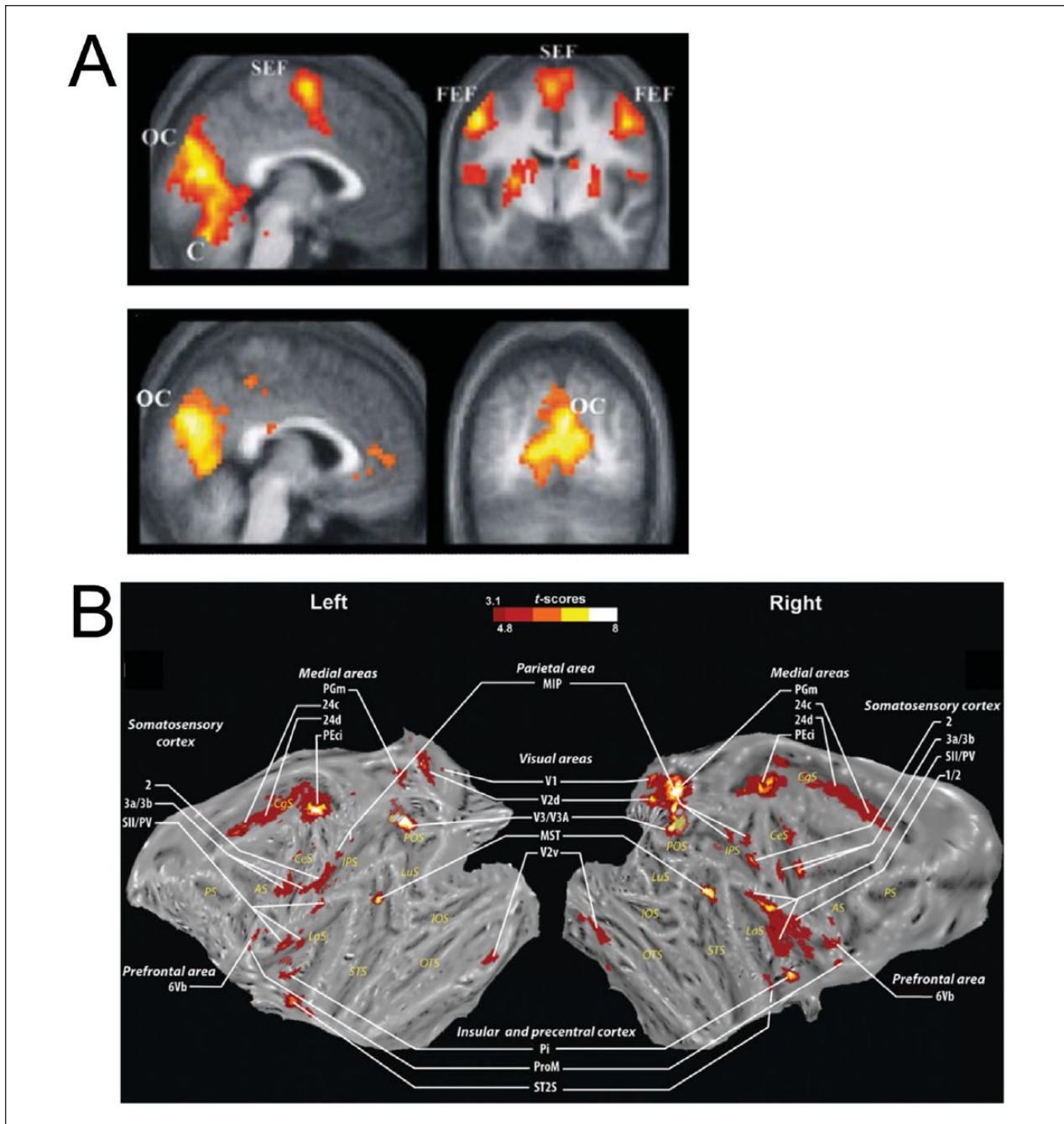
Figure 2. Blinking activates multiple brain regions in humans and nonhuman primates as measured with blood oxygen level–dependent (BOLD) functional magnetic resonance imaging (fMRI). (A) Top, brain regions showing significant responses to voluntary blinking. Bottom, brain regions showing significant responses to external darkening. Note that these are separate sets of brain regions, showing the response to blinking is not just due to a transient removal of visual input. Occipital cortex (OC), frontal eye field (FEF), cerebellum (C). (B) Brain regions in the monkey brain that shown significant correlations with the spontaneous blink rate, demonstration spontaneous blinking is associated with distributed patterns of brain activation. (A) adapted from Bristow and others (2005a) with permission; (B) adapted from Guipponi and others (2014) with permission.

bilaterally increases firing rates in brainstem, thalamic and cortical motor somatosensory areas (de Kock and Sakmann 2009; Hill and others 2011; Moore and others 2015; Urbain and others 2015).

Whisking is driven by a variety of stimuli and activates many brain regions (Fig. 3). While awake rodents are extensively used for brain-wide imaging studies using fMRI (Ferenczi and others 2016; Gao and others 2017),
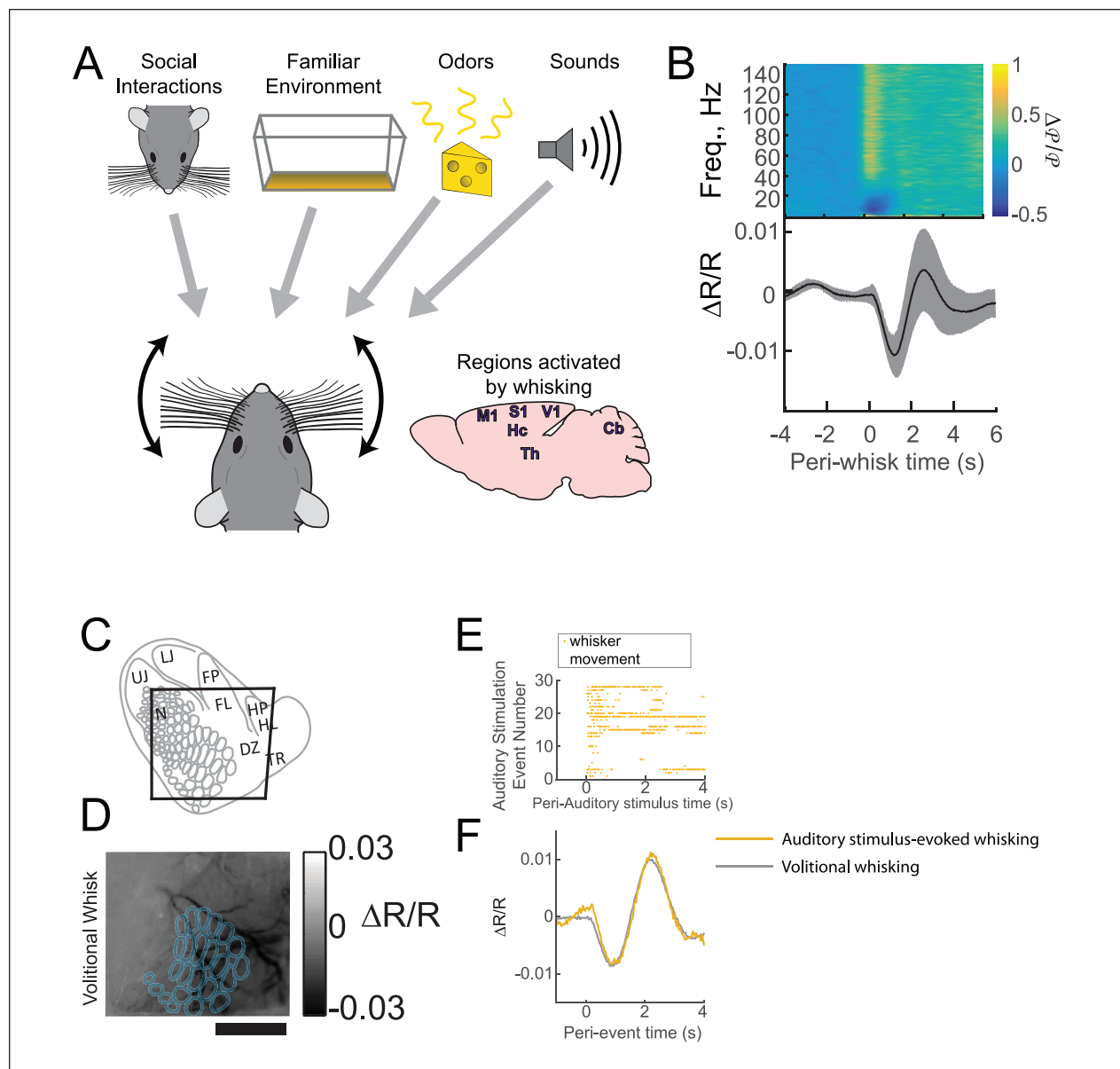
Figure 3. Whisking is elicited by multiple stimuli and activates many brain regions. (A) Volitional whisking can be evoked by conspecifics, presentation of the home cage, odors, and auditory stimuli. Volitional whisking activation is accompanied by increases in neural activity not only in motor cortex (M1) and somatosensory cortex (S1) but also in thalamus (Th), cerebellum (Cb), hippocampus (Hc), and visual cortex (V1). Other brain regions not typically associated with somatosensation may be activated as well. (B) Top, average volitional whisking-evoked changes in local field potential power aligned to the onset of volitional whisking bouts. Bottom, average change in the intrinsic optical signal (a measure of blood volume) during volitional whisking bouts. A decrease in Δ*R/R* is caused by an increase in blood volume (vasodilation). (C) Location of imaging window (black rectangle) relative to specific regions in the somatosensory cortex. Upper jaw (UJ), lower jaw (LJ), nose (N), forepaw (FP), forelimb (FL), hindpaw (HP), hindlimb (HL), trunk (TR), dysgranular zone (DZ). (D) Averaged reflectance changes relative to baseline for a representative animal during volitional whisking. Brightness shows the mean normalized reflectance change from baseline. The light blue circular regions show the positions of individual macro-vibrissae barrel reconstructed from layer IV cytochrome oxidase staining. (E) Whisking is evoked by auditory stimulation. Whisker movements (yellow dots) are shown aligned to the presentation of an auditory stimulus in 24 representative trials. Whisking is reliably elicited in time-locked manner by sound. (F) Changes in the intrinsic optical signal (Δ*R/R*) in the somatosensory cortex from the example animal in (E) in response aligned to volitional whisking onset (gray) or auditory stimulus onset (yellow). The "cross-modal" response in somatosensory cortex is actually driven by whisking. (B)-(E) adapted from Winder and others (2017).
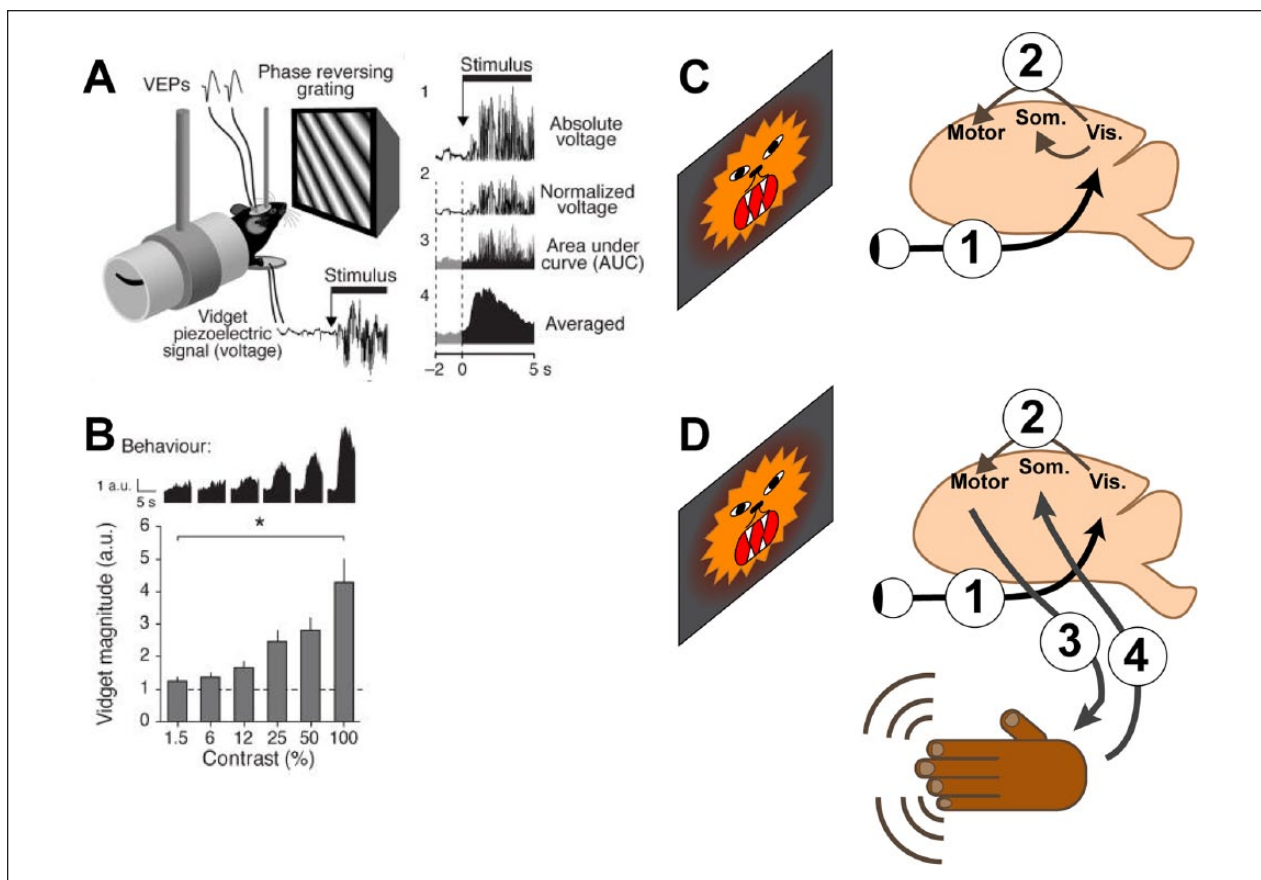
Figure 4. Stimulus-evoked fidgeting or direct neuronal projections can drive brain-wide signals in response to a stimulus. (A) Mice naturally and spontaneously generate motor responses to visual stimuli. Presentation of a grating induces a "vidget," a visually evoked fidget (left), and the movement is detected with a piezo sensor (right). (B) The amplitude of the vidget behavior increases with the contrast of the visual stimulus. (A) and (B) adapted from Cooke and others (2015) with permission. (C) A visual stimulus drives activations of visual cortex (Vis.) (1), whose neuronal projections cause activation in somatosensory (Som.) and motor cortices (2). (B) Alternatively, the visual stimulation could drive neural activity in visual cortex (1), which drives neural activity in motor cortex (2), leading to body movements and activation of cutaneous and proprioceptive somatosensory afferents (3), which then lead to somatosensory cortex activation (4). Global activation as in (A) is often interpreted as being due to visual cortex sending signals directly to other brain regions. Note that the two possibilities are not mutually exclusive.

voltage-sensitive indicators (Mohajerani and others 2013), and genetically encoded calcium indicators (Allen and others 2017; Ma and others 2016; Murphy and others 2016), whisking is typically only monitored when it is important for the task at hand (Chen and others 2017b; Winder and others 2017). Whisking can be elicited by social interaction (Bobrov and others 2014; Lenschow and Brecht 2015), a familiar environment (Ganguly and Kleinfeld 2004), odorants (Kurnikova and others 2017; Moore and others 2013), or an auditory stimulus (Winder and others 2017). Whisking can also phase lock to the hippocampal theta rhythm (Grion and others 2016; Macrides and others 1982). Contact with an object is not required to drive changes in neural activity, as whisking in air drives increases in activity in the somatosensory cortex (de Kock and Sakmann 2009; Ganguly and Kleinfeld 2004; Gentet and others 2010; O'Connor and

others 2010), thalamus (Urbain and others 2015), motor cortex (Sreenivasan and others 2016), and the cerebellum (Chen and others 2017a; O'Connor and others 2002). While these increases in neural activity may not be as dramatic as those elicited by passive whisker stimulation, they are large enough to cause hemodynamic signals in the somatosensory cortex (Winder and others 2017) (Fig. 3). Whisking-related activity is likely to be present in many different brain regions, as voltage-sensitive dye recording have shown cortex-wide waves of depolarization following the initiation of spontaneous whisking in mice (Ferezou and others 2007). A recent report making use of large-scale recordings of neural activity in visual cortex of awake mouse found a substantial portion of the spontaneous activity in the visual cortex was correlated to orofacial movements and whisking (Stringer and others 2018).

Many nontactile stimuli drive whisking, and whisking drives activation of many brain regions, including those not canonically related to somatosensation (Fig. 3). Thus, nonsomatosensory stimuli or tasks will frequently induce whisker movement, as well as corresponding changes in neural activity and hemodynamic signals. Whisking-related changes in neural activity (and likely hemodynamic signals) will not be restricted to the somatosensory cortex but will be present throughout the brain.

Head and Body Motions and Postural Adjustments Are Ongoing in Awake Animals and Humans

While optical and electrophysiological studies in rodents usually use head-fixation during imaging (Dombeck and others 2007; O'Connor and others 2009), human and rodent fMRI studies typically do not tightly restrain the head. Head motion will generate two kinds of signals in fMRI, an artifactual activation due to spin history effects, another due to "true" activation reflecting the motion-related changes in neural activity. As head motion is generated by activity in the brain and will cause somatosensory activity (driven by both cutaneous and proprioceptive input), it will also be accompanied by changes in neural activity in motor and somatosensory areas, leading to true functional signals (Yan and others 2013). It is now well established that spontaneous head motion causes artifacts in resting-state fMRI studies, and that head motion can be larger in children, psychiatric patients, and autistic subjects than in controls (Engelhardt and others 2017; Huijbers and others 2017; Power and others 2012; Satterthwaite and others 2012; Satterthwaite and others 2017; Van Dijk and others 2012). Head motion is stable within subjects (Zeng and others 2014) and is heritable (Couvy-Duchesne and others 2014; Engelhardt and others 2017; Hodgson and others 2016). Individual differences in mind-wandering are positively correlated to fidgeting (Carriere and others 2013; Seli and others 2014), which could also generate spurious correlations between brain activity and self-reported mental state. Head motion is also strongly correlated with body mass index (BMI), IQ, and other traits (Siegel and others 2016). Head motion may also covary with arousal level (Yuan and others 2013; Zeng and others 2014), and these changes in arousal may drive differential patterns of network activity. These results suggest that fidgeting is a stable individual trait that is correlated with many other cognitive and noncognitive traits.

Because large head movement are readily apparent in fMRI scans, there has been a great deal of work devoted to removing and minimizing head motion–related artifacts (Liu 2016; Power and others 2014; Satterthwaite

and others 2012; Van Dijk and others 2012). However, functional activation of motor and somatosensory areas will occur with any motion, and body motion is not monitored in most studies. Relatively small body motions are accompanied by robust motor cortex activation, which is clearly apparent in fMRI (Birn and others 1999; Bright and Murphy 2015; Lotze and others 2000; Meier and others 2008; Yan and others 2013). Scrubbing frames with motion from the data set will not completely remove this functional activation, as the functional activity will lag the motion events and persist for seconds, well beyond the period of the motion due to the slow time course of the hemodynamic response function (Birn and others 1999). One should bear in mind that not all body or head motion will cause detectable brain displacement due the relative low spatial resolution of MRI, so it cannot be assumed that there is no motion even if none is visible, since even small motions can drive functional activation.

Optical imaging studies in animals rely on head restraint to minimize head motion (Gao and others 2017), but similar confounds are present in these studies. Rodents are often imaged on top a spherical treadmill (Dombeck and others 2007), which allow a great deal of body motion. Because the ball motion, not the legs are monitored, animals will be free to engage in movements (e.g., stomping, grooming, twitching) (Powell and others 2015) that may not be detected unless they drive appreciable movement of the treadmill. In head-fixed mice, body and limb movements, even postural adjustments, drive localized increases in blood flow and arterial dilation in the somatosensory cortex, and venous distension across the cortex (Gao and Drew 2016; Gao and others 2015; Huo and others 2014; Huo and others 2015a; Huo and others 2015b) as well as increases in neural activity and blood flow in the cerebellum (Nimmerjahn and others 2009).

In addition to small, spontaneous postural movements of the head, the neck muscle become engaged prior to other movements and in a task- and stimulus-locked manner. These same neck muscles are activated during movement and posture changes (Corneil and others 2001), and these neck muscles are activated during eye movements even in head-fixed animals (Lestienne and others 1984). There are anticipatory neck muscle activations in humans and nonhuman primates (Goonetilleke and others 2015). Visual stimuli in humans produce stimulus-locked responses in limb skeletal muscle electromyograms (EMGs) (Gu and others 2016; Pruszynski and others 2010; Wood and others 2015). In rodents, visual stimulation induces body movements (visually evoked fidgets, "vidgets") (Cooke and others 2015) (Fig. 4). There is extensive evidence for overt anticipatory movements during covert attention tasks and in response

to sensory stimulation, likely mediated through the superior colliculus (Corneil and Munoz 2014). Recent wide-field GCaMP (a genetically coded calcium indicator) imaging in mice performing a decision-making task has shown that movement-related changes in neural activity are present across the whole cortex, and these movement related signals are larger than task-related neural activity (Musall and others 2018). To summarize, many sorts of tasks and stimuli (including ones that are not overly motor), are preceded, accompanied, and/or followed by muscle activation in both humans and animals. These muscle activations will generate proprioceptive and cutaneous feedback that will activate somatosensory areas, as well as in brain regions that receive input from the superior colliculus (Corneil and Munoz 2014). While it may be tempting to use anesthesia to remove these movements, anesthesia causes enormous disruptions of normal brain function (see Discussion) that make it inappropriate for use in studying normal brain function.

Respiration and Sniffing Behaviors Are Modulated by Tasks and Nonolfactory Stimuli

Breathing is a periodic behavior, with slow variations in rate, punctuated by sighs (Li and others 2016) that occur every few minutes. Respiration-related nuclei project to the locus coeruleus, and sighing can change arousal levels (Yackle and others 2017), but respiration by itself probably does not drive time-locked brain-wide electrical responses (Parabucki and Lampl 2017). As the somatosensory cortex receives sensory input from the phrenic nerve (Davenport and others 2010), movement of the torso during respiration may drive bilateral somatosensory activation, and slow modulation of respiration would cause corresponding slow variations in neural activity in the trunk and visceral representations in somatosensory cortex. The confounds of respiration on brain-wide BOLD signals (the so-called "global signal") are well known (Birn and others 2008a; Birn and others 2008b; Birn and others 2009; Murphy and others 2013). In humans, cognitive tasks can drive task-linked breathing (Birn and others 2009). In rodents, sniffing behaviors increase in a time-locked manner during non-olfactory tasks (Wesson and others 2008). Sniffing in rodents is accompanied by complex movements of the nose (Kurnikova and others 2017), which likely involve somatosensory and motor areas of the brain, just as whisking does. While obviously respiration-related neural and hemodynamic signals cannot be avoided, respiration frequency, amplitude and end-tidal CO_2 can be monitored in animals (Moore and others 2013) and humans (Birn and others 2008a).

Tongue Movements and Swallowing Activate Sensory and Motor Areas

Finally, movement of the tongue and mouth may contribute to spontaneous activity. While whisker, body and head movements and blinking are often readily observable, movements of the tongue and pharynx may not be outwardly visible. These oral movements will drive activity in sensory, motor, and higher brain structures. Tongue motion is associated with motor cortex activation in humans (Meier and others 2008), and motor cortex and frontal areas in mice (Chen and others 2017b; Komiyama and others 2010). Swallowing also causes bilateral motor cortex activation, as well as the insula and somatosensory cortex (Birn and others 1999; Hamdy and others 1999; Martin and others 2001; Mihai and others 2014). Spontaneous swallowing events occur 20 to 30 times per hour in humans (Lear and others 1965), often enough to occur several times during a typical resting-state scan (10-20 minutes). Jaw muscle electromyography (EMG) are very sensitive (Miller 1978), and jaw motion leads to distributed patterns of brain activation visible in human neuroimaging experiments (Tamura and others 2003).

Possible Physiological Roles of Fidgeting-Like Behaviors

While fidgeting behaviors are ubiquitous, their purpose is poorly understood. Active sensing behaviors and blinking have clear perceptual and physiological roles, though why humans and animals constantly make small bodily motions is not clear. There are several plausible, non-exclusive origins for these movements. Muscles exhibit thixotropy, a use-dependent reduction in their passive stiffness (Campbell and Lakie 1998; Lakie and Robinson 1988; Vernooij and others 2016). Contraction reduces the passive stiffness of the muscle, and this stiffness increases gradually over several seconds following a movement (Lakie and Robson 1988). Muscle twitches every few seconds will keep muscles from becoming too stiff and keep the muscles in a range of roughly constant stiffness, making it easier to generate precise movements. Because sensory neurons adapt their dynamic range to match recent stimulus statistics (Brenner and others 2000; Fairhall and others 2001), another possibility is that periodic motion serves to help "pre-adapt" somatosensory and proprioceptive neurons. Occasional twitches or movements might serve to put sensory neurons in the appropriate coding regime, so that when a substantial movement is made, proprioceptive neurons can more accurately encode the resulting somatosensory stimulus. Another possible origin of fidgeting behavior is that it represents "leakage" of motor commands from the brain.

Motor movements are typically controlled by populations of neurons that require pre-movement preparatory activity (Churchland and others 2010), but usually this preparatory activity in the motor cortex effectively cancels out at the level of motor outputs (Kaufman and others 2014). Twitching movements might represent imperfect cancellations. Finally, fidgeting movements may play an important role generating accurate sensory-motor maps (Blumberg and others 2013). Whisker twitches during sleep in juvenile animals serve an instructive role in sensory map formation (Blumberg and others 2015; Tiriac and others 2012), and such movements may play a similar role sharpening and maintaining maps in awake adults. None of these proposed purposes categorically excludes any of the others, and different types of spontaneous movements may serve different roles. Comparative ethological studies examining species-specific differences in fidgeting may help telucidate the function of these movements (Brenowitz and Zakon 2015).

Discussion

Ameliorating the Confounds of Fidget-Like and Spontaneous Movements in Systems Neuroscience and Neuroimaging Studies

Spontaneous fidgeting movements in both humans and animals drive activation of multiple sensory-motor brain regions. These behaviors are not uniform in time, as they show temporal correlations, and their rates and timing are modulated by tasks, sensory stimulation, and arousal levels. Because of this, spontaneous fidgeting motions cannot be treated simply as "background" and ignored. As these behaviors are unavoidable in awake animals, they will contribute to whole-brain behaviorally triggered activation patterns and "spontaneous" activity. Because these behaviors are accompanied by synchronous increases in neural activity in sensory and motor regions, they will show up in resting-state studies as functionally connected brain regions that could be erroneously interpreted as arising from direct neuronal connections (Fig. 4). When the fidgeting behaviors are triggered by a stimulus (e.g., visual stimulation), there could be an accompanying activation of somatosensory and motor areas that could be erroneously interpreted as a cross-modal activation by the visual stimulus. Seemingly innocuous differences in the environmental conditions could potentially have impacts on spontaneous fidgeting motions, which will then drive changes in neural activity. For a plausible, but speculative example of how small environmental changes could have an effect on measured brain responses, variations in the humidity will alter blink rate (Nakamori and others 1997), and these alterations of blink rate could have an impact on the default network (Nakano and others 2013). Another example is presentation of a visual stimulus which elicits movement (Fig. 4). This movement will drive cutaneous and proprioceptive sensory neurons, which will in turn drive activity in the somatosensory cortex. Without measuring and accounting for behavioral changes, differences in the fidgeting behavior across subjects could show as differences in functional connectivity or patterns of global brain activation.

Fidgeting behaviors may also be related to the "global signal" (Fox and others 2009; Murphy and others 2009) seen in the blood oxygen and cerebral volume measures (Scholvinck and others 2010). The global signal is associated with head motion (Power and others 2017). While the processing steps that remove the global signal are controversial (Fox and others 2009; Liu 2016; Murphy and others 2009; Power and others 2017), there is increasing evidence that these signals are related to arousal levels and transitions (Chang and others 2016; Liu and others 2018; Turchi and others 2018; Wong and others 2013). Global signals are often linked to respiration changes (Power and others 2017) and may be linked to sighing. The relationship between fidgeting movements and arousal level may be complex or bimodal or have species-specific differences. High arousal levels could result in more head movements, as could low arousal via a loss of self-control or muscle tone.

While fidgeting-like behaviors can be stopped by anesthesia, using anesthesia to study brain-wide dynamics is akin to "destroying the village in order to save it." Anesthesia catastrophically disrupts nearly every aspect of normal brain function (Brown and others 2010; Gao and others 2017), making it an unacceptable alternative for studying brain dynamics for most questions. Anesthesia drastically lowers brain metabolism, decreasing it by 50% (Alkire and others 1995; Alkire and others 1997), which is comparable to the decrease seen in vegetative comas (Levy and others 1987). Anesthesia disrupts neurovascular coupling, the relationship between neural activity and increases in blood flow that underlie fMRI and other hemodynamic imaging techniques (Desai and others 2011; Drew and others 2011; Knutsen and others 2016; Martin and others 2002; Pisauro and others 2013). Anesthesia also profoundly disrupts astrocyte calcium dynamics (Nimmerjahn and others 2009; Thrane and others 2012), neural activity and neural responsiveness to sensory stimuli (Cardin and Schmidt 2004; Chapin and Woodward 1981; Ferezou and others 2007; Rinberg and others 2006), and baseline brain oxygenation levels (Lyons and others 2016). The brain extracellular space is increased under anesthesia relative to the awake animal (Xie and others 2013), while the brain temperature is markedly decreased by anesthesia (Kalmbach and Waters 2012; Shirey and others 2015). Resting-state functional connectivity in both humans and animals is greatly

disrupted by anesthesia (Akeju and others 2014; Ferenczi and others 2016; Lewis and others 2012; Liang and others 2012; Liang and others 2015; Liu and others 2011; Liu and others 2013; Moeller and others 2009; Nallasamy and Tsao 2011). However, if anesthesia must be used for a study, there are anesthetic paradigms that minimize the functional connectivity differences between the anesthetized and awake state (Paasonen and others 2018). Given that anesthesia causes profound disruptions of normal brain functions, it is not appropriate for most human studies, and that task and cognitive studies cannot be done under anesthesia, it is not a viable option for dealing with fidget-like behaviors for most experiments.

As fidgeting behaviors can only be stopped by anesthesia, the best way of dealing with them is by detecting and accounting for these movements. Fortunately, several recent technological advances have made the detection and quantification of these fidgeting behaviors easier. First, there have been large improvements in computer vision, specifically in its application to the high-throughput detection and quantification of behavior and movement in animals (Guo and others 2015; Robie and others 2017b). High-speed cameras coupled with better computer vision algorithms can enable behavioral monitoring from multiple angles (Guo and others 2015; Winder and others 2017), as well as stereoscopic observation (Hong and others 2015), allowing very sensitive tracking of body and limb movements (Giovannucci and others 2018; Machado and others 2015). As these technologies become standardized and commodified, behavioral monitoring of fidgeting will become easier. While there has been a recent push to monitor eye position and blinking in nonhuman primate fMRI studies (Chang and others 2016), this sort of behavioral monitoring is not usually employed in human fMRI studies. Second, improvements in the miniaturization of electrodes for bioelectric potential monitoring will enable high-resolution monitoring of EMG signals from muscles. Many of the technologies developed ostensibly for the monitoring of neural activity in the brain are easily adapted to monitoring muscles peripherally. For example, "neural dust," small untethered electrodes that communicate via ultrasound, can be used to monitor electrical activity (Seo and others 2016). Combined with improvements in wireless powering and transmission of signals (Kim and others 2013; Szuts and others 2011), these electrodes could be modified to perform high density monitoring of muscle activity throughout the body.

Detecting these fidget-driven responses in hemodynamic or other signals is the first step, the second step is determining their contributions to the observed neural and hemodynamic signals. The neuroimaging community has made large advances in data analysis techniques to remove systemic physiological signals from both humans and animals (Birn and others 2009; Birn and others 2014; Keilholz and others 2017; Liu 2016; Murphy and others 2013), and these techniques can be adapted to regressing out fidget-induced signals. While the quantitative relationship between the underlying neural activity and the hemodynamic response differs across brain regions (Devonshire and others 2012; Handwerker and others 2004; Huo and others 2014), at least in somatosensory cortex neurovascular coupling is constant across behaviors (Winder and others 2017). Because the hemodynamic signal in the somatosensory cortex is highly correlated with movement (Huo and others 2014; Huo and others 2015a; Huo and others 2015b), it is likely that these regression techniques will be able to "clean up" the signal in some brain regions to reveal neural dynamics driven by direct connections between brain regions. Recent work in awake mice have shown that dimensionality-reduction analysis techniques can separate out the components of neural activity that are correlated with spontaneous behaviors (Musall and others 2018; Stringer and others 2018). Once neural activity can be partitioned in such a way, the contributions of spontaneous fidgeting motions can be correctly accounted for.

Systems neuroscience has been increasingly concerned with the role of behavior, particularly natural behavior (Krakauer and others 2017). This ethological focus, coupled with better "big-data" analysis methods (Gao and Ganguli 2015; Gomez-Marin and others 2014; Robie and others 2017a; Wiltschko and others 2015), has poised the field for large advances in relating neural activity (at multiple scales) to behavior. However, the role of ubiquitous and spontaneous fidget-like behaviors in generating brain-wide dynamics has been underappreciated. As the rate and timing of fidget-like behaviors will be impacted by common experimental manipulations and pathologies, the solution is to monitor these behaviors, and either subtract out or censor their effects. We argue that detailed monitoring of these spontaneous behaviors is an import step in understanding brain dynamics during whole-brain neural or hemodynamic imaging.

ORCID iDs

Patrick J. Drew iD https://orcid.org/0000-0002-7483-7378
Qingguang Zhang iD https://orcid.org/0000-0003-4500-813X

References

Akeju O, Loggia ML, Catana C, Pavone KJ, Vazquez R, Rhee J, and others. 2014. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. Elife 3:e04499.

Alkire MT, Haier RJ, Barker SJ, Shah NK, Wu JC, Kao YJ. 1995. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 82(2):393–403.

Alkire MT, Haier RJ, Shah NK, Anderson CT. 1997. Positron emission tomography study of regional cerebral metabolism in humans during isoflurane anesthesia. Anesthesiology 86(3):549–57.

Allen WE, Kauvar IV, Chen MZ, Richman EB, Yang SJ, Chan K, and others. 2017. Global representations of goal-directed behavior in distinct cell types of mouse neocortex. Neuron 94(4):891–907.e6.

Birn RM, Bandettini PA, Cox RW, Shaker R. 1999. Event-related fMRI of tasks involving brief motion. Hum Brain Mapp 7(2):106–14.

Birn RM, Cornejo MD, Molloy EK, Patriat R, Meier TB, Kirk GR, and others. 2014. The influence of physiological noise correction on test-retest reliability of resting-state functional connectivity. Brain Connect 4(7):511–22.

Birn RM, Murphy K, Bandettini P. 2008a. The effect of respiration variations on independent component analysis results of resting state functional connectivity. Hum Brain Mapp 29(7):740–50.

Birn RM, Murphy K, Handwerker DA, Bandettini PA. 2009. fMRI in the presence of task-correlated breathing variations. Neuroimage 47(3):1092–104.

Birn RM, Smith MA, Jones TB, Bandettini PA. 2008b. The respiration response function: the temporal dynamics of fMRI signal fluctuations related to changes in respiration. Neuroimage 40(2):644–54.

Blount WP. 1927. Studies of the movements of the eyelids of animals: blinking. Q J Exp Physiol 18(2):111–25.

Blumberg MS, Coleman CM, Sokoloff G, Weiner JA, Fritzsch B, McMurray B. 2015. Development of twitching in sleeping infant mice depends on sensory experience. Curr Biol 25(5):656–62.

Blumberg MS, Marques HG, Iida F. 2013. Twitching in sensorimotor development from sleeping rats to robots. Curr Biol 23(12):R532–7.

Bobrov E, Wolfe J, Rao RP, Brecht M. 2014. The representation of social facial touch in rat barrel cortex. Curr Biol 24:109–15.

Brenner N, Bialek W, de Ruyter van Steveninck R. 2000. Adaptive rescaling maximizes information transmission. Neuron 26(3):695–702.

Brenowitz EA, Zakon HH. 2015. Emerging from the bottleneck: benefits of the comparative approach to modern neuroscience. Trends Neurosci 38(5):273–8.

Bright MG, Murphy K. 2015. Is fMRI "noise" really noise? Resting state nuisance regressors remove variance with network structure. Neuroimage 114:158–69.

Bristow D, Frith C, Rees G. 2005a. Two distinct neural effects of blinking on human visual processing. Neuroimage 27(1):136–45.

Bristow D, Haynes JD, Sylvester R, Frith CD, Rees G. 2005b. Blinking suppresses the neural response to unchanging retinal stimulation. Curr Biol 15(14):1296–300.

Brown EN, Lydic R, Schiff ND. 2010. General anesthesia, sleep, and coma. N Engl J Med 363(27):2638–50.

Campbell KS, Lakie M. 1998. A cross-bridge mechanism can explain the thixotropic short-range elastic component of relaxed frog skeletal muscle. J Physiol 510(Pt 3):941–62.

Cardin JA, Schmidt MF. 2004. Noradrenergic inputs mediate state dependence of auditory responses in the avian song system. J Neurosci 24(35):7745–53.

Carriere JS, Seli P, Smilek D. 2013. Wandering in both mind and body: individual differences in mind wandering and inattention predict fidgeting. Can J Exp Psychol 67(1):19–31.

Chang C, Glover GH. 2010. Time-frequency dynamics of resting-state brain connectivity measured with fMRI. Neuroimage 50(1):81–98.

Chang C, Leopold DA, Scholvinck ML, Mandelkow H, Picchioni D, Liu X, and others. 2016. Tracking brain arousal fluctuations with fMRI. Proc Natl Acad Sci U S A 113(16):4518–23.

Chapin JK, Woodward DJ. 1981. Modulation of sensory responsiveness of single somatosensory cortical cells during movement and arousal behaviors. Exp Neurol 72(1):164–78.

Chen S, Augustine GJ, Chadderton P. 2017a. Serial processing of kinematic signals by cerebellar circuitry during voluntary whisking. Nat Commun 8(1):232.

Chen TW, Li N, Daie K, Svoboda K. 2017b. A map of anticipatory activity in mouse motor cortex. Neuron 94(4):866–79.e4.

Churchland MM, Cunningham JP, Kaufman MT, Foster JD, Nuyujukian P, Ryu SI, and others. 2012. Neural population dynamics during reaching. Nature 487(7405):51–6.

Churchland MM, Cunningham JP, Kaufman MT, Ryu SI, Shenoy KV. 2010. Cortical preparatory activity: representation of movement or first cog in a dynamical machine? Neuron 68(3):387–400.

Clack NG, O'Connor DH, Huber D, Petreanu L, Hires A, Peron S, and others. 2012. Automated tracking of whiskers in videos of head fixed rodents. PLoS Comput Biol 8(7):e1002591.

Cooke SF, Komorowski RW, Kaplan ES, Gavornik JP, Bear MF. 2015. Visual recognition memory, manifested as long-term habituation, requires synaptic plasticity in V1. Nat Neurosci 18(2):262–71.

Corneil BD, Munoz DP. 2014. Overt responses during covert orienting. Neuron 82(6):1230–43.

Corneil BD, Olivier E, Richmond FJ, Loeb GE, Munoz DP. 2001. Neck muscles in the rhesus monkey. II. Electromyographic patterns of activation underlying postures and movements. J Neurophysiol 86(4):1729–49.

Couvy-Duchesne B, Blokland GA, Hickie IB, Thompson PM, Martin NG, de Zubicaray GI, and others. 2014. Heritability of head motion during resting state functional MRI in 462 healthy twins. Neuroimage 102(Pt 2):424–34.

Davenport PW, Reep RL, Thompson FJ. 2010. Phrenic nerve afferent activation of neurons in the cat SI cerebral cortex. J Physiol 588(Pt 5):873–86.

de Kock CPJ, Sakmann B. 2009. Spiking in primary somato-
    sensory cortex during natural whisking in awake head-
    restrained rats is cell-type specific. Proc Natl Acad Sci U S
    A 106(38):16446–50.

Desai M, Kahn I, Knoblich U, Bernstein J, Atallah H, Yang
    A, and others. 2011. Mapping brain networks in awake
    mice using combined optical neural control and fMRI. J
    Neurophysiol 105(3):1393–405.

Devonshire IM, Papadakis NG, Port M, Berwick J, Kennerley
    AJ, Mayhew JEW, and others. 2012. Neurovascular cou-
    pling is brain region-dependent. Neuroimage 59(3):1997–
    2006.

Dombeck DA, Khabbaz AN, Collman F, Adelman TL, Tank
    DW. 2007. Imaging large-scale neural activity with cellular
    resolution in awake, mobile mice. Neuron 56(1):43–57.

Dotson NM, Hoffman SJ, Goodell B, Gray CM. 2017. A large-
    scale semi-chronic microdrive recording system for non-
    human primates. Neuron 96(4):769–82.e2.

Drew PJ, Shih AY, Kleinfeld D. 2011. Fluctuating and sensory-
    induced vasodynamics in rodent cortex extend arteriole
    capacity. Proc Natl Acad Sci U S A 108(20):8473–8.

Engelhardt LE, Roe MA, Juranek J, DeMaster D, Harden
    KP, Tucker-Drob EM, and others. 2017. Children's head
    motion during fMRI tasks is heritable and stable over time.
    Dev Cogn Neurosci 25:58–68.

Fairhall AL, Lewen GD, Bialek W, de Ruyter Van Steveninck
    RR. 2001. Efficiency and ambiguity in an adaptive neural
    code. Nature 412(6849):787–92.

Feldman JL, Del Negro CA, Gray PA. 2013. Understanding the
    rhythm of breathing: so near, yet so far. Annu Rev Physiol
    75:423–52.

Ferenczi EA, Zalocusky KA, Liston C, Grosenick L, Warden
    MR, Amatya D, and others. 2016. Prefrontal cortical regu-
    lation of brainwide circuit dynamics and reward-related
    behavior. Science 351(6268):aac9698.

Ferezou I, Haiss F, Gentet LJ, Aronoff R, Weber B, Petersen
    CCH. 2007. Spatiotemporal dynamics of cortical sensorim-
    otor integration in behaving mice. Neuron 56(5):907–23.

Fox MD, Raichle ME. 2007. Spontaneous fluctuations in brain
    activity observed with functional magnetic resonance
    imaging. Nat Rev Neurosci 8(9):700–11.

Fox MD, Zhang D, Snyder AZ, Raichle ME. 2009. The global
    signal and observed anticorrelated resting state brain net-
    works. J Neurophysiol 101(6):3270–83.

Galton F. 1885. The measure of fidget. Natue 32:174–5.

Ganguly K, Kleinfeld D. 2004. Goal-directed whisking
    increases phase-locking between vibrissa movement and
    electrical activity in primary sensory cortex in rat. Proc
    Natl Acad Sci U S A 101(33):12348–53.

Gao P, Ganguli S. 2015. On simplicity and complexity in the
    brave new world of large-scale neuroscience. Curr Opin
    Neurobiol 32:148–55.

Gao YR, Drew PJ. 2016. Effects of voluntary locomotion and
    calcitonin gene-related peptide on the dynamics of single
    dural vessels in awake mice. J Neurosci 36(8):2503–16.

Gao YR, Greene SE, Drew PJ. 2015. Mechanical restriction
    of intracortical vessel dilation by brain tissue sculpts the
    hemodynamic response. Neuroimage 115:162–76.

Gao YR, Ma Y, Zhang Q, Winder AT, Liang Z, Antinori L,
    and others. 2017. Time to wake up: studying neurovascular
    coupling and brain-wide circuit function in the un-anesthe-
    tized animal. Neuroimage 153:382–98.

Gawne TJ, Martin JM. 2000. Activity of primate V1 cortical
    neurons during blinks. J Neurophysiol 84(5):2691–4.

Gentet LJ, Avermann M, Matyas F, Staiger JF, Petersen CCH.
    2010. Membrane potential dynamics of GABAergic neurons
    in the barrel cortex of behaving mice. Neuron 65(3):422–35.

Giovannucci A, Pnevmatikakis EA, Deverett B, Pereira T,
    Fondriest J, Brady MJ, and others. 2018. Automated gesture
    tracking in head-fixed mice. J Neurosci Methods 300:184–95.

Golan T, Davidesco I, Meshulam M, Groppe DM, Megevand P,
    Yeagle EM, and others. 2016. Human intracranial record-
    ings link suppressed transients rather than 'filling-in' to
    perceptual continuity across blinks. Elife 5:e17243.

Gomez-Marin A, Paton JJ, Kampff AR, Costa RM, Mainen ZF.
    2014. Big behavioral data: psychology, ethology and the
    foundations of neuroscience. Nat Neurosci 17(11):1455–62.

Gonzalez-Castillo J, Saad ZS, Handwerker DA, Inati SJ,
    Brenowitz N, Bandettini PA. 2012. Whole-brain, time-
    locked activation with simple tasks revealed using massive
    averaging and model-free analysis. Proc Natl Acad Sci U S
    A 109(14):5487–92.

Goonetilleke SC, Katz L, Wood DK, Gu C, Huk AC, Corneil BD.
    2015. Cross-species comparison of anticipatory and stimu-
    lus-driven neck muscle activity well before saccadic gaze
    shifts in humans and nonhuman primates. J Neurophysiol
    114(2):902–13.

Grillner S. 2006. Biological pattern generation: the cellular
    and computational logic of networks in motion. Neuron
    52(5):751–66.

Grion N, Akrami A, Zuo Y, Stella F, Diamond ME. 2016.
    Coherence between rat sensorimotor system and hippo-
    campus is enhanced during tactile discrimination. PLoS
    Biol 14(2):e1002384.

Gu C, Wood DK, Gribble PL, Corneil BD. 2016. A trial-by-trial
    window into sensorimotor transformations in the human
    motor periphery. J Neurosci 36(31):8273–82.

Guipponi O, Odouard S, Pinede S, Wardak C, Ben Hamed S.
    2014. fMRI cortical correlates of spontaneous eye blinks in
    the nonhuman primate. Cereb cortex 25(9):2333–45.

Guo JZ, Graves AR, Guo WW, Zheng J, Lee A, Rodriguez-
    Gonzalez J, and others. 2015. Cortex commands the perfor-
    mance of skilled movement. Elife 4:e10774.

Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, and
    others. 1999. Cortical activation during human volitional
    swallowing: an event-related fMRI study. Am J Physiol
    277(1 Pt 1):G219–25.

Handwerker DA, Ollinger JM, D'Esposito M. 2004. Variation
    of BOLD hemodynamic responses across subjects and
    brain regions and their effects on statistical analyses.
    Neuroimage 21(4):1639–51.

Hanks TD, Summerfield C. 2017. Perceptual decision making
    in rodents, monkeys, and humans. Neuron 93(1):15–31.

Harris KD, Quiroga RQ, Freeman J, Smith SL. 2016. Improving
    data quality in neuronal population recordings. Nat
    Neurosci 19(9):1165–74.

He BJ, Zempel JM, Snyder AZ, Raichle ME. 2010. The temporal structures and functional significance of scale-free brain activity. Neuron 66(3):353–69.

Hill DN, Curtis JC, Moore JD, Kleinfeld D. 2011. Primary motor cortex reports efferent control of vibrissa motion on multiple timescales. Neuron 72(2):344–56.

Hodgson K, Poldrack RA, Curran JE, Knowles EE, Mathias S, Goring HH, and others. 2016. Shared genetic factors influence head motion during MRI and body mass index. Cereb Cortex 27(12):5539–46.

Holland MK, Tarlow G. 1972. Blinking and mental load. Psychol Rep 31(1):119–27.

Hong W, Kennedy A, Burgos-Artizzu XP, Zelikowsky M, Navonne SG, Perona P, and others. 2015. Automated measurement of mouse social behaviors using depth sensing, video tracking, and machine learning. Proc Natl Acad Sci U S A 112(38):E5351–60.

Huijbers W, Van Dijk KR, Boenniger MM, Stirnberg R, Breteler MM. 2017. Less head motion during MRI under task than resting-state conditions. Neuroimage 147:111–20.

Huo BX, Gao YR, Drew PJ. 2015a. Quantitative separation of arterial and venous cerebral blood volume increases during voluntary locomotion. Neuroimage 105:369–79.

Huo BX, Greene SE, Drew PJ. 2015b. Venous cerebral blood volume increase during voluntary locomotion reflects cardiovascular changes. Neuroimage 118:301–12.

Huo BX, Smith JB, Drew PJ. 2014. Neurovascular coupling and decoupling in the cortex during voluntary locomotion. J Neurosci 34(33):10975–81.

Hupe JM, Bordier C, Dojat M. 2012. A BOLD signature of eyeblinks in the visual cortex. Neuroimage 61(1):149–61.

Kalmbach AS, Waters J. 2012. Brain surface temperature under a craniotomy. J Neurophysiol 108(11):3138–46.

Kaminer J, Powers AS, Horn KG, Hui C, Evinger C. 2011. Characterizing the spontaneous blink generator: an animal model. J Neurosci 31(31):11256–67.

Karson CN. 1979. Oculomotor signs in a psychiatric population: a preliminary report. Am J Psychiatry 136(8):1057–60.

Karson CN. 1983. Spontaneous eye-blink rates and dopaminergic systems. Brain 106 (Pt 3):643–53.

Karson CN, Dykman RA, Paige SR. 1990. Blink rates in schizophrenia. Schizophr Bull 16(2):345–54.

Kaufman MT, Churchland MM, Ryu SI, Shenoy KV. 2014. Cortical activity in the null space: permitting preparation without movement. Nat Neurosci 17(3):440–8.

Keilholz SD, Pan WJ, Billings J, Nezafati M, Shakil S. 2017. Noise and non-neuronal contributions to the BOLD signal: applications to and insights from animal studies. Neuroimage 154:267–81.

Khazali MF, Pomper JK, Smilgin A, Bunjes F, Thier P. 2016. A new motor synergy that serves the needs of oculomotor and eye lid systems while keeping the downtime of vision minimal. Elife 5:e16290.

Kim TI, McCall JG, Jung YH, Huang X, Siuda ER, Li Y, and others. 2013. Injectable, cellular-scale optoelectronics with applications for wireless optogenetics. Science 340(6129):211–6.

Kleinfeld D, Ahissar E, Diamond ME. 2006. Active sensation: insights from the rodent vibrissa sensorimotor system. Curr Opin Neurobiol 16(4):435–44.

Kleinfeld D, Deschênes M. 2011. Neuronal basis for object location in the vibrissa scanning sensorimotor system. Neuron 72(3):455–68.

Knutsen PM, Mateo C, Kleinfeld D. 2016. Precision mapping of the vibrissa representation within murine primary somatosensory cortex. Philos Trans R Soc Lond B Biol Sci 371(1705):20150351.

Komiyama T, Sato TR, Connor DHO, Zhang Y-X, Huber D, Hooks BM, and others. 2010. Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. Nature 464(7292):1182–6.

Krakauer JW, Ghazanfar AA, Gomez-Marin A, MacIver MA, Poeppel D. 2017. Neuroscience needs behavior: correcting a reductionist bias. Neuron 93(3):480–90.

Kurnikova A, Moore JD, Liao SM, Deschenes M, Kleinfeld D. 2017. Coordination of orofacial motor actions into exploratory behavior by rat. Curr Biol 27(5):688–96.

Lakie M, Robinson LG. 1988. Thixotropic changes in human muscle stiffness and the effects of fatigue. Exp Physiol 73(4):487–500.

Lakie M, Robson LG. 1988. Thixotropy: stiffness recovery rate in relaxed frog muscle. Q J Exp Physiol 73:237–9.

Lear CS, Flanagan JB Jr, Moorrees CF. 1965. The frequency of deglutition in man. Arch Oral Biol 10:83–100.

Lenschow C, Brecht M. 2015. Barrel cortex membrane potential dynamics in social touch. Neuron 85(4):718–25.

Leopold DA, Murayama Y, Logothetis NK. 2003. Very slow activity fluctuations in monkey visual cortex: implications for functional brain imaging. Cereb Cortex 13(4):422–33.

Lestienne F, Vidal PP, Berthoz A. 1984. Gaze changing behaviour in head restrained monkey. Exp Brain Res 53(2):349–56.

Levy DE, Sidtis JJ, Rottenberg DA, Jarden JO, Strother SC, Dhawan V, and others. 1987. Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann Neurol 22(6):673–82.

Lewis LD, Weiner VS, Mukamel EA, Donoghue JA, Eskandar EN, Madsen JR, and others. 2012. Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc Natl Acad Sci U S A 109(49):E3377–86.

Li JM, Bentley WJ, Snyder LH. 2015. Functional connectivity arises from a slow rhythmic mechanism. Proc Natl Acad Sci U S A 112(19):E2527–35.

Li P, Janczewski WA, Yackle K, Kam K, Pagliardini S, Krasnow MA, and others. 2016. The peptidergic control circuit for sighing. Nature 530(7590):293–7.

Liang Z, King J, Zhang N. 2012. Anticorrelated resting-state functional connectivity in awake rat brain. Neuroimage 59(2):1190–9.

Liang Z, Liu X, Zhang N. 2015. Dynamic resting state functional connectivity in awake and anesthetized rodents. Neuroimage 104:89–99.

Liu JV, Hirano Y, Nascimento GC, Stefanovic B, Leopold DA, Silva AC. 2013. fMRI in the awake marmoset: somatosensory-evoked responses, functional connectivity, and comparison with propofol anesthesia. Neuroimage 78(C):186–95.

Liu TT. 2016. Noise contributions to the fMRI signal: an overview. Neuroimage 143:141–51.

Liu X, de Zwart JA, Scholvinck ML, Chang C, Ye FQ, Leopold DA, and others. 2018. Subcortical evidence for a contribution of arousal to fMRI studies of brain activity. Nat Commun 9(1):395.

Liu X, Zhu XH, Zhang Y, Chen W. 2011. Neural origin of spontaneous hemodynamic fluctuations in rats under burst-suppression anesthesia condition. Cereb Cortex 21(2): 374–84.

Lotze M, Erb M, Flor H, Huelsmann E, Godde B, Grodd W. 2000. fMRI evaluation of somatotopic representation in human primary motor cortex. Neuroimage 11(5 Pt 1):473–81.

Lyons DG, Parpaleix A, Roche M, Charpak S. 2016. Mapping oxygen concentration in the awake mouse brain. Elife 5:e12024.

Ma Y, Shaik MA, Kozberg MG, Kim SH, Portes JP, Timerman D, and others. 2016. Resting-state hemodynamics are spatiotemporally coupled to synchronized and symmetric neural activity in excitatory neurons. Proc Natl Acad Sci U S A 113(52):E8463–71.

Machado AS, Darmohray DM, Fayad J, Marques HG, Carey MR. 2015. A quantitative framework for whole-body coordination reveals specific deficits in freely walking ataxic mice. Elife 4:e07892.

Macrides F, Eichenbaum HB, Forbes WB. 1982. Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. J Neurosci 2(12):1705–17.

Marder E. 2012. Neuromodulation of neuronal circuits: back to the future. Neuron 76(1):1–11.

Martin C, Berwick J, Johnston D, Zheng Y, Martindale J, Port M, and others. 2002. Optical imaging spectroscopy in the unanaesthetised rat. J Neurosci Methods 120(1):25–34.

Martin RE, Goodyear BG, Gati JS, Menon RS. 2001. Cerebral cortical representation of automatic and volitional swallowing in humans. J Neurophysiol 85(2):938–50.

Meier JD, Aflalo TN, Kastner S, Graziano MS. 2008. Complex organization of human primary motor cortex: a high-resolution fMRI study. J Neurophysiol 100(4):1800–12.

Mihai PG, Otto M, Platz T, Eickhoff SB, Lotze M. 2014. Sequential evolution of cortical activity and effective connectivity of swallowing using fMRI. Hum Brain Mapp 35(12): 5962–73.

Miller AJ. 1978. Spectral analysis of the electromyogram of the temporal muscle in the rhesus monkey (Macaca mulatta). Electroencephalogr Clin Neurophysiol 44(3):317–27.

Moeller S, Nallasamy N, Tsao DY, Freiwald WA. 2009. Functional connectivity of the macaque brain across stimulus and arousal states. J Neurosci 29(18):5897–909.

Mohajerani MH, Chan AW, Mohsenvand M, Ledue J, Liu R, McVea DA, and others. 2013. Spontaneous cortical activity alternates between motifs defined by regional axonal projections. Nat Neurosci 16(10):1426–35.

Moore JD, Deschênes M, Furuta T, Huber D, Smear MC, Demers M, and others. 2013. Hierarchy of orofacial rhythms revealed through whisking and breathing. Nature 497:205–210.

Moore JD, Mercer Lindsay N, Deschenes M, Kleinfeld D. 2015. Vibrissa self-motion and touch are reliably encoded along the same somatosensory pathway from brainstem through thalamus. PLoS Biol 13(9):e1002253.

Murphy K, Birn RM, Bandettini PA. 2013. Resting-state fMRI confounds and cleanup. Neuroimage 80(C):349–59.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44(3):893–905.

Murphy TH, Boyd JD, Bolanos F, Vanni MP, Silasi G, Haupt D, and others. 2016. High-throughput automated home-cage mesoscopic functional imaging of mouse cortex. Nat Commun 7:11611.

Musall S, Kaufman MT, Gluf S, Churchland AK. 2018. Movement-related activity dominates cortex during sensory-guided decision making. bioArXiV. doi:10.1101/308288

Nakamori K, Odawara M, Nakajima T, Mizutani T, Tsubota K. 1997. Blinking is controlled primarily by ocular surface conditions. Am J Ophthalmol 124(1):24–30.

Nakano T, Kato M, Morito Y, Itoi S, Kitazawa S. 2013. Blink-related momentary activation of the default mode network while viewing videos. Proc Natl Acad Sci U S A 110(2): 702–6.

Nakano T, Yamamoto Y, Kitajo K, Takahashi T, Kitazawa S. 2009. Synchronization of spontaneous eyeblinks while viewing video stories. Proc Biol Sci 276(1673):3635–44.

Nallasamy N, Tsao DY. 2011. Functional connectivity in the brain: effects of anesthesia. Neuroscientist 17(1):94–106.

Nimmerjahn A, Mukamel EA, Schnitzer MJ. 2009. Motor behavior activates Bergmann glial networks. Neuron 62(3):400–12.

O'Connor DH, Huber D, Svoboda K. 2009. Reverse engineering the mouse brain. Nature 461(7266):923–9.

O'Connor DH, Peron SP, Huber D, Svoboda K. 2010. Neural activity in barrel cortex underlying vibrissa-based object localization in mice. Neuron 67(6):1048–61.

O'Connor SM, Berg RW, Kleinfeld D. 2002. Coherent electrical activity between vibrissa sensory areas of cerebellum and neocortex is enhanced during free whisking. J Neurophysiol 87(4):2137–48.

Paasonen J, Stenroos P, Salo RA, Kiviniemi V, Grohn O. 2018. Functional connectivity under six anesthesia protocols and the awake condition in rat brain. Neuroimage 172:9–20.

Parabucki A, Lampl I. 2017. Volume conduction coupling of whisker-evoked cortical LFP in the mouse olfactory bulb. Cell Rep 21(4):919–25.

Payne HL, Raymond JL. 2017. Magnetic eye tracking in mice. Elife 6:e29222.

Petersen CCH. 2007. The functional organization of the barrel cortex. Neuron 56(2):339–55.

Pisauro MA, Dhruv NT, Carandini M, Benucci A. 2013. Fast hemodynamic responses in the visual cortex of the awake mouse. J Neurosci 33(46):18343–51.

Powell K, Mathy A, Duguid I, Hausser M. 2015. Synaptic representation of locomotion in single cerebellar granule cells. Elife 4:e07290.

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59(3):2142–54.

Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84:320–41.

Power JD, Plitt M, Laumann TO, Martin A. 2017. Sources and implications of whole-brain fMRI signals in humans. Neuroimage 146:609–25.

Pruszynski JA, King GL, Boisse L, Scott SH, Flanagan JR, Munoz DP. 2010. Stimulus-locked responses on human arm muscles reveal a rapid neural pathway linking visual input to arm motor output. Eur J Neurosci 32(6):1049–57.

Rinberg D, Koulakov A, Gelperin A. 2006. Sparse odor coding in awake behaving mice. J Neurosci 26(34):8857–65.

Ritt JT, Andermann ML, Moore CI. 2008. Embodied information processing: vibrissa mechanics and texture features shape micromotions in actively sensing rats. Neuron 57(4):599–613.

Robie AA, Hirokawa J, Edwards AW, Umayam LA, Lee A, Phillips ML, and others. 2017a. Mapping the neural substrates of behavior. Cell 170(2):393–406 e28.

Robie AA, Seagraves KM, Egnor SE, Branson K. 2017b. Machine vision methods for analyzing social interactions. J Exp Biol 220(Pt 1):25–34.

Satterthwaite TD, Ciric R, Roalf DR, Davatzikos C, Bassett DS, Wolf DH. 2017. Motion artifact in studies of functional connectivity: characteristics and mitigation strategies. Hum Brain Mapp. Nov 1 Epub. doi:10.1002/hbm.23665

Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, and others. 2012. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage 60(1):623–32.

Scholvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. 2010. Neural basis of global resting-state fMRI activity. Proc Natl Acad Sci U S A 107(22):10238–43.

Seli P, Carriere JS, Thomson DR, Cheyne JA, Martens KA, Smilek D. 2014. Restless mind, restless body. J Exp Psychol Learn Mem Cogn 40(3):660–8.

Seo D, Neely RM, Shen K, Singhal U, Alon E, Rabaey JM, and others. 2016. Wireless recording in the peripheral nervous system with ultrasonic neural dust. Neuron 91(3):529–39.

Shirey MJ, Smith JB, Kudlik DE, Huo BX, Greene SE, Drew PJ. 2015. Brief anesthesia, but not voluntary locomotion, significantly alters cortical temperature. J Neurophysiol 114(1):309–22.

Siegel JS, Mitra A, Laumann TO, Seitzman BA, Raichle M, Corbetta M, and others. 2016. Data quality influences observed links between functional connectivity and behavior. Cereb Cortex 27(9):4492–502.

Sreenivasan V, Esmaeili V, Kiritani T, Galan K, Crochet S, Petersen CCH. 2016. Movement initiation signals in mouse whisker motor cortex. Neuron 92(6):1368–82.

Stern JA, Boyer D, Schroeder D. 1994. Blink rate: a possible measure of fatigue. Hum Factors 36(2):285–97.

Stern JA, Walrath LC, Goldstein R. 1984. The endogenous eye-blink. Psychophysiology 21(1):22–33.

Stringer C, Pachitariu M, Steinmetz N, Bai Reddy C, Carandini M, Harris KD. 2018. Spontaneous behaviors drive multi-dimensional, brain-wide population activity. bioArXiV. doi:org/10.1101/306019

Szuts TA, Fadeyev V, Kachiguine S, Sher A, Grivich MV, Agrochão M, and others. 2011. A wireless multi-channel neural amplifier for freely moving animals. Nat Neurosci 14(2):263–9.

Tamura T, Kanayama T, Yoshida S, Kawasaki T. 2003. Functional magnetic resonance imaging of human jaw movements. J Oral Rehabil 30(6):614–22.

Thrane AS, Thrane VR, Zeppenfeld D, Lou N, Xu Q, Nagelhus EA, and others. 2012. General anesthesia selectively disrupts astrocyte calcium signaling in the awake mouse cortex. Proc Natl Acad Sci U S A 109(46):18974–9.

Tiriac A, Uitermarkt BD, Fanning AS, Sokoloff G, Blumberg MS. 2012. Rapid whisker movements in sleeping newborn rats. Curr Biol 22(21):2075–80.

Turchi J, Chang C, Ye FQ, Russ BE, Yu DK, Cortes CR, and others. 2018. The basal forebrain regulates global resting-state fMRI fluctuations. Neuron 97(4):940–52.e4.

Urbain N, Salin PA, Libourel PA, Comte JC, Gentet LJ, Petersen CC. 2015. Whisking-related changes in neuronal firing and embrane potential dynamics in the somatosensory thalamus of awake mice. Cell Rep 13(4):647–56.

Vallentin D, Kosche G, Lipkind D, Long MA. 2016. Neural circuits. Inhibition protects acquired song segments during vocal learning in zebra finches. Science 351(6270):267–71.

Van Dijk KR, Sabuncu MR, Buckner RL. 2012. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 59(1):431–8.

Van Orden KF, Limbert W, Makeig S, Jung TP. 2001. Eye activity correlates of workload during a visuospatial memory task. Hum Factors 43(1):111–21.

Vernooij CA, Reynolds RF, Lakie M. 2016. Physiological tremor reveals how thixotropy adapts skeletal muscle for posture and movement. R Soc Open Sci 3(5):160065.

Wesson DW, Donahou TN, Johnson MO, Wachowiak M. 2008. Sniffing behavior of mice during performance in odor-guided tasks. Chem Senses 33(7):581–96.

Wiltschko AB, Johnson MJ, Iurilli G, Peterson RE, Katon JM, Pashkovski SL, and others. 2015. Mapping sub-second structure in mouse behavior. Neuron 88(6):1121–35.

Winder AT, Echagarruga C, Zhang Q, Drew PJ. 2017. Weak correlations between hemodynamic signals and ongoing neural activity during the resting state. Nat Neurosci 20(12):1761–9.

Wong CW, Olafsson V, Tal O, Liu TT. 2013. The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures. Neuroimage 83(C):983–90.

Wood DK, Gu C, Corneil BD, Gribble PL, Goodale MA. 2015. Transient visual responses reset the phase of low-frequency oscillations in the skeletomotor periphery. Eur J Neurosci 42(3):1919–32.

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, and others. 2013. Sleep drives metabolite clearance from the adult brain. Science 342(6156):373–7.

Xie Y, Chan AW, McGirr A, Xue S, Xiao D, Zeng H, and others. 2016. Resolution of high-frequency mesoscale intracortical maps using the genetically encoded glutamate sensor iGluSnFR. J Neurosci 36(4):1261–72.

Yackle K, Schwarz LA, Kam K, Sorokin JM, Huguenard JR, Feldman JL, and others. 2017. Breathing control center neurons that promote arousal in mice. Science 355(6332):1411–5.

Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, and others. 2013. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage 76:183–201.

Yuan H, Zotev V, Phillips R, Bodurka J. 2013. Correlated slow fluctuations in respiration, EEG, and BOLD fMRI. Neuroimage 79:81–93.

Zeng LL, Wang D, Fox MD, Sabuncu M, Hu D, Ge M, and others. 2014. Neurobiological basis of head motion in brain imaging. Proc Natl Acad Sci U S A 111(16): 6058–62.