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Twitches, blinks, and fidgets: Important generators of ongoing neural activity

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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 of neural activity in the 0.01 to 0.1 Hz frequency range that will show up in fMRI 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 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 in order to differentiate fidget-driven activity from internally-driven neural dynamics.

Keywords

whisking; spontaneous activity; resting-state; sensorimotor; twitch

Introduction

"But when the audience is bored...they sway from side to side..."

Francis Galton, 1885 (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

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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 (Figure 1), are affected by tasks and brain state, and will consequently 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 (non-exclusive) origins. Neural activity associated to 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 towards whole-brain imaging using voltage-sensitive probes (Ferezou and others, 2007; Mohajerani and others, 2013) and genetically-encoded indicators in awake animals (Allen and others, 2017; Chen and others, 2017b; Murphy and others, 2016; Xie and others, 2016), or 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 of 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; Karson 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 found in early visual areas, but are also seen in higher areas throughout the brain (Figure 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 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). Due to 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-0.1Hz), and these variations can drive correlated activity in multiple brain regions. The inter-blink 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 auto-correlated, 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 non-stationarity 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, which 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 pre-eminent 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 for 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 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 (Figure 3). While awake rodents are extensively used for brain-wide imaging studies using fMRI (Ferenczi and others, 2016; Gao and others, 2017), 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) (Figure 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 non-tactile stimuli drive whisking, and whisking drives activation of many brain regions, including those not canonically related to somatosensation (Figure 3). Thus, non-somatosensory 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 the 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, 2017; Satterthwaite and others, 2012; Van Dijk and others, 2012). Head motion is stable within subjects (Zeng and others, 2014) and is heritable (Couvry-Duchesne and others, 2014; Engelhardt and others, 2017; Hodgson and others, 2016). Individual differences in mind-wandering is 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 co-vary 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 non-cognitive 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 these small motions can drive functional activation.

Optical imaging studies 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, 2015a; Huo and others, 2015b; Huo and others, 2014) 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 non-human 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)) (Figure 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 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 non-olfactory 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, 2009; Birn and others, 2008b; 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 CO₂ 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 20–30 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 lead 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. Lastly, fidgeting movements may play an important role generating accurate sensory-motor maps (Blumberg and others, 2013). Whisker twitches during sleep in juvenile animals serves an instructive role in sensory map formation (Blumberg and others, 2015; Tiriack 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 to elucidate 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 (Figure 4). When the fidgeting behaviors are triggered by a stimulus (for example, 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 (Figure 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 also 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, 2013; Liu and others, 2011; 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 these fidgeting behaviors can only be stopped by anesthesia, the best way of dealing with them is detecting and accounting for these movements and behaviors. 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 (Machado and others, 2015; Giovannucci and others, 2018). 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 non-human primate fMRI studies (Chang and others, 2016), this sort of behavioral monitoring is not usually employed in human fMRI studies. Secondly, 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, 2014; Birn and others, 2009; 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, 2015a; Huo and others, 2015b; Huo and others, 2014), 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 focus, coupled with better ethological big data analysis methods (Gao and Ganguli 2015; Gomez-Marin and others, 2014; Robie and others, 2017a; Wilschko 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.

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Figure 1). Spontaneous behaviors have characteristic timescales on the range from seconds to thousands of seconds.

For each behavior, the inter-behavior interval (typical time between behaviors or timescale on which the behavior varies) is plotted. Note that many behaviors vary on the 10–100 second timescale. Top shows humans, bottom rodents. The same range of timescales is used to assay functional connectivity in fMRI experiments (0.01 Hz–0.1 Hz). See relevant sections for references.

Figure 2). Blinking activates multiple brain regions in humans and non-human primates as measured with BOLD 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.

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 in motor cortex (M1) and somatosensory cortex (S1), but also 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 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 ($\Delta R/R$) in the somatosensory cortex from the example animal in (E) in response aligned to volitional whisking onset (grey) 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.