Cortical circuits for integration of self- and visual motion signals

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Highlights

- ◦ Neurons in V1 receive locomotion signals from cortical and non-cortical areas.
- ◦ Neurons in layer 6 of V1 receive vestibular input via the retrosplenial cortex.
- ◦ V1 combines internally and externally generated motions signals.
- ◦ We present an experimental road map for understanding why self and external motion signals are integrated in the visual cortex.

Abstract

The cerebral cortex contains cells which respond to movement of the head, and these cells are thought to be involved in the perception of self-motion. In particular, studies in the primary visual cortex of mice shows that both running speed and passive whole-body rotation modulates neuronal activity, and modern genetically-targeted viral tracing approaches have begun to identify previously unknown circuits that underlie these responses. Here we review recent experimental findings and provide a road map for future work in mice to elucidate the functional architecture and emergent properties of a cortical network potentially involved in the generation of egocentric-based visual representations for navigation.

Introduction

The neural circuits that support the integration of information relayed from the sensory organs are fundamental to survival. The cerebral cortex is one of the defining brain structures of the mammalian brain and receives inputs from all sensory modalities, and furthermore, is known to play a key role in multisensory integration. The classical view of multisensory integration in the cortex is that each sensory modality is processed separately by a series of specialised cortical areas, and then integrated in higher-order association areas in a feed forward manner [1,2]. This "distributed hierarchical system" model, however, has been challenged by a growing body of evidence showing that 'unimodal' sensory brain regions can process both cross-modal sensory [3] and motor related signals. One such brain region where multisensory information converges with motor signals is the visual cortex, which in mice has been shown to integrate multi-modal self-motion signals (i.e. motion of the head): both locomotion [4–6] and vestibular signals [7–10].

There are several possible reasons why visual and non-visual self-motion signals, caused by motion of the head in space, should be integrated in visual cortex. One reason is that self-motion causes the visual image on the retina to move, and the visual system needs to distinguish self-motion from the movement of objects [11–14]. A second reason is to distinguish the visual motion that arises during active movements (e.g. locomotion, head movements) from passive movements (external forces that displace the animal), or similarly, mismatches between motor commands and visual motion [4,15,16]. Although it is currently unclear if vestibular activation still modulates neuronal responses in visual cortex when an animal actively moves [17,18], responses to active head movements have been observed in the parieto-insular vestibular cortex of macaques [19] and in the primary visual cortex of mice [20]. Finally, the integration of multimodal self-motion cues can result in faster and more accurate estimates of self-motion [21,22] and indeed the activity in the visual cortex of macaques is causally related to self-motion perception [23,24].

In this review, we examine what is currently known of the cortical circuits that mediate the integration of self-motion cues in the visual processing regions of the mouse visual cortex. Mice are a particularly useful animal model at this level of analysis since they afford the most detailed dissection of mammalian cortical circuits and cell types, which will build on and complement previous studies in primates. Furthermore, we discuss some of the recent advances in experimental methodologies that will allow a deeper and more complete understanding of these circuits in realistic behaviours.

Circuitry for self-motion integration in the visual cortex

The classic model of visual processing in the cerebral cortex holds that the visual cortex processes visual information in a hierarchical, feed-forward manner. Visual inputs from the dorsolateral geniculate nucleus of the thalamus (dLGN) arrive at the primary visual cortex (V1), and V1 sends it's outputs to higher level visual areas (HVAs), which in turn send projections to multimodal association areas [1,25,26]. How then do non-visual self-motion signals arrive in V1? Vestibular signals for horizontal rotation are known to arrive in layer 6 of V1, at least in part, by way of a population of cells in retrosplenial cortex (RSP, Figure 1) [10,27]. At least a fraction of this population of RSP cells receives input from the anterior thalamic nuclei [10], which forms part of the anterior ascending vestibular pathway [17] (Figure 1). Rotation strongly modulates activity in a large fraction of cells in layers 5 and 6 with little or no activation of superficial layers [10]. The lack of observed responses in V1 superficial layers may mean that vestibular signalling is a deep layer process, or that the whole cortical column might only be engaged in specific contexts [28–30].

Several anatomical substrates for locomotion signals in V1 have been identified (Figure 1) [31,32]. In darkness, at least some of these locomotion signals arise from projections in the mesencephalic locomotor region and the basal forebrain, and these projections increase activity in V1 through a disinhibition process, in which vasoactive intestinal peptide (VIP) neurons inactivate the inhibitory somatostatin (SOM) neurons, which in turn increases activity in layer 2/3 cells [32–34]. However, during visual stimulation, locomotion increases activity in both VIP and SOM neurons, suggesting the mechanism for locomotion signals is context dependant [28]. Several other sources of motor inputs to V1 have been identified – notably the anterior cingulate (ACC) and secondary cortex (M2), which sends projections to mainly to neurons in layers 1, 2/3 and 6 of V1 [15]. ACC, but not M2, also receives input from both V1 and HVAs [35]. Other areas have been shown to provide locomotion signals include the dLGN and lateral posterior (LP) nuclei of the thalamus [36,37], but the source of this thalamic locomotion signal is not known – it may originate from the mesencephalic locomotor region, or may arise from cortical feedback, possibly from V1 [37].

Another key region in the cortical circuit that mediates integration of self-motion is the retrosplenial cortex (RSP) [38]. Classically known for its role in spatial navigation and high-level cognitive functions [39], RSP neurons also show vestibular, motor, and visual responses [10,38,40,41]. Therefore RSP has the characteristics of a multimodal association area, and in the classical model, would act as the locus for integration of self-motion cues. But the presence of non-visual self-motion signals in visual cortex raises interesting questions about the role of RSP in this network [42]. For example, does RSP

perform any multisensory integration itself, or does it relay non-visual signals to visual cortex [43] and receive integrated signals in return? If it does perform integrative operations, how do they differ to those in visual cortex? The abundance of projections from RSP to V1 [27,43,44], suggest that RSP likely contributes more than vestibular signals - it may also act as task dependant, selective gateway for non-visual signals such as motor planning or spatial navigation [45], as it receives strong inputs from ACC/M2 [15,35] and the hippocampal formation [46].
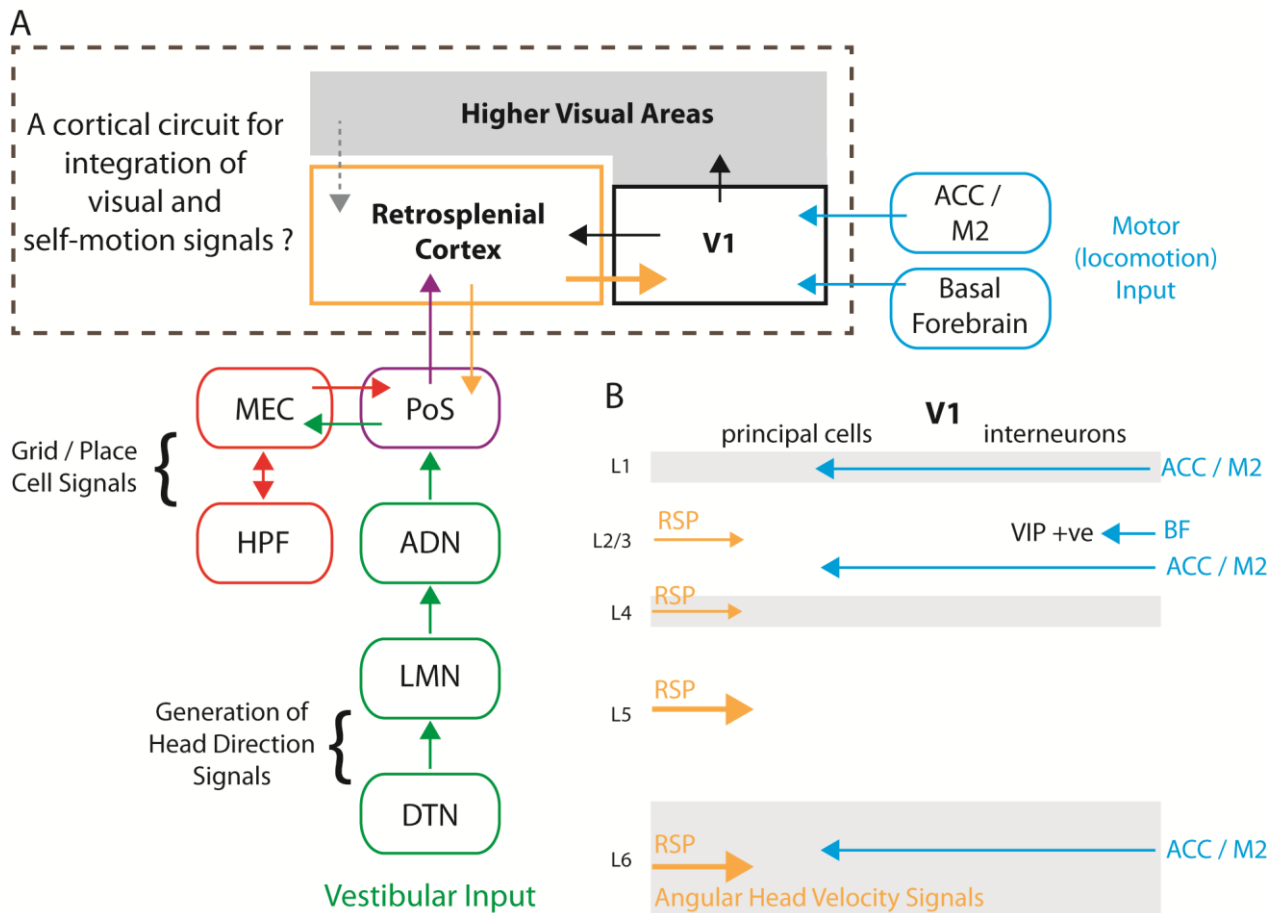

Figure 1: A: The circuitry that links the motor, vestibular and spatial navigation systems to the visual cortex. The primary visual cortex (V1) receives inputs from motor regions (blue, anterior cingulate/secondary motor cortex [ACC/M2], and the basal forebrain [bf]) and the retrosplenial cortex (orange). V1 is connected with higher level visual areas (grey) forming a network of cortical areas for self-motion processing (dashed arrow indicates likely connection). Retrosplenial cortex receives a variety of inputs, including grid/place signals from the medial entorhinal cortex (MEC) via the hippocampal formation (HPF), as well as head direction and vestibular signals from the postsubiculum (PoS) via the head direction network (ADN – anterior dorsal thalamic nucleus, LMN – lateral mammillary nucleus, DTN – dorsal tegmental nucleus). Retrosplenial cortex is therefore capable of providing a range of different self-motion signals to the visual cortex. B: Retrosplenial and motor region inputs to V1. Vestibular signals from the retrosplenial cortex arrive at L6, but L5 neurons also respond to vestibular stimulation in darkness. Motor signals from the basal forebrain modulate layer 2/3 activity through VIP interneurons, and motor inputs from ACC/M2 arrive

at layers 1, 5 & 6. In contrast to V1, no study to our knowledge has characterised the layer specific inputs and circuitry in HVAs, or RSP for self-motion signals.

In summary, good progress has been made in understanding the circuitry that supports the integration of self-motion signals in V1, but a detailed wiring diagram of cell types that incorporates HVAs and RSP is still lacking. Further studies are also needed to determine the functional characteristics of the neurons that send self-motion cues to HVAs, possibly using disynaptic rabies tracing in combination with Cre lines [27,47,48] to express calcium or voltage indicators, or alternatively, by imaging calcium activity in the axons of input neurons [37,49].

Integration of visual and non-visual self-motion signals

The presence of non-visual activity in visual cortex has been clearly demonstrated by recording neural activity in complete darkness, i.e. without any visual stimulus present. In terms of self-motion, passive rotation evokes spiking activity and changes in membrane potential in V1 neurons in complete darkness, and responses are often direction selective [10]. Similarly, locomotion related activity has been observed in V1 of head-fixed mice running on treadmills in complete darkness, as both calcium modulations [4,50] and spiking [6,36], and responses are often tuned for running speed. In combination with a study demonstrating that mouse V1 plays a clear role in visual motion processing [51], the multisensory nature of V1 for self-motion processing is well established.

Although recording neural responses in darkness can be very useful to confirm the presence of non-visual responses, the ultimate goal is to understand how non-visual stimuli are integrated with the neural responses to visual stimuli [52]. In V1, visual-vestibular evoked membrane potential responses to passive rotation have been shown to be an arithmetic sum of the visual and vestibular responses [10] indicating that self-motion information is not simply subtracted to isolate external visual motion. Similarly, spiking activity in response to locomotion and visual stimulation is a weighted sum of the two conditions [6], but the effects of locomotion of visual processing have also been investigated in terms of gain modulation [5,53], increased reliability of responses [54], surround suppression [36,55], and mismatch signals [4]. There have been far fewer such studies in HVAs [56] and RSP, and so more studies outside V1 are required in order to understand the function of the wider self-motion cortical circuit.

One limitation with previous studies of self-motion integration is that they typically utilise only two of the three self-motion cues (of visual, vestibular and motor), but the vast majority of natural behaviours include all three (Figure 2A). For example, visual and

vestibular stimulation without a motor command corresponds to being passively moved by some external force, but this is a relatively rare occurrence compared to most real-world self-motion. Active head movements, including locomotion, without vestibular stimulation (e.g. head fixed animals on treadmills) does not correspond to any common natural behaviour, since vestibular activation always occurs when animals are actively moving. Finally, although mice are often active in complete darkness and thus experience vestibular and motor signals without vision, it is unclear what role visual cortex activity plays in self-motion perception in this context, but lesion studies in rats suggest that V1 may be important for spatial learning in darkness [57].

A

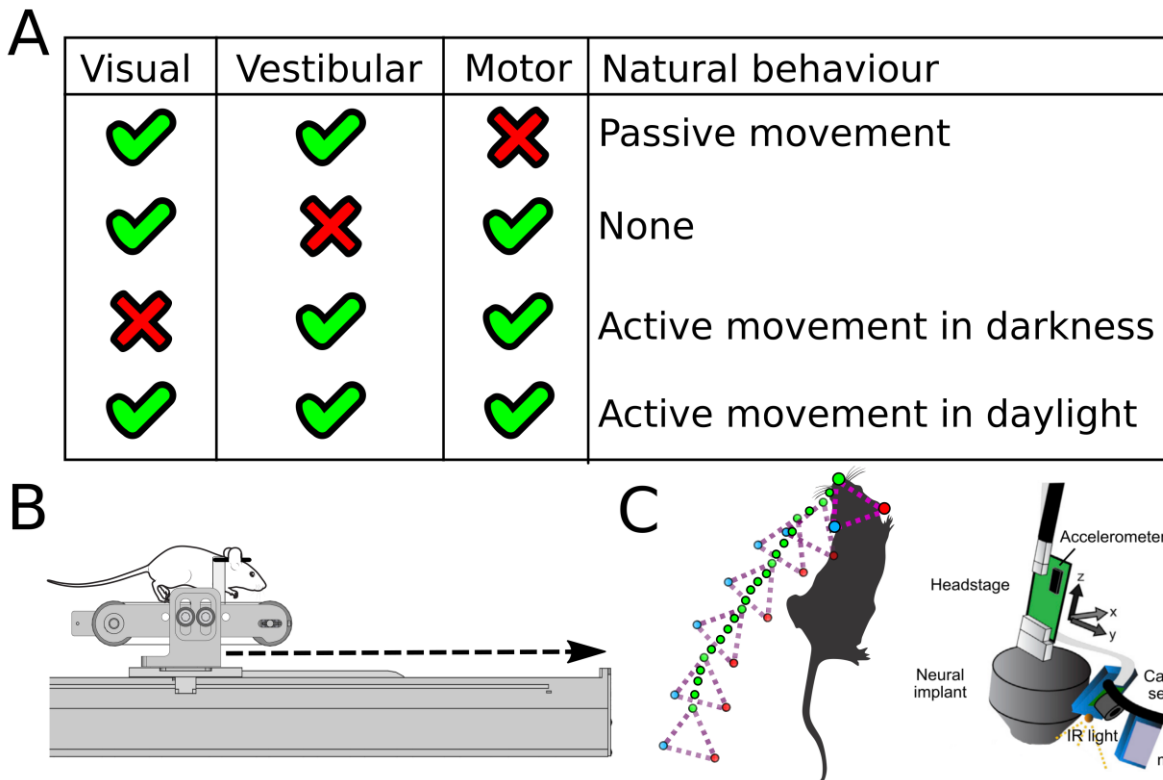| Visual	Vestibular	Motor	Natural behaviour
✔	✔	✘	Passive movement
✔	✘	✔	None
✘	✔	✔	Active movement in darkness
✔	✔	✔	Active movement in daylight

B

C

Figure 2: A: The different combinations of visual, vestibular and movement conditions in current experimental paradigms, and the corresponding natural behaviours. Although studies using only two of these conditions have been extremely useful, they relate to a relatively limited range of natural situations and behaviours. To fully understand the role of non-visual self-motion signals in visual cortex, new experiments are needed that incorporate all three conditions. B: A possible head-fixed, controlled experimental paradigm that would allow visual and vestibular stimulation with locomotion, in which a mouse runs on a treadmill that physically translates in space. C: New advances in tracking head and body position (left, coloured circles represent the tracked position of the head through time)*, as well as measurements of eye position with head speed and acceleration (right, from [20], see also [58]) should allow more detailed measurements the relevant self-motion parameters in freely moving paradigms.*

Furthermore, the extent to which a motor action command (e.g. a running speed signal) might be used by visual cortical areas as a reliable predictor of expected optic flow remains, to our mind, uncertain. Experiments thus far in head-fixed mice that run either on a spherical or horizontal treadmill in which the speed is coupled to the flow of a visual stimulus, show that when the locomotion and visual flow speed are suddenly decoupled, approximately 13% of visual cortical cells change their firing behaviour [4]. However in nature, the biomechanics of running and the subsequent speed of motion (and thus the expected optic flow) are strongly dependent on external conditions such as the integrity of the substrate and slope of the surface on which such activity is taking place [59–61]. Therefore in order to determine running speed, the brain would likely need to also at least integrate proprioceptive signals with the locomotion motor plan. Secondly the body speed of an animal does not reflect the moment-to moment changes in the motion status of the head. The fact that evolution has provided an organ that reports head acceleration and is ideally located adjacent to the visual sensory organs suggests vestibular stimulation is an indispensable component of self- and visual-motion perception.

It seems conceivable that if self-motion cues are fundamental to the perception of external visual motion as well as spatial navigation [62], then these two systems could be integrated to form an internal reference framework for coding allocentric visual information for visual-based navigation. Interestingly, place field like spatial signals have been found the same cortical areas that contain self-motion signals: V1 [28,45,63–65], HVAs [65] and RSP [38,66]. The precise circuitry that supports spatial navigation encoding in V1 and HVAs is not known, but it is likely mediated by RSP, as it is well known to encode spatial signals [39,66] and it is ideally situated as gateway between visual cortex and hippocampal formation [46]. It is currently unclear whether the cells that encode allocentric spatial information (i.e. place or head direction) in these areas are the same cells that encode self-motion processing (e.g. vestibular responses in V1 layer 6, locomotion responses in V1 layer 2/3), or if these two processes are supported by separate circuits [43,44].

In summary, the activity in visual cortex that was reported in previous experiments may represent special or somewhat limited cases of the function of visual cortex. Thus new experiments are needed that allow combined visual and vestibular stimulation in conjunction with active movement if we are to fully understand the function of the non-visual self-motion cues in visual processing.

Active movement paradigms

Experimental paradigms that allow active self-motion with both visual and vestibular stimulation present several new opportunities and challenges. Such experiments could still

utilise head-fixation and tight control of stimulus parameters. For example, one previous study used a virtual reality system and head-fixed mice that can physically rotate their heads in space while walking on a ball [67], and therefore receive vestibular stimulation for rotational (but not translational) movements. A complementary experiment could involve a head-fixed mouse running on a treadmill that can be physically translated according to the speed at which the animal runs (Figure 2B). In either case, decoupling an animal's motor actions from the physical rotation/translation would recreate the motor only condition of previous experiments, or similarly, locking the ball/treadmill during rotation/translation would recreate the passive vestibular stimulation type of experiment. By adding (or removing) visual optic flow cues, the complete set of unimodal, bimodal and trimodal conditions can be studied in a highly controlled manner [68].

However, such experiments still lack many key aspects of natural self-motion. First of all, the animals are restricted to move in only a single dimension, e.g. head rotation or running forwards, which represents a significant under sampling of natural movements. Second, movements under head-fixation may be too dissimilar from natural movements, e.g. pivoting around the centre of the head instead of the body, or modified running gaits on treadmills. Finally, since the experimenter is responsible for the control of visual and vestibular stimulation, then an appropriate range and sequence of stimulus conditions, such as speed, need to be selected on the passive motion trials. While these can be derived from freely moving behavioural data [69,70], a fully naturalistic sequence and distribution of stimulus parameters can be difficult to generate and deploy in a controlled experimental setting, since most experimental setups do not allow for 3 dimensional rotation and translation.

Freely moving experiments, in which the animal is free to move in all possible directions with natural body movements, presents an opportunity to overcome many of limitations of head-fixed studies. First, the movement patterns are by definition naturalistic (not withstanding effects of head-mounted recording devices). While it is true that the movement patterns produced by freely moving animals are complex and can be difficult to measure, several recent advances may alleviate this problem (Figure 2C). Head-mounted gyroscopes and accelerometers, which measure head angular velocity and acceleration, are now light enough for use in mice [58]. Furthermore, these can be combined with miniature cameras [20] to provide eye tracking, which is often critical in studies of visual processing [71]. Recent advances in deep learning have enabled neural networks to provide highly accurate pose estimation [72] for tracking the head and body position in space [73]. Although behaviour in freely moving experiments is not as stereotyped as more controlled, trial-based, head-fixed studies, advances in statistical modelling now provide the tools for analysing continuous and naturalistic behaviours [74,75]. Freely moving studies do not allow uni- or bimodal conditions (except the darkness condition), but as discussed, these conditions may be limiting for understanding the function of these signals in visual cortex (Figure 2A). One other possibility is to combine head-fixed and freely

moving paradigms into a single study, in which the neural activity is first characterised in a head-fixed condition, and then animal is released to allow unrestrained movement. This may provide the best of both worlds – a systematic investigation of neuronal responses with respect to a particular set of self-motion stimuli, and then measurements under naturalistic and unconstrained behaviour. Recording the activity of the same neurons under both paradigms could provide new insights into the generalizability of the controlled, head-fixed experiments [67].

Several recent advances in experimental techniques have made it possible to record the activity of specific types of neurons in freely moving paradigms, which will be critical to understand the function of the relevant visual cortex circuits. Optogenetic tagging allows the identification of cell type for extracellularly recorded neurons in freely moving animals [76,77], and head-mounted one and two photon microscopes allow the direct visualisation of cell type specific calcium activity [78,79]. But to our knowledge, these methods have not yet been used to study self-motion in the visual cortex of freely moving animals. Head-mounted two-photon microscopes [78] also allow for dendritic calcium recordings in freely moving experiments, which enables investigations of self-motion multisensory integration at the level of dendrite and spine [80]. In summary, these technologies should greatly aid the mapping of the cortical circuitry that supports self-motion integration in the visual cortex.

Conclusions and outlook

Our understanding of V1 processing has immensely benefited very recently from the discovery of novel functional properties and identification of previously unknown cortico-cortical connections, but a more detailed and complete wiring diagram is needed and should be extended to the higher level visual areas, as well as the RSP. The widespread presence of non-visual motion signals in visual cortex raises interesting questions about the role of the visual cortex in non-visual functions, as well as the role of traditional multisensory areas, such as RSP, in this network. Furthermore, the presence of spatial navigation signals in potentially the same visual cortex circuits raises further questions about the relationships between the self-motion, vision and spatial navigation systems. Achieving a complete understanding of this will require new experiments that entail both active movement with both visual and vestibular stimulation, and in particular, freely moving studies.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

Annotated references

Papers of outstanding interest (**):

1. Cullen 2019. The most up-to date and comprehensive review on the vestibular system and active motion.

2. Leinweber et al. 2017. A detailed study examining the circuitry and integration of motor signals in V1.

3. Mathis et al. 2017. A breakthrough in animal tracking which will be greatly informative in freely moving studies.

4. Vélez-Fort et al. 2018. A recent study demonstrating the existence of strong vestibular input to mouse V1 circuits.

5. Zong et al. 2017. A new development in head mounted 2-photon microscopes that is ideally suited to studying self motion circuits in mice.

Papers of special interest (*):

1. Aharoni et al. 2019.

2. Chen et al. 2018.

3. Cullen and Taube 2017.

4. Khan and Hofer 2018.

5. Krummin et al. 2018.

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