PRACTICAL GUIDE

Functional neuroanatomy of the human eye movement network: a review and atlas

Benjamin Coiner[1,2,3] · Hong Pan[1,2] · Monica L. Bennett[1,2] · Yelena G. Bodien[2,4,5] · Swathi Iyer[1,2,6] · Therese M. O'Neil-Pirozzi[5,7] · Lorene Leung[1,2,8] · Joseph T. Giacino[2,5] · Emily Stern[1,2,9]

Abstract
The human eye movement network is a complex system that requires the integration of sensory, motor, attentional, and executive processes. Here, we review the neuroanatomy of the eye movement network with an emphasis on functional neuroimaging applications. We consolidate the literature into a concise resource designed to be immediately accessible and applicable to diverse research interests, and present the novel Functional Oculomotor System (FOcuS) Atlas—a tool in stereotaxic space that will simplify and standardize the inclusion of the eye movement network in future functional neuroimaging studies. We anticipate this review and the FOcuS Atlas will facilitate increased examination of the eye movement network across disciplines leading to a thorough understanding of how eye movement network function contributes to higher-order cognition and how it is integrated with other brain networks. Furthermore, functional examination of the eye movement network in patient populations offers the potential for deeper insight into the role of eye movement circuitry in functional network activity, diagnostic assessments, and the indications for augmentative communication systems that rely on eye movement control.

Abbreviations
EMN   Eye movement network
FOcuS   Functional Oculomotor System (Atlas)

Joseph T. Giacino and Emily Stern contributed equally to the senior authorship of this manuscript.

✉ Emily Stern
  estern@bwh.harvard.edu

[1] Department of Psychiatry, Brigham and Women's Hospital, 221 Longwood Avenue, BLI442, 75 Francis St, Boston, MA 02115, USA

[2] Harvard Medical School, 25 Shattuck St, Boston, MA 02115, USA

[3] Eskind Family Biomedical Library and Learning Center, Vanderbilt University School of Medicine, 2209 Garland Avenue, Nashville, TN 37240, USA

[4] Department of Neurology, Center for Neurotechnology and Neurorecovery, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114, USA

[5] Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, 300 First Ave, Charlestown, MA 02129, USA

[6] The MathWorks, Inc, 1 Apple Hill Drive, Natick, MA 01760, USA

[7] Department of Communication Sciences and Disorders, Northeastern University, 360 Huntington Ave, Boston, MA 02115, USA

[8] Boston University School of Medicine, 72 E Concord St, Boston, MA 02118, USA

[9] Department of Radiology, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, USA

Introduction

Functional neuroimaging techniques have proven exceptionally well suited to study the human eye movement network (EMN). In addition, methodological advancements including the development of high-field functional magnetic resonance imaging (fMRI) have recently allowed for functional examination of the small subcortical regions and brainstem nuclei crucial for the execution of eye movements (Wall et al. 2009; Krebs et al. 2010). Unfortunately, few resources

combine structural and functional data to provide a comprehensive review of key cortical, subcortical, and cerebellar regions underlying the initiation and control of eye movement. Furthermore, though many fMRI and positron emission tomography (PET) studies have investigated oculomotor function, few present clear anatomical boundaries for relevant brain regions studied or regions of interest (ROIs) used. To our knowledge, no resource exists to facilitate the inclusion of the EMN in functional neuroimaging studies, making its consideration difficult and standardization across studies nearly impossible. In this review, we outline the regions and circuitry underlying human oculomotor control and provide a tool to simplify and standardize inclusion of the EMN in future neuroimaging studies. This downloadable tool, the Functional Oculomotor System (FOcuS) Atlas, includes the cortical, subcortical, cerebellar, and brainstem regions within the human EMN that are reliably imaged using functional neuroimaging techniques.

Though many functional neuroimaging studies have investigated the EMN, the majority of these eye movement studies are limited to pure oculomotor tasks. We hope to explain the relevance of the EMN to healthy, higher-order cognition and across various injury and disease states, motivating increased consideration and investigation of the EMN in these contexts. Improving our understanding of the complex network of regions and pathways underlying human eye movement is critical for the continued examination of healthy cognitive function and impairments resulting from disease and injury.

In this review, we present the FOcuS Atlas, outline the structural and functional components of the human EMN, and provide guidance for inclusion of the network in future neuroimaging studies. We begin by describing EMN regions in the cerebral cortex, proceed downward through subcortical structures, and end with brainstem motor nuclei and the cerebellum. We then describe each individual region in the context of the complex connectome that drives human EMN function, present a schematic diagram synthesizing the functions and complex interactions of EMN brain regions (see Fig. 3) and offer directions for future research.

FOcuS Atlas and region of interest review

The FOcuS Atlas, shown in Fig. 1, includes 25 ROIs presented in MNI stereotaxic space that facilitate and/or contribute to the initiation and control of human eye movements. This resource, freely disseminated to the academic community, will facilitate ongoing EMN research. Table 1 summarizes the function, location, and definition of each EMN ROI included in the FOcuS Atlas. Figure 2 presents a schematic of ROI location and separates ROIs into four functional components of eye movement: the initial processing of

visual stimuli, externally driven components (e.g., reflexive movements and visuospatial processing), internally generated components (e.g., intentional movements), and the oculomotor circuitry in the brainstem and cerebellum. The FOcuS Atlas is available for download in the supplementary materials.

Cortex

Given the diverse processes involved in eye movements, regions of the EMN are found throughout the human cerebral cortex. Frontal and cingulate cortices are primarily involved in executive, intentional, and other internally generated components of eye movement. Parietal cortex is involved in externally driven components of eye movement. Occipital and occipitotemporal cortices contribute sensory functions, encoding different properties of visual stimuli. After incoming visual stimuli are initially processed in primary visual cortex (CAL) located in the calcarine sulcus, continued processing in occipital, parietal, frontal, and cingulate cortices is necessary for the initiation of motor commands and continued monitoring of eye movements.

Frontal eye fields

Evidence has mounted supporting the presence of two distinct frontal eye field regions situated along the precentral sulcus (Müri 2006; McDowell et al. 2008; Pierrot-Deseilligny et al. 2004). Attempts to distinguish between what was classically referred to as the frontal eye field (FEF) and the more recently identified locus of eye field activity, located more inferiorly along the precentral sulcus, have produced many names for the two regions. The 'classic' FEF may be referred to as the superior or medial FEF, and the 'new' frontal eye field bears several names, including the premotor eye field, lateral FEF, and inferior FEF. Here, we use superior and inferior FEF (s/iFEF) when referencing these two regions.

The sFEF is located bilaterally at the intersection of the precentral sulcus and the superior frontal sulcus (Amiez and Petrides 2009; Jamadar et al. 2013; Pierrot-Deseilligny et al. 2004). The sFEF is one of the most important and widely connected regions of oculomotor control, with diffusion tensor imaging (DTI) studies indicating connectivity with the superior parietal lobule, dorsal prefrontal cortex, and cingulate cortex (Tomassini et al. 2007), as well as regions in the dorsal visuospatial attention network: intraparietal sulcus, supramarginal gyrus, superior temporal gyrus, and extrastriate visual areas (Umarova et al. 2010). sFEF is involved in essentially all eye movements, namely the preparation and initiation of both intentional saccades and pursuit eye movements, and the maintenance of fixation (O'Driscoll et al. 2000; Krauzlis 2004; Matsuda et al. 2004; Ettinger
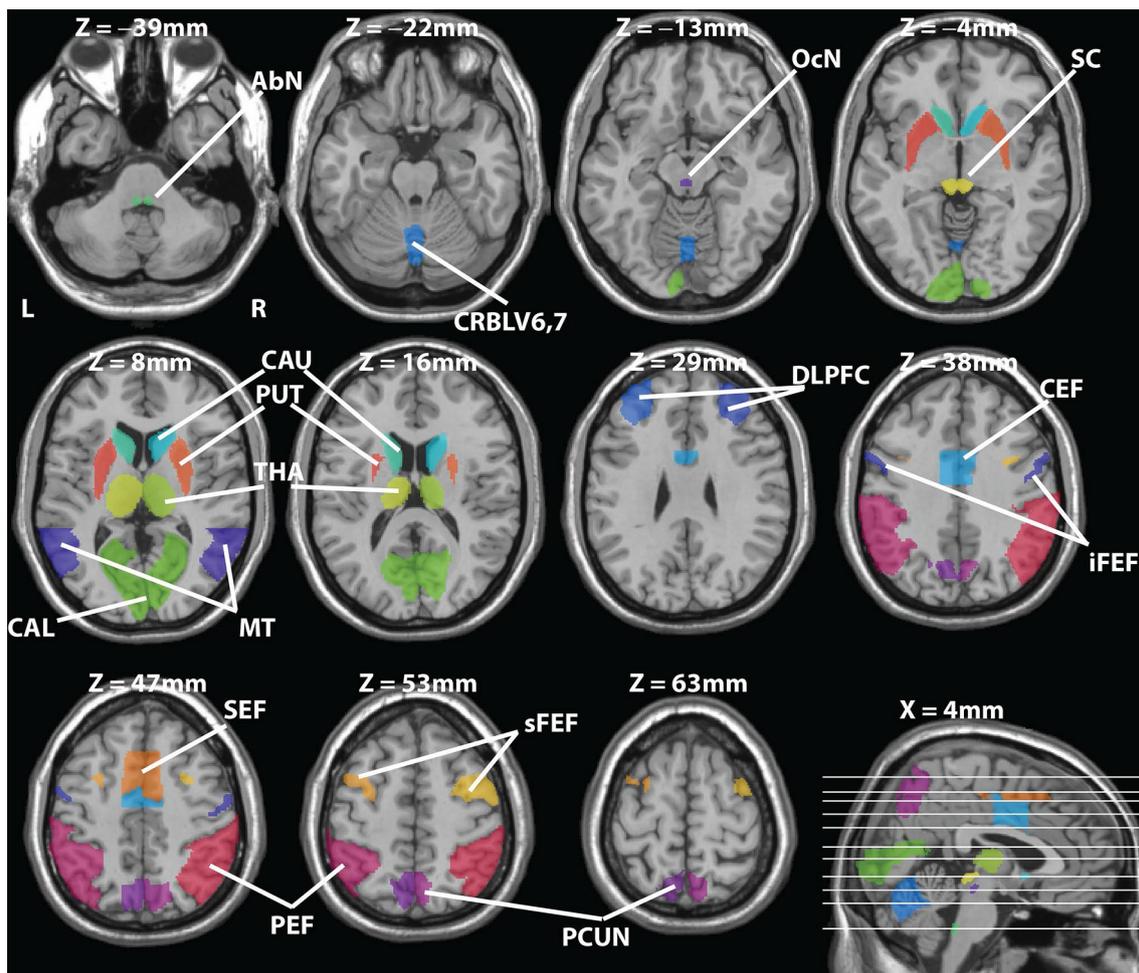
Fig. 1 Visualization of the Functional Oculomotor System (FOcuS) Atlas. Axial slices showing all twenty-five eye movement regions of interest (ROIs) in the FOcuS Atlas. ROIs are shown on the spatially normalized MNI MRI Single-Subject Brain. Abbreviations correspond to abbreviations found in the downloadable atlas and provided in Table 1. *AbN* abducens nucleus, *CRBLV6,7* cerebellar ver- mis lobules VI and VII, *OcN* oculomotor nucleus, *SC* superior col- liculus, *CAL* primary visual cortex (calcarine sulcus), *CAU* caudate, *PUT* putamen, *THA* thalamus, *MT* middle temporal complex, *DLPFC* dorsolateral prefrontal cortex, *CEF* cingulate eye field, *iFEF* inferior frontal eye field, *sFEF* superior frontal eye field, *SEF* supplementary eye field, *PEF* parietal eye field, *PCUN* precuneus

et al. 2008; Leigh and Zee 2015; Berman et al. 1999; Ding et al. 2009; Heide et al. 2001; Jamadar et al. 2013; Neggers et al. 2012; Petit and Beauchamp 2003; Petit and Haxby 1999; Sugiura et al. 2004). Distinct saccade and pursuit-related subregions of the sFEF accomplish these functions (Petit and Haxby 1999; Krauzlis 2004). We offer the caveat that significant interindividual variability has been found regarding the positioning of the sFEF on the medio-lateral dimension via PET (Paus 1996).

The iFEF is located bilaterally in the dorsal branch of the inferior precentral sulcus (Amiez and Petrides 2009). More specifically, saccade-related iFEF activation has been localized to the lateral and posterior portions of the inferior precentral sulcus, sometimes extending to parts of the precentral gyrus and lateral central sulcus (Derrfuss et al. 2012). The precise function of the iFEF is not clear.

As with the sFEF, iFEF activations are reported during pursuit eye movements (Berman et al. 1999) and various types of volitional saccades (Berman et al. 1999; Heide et al. 2001; Ettinger et al. 2008; Derrfuss et al. 2012; Sugiura et al. 2004). Visually guided eye, head, and combined eye/head movements similarly elicit activations in both sFEF and iFEF (Petit and Beauchamp 2003). Activation in the iFEF is also observed during eye blinks (Kato and Miyauchi 2003). While DTI has shown that the two frontal eye fields have different connections to frontal and pari- etal areas (Tomassini et al. 2007), the extent of functional differences between the sFEF and iFEF remains undeter- mined. McDowell et al. (2008) suggest that sFEF may be more associated with volitional movements and the iFEF more associated with reflexive movements, but reiterate the need for additional research. Neggers et al. (2012)

Table 1 Eye movement network regions of interest

Region of interest	Function	Anatomical location	Region of interest definition
Cortex			
Primary visual cortex (CAL)	Receives visual stimulus input	Occipital cortex; along calcarine sulcus	AAL 043/044 Calcarine L/R combined
Middle temporal complex (MT)	Perception of motion; role in smooth pursuit and visual stability	Lateral occipitotemporal cortex; within posterior aspects of inferior temporal sulcus	AAL 081 Temporal Sup L with -4 mm $< Y < 12$ mm, -85 mm $< Y < -50$ mm, + AAL 085 Temporal Mid L with -4 mm $< Z < 12$ mm, -85 mm $< Y < -40$ mm; AAL 082/086 Temporal Sup R + Temporal Mid R -4 mm $< Z < 12$ mm, -85 mm $< Y < -40$ mm
Precuneus (PCUN)	Elements of visuospatial processing and directing attention	Parietal cortex; BA 7	AAL 067/068 Precuneus L/R intersect with BA7
Parietal eye field (PEF)	Generation of reflexive saccades; role in visuospatial processing and attention	Parietal cortex; within posterior aspect of intraparietal sulcus	AAL 061/062/063/064/065/066 Angular, Supramarginal, Inferior Parietal gyri L/R ($Z > 30$ mm)
Supplementary eye field (SEF)	Preparation of volitional saccades; important for cognitively complex saccades and motor programs; role in predictive eye movements	Frontal cortex; in anterior supplementary motor area; on medial wall of paracentral sulcus	AAL 019/020 SMA L/R $Z < 52$ mm
Superior frontal eye fields (sFEF)	Preparation and initiation of intentional saccades and pursuit; maintenance and correction during pursuit and fixation	Frontal cortex; intersection of precentral sulcus and superior frontal sulcus	AAL 007/008 Mid Frontal L/R, intersect with BA6
Inferior frontal eye fields (iFEF)	Precise function unclear; role in pursuit and saccadic eye movements	Frontal cortex; within lateral and posterior aspects of the dorsal branch of inferior precentral sulcus	AAL 001/002 Precentral Gyrus L/R 36 mm $< Z < 48$ mm, $X < -45$ mm for L, $X > 45$ mm for R, and the posterior wall of 5 mm in thickness
Cingulate eye field (CEF)	Modulation of eye movements through conflict monitoring, motivation, and performance evaluation	Cingulate cortex; posterior aspect of anterior cingulate; at limit of BA 23 and 24	AAL 031/032/033/034 Ant & Mid Cingulate L/R, bordered on the boundary between BA23 and BA24 (-12 mm $< Y < 12$ mm)
Dorsolateral prefrontal cortex (DLPFC)	Higher-order cognitive processes, e.g., saccade inhibition and predictive eye movements	Prefrontal cortex; in middle frontal gyrus; mainly BA 46	BA46 L/R (20 mm $< Z < 30$ mm)
Thalamus and striatum			
Thalamus (THA)	Involved in control of eye movements and directing visual attention; relays info from subcortical structures to cortex for modifying motor commands		AAL 077/078 L/R
Putamen (PUT)	Part of BG excitatory and inhibitory pathways to SC; context/reward dependent control of eye movements; predominant site for oculomotor cortical connectivity	Dorsal Striatum	AAL 073/074 L/R
Caudate (CAU)	Part of BG excitatory and inhibitory pathways to SC; context/reward dependent control of eye movements	Dorsal Striatum	AAL 071/072 L/R

Table 1 (continued)

Region of interest	Function	Anatomical location	Region of interest definition
Brainstem and cerebellum			
Lobules VI and VII of cerebellar vermis (CRBLV6,7)	Coordination of eye movements via interactions with SC and brainstem circuitry; motor adaptation based on visuomotor feedback	Superior portion of posterior cerebellar vermis, a narrow midline region separating the posterior cerebellar hemispheres	AAL 112/113 combined
Superior colliculus (SC)	Integration of internal and external information to plan and initiate eye movements; "trigger" for initiating eye movements; role in visual attention	Superior midbrain tectum structure	Manually delineated
Abducens nucleus (AbN)	Innervates the lateral rectus muscle	Bilateral pontine nuclei, on floor of fourth ventricle	Manually delineated
Oculomotor nucleus (OcN)	Innervates the superior rectus, inferior rectus, medial rectus, and inferior oblique muscles	Bilateral midbrain nuclei; in floor of cerebral aqueduct	Manually delineated

Additional details regarding ROI definitions are provided in the supplementary materials

AAL automated anatomical labeling atlas, *L* left, *R* right, *BA* Brodmann area, *BG* basal ganglia

propose a strictly motor role of the iFEF and that the sFEF may contribute to both motor and planning functions.

Supplementary eye field

The supplementary eye field (SEF) is situated within the anterior supplementary motor area (SMA), on the medial wall of the paracentral sulcus (Amiez and Petrides 2009; Grosbras et al. 2001). Like the sFEF, SEF is involved in the preparation and execution of saccadic and pursuit eye movements (Berman et al. 1999; O'Driscoll et al. 2000; Matsuda et al. 2004; Ettinger et al. 2008; Leigh and Zee 2015; Jamadar et al. 2013; Petit and Haxby 1999; Thakkar et al. 2014). However, the SEF is typically more active during increasingly cognitively demanding tasks, such as performing sequences of several saccades (Heide et al. 2001; Thakkar et al. 2014), or saccades combined with body movements (Petit and Beauchamp 2003). A purported pre-SEF, located slightly anterior to SEF, has been implicated in the motor learning necessary for SEF to prepare new or more complex motor sequences (Grosbras et al. 2001; Heide et al. 2001; Pierrot-Deseilligny et al. 2004). Evidence also suggests a crucial role of the SEF in predictive eye movements, including both predictive saccades and anticipatory tracking (O'Driscoll et al. 2000; Heide et al. 2001; Alvarez et al. 2010; Leigh and Zee 2015).

Dorsolateral prefrontal cortex

The dorsolateral prefrontal cortex (DLPFC) is located in the middle frontal gyrus, mainly constituted by BA 46 (Pierrot-Deseilligny et al. 2005). Though the DLPFC is not specific to the EMN, its role in higher-order cognitive processes necessarily applies to the executive control of eye movement. The DLPFC is in fact thought to be crucial for the decisional processes governing eye movements (Pierrot-Deseilligny et al. 2003, 2004). Behavioral effects of lesions to the human DLPFC and neuroimaging studies indicate its clear involvement in the inhibition of saccades (Pierrot-Deseilligny et al. 2003; Matsuda et al. 2004; Ettinger et al. 2008; Jamadar et al. 2013; Leigh and Zee 2015). Another main contribution of the DLFPC to oculomotor function is in predictive eye movements. The DLPFC appears to facilitate both anticipatory saccades (Pierrot-Deseilligny et al. 2003; Alvarez et al. 2010) and predictive tracking (Ding et al. 2009). The DLPFC is also thought to act as a site of short-term spatial memorization for use in future intentional saccades (Pierrot-Deseilligny et al. 2003). However, fMRI studies investigating memory-guided saccades have often failed to find significant involvement of the DLPFC (Heide et al. 2001; Sugiura et al. 2004). A recent study of patients with surgical resections from the DLPFC found that this
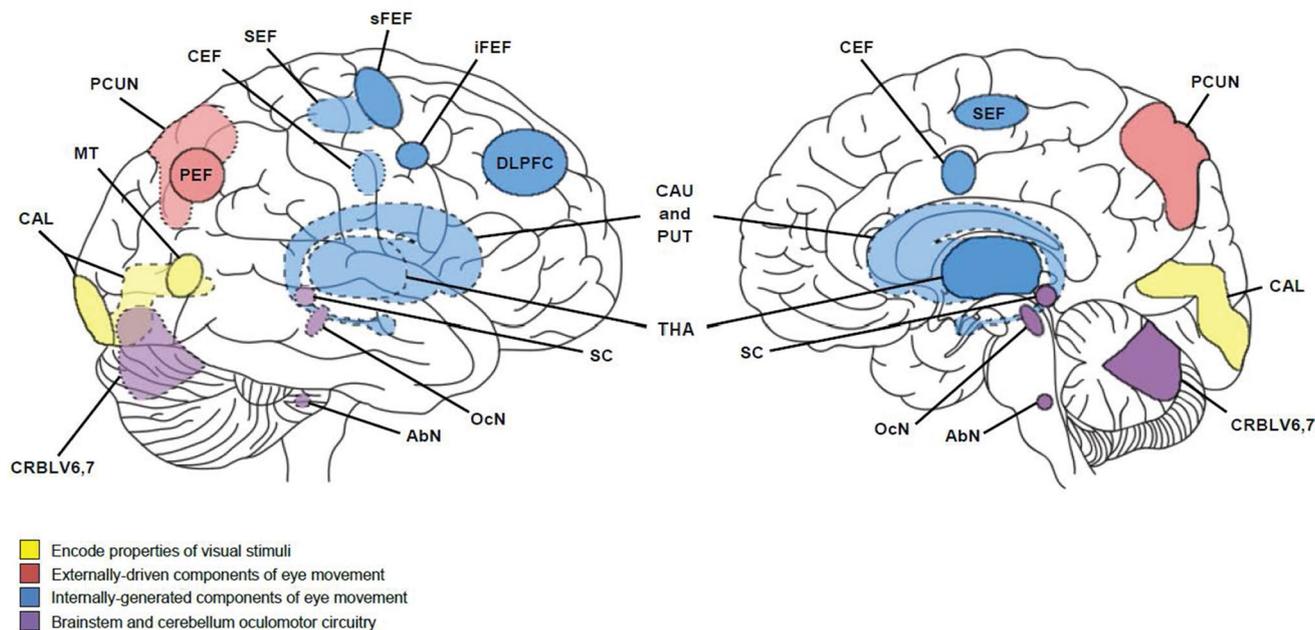
Fig. 2 Localization of eye movement network regions of interest. *AbN* abducens nucleus, *CRBLV6,7* cerebellar vermis lobules VI and VII, *OcN* oculomotor nucleus, *SC* superior colliculus, *CAL* primary visual cortex (calcarine sulcus), *CAU* caudate, *PUT* putamen, *THA* thalamus, *MT* middle temporal complex, *DLPFC* dorsolateral prefrontal cortex, *CEF* cingulate eye field, *iFEF* inferior frontal eye field, *sFEF* superior frontal eye field, *SEF* supplementary eye field, *PEF* parietal eye field, *PCUN* precuneus

damage had no effect on the accuracy of memory-guided saccades (Mackey et al. 2016), altogether suggesting that the DLPFC may not be necessary for the spatial working memory processes involved in memory-guided saccades or other eye movements.

Cingulate eye field

Lesion and functional neuroimaging studies show that the posterior aspect of the anterior cingulate cortex (ACC) is involved in intentional oculomotor control (Petit et al. 1993; Gaymard et al. 1998; Berman et al. 1999; Matsuda et al. 2004; Sugiura et al. 2004; Amiez and Petrides 2009; Jamadar et al. 2013). This purported cingulate eye field (CEF) is suggested to be located at the limit of BA 23 and 24 (Müri 2006; Pierrot-Deseilligny et al. 2004) in the dorsal bank of the cingulate sulcus and within the rostral part of the cingulate motor area (Amiez and Petrides 2009). The CEF reliably displays activation during saccade and pursuit tasks (Petit et al. 1993; Matsuda et al. 2004; Sugiura et al. 2004; Berman et al. 1999) and is thought to evaluate and optimize oculomotor performance, especially during complex tasks, through processes such as conflict and performance monitoring (Leigh and Zee 2015; Jamadar et al. 2013). The CEF likely incorporates motivation, reward, and past experience to prepare the

frontal oculomotor areas involved in the generation of intentional eye movements (Gaymard et al. 1998; Leigh and Zee 2015). Though there is some discrepancy regarding the exact location of the CEF (Jamadar et al. 2013), the involvement of the posterior ACC in intentional eye movements is clear.

Parietal eye field

The parietal eye field (PEF) is located bilaterally within the posterior intraparietal sulcus (IPS), adjacent laterally to the anterior portion of the angular gyrus (BA 39) and medially to the posterior part of the superior parietal lobule (BA 7) (Pierrot-Deseilligny et al. 1991, 2004; Leigh and Zee 2015). A more precise location of PEF, however, has proven difficult to define. Topographic anatomy of posterior parietal cortex (PPC), and thus the IPS, is quite variable between individuals, and much of the IPS outside of the PEF also contributes to elements of visuomotor and visuospatial function (Grefkes and Fink 2005; Müri 2006). PEF likely plays a role in attention and visuospatial integration in conjunction with other regions in IPS/PPC (Grefkes and Fink 2005; Leigh and Zee 2015) and is crucial for the generation of reflexive saccades (Pierrot-Deseilligny et al. 1991; Leigh and Zee 2015). PEF also reliably activates during pursuit-related tasks (Petit and Haxby 1999; Berman et al. 1999) and
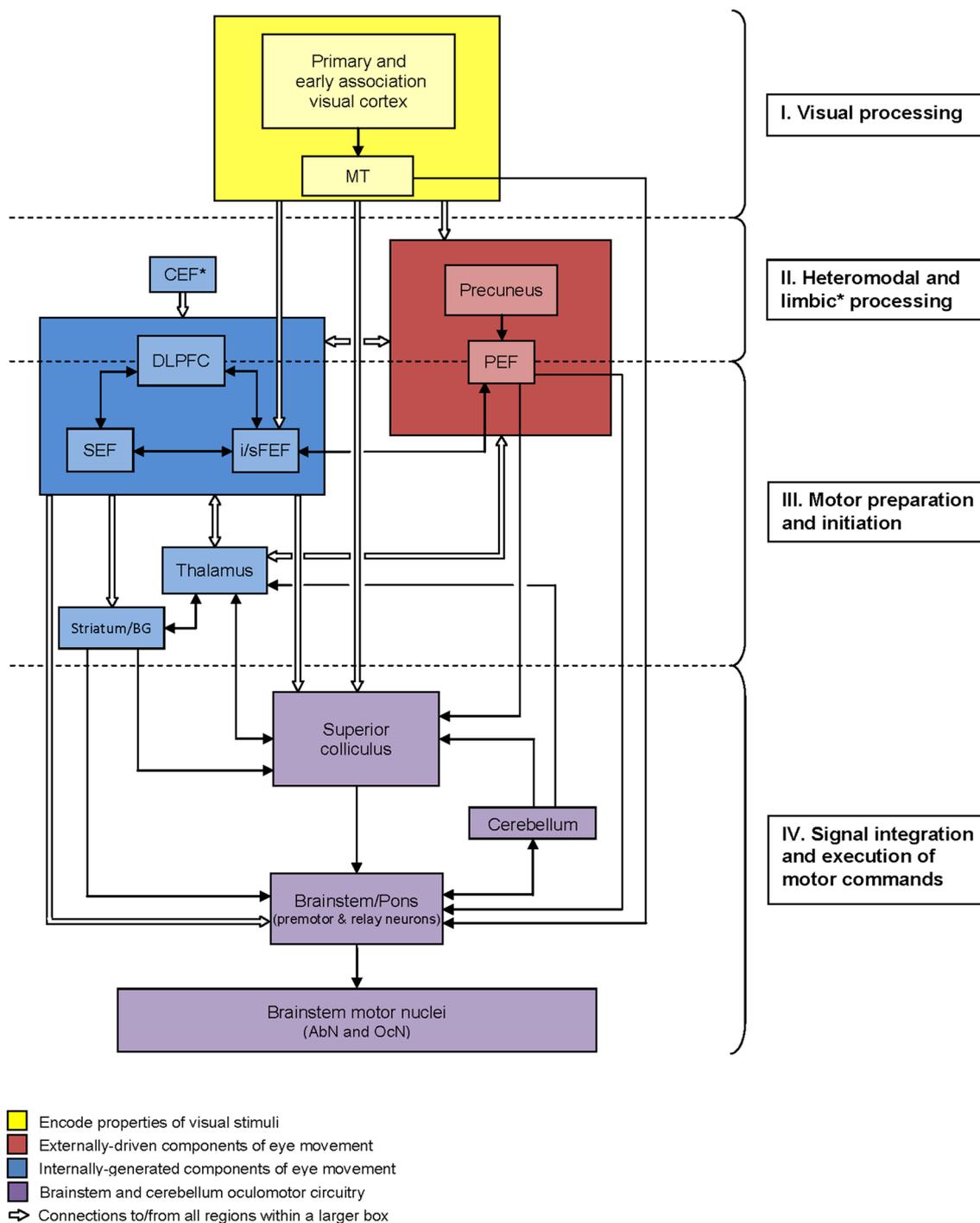
Fig. 3 Functional–anatomic connections within the human eye movement network. (I, yellow) Primary visual cortex and extrastriate visual areas process basic properties of incoming visual stimuli. (II, red) Posterior parietal cortex integrates heteromodal sensory information in order to direct spatial attention and create a spatial representation of the external environment. (II, blue) Prefrontal and cingulate cortex are responsible for executive and motivational components of volitional eye movements. (III, red) Motor commands from PEF in parietal cortex generate reflexive eye movements via direct projections to the superior colliculus. (III, blue) Motor commands from frontal cortex generate volitional eye movements and inhibit reflexive eye movements via projections to the superior colliculus; include direct collicular projections and pathways through the basal ganglia. (IV, purple) Brainstem oculomotor circuitry integrates incoming motor commands to generate appropriate eye movements; the cerebellum is crucial for ongoing coordination of oculomotor activity and is a key site for providing visuomotor feedback to frontal oculomotor areas (via the thalamus); cortical areas project to the brainstem and to the cerebellum via pontine neurons. *MT* middle temporal complex, *PEF* parietal eye field, *CEF* cingulate eye field, *SEF* supplementary eye field, *iFEF* inferior frontal eye field, *sFEF* superior frontal eye field, *DLPFC* dorsolateral prefrontal cortex, *OcN* oculomotor nucleus, *AbN* abducens nucleus

volitional saccade tasks (Berman et al. 1999; Heide et al. 2001; Matsuda et al. 2004; Müri 2006), likely reflecting its various external processing functions.

Precuneus

The precuneus (PCUN) is a large area in medial parietal cortex. The portion involved in the EMN is in part defined by BA 7. Like the DLPFC, the precuneus is not specific to the EMN, but its role in attention and visuospatial processing makes it relevant to oculomotor processes (Zhang and Li 2012). Specific to eye movement, dorsal precuneus has been shown to encode eye position (Williams and Smith 2010), and activity in the precuneus is consistently reported during pursuit (Berman et al. 1999; Petit and Haxby 1999) and a variety of saccade behaviors (Berman et al. 1999; Petit and Haxby 1999; Heide et al. 2001; Petit and Beauchamp 2003; Jamadar et al. 2013). Across studies, oculomotor activity in the precuneus does not involve the whole region, rather, more dorsal, medial, and posterior portions of the region (see Jamadar et al. 2013).

Middle temporal complex

The human middle temporal complex (MT), also known as V5, is located bilaterally in lateral occipitotemporal cortex (Zeki et al. 1991; Petit and Haxby 1999) and is most commonly found within the ascending limb or posterior continuation of the inferior temporal sulcus (Dumoulin et al. 2000). MT is subdivided into middle temporal and medial superior temporal (MST) areas and is primarily involved in the perception of motion (Zeki et al. 1991). Given its role in processing the visual motion that drives pursuit, MT is central in models of the smooth pursuit eye movement system (Krauzlis 2004; Leigh and Zee 2015). In neuroimaging studies, MT demonstrates both saccade- and pursuit-related activity (Petit and Haxby 1999; O'Driscoll et al. 2000), but deactivation in MT during saccades has also been observed (Kleiser et al. 2004). This is largely attributed to a suppression of MT activity that reduces visual sensitivity during saccades (Kan et al. 2008). Functional differences between middle temporal and MST areas may further reconcile activation differences found in MT across fMRI studies. It has been suggested that both middle temporal and MST areas contribute to the control of pursuit eye movements and maintenance of visual stability, but that saccade-related activity only occurs in MST (Kan et al. 2008). It is also suggested that extraretinal signals related to eye movements project to MST (Leigh and Zee 2015).

Thalamus and striatum

The thalamus and striatum are critical for the voluntary control of eye movements. Internally generated motor commands from frontal oculomotor brain regions are modulated by these subcortical structures.

Thalamus

The thalamus (THA) is a widely connected subcortical structure whose functions include directing attention and relaying the sensory, motor, and contextual information necessary for oculomotor control (Leigh and Zee 2015). Functional neuroimaging has demonstrated a clear role of thalamus in directing visual attention (LaBerge and Buchsbaum 1990; Kastner et al. 2004). Continued research in humans has more recently identified thalamic contributions specific to eye movement functions. fMRI shows thalamic activation during antisaccades (Matsuda et al. 2004; Ettinger et al. 2008; Jamadar et al. 2013) and during the reactive control of saccades (Thakkar et al. 2014). Significant thalamic activation in neuroimaging studies has also been reported during voluntary, self-paced saccades performed in darkness (Petit et al. 1993), but others report only trend level (Neggers et al. 2012) or no thalamic activation altogether (Matsuda et al. 2004) under the same experimental conditions. Moreover, the thalamus displays more activation during antisaccades than during reflexive saccades (Tu et al. 2006). In addition to attention, the predominant role of the thalamus thus appears to be in the control processes, rather than the direct generation, of eye movements.

Striatum

The dorsal striatum, comprising the caudate (CAU) and putamen (PUT), is the site of cortical oculomotor input to the basal ganglia (BG) (Neggers et al. 2012; Leigh and Zee 2015). Pathways through the BG to the superior colliculus (SC) are a key means by which frontal cognitive resources enact their control over eye movements (Leigh and Zee 2015; Thakkar et al. 2014). Both the caudate and putamen show increased activation when the inhibition of a saccade is required, e.g., antisaccades (Jamadar et al. 2013) or during the reactive redirection of initially planned saccades (Thakkar et al. 2014). Cortical oculomotor areas are thought to similarly utilize the BG for internally generated control of pursuit behavior (Krauzlis 2004; Leigh and Zee 2015). While the caudate has historically been considered the oculomotor portion of the striatum, functional neuroimaging studies in humans consistently report activation in putamen alone during visually guided saccades (Krebs et al. 2010; Neggers et al. 2012; Thakkar et al. 2014). In agreement with

other imaging results, DTI has revealed that the frontal eye fields are mainly connected to the putamen (Neggers et al. 2012). Though the precise oculomotor roles of caudate and putamen remain uncertain, the striatum is a critical component of evaluative pathways through the BG necessary for the initiation and control of eye movements.

Brainstem and cerebellum

The brainstem and cerebellum contain the regions of the EMN that are directly responsible for executing accurate and meaningful eye movements. While the intricate neuronal circuitry of these processes is beyond the scope of this review, we highlight the superior colliculus, necessary for the translation of cortical motor commands into trigger signals for motor nuclei, the brainstem motor nuclei that innervate the extraocular muscles, and portions of the cerebellum that coordinate eye movements.

Superior colliculus

The SC is located in the midbrain and receives inputs from areas including the retina, cortical eye fields, visual cortex, BG, and thalamus (Leigh and Zee 2015). As a consequence of its small size and deep subcortical location near sources of pulsatile noise (Wall et al. 2009; Krebs et al. 2010), relatively few neuroimaging studies investigating the SC exist. Years of studies in animals strongly suggest an important role of the SC in the initiation and coordination of eye movements (Robinson and Fuchs 2001). Recent methodological advancements have allowed fMRI studies of human SC to build off this foundation, showing increases in activity while executing (Petit and Beauchamp 2003; Krebs et al. 2010; Linzenbold et al. 2011; Thakkar et al. 2014; Furlan et al. 2015; Tyler et al. 2015) and preparing for saccades (Furlan et al. 2015). The SC may also contribute to pursuit eye movements (Krauzlis 2004). Beyond eye movements themselves, the SC plays a role in visual attention. The SC is suggested to modulate attentional signals from higher cortical areas as part of a greater top-down attention network (Anderson and Rees 2011; Schneider and Kastner 2009). On the other hand, others suggest a more active role of the SC in attention, potentially generating specific attentional mechanisms (Sapir et al. 1999) and orienting covert spatial attention by combining information from cognitive and multisensory collicular inputs (Katyal and Ress 2014). Human midbrain degeneration and SC lesions lead to loss of voluntary saccades (Posner et al. 1982) and impairments to attentional mechanisms (Posner et al. 1982; Sapir et al. 1999), further supporting the SC's central role in attention and initiating eye movements. While additional research is needed to more fully understand the attentional functions of the SC and their interactions with its known oculomotor mechanisms, overall,

the SC is important for the integration of diverse sensory and attention-related information, which it then translates into a trigger signal for brainstem premotor neurons controlling the appropriate motor nuclei. In addition, the SC has connectivity to multiple other components of the EMN (see 'The eye movement network' section below), which further illustrates the central role that the SC plays in eye movement control.

Brainstem motor nuclei

Brainstem motor circuitry is directly responsible for generating all eye movements (Robinson and Fuchs 2001; Krauzlis 2004). The abducens and oculomotor nuclei (AbN and OcN) are two bilateral pairs of motor nuclei that together coordinate the contraction of five of the six extraocular muscles. The AbN innervates the lateral rectus muscles and the OcN innervates all extraocular muscles except for the lateral rectus and superior oblique muscles. The paramedian pontine reticular formation (PPRF) is another important brainstem structure, which houses oculomotor premotor circuitry. Though all three of these brainstem regions may be imaged with modern fMRI methods (Linzenbold et al. 2011), we did not define a PPRF ROI due to its relatively small activations (Linzenbold et al. 2011; Tyler et al. 2015). In addition to those previously discussed, the trochlear nucleus innervates the superior oblique muscle of the eye and is located immediately inferior to the OcN. However, to our knowledge, there have been no fMRI studies to date that imaged the trochlear nucleus; future studies may better elucidate the functional role of this nucleus.

Cerebellum

Consistent with its role in coordination of somatic motor control, the cerebellum is crucial for the control—but not the initiation—of eye movements. To fine-tune eye movements, the cerebellum projects to brainstem regions containing oculomotor premotor neurons (Robinson and Fuchs 2001; Leigh and Zee 2015). Stimulation of the posterior cerebellar vermis in monkeys identified vermal lobules VI and VII (CRBLV6,7) as the so-called 'oculomotor vermis' (Robinson and Fuchs 2001). While fMRI studies in humans parallel this finding, the complete role of the cerebellum in oculomotor control is much more intricate. Saccade-related activations in vermal lobules VI and VII are indeed reported, but saccade-related activity is also found in the cerebellar hemispheres and paravermal regions (Nitschke et al. 2005; Liem et al. 2013). More complex eye movement tasks elicit additional variations in cerebellar oculomotor activity (Nitschke et al. 2005; Jamadar et al. 2013). The significant degree to which eye movements and shifts of attention are linked undoubtedly contributes to this complexity. However, fMRI has begun to distinguish between

cerebellar involvement in attention and eye movements, showing unique, saccade-related activity in the posterior vermis, and covert attention-related activity in the cerebellar hemispheres (Corbetta et al. 1998). Neuroimaging also reveals variability in activations related to the error-monitoring function of the cerebellum, showing a relationship between cerebellar activation and saccadic inaccuracies (Liem et al. 2013). Pathways through the cerebellar vermis are also important for the control of pursuit (Krauzlis 2004; Leigh and Zee 2015; O'Driscoll et al. 2000). The clear and consistent role of the cerebellar vermis in oculomotor control, contrasted with the task and context-dependent activations observed elsewhere in the cerebellum, led us to limit our cerebellar ROI to vermal lobules VI and VII.

The eye movement network

From cortex to brainstem, all regions involved in eye movement are highly interconnected to integrate the diverse sensory, attentional, and motor information required for accurate oculomotor activity. This widespread connectivity is also necessary for visuomotor feedback and higher-order cognitive processes. Loss of function in even one region within the EMN often significantly impairs certain eye movement behaviors (Gaymard et al. 1998; Pierrot-Deseilligny et al. 1991).

Figure 3 shows a schematic representation of connections within the human EMN, organized according to the primary function(s) of each region. Visual information first travels from the retina, through the LGN, to primary visual cortex (Fig. 3, I, yellow). Information undergoes preliminary processing in extrastriate visual areas, including MT, which is involved in the perception of motion. Visual areas then project to the PPC, primarily involved in the externally driven components of eye movement (Fig. 3, II, red). Here, regions including the precuneus and PEF are responsible for constructing a spatial representation of the external environment and directing spatial attention. PEF and precuneus have reciprocal connections with the thalamus that likely mediate attention (LaBerge and Buchsbaum 1990; Leigh and Zee 2015). While visual areas also project to the FEF and SC, PPC is the main interface between sensory and motor processing (Grefkes and Fink 2005).

After processing in the PPC, appropriate motor commands are generated in response to the current context. If external stimuli are particularly salient, PEF generates reflexive saccades via direct projections to SC (Fig. 3, III, red) (Pierrot-Deseilligny et al. 1991, 2004; Leigh and Zee 2015). To undergo any cognitive processing or generate volitional eye movements, information must pass from parietal to frontal cortex. Accordingly, reciprocal connections exist between PPC and the frontal oculomotor areas (McDowell et al. 2008; Leigh and Zee 2015). Within the frontal cortex are strong, reciprocal connections between oculomotor areas (Leigh and Zee 2015), which are responsible for internally generated elements of eye movement. DLPFC and the CEF are the main sites of executive/higher-order cortical control of eye movement, with DLPFC involved in decisional and predictive processes and CEF involved in performance monitoring and motivation (Fig. 3, II, blue). DLPFC and CEF modulate motor commands originating in the SEF and i/sFEF, and CEF is also thought to exert its control over the DLPFC (Gaymard et al. 1998). Oculomotor commands from the frontal cortex then reach the SC via direct connections and indirect connections through the basal ganglia (Fig. 3, III, blue). DLPFC, i/sFEF, and SEF project both directly and indirectly to the SC (Krauzlis 2004; Neggers et al. 2012; Leigh and Zee 2015). Direct projections are involved in initiation and suppression of eye movements, whereas projections through the BG—beginning in the dorsal striatum—are related to the significance of the action, e.g., target selection when considering behavioral context and reward (Leigh and Zee 2015). These descending pathways through the BG allow for the excitation and inhibition of the SC.

The SC triggers eye movement through projections to complex premotor circuitry in the brainstem, including neurons of the PPRF (Fig. 3, IV, purple). Premotor circuitry is a crucial site for initiation and control of eye movements, as it controls the motor neurons innervating the extraocular muscles, e.g., AbN and OcN. The cerebellum directly modifies eye movements via projections to this brainstem premotor circuitry and to the SC (Robinson and Fuchs 2001). The cerebellum, along with the SC and BG, also projects to the thalamus, which relays subcortical information to frontal oculomotor regions for cognitive appraisal and the ongoing control of oculomotor behavior (Doron et al. 2010; Leigh and Zee 2015). Cortical areas, too, have direct projections to the brainstem, likely for increased communication, control, and efficiency of the oculomotor system. DLPFC, FEF, SEF, PEF, and MT exhibit small direct projections to brainstem premotor neurons and project to the cerebellum via pontine relay nuclei (Leigh and Zee 2015).

Implications, applications and future directions

Below, we outline the importance of the EMN in cognitive function and its relevance when studying brain injury and disease states. Finally, we highlight components of the EMN that are not well understood and should be main targets of continued research.

Eye movement and cognition

Eye movements facilitate a host of behavioral functions that are recruited to carry out both automatic and cognitively effortful daily activities, ranging from simple visual scanning while reading a book to driving a car on unfamiliar, highly trafficked roadways. These behaviors require integration of diverse sensory, attentional, and executive processes. Oculomotor tests are frequently used to probe cognitive functions such as memory, planning, and expectation (Luna et al. 2008), required for fluent execution of everyday activities (Land and Hayhoe 2001; Land and Furneaux 1997). While assessment of oculomotor function has historically relied on behavioral observations (e.g., eye tracking) and neurophysiological techniques, there is increasing recognition of the need for better understanding of the brain circuitry underlying the reciprocal relationship between eye movements and cognitive functions. Eye movement circuitry is inherently involved in every functional neuroimaging paradigm that presents visual stimuli but is not routinely investigated in studies that do not focus on the oculomotor system. Moreover, the bulk of knowledge about brain mechanisms of eye movement control provided by functional neuroimaging has been obtained using oculomotor tasks under experimental conditions [e.g., performing self-paced horizontal and vertical saccades while blindfolded (Neggers et al. 2012)], not extracted from real-world contexts.

Recent functional neuroimaging studies have begun investigating eye movement in naturalistic contexts, such as reading and viewing scenes (Choi and Henderson 2015; Choi et al. 2014), but the role of the EMN in these real-world, higher-order cognitive functions remains relatively unstudied. Studies investigating how the EMN functions during higher-order tasks like reading music, solving math problems, navigating complex spatial tasks, and completing classic cognitive tasks (e.g., Wisconsin Card Sorting) may help to elucidate how the EMN and other brain networks involved in cognitive control work in unison. For example, the role of the EMN in real-world activities such as athletics, driving, and various occupational tasks can be investigated in an MRI scanner using images, videos, or virtual reality technology and may yield new insights into the interdependencies between the EMN and other special-purpose networks (e.g., executive control, salience, sensorimotor) that enable quotidian function. More generally, as the EMN is involved in all visual task-based studies, its contribution as a network should be routinely examined in the context of its interaction with other functional networks when designing visual imaging paradigms and interpreting functional neuroimaging data.

Eye movement in disease and injury

Deficits in oculomotor performance are characteristic of many medical conditions, including Alzheimer's disease (Molitor et al. 2015), neurodegenerative movement disorders such as Parkinson's disease (Gorges et al. 2014), and psychiatric disorders including schizophrenia and bipolar disorder (O'Driscoll and Callahan 2008; Martin et al. 2011). Impaired oculomotor performance is also frequently present after brain injury and concussion (Samadani et al. 2015; Tyler et al. 2015). Though assessment of eye movements has proven diagnostic utility (Donaghy et al. 2011; Leigh and Zee 2015), integration of functional neuroimaging techniques with existing clinical methods presents an opportunity to better characterize oculomotor pathology and diagnose patients. Illustrating how neuroimaging techniques and the EMN may be used together to better inform clinical management, a recent fMRI study of patients in the subacute phase of concussion found lingering functional alterations in otherwise clinically asymptomatic patients while they performed a battery of oculomotor tests (Johnson et al. 2015). In addition, eye tracking technology has shown promise as a tool for diagnosis and assessment of everyday function in autism, mild cognitive impairment and other conditions (Frazier et al. 2016; Seligman and Giovannetti 2015; Kasneci et al. 2017). In contrast, neurodegenerative diseases (e.g., amyotrophic lateral sclerosis) and neurodevelopmental disorders (e.g., cerebral palsy, Rett syndrome) may spare oculomotor function in the setting of severe impairments in speech and motor function that compromise or prevent communication through conventional channels. The EMN may enable an alternative means of reliable communication through its connectivity to visual processing, attention, and volitional control networks. Computer-based eye gaze technologies illustrate the importance and clinical utility of the EMN in augmentative communication in individuals who no longer have access to behaviors mediated by speech and motor circuits (Myrden et al. 2014; Spataro et al. 2014; Townend et al. 2016). Functional neuroimaging used in tandem with in-scanner eye tracking offers the potential to establish diagnostic biomarkers by identifying subtle functional differences associated with the cognitive changes that follow disease and injury and to detect preserved cognitive functions (including communication ability) that might otherwise be missed in patient populations with severe impairments in oculomotor, motor and speech functions.

Severe injury to the CNS, including high cervical spinal cord injury and locked-in syndrome, may also impair communication, either through local disruption of corticospinal and corticobulbar tracts, or more generally via injury to mesodiencephalic structures responsible for arousal and drive functions. Assessment of level of consciousness

often relies heavily on eye movements because of loss of speech and active limb movement. However, making accurate diagnostic decisions based on simple observation of eye gaze is challenging and may contribute to high rates of misdiagnosis (Schnakers et al. 2009). fMRI activation studies assessing residual cognitive function in patients with disorders of consciousness (DOC) demonstrate how fMRI has informed the manner in which the EMN interacts with networks subserving visual processing, language and self-awareness (Owen and Coleman 2008; Monti et al. 2013).

Future directions for EMN research

Though much of the EMN is well understood, the contributions of certain regions of the EMN remain less clear. A more precise functional definition of the recently identified iFEF and clarification of functional distinctions between iFEF and sFEF, pre-SEF and SEF, caudate and putamen, and middle temporal and medial superior temporal subregions of MT are needed. Other EMN regions, namely the CEF and PEF, have fairly well-established functionality, but less certain anatomic localization. Use of ultrahigh-field fMRI may be beneficial in answering these questions and in identifying subtle differences in the role that distinct EMN regions play in specific cognitive and behavioral activities. Continued work to disentangle attentional and oculomotor functions of the thalamus, SC, and cerebellum is needed. Network connectivity studies will elucidate how individual regions in the EMN work in concert, and how the EMN interacts with other brain circuits.

Conclusions

The EMN is a complex system of diverse brain regions and circuits that contribute to the vast array of brain functions that involve visual perception. We advocate for increased examination of the EMN in functional neuroimaging studies, which will lead to a better understanding of naturalistic and pathological oculomotor function. The FOcuS Atlas is a resource designed to standardize the functional neuroanatomy of the EMN to assist investigators in planning and interpreting functional neuroimaging studies. Ultimately, this may lead to improvements in care related to brain injury and disease.

Compliance with ethical standards

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