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The Insula

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Review

The Insula: A "Hub of Activity" in Migraine

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Abstract

The insula, a "cortical hub" buried within the lateral sulcus, is involved in a number of processes including goal-directed cognition, conscious awareness, autonomic regulation, interoception, and somatosensation. While some of these processes are well known in the clinical presentation of migraine (i.e., autonomic and somatosensory alterations), other more complex behaviors in migraine, such as conscious awareness and error detection, are less well described. Since the insula processes and relays afferent inputs from brain areas involved in these functions to areas involved in higher cortical function such as frontal, temporal, and parietal regions, it may be implicated as a brain region that translates the signals of altered internal milieu in migraine, along with other chronic pain conditions, through the insula into complex behaviors. Here we review how the insula function and structure is altered in migraine. As a brain region of a number of brain functions, it may serve as a model to study new potential clinical perspectives for migraine treatment.

Keywords

interoception, pain, autonomic function, brain connectivity, salience network, headache, functional networks, sensory processing, emotional processing, brain imaging, fMRI, PET, lateral sulcus

Introduction

The focus of brain systems biology has trended toward integrated networks, which comprise a jigsaw of interacting brain regions. One region, the insula, located bilaterally in the lateral sulcus, plays a complex role in emotion, homeostasis (including error detection), autonomic function, sensation, salience, and awareness (Nieuwenhuys 2012). It is also known to be involved in specific behaviors related to disease conditions such as migraine. Migraine attacks involve a wide range of sensory, emotional, and cognitive symptomology. It is thus conceivable that the insula may serve as a cortical hub, processing many of the complex sensory and emotional aspects known to be present in the migraine condition.

In this review, we explore known functional components of the insula and their potential role in migraine. Specifically, we first summarize "Anatomical Aspects of the Insula" in the first section and then briefly outline "Functional Divisions of the Insula." Second, we discuss "The Functional Insula in Migraine," on how the insula that may contribute to some of the observed sensory, physiological, psychological, and cognitive changes in migraine. In the fourth section, "Migraine Therapy: Targeting Insular Function," we review data that support modulation of insula function in therapies used in migraine treatment. "Conclusions" are in the final section. The review attempts to provide an overview of insular function with regard to migraine. Clearly, migraine is not "an insula disease." However, since the insula is involved in complex behaviors associated with the migraine state, both ictally (the period of the migraine attack) and interictally (the period between migraine attacks), the insula could play an important role in integrating many of the dynamic processes know to be involved in migraine (e.g., sensory, autonomic, cognitive). In addition, while attempting to provide a review of current information regarding this region's involvement

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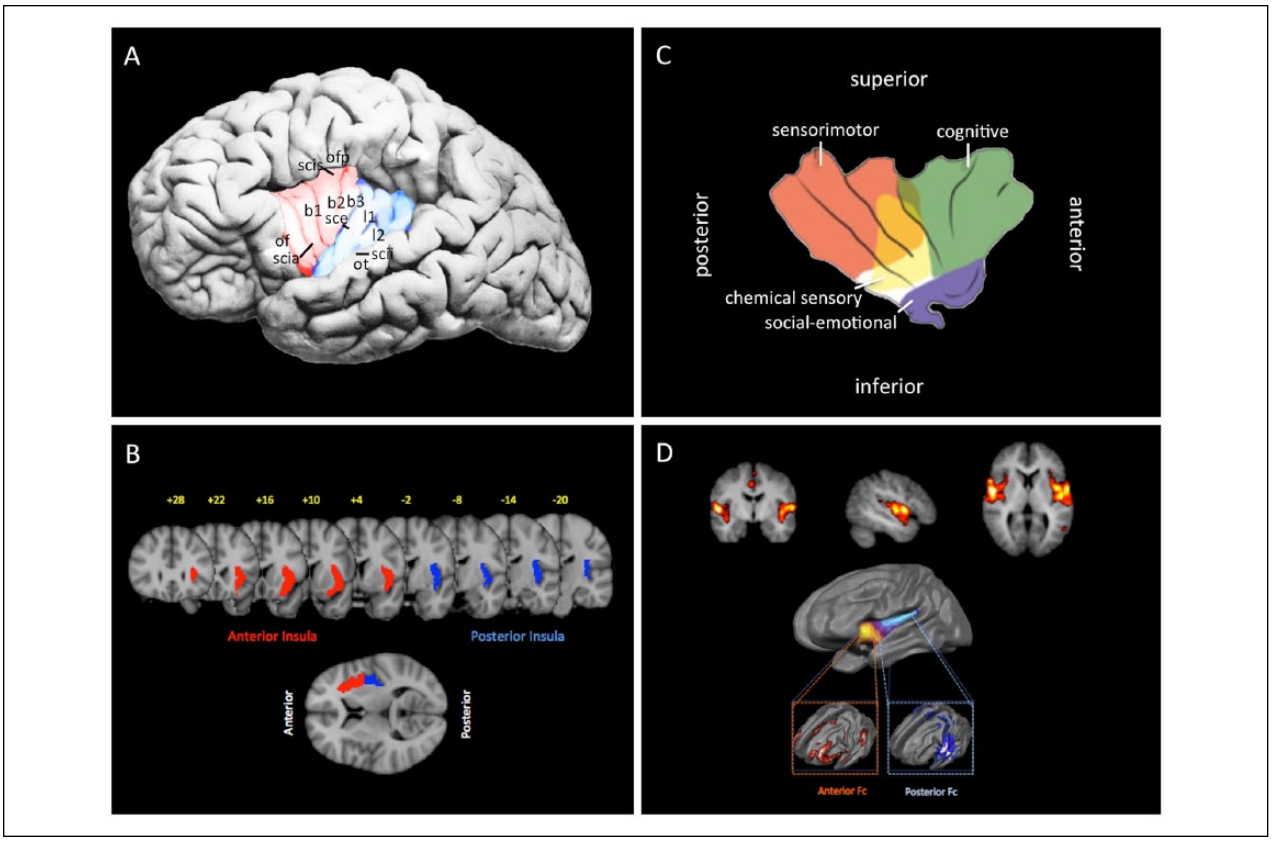

Figure 1. Structural and functional anatomy of the insula. (A) Gross anatomy: Gross anatomy of the insula showing the insular gyri. The shaded red corresponds with the anterior insula, shaded blue with the posterior insula (as shown in Figure 2). of = operculum orbitofrontale; scia = sulcus circularis insulae pars anterior; b1 = gyrus brevis primus; b2 = gyrus brevis secundus; b3 = gyrus brevis tertius; sce = sulcus centralis insulae; l1 = gyrus longus primus; l2 = gyrus longus secundus; scii = sulcus circularis insulae pars inferior; ot = operculum temporale; scis = sulcus circularis insulae pars superior; ofp = operculum frotoparietale. Adapted from (Nieuwenhuys 2012) with permission. (B) MRI of insula in humans: The figure was constructed from FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Anterior/posterior insula were obtained from the Harvard-Oxford probabilistic atlas included in the FSL distribution. Anterior/posterior insula probabilistic maps were thresholded at 25% and rendered over the standard MNI152 2-mm anatomical image. (C) Functional divisions: Functional areas in the insula are shown according to Kurth and others (2010). Adapted from (Klein and others 2013b) with permission. (D) Functional connectivity: (Top) The insula is involved in the Salience network—which has been defined as a network that includes the insula, anterior cingulate and orbitofrontal cortices with strong connectivity to subcortical and limbic structures (Seeley and others 2007) and the network has been considered to play a prominent role in pain and analgesia (Borsook and others 2013b). (Bottom) The figure shows the two major divisions of the insula, anterior and posterior ((Cauda and others 2011) with permission). The anterior ventral insula is functional connected to the salience detection network, while the dorsal insula is functional connected to a visuomotor integration network.

in migraine, it is a brain region involved in other conditions (i.e., fibromyalgia, chronic lower back pain, etc.) and needs to be considered in this context.

Anatomical Aspects of the Insula

The insula is a brain region located within the Sylvian fissure in the fronto-parietal and temporal opercula (Guenot and others 2004). Figure 1A shows the gross anatomy of the insula. The insula consists of 5 to 7 lobes in humans, which are divided into anterior and posterior portions by the central insular sulcus. Further anatomical divisions have been described elsewhere (Ture and others 1999). All insular gyri are interconnected, except the anterior and posterior short gyrus (Almashaikhi and others 2014). Recent studies in humans using tractography (the process of tracing white matter tracts using MRI) reveals that the anterior insula is predominantly connected to limbic and paralimbic brain regions as well as the anterior parts of the inferior frontal gyrus, while the posterior insula is connected with parietal and posterior temporal cortices (Cerliani and others 2012). These findings correlated with connections have also been reported in anatomical tract tracing studies in primates (reviewed

by (Augustine 1996)). The insula also has various connections with other cortical areas that include the visceral sensory area, visceral motor area, motor association area, vestibular area, as well as subcortical connections to the amygdala (Sah and others 2003) and thalamus (Mufson and Mesulam 1984). Accordingly, the insula is highly interconnected throughout the brain, thus providing the underpinnings of its involvement in a wide range of functions. Figure 1B shows horizontal and coronal sections through the insula providing a guide for the relative locations of the activations or gray matter changes shown in Figures 3 and 4.

In addition to the complex connectivity, the neuronal population of the insula varies across the different subregions of the brain structure: from granular neocortex in the posterior-dorsal insula to agranular neocortex in the anterior-ventral insula (Bauernfeind and others 2013). Specialized neurons, called von Economo neurons (VENs), have been found in the insula (Allman and others 2011; Evrard and others 2012), specifically in the agranular frontoinsular (rostro-ventral) part (Bauernfeind and others 2013). In humans, VENs are observed in the 36th week of gestation, are rare at birth, and increase in number during the first 8 months after birth (Allman and others 2011). As they develop, there is a laterality with more found in the right insula (Allman and others 2010), which shows dominance for a number of functions (see following text). It has been therefore suggested that they play a critical role in complex characteristics like self-awareness and social cognition (Critchley and Seth 2012). Differences in biochemical specificity that have been reported in VENs in humans versus other hominids may relate to evolutionary development of specific processing such as interoception (Stimpson and others 2011).

Functional Divisions of the Insula

The insula can also be functionally divided into anterior and posterior parts and exhibit functional divisions involved in somatosensory, autonomic, interoceptive, salience, and cognitive processing (see Fig. 1C). The variation in function of the human insula (Cloutman and others 2012) seems to correlate with structural connectivity noted above (Cerliani and others 2012). Functionally, the anterior insula shows connections within the middle and inferior temporal cortex and anterior cingulate cortex, and is primarily related to limbic regions, which play a role in emotional modulations (Cauda and others 2011). Furthermore, the anterior insula may also serve as a hub that integrates interactions with large-scale brain networks (Menon and Uddin 2010) as it forms an integral part of the salience network (Damoiseaux and others 2006), thus potentially incorporating behavioral responses with internal or external salient stimuli (Borsook and others 2013b). The posterior region is more closely connected to the premotor, sensorimotor, supplementary motor and middle-posterior cingulate cortices, indicating a role for the posterior insula in sensorimotor integration (Cauda and others 2011). Finally, anterior and posterior divisions of the insula are also functionally connected (Cauda and others 2011) (see Fig. 1D). Further details of the functional role of the insula are reviewed elsewhere (Afif and Mertens 2010; Bauernfeind and others 2013). It should also be noted that other authors have offered a slightly different version of subregional functions of the insula (Cauda and others 2011; Deen and others 2011; Kurth and others 2010).

Although multiple functional features of the insula have been described, an understanding of the details of the functional anatomy of the insula is still elusive. There are some overarching features such as converting physiological states into emotions related to feeling and a sense of being. However, based on surgical, electrophysiological and imaging studies, different anatomical regions may have specific functional domains (Cauda and others 2014; Dupont and others 2003). Direct stimulation of the anterior insula in humans elicits very few reportable responses, whereas stimulation of the mid and posterior parts of the insula results in gustatory and somatosensory symptoms (Stephani and others 2011). Painful sensations have also been reported following stimulation of the posterior insula (Mazzola and others 2009), with more specificity noted in the upper posterior part of the human insular cortex and right-sided lateralization (Ostrowsky and others 2002). This latter finding has been confirmed by functional magnetic resonance imaging (fMRI) studies showing that the insula is somatotopically organized (Brooks and others 2005). Interestingly, the integration of visceral and somatic inputs into more complex outputs from the insula may relate to intrainsular functional connectivity, as significant connectivity between anterior and posterior subregions has been observed during neurosurgical evaluation in patients with refractory epilepsy (Almashaikhi and others 2014).

Figure 2 summarizes afferent and efferent pathways involved in basic functions of the insula (viz., somatosensory, visceroception, cognition, etc.). These connections form the basis for many of the altered functions observed in migraine. Inputs include pain through trigeminovascular afferents, dizziness through vestibular afferents, and visceral connections that may provide a basis for abdominal symptoms and autonomic changes. Insular outputs to subcortical and brainstem regions that contribute to cortical control of autonomic function, the cingulate cortex contributing to interoceptive responses, and to the frontal lobe that is related to cognitive processing.

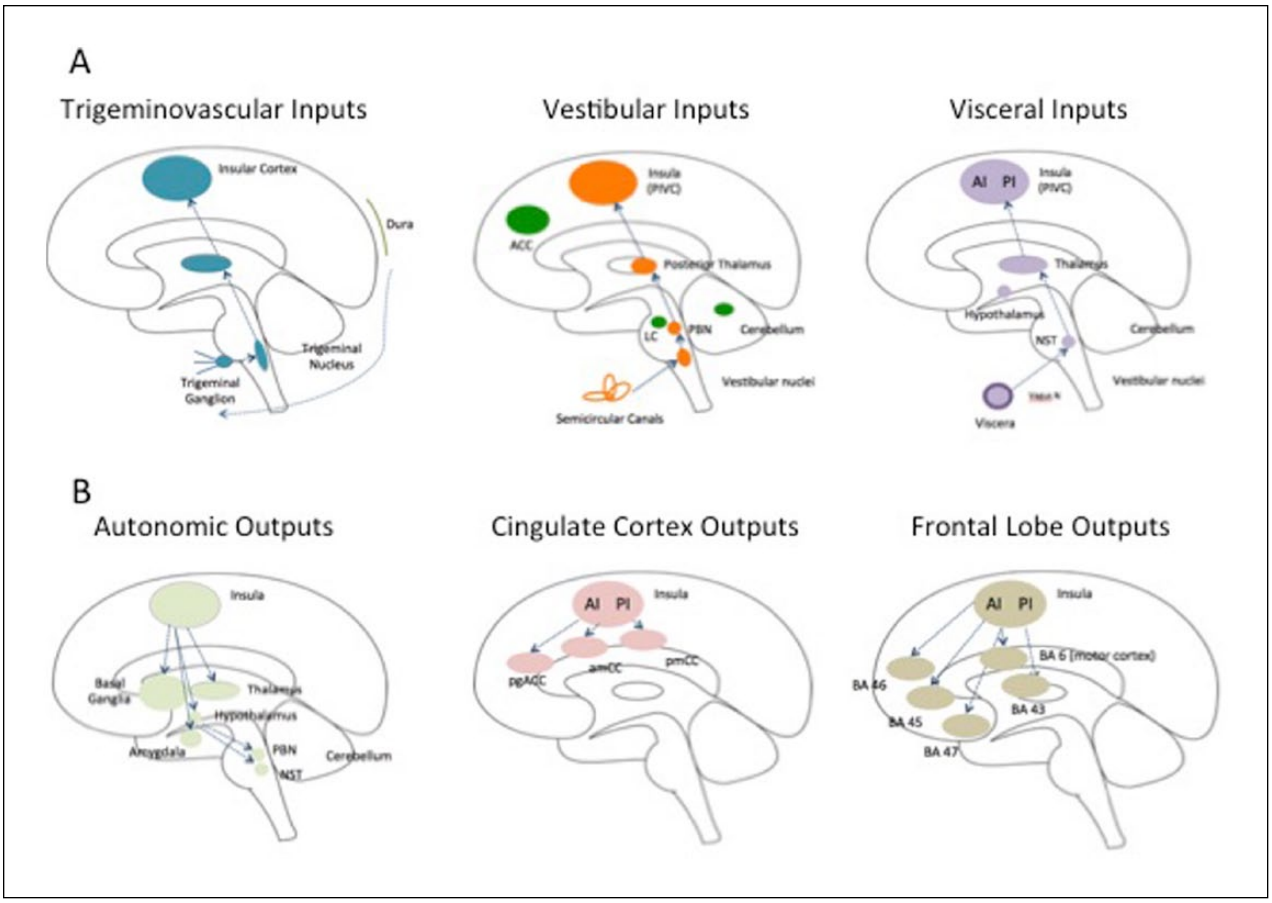

Figure 2. Important afferent and efferent insular pathways in migraine. (A) Afferent inputs (top row): *Trigeminovascular*: The trigeminal system includes afferent inputs from the three major divisions of the trigeminal nerve (ophthalmic, maxillary, and mandibular) that send their inputs to the trigeminal nuclear complex (Willis and Westlund 1997). Projections from here are primarily to the thalamus and to the amygdala and hypothalamus through trigeminothalamic (Matsushita and others 1982), trigemino-parabrachial-amygdala (Bernard and Besson 1990), and trigeminohypothalamic (Malick and Burstein 1998) tracts. Projections from these regions to the insula have been described for each primary projection complex (thalamo-insula (Mufson and Mesulam 1984); hypothalamo-insula (Saper 2000) and amygdalo-insula (Kevetter and Winans 1981). As noted in the text some of these connections have been reported in functional imaging studies in migraine patients. *Vestibular*: Vestibular inputs originate from the semicircular canals in the inner ear and project to the vestibular nuclei in the brainstem. The afferent pathway to the insula includes the parabrachial nuclei, posterior thalamus to the parieto-insula vestibular cortex (Brandt and Dieterich 1999). These pathways are reviewed elsewhere (Angelaki and Cullen 2008). *Visceral*: Visceral inputs to the insula include pathways from the viscera (e.g., vagus nerve) to the nucleus of the solitary tract (NTS) (McDougal and others 2011). Projections from the thalamus to the posterior insula relay visceral sensory information (Cechetto 2014). (B) Efferent outputs (bottom row): *Autonomic*: The insula is involved in cortical regulation of autonomic control (Jones 2011; Nagai and others 2010). Efferents from the insula connect with multiple subcortical (basal ganglia, thalamus, and hypothalamus) and brainstem regions (e.g., parabrachial nucleus, nucleus of the solitary tract) (Beissner and others 2013; Benarroch 1993). *Cingulate cortex*: Connections between the insula and cingulate cortex are part of a number of networks. It has been postulated that the interactions between the insula and the cingulate are involved in *integrating interoceptive information with emotional salience* (pACC/aMCC) or involved in *environmental monitoring, response selection, and skeletomotor body orientation* (MCC) (Taylor and others 2009). Pathways that are part of a circuit for processes such as empathy for pain (Engen and Singer 2013; Singer and others 2009; Singer and others 2004) or the initiation of goal-directed behaviors (Devinsky and others 1995). *Frontal lobe*: Pathways projecting from the insula to the frontal and motor cortex. The anterior insula connects to Brodmann areas (BA) 45, 46, 47, and 6 (motor cortex), while the posterior insula has connections with 43. These connections are implicated in cognitive processing, speech, memory encoding, and recognition (Ramnani and Owen 2004; Wood and Grafman 2003). ACC = anterior cingulate cortex; PIVC = parieto-insular vestibular cortex; LC = locus coeruleus; PBN = parabrachial nucleus; AI = anterior insula; PI = posterior insula; NST = solitary nucleus; pgACC = pregenual anterior cingulate cortex; amCC = anterior midcingulate cortex; pmCC = posterior midcingulate cortex; BA = Brodmann area.

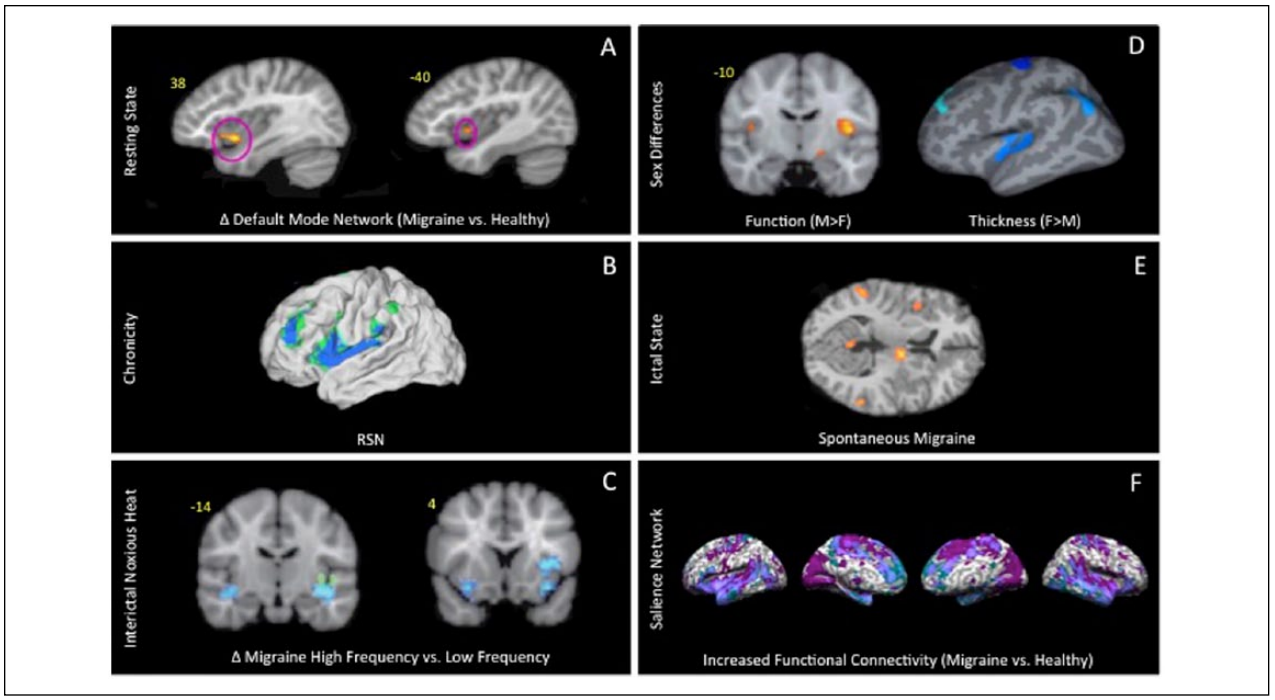

Figure 3. Insula activation in migraine. (A) Resting state: Group comparison maps showing higher default mode network connectivity in migraine versus healthy controls in the right and left anterior insula respectively. Adapted from (Xue and others 2012) with permission. (B) Chronicity: Functional connections with affective pain regions have been shown to differ between patients with chronic migraine (CM) and healthy controls. The connectivity strength of the anterior insula was correlated with the number of years of CM ((from Schwedt and others 2013) with permission). (C) Interictal noxious heat: fMRI contrast analysis of high-frequency versus low-frequency migraineurs in response to a +1°C pain threshold shows significant differences in the contralateral anterior insula in addition and bilateral inferior circular insula. These findings were co-localized with observed structural differences in the inferior circular insula (shown in green). Adapted from (Maleki and others 2012a) with permission. (D) Sex differences: Maps illustrating sex differences between male and female migraineurs in the insula. (Left) Males have higher fMRI activation in response to painful heat in the insula compared with females; whereas (right) insula cortical thickness is increased in females compared with males. Adapted from (Maleki and others 2012b) with permission. (E) Ictal state: PET measures of spontaneous migraine show right insula activation. Adapted from Afridi and others (2005a) with permission. (F) Salience network: fMRI resting state functional connectivity using the left anterior insula (aINS) as a seed region. Teal represents resting state functional connectivity for healthy controls and purple for migraine subjects. Light violet represents the areas showing overlap. Shows connectivity patterns consistent with the salience network (SN). Results indicate an increased connection to the SN in migraine subjects. Adapted from (Hubbard and others 2014) with permission.

The Functional Insula in Migraine

Based on its functional role and widespread connectivity with cortical and subcortical brain regions the insula has been proposed to play a significant role in neuropsychiatric disorders (Nagai and others 2007) including mood and anxiety disorders (Buse and others 2013; Sheftell and Atlas 2002), temporal lobe epilepsy (Ostrowsky and others 2000), craving and drug seeking in addiction (Naqvi and others 2014), pain (Mazzola and others 2009; Ostrowsky and others 2002), and non-motor symptoms of Parkinson's disease (Christopher and others 2014). In fact, damage of the insula affects a number of important behaviors and perceptions including individuals' sense of being, apathy or tiredness (Manes and others 1999), neglect (Manes and others 1999), temperature perception (Baier and others 2014), dysarthria (Baier and others 2011), auditory agnosia (Bamiou and others 2003), processing of empathy (Gu and others 2012), and drug craving (Garavan 2010).

As noted above, many of the putative functions ascribed to the insula also appear as symptoms in migraine so studying insular function and dysfunction may lead to further understanding and treatment. Table 1 lists imaging studies on migraine reporting insular changes (see criteria for PubMed search in table key). Migraine is more than a headache. It involves altered sensory, emotional, and cognitive processes (Charles 2013). In the following sections, we will explore four principal domains of altered function (sensory, physiological, psychological, and cognitive) in migraine and the putative involvement of the insula in these functions. Examples of insula activation across processes that can induce changes specific to migraine symptoms are

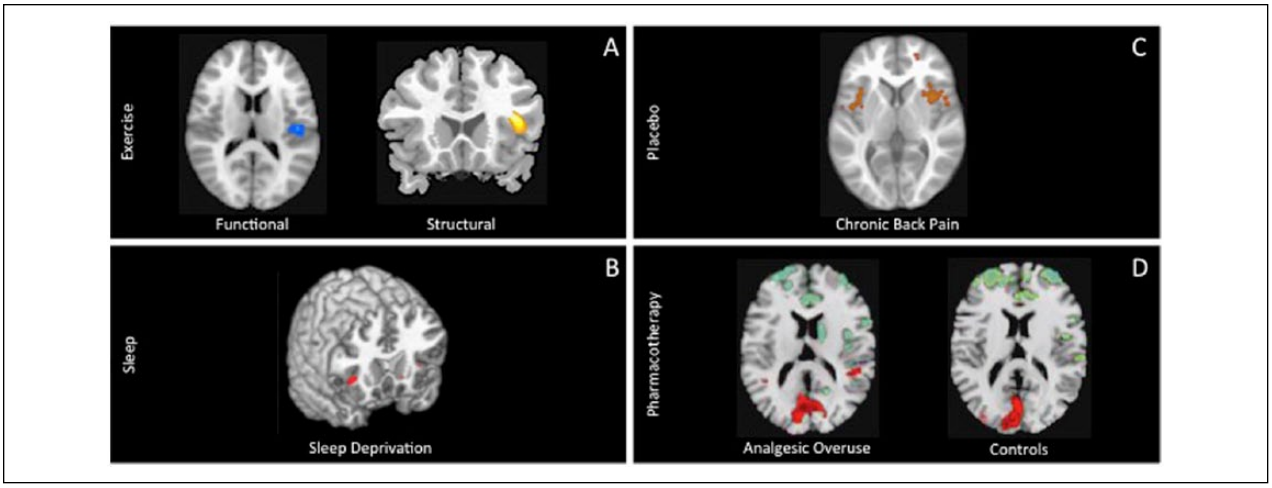

Figure 4. Treatment effects on the insula. (A) Exercise: (Left) A single bout of aerobic exercise has been shown to affect insular blood flow (decrease) as assessed with blood oxygen level–dependent (BOLD) fMRI using pseudo-continuous arterial spin labeling (pcASL) and to decrease activation by a "go/no-go" task (from (MacIntosh and others 2014), with permission). (Right) Cortical gray matter density in the right anterior insula has been shown to be strongly correlated with aerobic capacity ((Peters and others 2009), with permission). (B) Sleep deprivation: Sleep deprivation is associated with reduced activation in right anterior insula (Venkatraman and others 2011). (C) Placebo: Using fMRI, treatment-resistant chronic back pain patients showed higher activation in the bilateral insula compared with chronic back pain patients who experienced a pain decrease following treatment. Adapted from Hashmi and others (2012) with permission. (D) Pharmacotherapy: Using ^{18}F-FDG PET measurements, a significant increase in right insular metabolism has been reported in patients with chronic migraine (CM) and analgesic overuse (AO) compared to both patients with CM without AO and healthy controls ((from Di and others 2013), with permission).

those defined for underling functions in other studies including pain (Henderson and others 2008), autonomic function (Henderson and others 2012; James and others 2013), cognition (Wiech and others 2010), prediction error (Bossaerts 2010; Preuschoff and others 2008), and aversive processes such as disgust (Wright and others 2004), vestibular function (Fasold and others 2002), and nausea (Napadow and others 2013).

Figure 3A demonstrates an example of the functional changes to the insula observed in migraine subjects compared with healthy controls. There is an increase in insular activity that corresponds to the default mode network (DMN) (Xue and others 2012), a network associated with normal brain function while at rest. Figure 3B displays the correlation between the number of years with migraine and increased functional alterations to the resting state network (RSN) (Schwedt and others 2013), a network synonymous with the DMN. The results of these studies indicate that migraine may not only alter insular activity but over time, these repeated attacks might exert an ongoing effect on perturbing insula function.

Sensory Processes in Migraine

Pain. The major sensory symptom of migraine is head pain that is severe and debilitating (Silberstein 2004). The posterior insula has inputs from the thalamus conveying nociceptive signals to the insular cortex (Craig 2003; Craig and others 2000). The insula has been called "a multidimensional integration site for pain" (Brooks and Tracey 2007). Separation of innocuous (e.g., touch, proprioception, innocuous cold or warmth) and noxious stimuli (heat) has been reported in the human insula, as proprioception activates the contralateral mid-insula, innocuous cooling activates mid- and dorsal posterior insular parts, and pain activates the contralateral posterior insula, indicating that the insula may contribute to sensory-discriminative functions (Mazzola and others 2012). Most recently, data obtained using intracerebrally recorded nociceptive laser-evoked potentials (LEPs) from the full extent of the insula suggests that nociceptive input is first processed in the posterior insula, where it is coded in terms of intensity and anatomical location, after which it is conveyed to the anterior insula, where the emotional reaction to pain is processed (Frot and others 2014). Furthermore, both heat and pinprick stimuli demonstrated contralateral anterior and posterior insula activation (Baumgartner and others 2010), further supporting the notion that the insula may be involved in sensory integration in pain. In addition, the pain inputs may be further incorporated into complex networks, such as the salience network, through the anterior insula (Wiech and others 2010). Painful stimulation also leads to an increase in insula to periaqueductal grey functional connectivity (Linnman and others 2012). Functional connectivity data for anterior and posterior insular regions activated by noxious and

Table 1. Migraine Imaging Studies Reporting Changes in Insula Function and Structure.[a]

Migraine Type	State of Migraine	Method	Experimental Paradigm (Stimulation)	Subjects, N (M/F)	Effect (+/−)	Laterality (R/L)	Region(A/P)	Reference
Functional studies								
MWOA	Ictal	PET	GTN	1 (1/0)	+	R + L	P	Bahra and others (2001)
MWA(2)/MWOA(3)	Ictal/interictal	PET	Spontaneous	5 (0/5)	+	R + L	—	Afridi and others (2005a)
MWOA	Ictal/interictal	PET	GTN	8 (3/5)	+	R	—	Maniyar and others (2014)
MWA(8)/MWOA(16)	Ictal	PET	GTN	24 (10/14)	+	R + L	—	Afridi and others (2005b)
Vestibular	Ictal/interictal	PET	Spontaneous	2 (0/2) + MC	+	R	P	Shin and others (2014)
MWOA	Ictal	SPECT	Magnesium/placebo	40 (5/35)	+	R	—	Koseoglu and others (2008)
MWA(4)/MWOA(6)	Interictal	fMRI	Verbal stimuli	10 (1/9) + MC	+	R + L	A + P	Eck and others (2011)
MWA(6)/MWOA(14)	Ictal/interictal	fMRI	Olfactory stimuli	20 (5/15)	+	R	A + P	Stankewitz and May (2011)
MWOA	Interictal	fMRI	Spontaneous	23 (6/17) + MC	+	R + L	A	Xue and others (2012)
MWA(11)/MWOA(11)	Interictal	fMRI	Spontaneous	22 (2/20) + C	+	R + L	A	Hadjikhani and others (2013)
Chronic	Interictal	fMRI	Spontaneous	20 (3/17)	+	R+L	A	Schwedt and others (2013)
MWA (20)/MWOA (10)	Ictal/interictal	fMRI	Spontaneous/ olfactory stimuli	20 (4/16)	+	R + L	A	Stankewitz and others (2013)
MWOA	Interictal	fMRI	Spontaneous	40 (12/28)+ MC	+	L	—	Zhao and others (2013)
Migraine + allodynia	Interictal	fMRI	Spontaneous	38 (6/32) + C	+	R	P	Schwedt and others (2014)
MWA(26)/MWOA(26)	Interictal	fMRI connectivity	Spontaneous	52 (18/34) + MC	− (MWA)	R	A	Niddam and others (2015)
MWOA	Interictal	fMRI connectivity	Spontaneous	15 (3/12) + MC	+	R + L	A	Tso and others (2015)
Structural studies								
Episodic	Interictal	MRI/ fMRI	Spontaneous	22 (11/11) + MC	+/−	L	P	Maleki and others (2012b)
MWOA	Interictal	MRI/fMRI	Spontaneous	40 (11/29) + MC	+	L	—	W. Yuan and others (2013)
MWOA	Interictal	MRI/VBM	Spontaneous	35 (3/32) + C	−	R	A	Schmidt-Wilcke and others (2008)
Drug effect studies								
Healthy + sumatriptan	—	fMRI	Soft brush	12 (4/8)	+/−	—	A/P	Kramer and others (2007)
Healthy + sumatriptan	—	fMRI	Electrical stimuli	12 (8/4)	+	R	A	K. Yuan and others (2013)
CM + PCA (AO)	Interictal	PET	Spontaneous	20 (7/13) + MC	+	R	—	Di and others (2013)
MWOA + acupuncture	Ictal	PET-CT	Acupuncture	30 (12/18) + MC	+	—	—	Yang and others (2012)

MWOA = migraine without aura; MWA = migraine with aura; MC = matched controls; GTN = glyceryl trinitrate; pMRI = perfusion MRI; DWI = diffusion weighted imaging; CM= chronic migraine; PCA = paracetamol caffeine aspirin; AO = analgesic overuse.

[a]Search Terms: Literature search of migraine and insula was undertaken using PubMed (http://www.ncbi.nlm.nih.gov/pubmed). Keywords used included the following: migraine, insula, anti-migraine drugs, gray matter, episodic migraine, and chronic migraine. Additional strategies included manual searches for relevant articles from the selected articles' reference lists as well as utilization of PubMed's related articles function.

non-noxious stimuli have led to further segregation of pain processing, showing that the anterior insula is more strongly functionally connected to affective and cognitive regions, whereas the posterior insula has strong connectivity with sensory-discriminative processing regions (Peltz and others 2011). The frequent activations of the anterior insula observed in pain fMRI studies may be interpreted as "heightened alertness of either stimulus- or task-driven origin, or both" that integrates internal and external stressors to maintain allostasis (Sterzer and Kleinschmidt 2010).

Given that the insula appears to be a brain hub or convergence point for afferent inputs (predominantly nociceptive) and emotional processing, one would expect similar activations in pain conditions such as migraine (notwithstanding that other sensory information may flow in parallel). Cortical projections from trigeminovascular neurons in the thalamus have been described to the insula—as well as other cortical areas (Noseda and others 2011). In patients with insula lesions, acute experimental noxious stimuli produce higher pain intensity ratings and an increased level of responses in the primary somatosensory cortex (S1) compared with healthy controls, suggesting that the insula is involved in "tuning cortical regions to appropriately use previous cognitive information during afferent processing" (Starr and others 2009). Furthermore, a case of an epileptic focus in the posterior insula has been described, which produced pain (as opposed to inducing post-seizure–related headaches) during a seizure and, in addition, stimulation of the same area elicited by pain (Isnard and others 2011). Mapping of seizure-induced pain in the insula has shown predominantly in the sensory region of the posterior insula (Ostrowsky and others 2002) supporting the notion that the posterior insula is involved in pain perception. Figure 3C demonstrates how high-frequency (HF) migraineurs show decreased activation to painful stimuli compared with low-frequency (LF) migraineurs (Maleki and others 2012a). Additional findings of decreased cortical thickness of the insula in the HF group indicate a dynamic nature of this region with pain. This suggests that insular dysfunction may result from increased migraine frequency (Maleki and others 2012a). Other insular changes in migraine are illustrated in Figure 3. The dynamic functional and morphological changes in the region include integrative process whereby sensory information is transferred to the anterior insula involved in emotional processing of pain (Frot and others 2014). In this way, repetitive migraine attacks may alter emotional processing through regions such as the insula.

Vestibular System. Other sensory alterations in migraine include vestibular dysfunction, which in turn contributes to symptoms of nausea and vomiting. Migraine may present a *forme fruste* "vestibular migraine" condition (Furman and others 2013); generally, many migraineurs have symptoms that are vestibular in nature. Small lesions of the insula may present with vertigo (Papacostas and others 2006) and posterior insula strokes may coincide with both pseudothalamic sensory and vestibular-like syndromes (Cereda and others 2002). Vestibular neurons in the insula have been found in monkeys (Grusser and others 1990) that were affected by neck and visual responses. One of the reasons patients with migraine typically obtain relief from laying down may therefore relate to limiting neck and visual inputs that may contribute to vestibular symptoms. Vestibular symptoms, while more common in children and adolescents (Weisleder and Fife 2001), are present in some 30% to 50% of migraine patients (Stolte and others 2015).

Viscerception. Migraine symptoms include a vast array of sensory alterations (i.e., photophobia, phonophobia, osmophobia, geumophobia, etc.) with the insula implicated to play a role as a driver behind these abnormally noxious responses. Although osmophobia, which produces burning smells described as olfactory aura, is uncommon in the general population, it is a symptom that may precede or come on with a migraine attack (Coleman and others 2011). Interestingly, in the interictal stage, about 35% of migraineurs report olfactory hypersensitivities (Marmura and others 2014; Stankewitz and May 2011) whereas in the ictal phase, some migraineurs have olfactory symptoms of microsmia or hyposmia (Marmura and others 2014). These different sensory alterations may be associated with the disruption of the insula and supported by a study showing increased activation induced by olfactory stimuli (rose odor) in the amygdala and insula during spontaneous migraine attacks (Stankewitz and May 2011). The insula cortex is the primary region involved not only in smell but in taste as well (Maffei and others 2012). Taste perception is integrated in the anterior insula, and may indicate why another common migraine symptom is both nausea and vomiting. In addition, many imaging studies support the notion of the insula playing a role in the disgust response (Phillips and others 2004; Sprengelmeyer and others 2011; Suzuki 2012; Wicker and others 2003; Wright and others 2004). Further support indicates the insula as a site for altered olfactory sensation from lesion studies of the insula showing to affect olfaction in humans (Mak and others 2005; Stevenson and others 2015), as well as diminished taste recognition and intensity deficits (Pritchard and others 1999). Accordingly, these findings confirm the complexity of visceral pathways in migraine, in which the insula may represent a major brain-processing site.

Physiological Processes in Migraine

The insula is involved in a wide range of physiological processes that are clinically altered in migraineurs, some of which are discussed in the following text.

Autonomic Function. In migraineurs, alterations in autonomic function have been well documented. Overall, adult patients with migraine exhibit autonomic nervous system hypofunction, as measured in the interictal period (Shechter and others 2002). Additionally, we have recently shown alterations in hypothalamic functional connectivity in episodic migraineurs compared with healthy controls (Moulton and others 2014), thus possibly reflecting an abnormal autonomic system. Altered hypothalamic function during migraine (Alstadhaug 2009) may also suggest that the autonomic nervous system can trigger migraine attacks. The insula is one of many cortical regions involved in autonomic control (Cechetto 2014; Jones 2011; Nagai and others 2010). Stimulation of cardiopulmonary afferents produce activation in the anterior insular cortex through a pathway that originates in the nucleus of the solitary tract and synapses in the parabrachial nucleus and the ventroposterior parvocellular nucleus of the thalamus (Cechetto 2014) (see Figure 2). Autonomic function in the insula in migraine is still to be evaluated, but based on evidence of pain-related activations of the insula and its role in autonomic regulation (Leone and others 2006), it is highly likely that altered regulation of autonomic function may also involve changes in insular functions (Geraud and Donnet 2013). Further evidence has been seen in strokes occurring in the insula that result in increased susceptibility to cardioautonomic dysfunction (Meyer and others 2004).

Sleep. Sleep disruption is reported in migraine patients (Jennum and Jensen 2002; Sahota and Dexter 1990). During rapid eye movement (REM) sleep there is a relative activation in a number of brain areas (limbic and paralimbic), including the insula compared with the awake-state as assessed by PET fluoro-deoxy glucose (FDG) imaging, suggesting that involvement of these regions is part of "the integration of neocortical function with basal forebrain-hypothalamic motivational and reward mechanisms" (Nofzinger and others 1997). In a follow-up study for slow wave sleep (SWS), the same group reported that whole brain metabolism decreased relative to the awake state, even after controlling for whole brain decreases, but no changes were observed in the insula (Nofzinger and others 2002). It has, however, been recently indicated that slow wave function may correlate with the thickness of the insula (Dube and others 2015). Others have also reported the role of the insula in the sleep-wake cycle including REM and non-REM components (Braun and others 1997). The potential interaction of the insula and migraine may relate to adaptive and restorative changes, since sleep deprivation alters insula function related to decision making (Venkatraman and others 2011) and autonomic function (Konishi and others 2013; Meerlo and others 2008), including neural circulatory control (Kato and others 2000). Given the important role of the insula in autonomic function and that alterations in cerebral blood flow may contribute to the headache phase (Asghar and others 2011), altered sleep may thus diminish resilience in migraineurs. Figure 4B shows another example of the importance and effect of sleep with a decrease in activation in the insula from sleep deprivation.

Interoception. The role of the insula in interoception was introduced by (Craig 2003) in the context of pain and sensation relating to mechanisms around "how do you feel" the physiological state of the body. While other brain regions may be involved in sense of self (Critchley and others 2004), the insula plays a key role in connecting these physiological interoceptive processes with feelings (Pollatos and others 2007). The dorsal posterior insula is involved in interoceptive awareness (Craig 2003), and more recently, the anterior insula has also been implicated in this process (Zaki and others 2012). The overall integration of interoception may involve contributions of "discrete modules" (Evrard and others 2014) and its integration in complex (e.g., salience-related; Borsook and others 2013b) circuitry and interpretation of sensory inputs to the posterior insula and integration of autonomic control from the anterior insula. Interoception is likely important in migraine since a migraineur's physiological internal state is different in ictal and interictal states. The physiological state in episodic migraine is manifestly altered in the peri-ictal phase with major sensory and autonomic changes that presumably have effects on interoceptive processing changing "feelings, energy, and effort" and thus the subjective state of being (Craig 2013).

Sex. Compared with males, females have a higher incidence and prevalence of migraine (Silberstein and Lipton 1993; Stewart and others 1994b). Sex differences relate to both brain and behavioral changes. Recently, our group reported structural and functional sex differences in the insula in female versus male migraineurs (Maleki and others 2012b). Furthermore, another study by our group shows that the insular cortex does not show normal thinning with age (Maleki and others 2015). The latter is of interest since in other clinical disorders such as major depressive disorder (MDD), patients displayed decreased gray matter volumes in the left dorsal anterior insula (Liu and others 2014). Figure 3D shows sex differences of insula gray matter volume in male and female migraineurs.

Age. The prevalence of migraine decreases significantly after the age of 65 years in both males and females (Victor and others 2010). Between the ages of 12 and 30 years, the fiber density decreases between the insula and the frontal and parietal cortices but increases between the insula and the temporal cortex (Dennis and others 2014).

Functional implications also relate to insular connectivity in chronic pain states where brain structure and function shift from being adaptive in younger to being maladaptive in older patients (Ceko and others 2013). The insula changes reported in aging (Foundas and others 1998) result in functional alterations in pain processing (Tseng and others 2013).

Psychological Processes in Migraine

Migraineurs exhibit significant psychiatric comorbidities (Buse and others 2013; Sheftell and Atlas 2002). In addition, migraineurs have altered processing in psychological domains such as mood (Marino and others 2010), tiredness (Raggi and others 2012), and disgust and/or unpleasantness of environmental stimuli (Demarquay and others 2006). The insula has been defined as a "limbic integration cortex" and is putatively involved in emotion. Some of these are discussed in more detail below.

Anxiety. As noted in a recent review, the insula may be involved in anxiety regulation (Paulus and Stein 2006; 2010). Anxiety-prone subjects show increased activity in the anterior insula (Simmons and others 2011); additionally, this subgroup showed increased insula activation in response to the anticipation of aversive stimuli (Simmons and others 2006). In migraineurs, anticipation may contribute to enhancing anxiety-related circuits that include the insula and thus "drive" a more anxious phenotype to expect the onset of the next migraine attack. Interestingly, panic attacks have a high comorbidity with migraine (Smitherman and others 2013; Stewart and others 1994a). Physical exercise (e.g., yoga) may modulate the nociceptive/pain afferent input and potentially the emotional reactions, such as anxiety, to the insula resulting in a change in insular brain anatomy and connectivity (Villemure and others 2014). Related to anxiety is the phenomenon of panic attacks that are comorbid with migraine (Smitherman and others 2013; Stewart and others 1994a).

Stress and Safety Signals. Migraine is a stressor (Borsook and others 2012; Radat 2013). Measures of cortisol in migraine patients were found to be higher than control subjects at most times tested (Ziegler and others 1979). "Safety signals are learned cues that predict stress-free periods whereas behavioral control is the ability to modify a stressor by behavioral actions" and in this way diminish the effects of stressors (Christianson and others 2008; Christianson and others 2011). Part of this stress inducing safety response may be through autonomic regulation (Cechetto 2014). In tracing studies in rats, there is a convergence of autonomic and limbic function that may underlie the interaction of viscera-somatic inputs and behavioral processes (Saper 1982). Taken together, the insula may be intimately involved in migraine, possibly through (1) integration of safety signals (Christianson and others 2011), (2) autonomic function (Mosek and others 1999; Shechter and others 2002) (see above), and (3) translation of stress (Bossaerts 2010) into behavioral outcomes (Craig 2010). As part of the salience network (Borsook and others 2013b), the region may help determine the resilience to stressors (i.e., repeated migraine attacks).

Affect and Lateralization. Neuroimaging studies have shown lateralization of affective pain and other processes (Duerden and others 2013; Mutschler and others 2012). Right-sided somatosensory lateralization of insula activation is evident from a number of studies in pain (Brooks and others 2002; Symonds and others 2006). In a PET study of spontaneous migraine, right-sided activation in the insula was present (Afridi and others 2005a) (see Figure 3F). Right-sided lateralization has also been observed in cortical thickness in female migraineurs compared to male migraineurs (Maleki and others 2015). In comparison, patients with MDD, exhibit insular hypoactivity with reported homeostatic shifts, suggesting a deficit in the ability to have a normal response to changes in the environment (Strigo and others 2010). The undulating onset and offset of migraine attacks may show micro episodes that parallel the MDD group, suggesting that mood swings reported in migraine may manifest in altered right insula processing (Coen and others 2009).

Fatigue. Fatigue affects some 70% to 84 % of migraine patients; it may last for days after the attack and is the most frequent psychosocial difficulty in these patients (Raggi and others 2012). As reports of insular damage show, a putative basis for these changes may result from a functional disconnection with brain structures (e.g., frontal lobe, anterior cingulate cortex) involved with willed motor behavior (Manes and others 1999).

Odd Perceptions. Migraine attacks may be accompanied by sensory distortions, including visual distortions (Huang and others 2003), synesthesia (Alstadhaug and Benjaminsen 2010), room tilt (Lopez Dominguez and others 2007), and the "Alice in Wonderland syndrome" (Bayen and others 2012; Ilik and Ilik 2014). These changes may also include somatoparaphrenia (the sense of ownership toward our own body parts, that usually involve multiple brain lesions) (Gandola and others 2012), which may be associated with "altered physiological index of perceptual analysis" to pain (Romano and others 2014). It has been described in migraine patients that involve a diffuse number of structures (Moreira and others 2010). In an fMRI study, abnormal, bilateral decreased activity is reported in the anterior insula in depressed patients that correlates with abnormal body

perception (Wiebking and others 2010). In patients with left posterior insular lesions, autoscopic abnormalities (visual illusory reduplication of their own body in extrapersonal space) have been described (Heydrich and Blanke 2013). In this context, it may be worth noting a long-standing clinical observation that migraine is rather uncommon in patients with schizophrenia (Mehta and others 1980), while insula structure and function (Wylie and Tregellas 2010) and insula responses to pain (Linnman and others 2013) are diminished in patients with schizophrenia.

Empathy. A circuit for empathy has been defined that includes the anterior insula and anterior midcingulate cortex (Engen and Singer 2013; Singer and others 2009). Empathy for pain also includes the anterior insula (Singer and others 2004). Individuals with greater empathy were found to have more gray matter in the insula, which also coincided with greater functional activation within the insula region (Bernhardt and others 2014). Intriguingly, female episodic migraine patients exhibit more gray matter in the insula than male migraineurs (Maleki and others 2012b). While the exact functional implications are not known, it has been suggested that "hyperempathy" exists in migraine patients most of whom are female (Wendt 2010), which is thought to reflect altered interactions with the amygdala, where increased insular connectivity was observed in migraine patients (Hadjikhani and others 2013).

Cognitive Processes in Migraine

Prediction Error. Prediction error and migraine are reviewed elsewhere (Borsook and others 2013a). Error awareness is the detection of the conscious and subconscious processing to evaluate physiological signals that are different from a baseline or homeostatic level (Borsook and others 2013a; Ullsperger and others 2010). The insula is considered to serve as an important hub in error awareness in a number of neurological conditions (Klein and others 2013a).

Task Level Control. Because the insula is involved in integrating aspects of sensory-"ceptive" information with emotional and motor responses (through the anterior cingulate cortex) (Nelson and others 2010), the inability to orchestrate "task level control" or attentional control may be compromised. The changes may relate to processes previously reported as "saliency, switching, attention and control" (Menon and Uddin 2010), which may relate to the inability to exclude information in migraine (Ditchfield and others 2006; Koppen and others 2011; Shepherd and others 2012; Tibber and others 2014; Wagner and others 2013). In Figure 3F we show how altered insula function is implicated in task error through the consequential effects on the salience network (SN), a network implicated in attention and learning. In fact, errors result in activation of the SN, which is driven by the anterior right insula (Ham and others 2013).

Migraine Therapy: Targeting Insular Function

Several approaches have been successfully used in routine clinical practice for the treatment of migraine patients, including exercise, stress reduction, pharmacotherapy, placebo, and cognitive behavioral therapy. It is conceivable that these methods mediate their effects through the insula. Next we review evidence on how treatments can affect insular cortex structure and function. It should be noted that while the insula may show activation, it might not mean that the insula mediates treatment directly, but that it may be part of an overall brain response to treatment. Treatment approaches have recently been focusing on altered interoceptive dysfunctions in other conditions such as drug addiction (Paulus and others 2013). The use of fMRI can elucidate processes involved in functional and structural insula alterations. Figure 4 summarizes the effects on insula activation by a number of approaches used in the treatment of migraine (exercise, Fig. 4A; sleep hygiene, Fig. 4B; placebo response, Fig. 4C) as well as the effect of analgesic overuse as a result of treatment resulting in insula dysfunction (Fig. 4D).

Exercise

Exercise has been considered to help brain health through active modulation of plasticity (Cotman and Berchtold 2002), including alterations in brain-derived neurotrophic factor (BDNF) (Gomez-Pinilla and others 2008). Aerobic exercise increases cortical gray matter in the right anterior insula (Peters and others 2009) and inhibits gray matter loss (Gondoh and others 2009), even in aging population (Colcombe and others 2006). Studies have suggested that aerobic exercise improves long-term outcomes in migraineurs (Lockett and Campbell 1992). "Training the brain" may enhance connectivity within the insula and improve the individual's pain and emotional processing. Indeed, diminished pain may be observed with enhanced insular health (Starr and others 2009), though underlying processes are still not understood.

Hydration

The insula plays a role in interoception—a process of evaluating internal physiological states (see above). Similar to responses observed with migraine patients, dehydration also produces enhanced pain to a cold pressor

test with increased activation in brain regions including the insula. With healthy dehydrated subjects, on rehydration, these effects are diminished (Ogino and others 2014). In the clinical setting, maintenance of good hydration has long been considered helpful for migraine patients (Ostfeld and Wolff 1955). Given the importance of the structure in autonomic function, and in particular cardiac function, hydration may have a biological foundation in the interactions of interoceptive processes and migraine.

Diminishing Stress

Under stressful conditions there may be increased susceptibility to migraine. The sensory insular cortex is involved in mitigating the effects of stress (Christianson and others 2008) through safety signals (Christianson and others 2011). Treatments that target stress may in part contribute to enhanced processing that diminishes stress not only through cognitive processes but also through training of the insula to limit afferent stress inputs (including pain). Indeed, there is enhanced pain in patients who anticipate pain (in migraineurs because of potentially and temporally ill-defined onsets of severe headaches) because negative context may affect immediate and future pain (Phillips and others 2003; Quartana and others 2009). Stress may be a major contributor to allostatic load (McEwen and Gianaros 2011) that may elicit and/or worsen migraine (Borsook and others 2012). In fact, migraine also affects other well-known brain regions involved in the stress response. For example, decreased functional connectivity has been reported between the hippocampus and the bilateral anterior insula (Maleki and others 2013).

Sleep

Migraineurs, both chronic and episodic suffer from poor sleep hygiene (Kelman and Rains 2005; Sancisi and others 2010; Walters and others 2014). Figure 4B shows a reduction in activation of the right anterior insula in healthy subjects who have undergone sleep deprivation (Venkatraman and others 2011) further implicating the role of sleep in insula function, which may also have an effect on migraine attacks. Good sleep hygiene may therefore contribute to a balanced homeostatic and interoceptive state in migraine.

Pharmacotherapy

The main pharmacological treatment modalities for migraine include abortive (e.g., triptans) and preventive treatments (e.g., antiseizure, antidepressant and potentially botulinum toxin). Unpleasant feelings can be induced in migraineurs taking triptans (Kramer and others 2007). Triptans produce a decrease of posterior insular cortex activation compared with the saline condition (Kramer and others 2007). In a different fMRI study, following sumatriptan injection, increased activation was observed in the anterior insula and pain-related brain regions to brush stimuli, thus suggesting "sumatriptan could disinhibit nociceptive signaling and make light touch less pleasant" (Kramer and others 2007). In the context of allodynia in migraine, triptans may be able to diminish the intensity and aversiveness of normally innocuous stimuli (Burstein and others 2000). Unmyelinated tactile afferents that are present in hairy skin only project to posterior insular cortex and serve affective aspects of tactile sensation (Liljencrantz and others 2013). This may be of significance given the recent report that botulinum toxin inhibits mechanoreceptors by altering the neuronal surface expression of high-threshold mechanosensitive ion channels (Burstein and others 2014). There is increasing excitement about the potential introduction of calcitonin gene-related peptide (CGRP) antagonists for migraine. Although most of the focus is on peripheral mechanisms, there are reports in preclinical studies of CGRP immunoreactivity in the insular cortex of rats that increase in response to aversive taste (Peyron and others 2004). We are unaware of any imaging studies reporting insula changes as a result of specific antimigraine therapies, whether symptomatic (e.g., nonsteroidals), abortive (e.g., triptans), or preventive (e.g., antidepressants, antiseizure) in nature. However, reports of direct pharmacological effects on insula dysfunction have been noted for paracetamol caffeine aspirin (PCA) powders in chronic migraine patients (Di and others 2013), amitriptyline in patients with irritable bowel syndrome and rectal pain (Morgan and others 2005) and sumatriptan in healthy subjects (Kramer and others 2007; W. Yuan and others 2013). Given our current understanding of multiple facets of insula function, it remains unclear how targeting normalization of insula function may be a key process in future migraine treatments, including pharmacotherapy. An initial approach may be to define normalization of function and structure that has recently been defined for other pain conditions (Becerra and others 2014; Erpelding and others 2014; Rodriguez-Raecke and others 2009; Seminowicz and others 2011).

Placebo

Placebo can reduce expectations (Benedetti and others 2011), diminish pain (Colloca and others 2013), lessen disgust (Schienle and others 2014), and enhance treatments (Bingel and others 2011). The opposite effect, nocebo, may enhance adverse outcomes such as pain (Colloca and Benedetti 2007). Interestingly, two basic systems are involved—opioidergic (Petrovic and others 2002) and non-opioidergic mechanisms (Benedetti and Amanzio 1997). Placebo is a powerful process in migraine

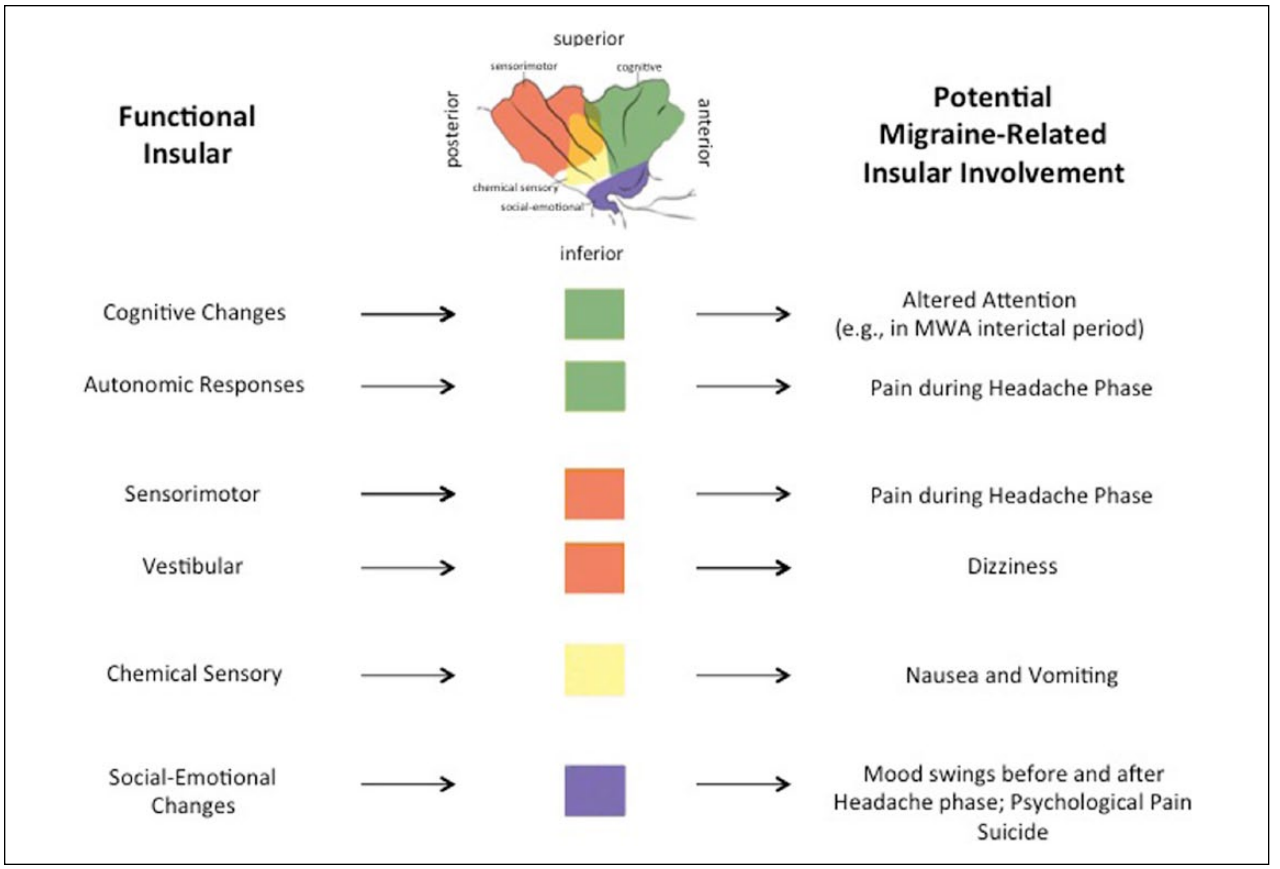

Figure 5. Summary of putative insular alterations in migraine. Many of the alterations in function in migraine involve insular processing of afferent and efferent information. The functional regions shown at the top of the figure are from Figure 1 (derived from (Klein and others 2013b), with permission).

(Kam-Hansen and others 2014). Accumulating data supports the notion that placebos may change the brain (Benedetti and others 2011). Moreover, the involvement of the insula in the placebo response has been repeatedly demonstrated in imaging studies (Hashmi and others 2012; Sarinopoulos and others 2006; Wager and others 2004). However, it is still unclear how best to harness the placebo effect in the clinic (Jubb and Bensing 2013). Migraine may be a perfect disease entity to embrace and use placebo in treatments. Figure 4D shows insula activation as a result of the placebo response. Few imaging studies have been performed evaluating the insula's role in placebo in migraine patients, but such studies should contribute to our understanding on insula function in placebo in migraine patients compared with healthy controls.

Cognitive Behavioral Therapy

Patients with migraine, and specifically chronic migraine headaches, often pose a challenge for practitioners. Especially in patients with a higher frequency of headaches, attention to psychological and behavioral issues become a more important part of the therapeutic approach (Weeks 2013). Cognitive behavioral therapy (CBT) may be an important and effective tool in the treatment of chronic pain and migraine, particularly when combined with pharmacological treatment. For example, a study in children and adolescents with chronic migraine showed that the use of CBT plus amitriptyline resulted in greater reductions in days with headache and migraine-related disability compared to headache education plus amitriptyline (Powers and others 2013). In anxiety, successful CBT resulted in an overall down regulation of initial abnormal hyperactivity in fear-related brain regions such as the insula, amygdala, and anterior cingulate cortex (Lipka and others 2014). Furthermore, CBT in patients with social anxiety disorder has been shown to reduce insular reactivity to fear-inducing stimuli over time (Klumpp and others 2013). In summary, there is evidence that CBT can modulate activity in the brain that may be successful in treating migraine. The insula response as measured by brain imaging may provide an objective measure of such interventions (Klumpp and others 2013).

Conclusions

The insula is involved in a wide range of functions. As such, it provides a cortical hub for the integration of extero- and interoceptive information inputs that can be transposed into higher level behavioral function—that is, it links "self-consciousness to the processing and integration of multisensory bodily signals" (Heydrich and Blanke 2013). Figure 5 summarizes the interactions of putative regional functions of the insula in these functional domains as proposed for normal insula function shown in Figure 1B (Klein and others 2013a). Accordingly, the insula constitutes an important brain region to study to further elucidate its role and plasticity in migraine and perhaps such an understanding may allow for measures for therapeutic modulation of those processes that are integrated by the insula in the migraine phenotype.

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