Uncovering the role of the insula in non-motor symptoms of Parkinson’s disease

Leigh Christopher,1,2,3 Yuko Koshimori,1,2,3 Anthony E. Lang,1 Marion Criaud2,3 and Antonio P. Strafella1,2,3

1 Morton and Gloria Shulman Movement Disorder Unit and E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, Ontario, Canada
2 Research Imaging Centre, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada
3 Research Institute, UHN, University of Toronto, Ontario, Canada

Correspondence to: Antonio P. Strafella, M.D. PhD FRCPC, Toronto Western Hospital and Institute, CAMH-Research Imaging Centre, University of Toronto, Toronto, ON, Canada, M5T 1R8
E-mail: antonio.strafella@uhnres.utoronto.ca or antonio.strafella@camhpet.ca

Patients with Parkinson’s disease experience a range of non-motor symptoms, including cognitive impairment, behavioural changes, somatosensory and autonomic disturbances. The insula, which was once thought to be primarily a limbic cortical structure, is now known to be highly involved in integrating somatosensory, autonomic and cognitive-affective information to guide behaviour. Thus, it acts as a central hub for processing relevant information related to the state of the body as well as cognitive and mood states. Despite these crucial functions, the insula has been largely overlooked as a potential key region in contributing to non-motor symptoms of Parkinson’s disease. The insula is affected in Parkinson’s disease by alpha-synuclein deposition, disruptions in normal neurotransmitter function, alterations in connectivity as well as metabolic and structural changes. Although research focusing on the role of the insula in Parkinson’s disease is scarce, there is evidence from neuroimaging studies linking the insula to cognitive decline, behavioural abnormalities and somatosensory disturbances. Here, we review imaging studies that provide insight into the potential role of the insula in Parkinson’s disease non-motor symptoms.

Keywords: Parkinson’s disease; neuroimaging; insula; cognition; behaviour

Introduction

The insula is a cortical region ‘hidden’ beneath the frontal, temporal and parietal lobes. Until recently its functional roles have remained largely unknown and often overlooked. The insula has long been considered part of the limbic cortical system (Mesulam and Mufson, 1982a), however, recent research suggests its involvement in a wide variety of functions. In fact, it seems that the insula may be a crucial brain region in humans, because of its role in processing subjective awareness, and integrating important homeostatic information from the body with higher level cognitive processes (Craig, 2009). In particular, the anterior division of the insula is expanded in humans compared to other closely related species, alluding to its role in higher-order awareness and social cognition (Bauernfeind et al., 2013). The insula is also thought to process visceral feelings or signals from the body, and these signals can assist in rapid decision-making processes involving risk, uncertainty or social interactions (Craig, 2002; Singer et al., 2009). This has also been described as the somatic marker hypothesis, which proposes that visceral and emotional information guide decisions...
in uncertain situations, rather than purely cognitive processes (Damasio, 1996). Recent research has suggested separate functional roles for the anterior and posterior insula in more cognitive/affective and viscero-sensory/somatosensory awareness, respectively (Chang et al., 2013).

How does the insula relate to Parkinson’s disease? Although once thought to be primarily a motor disorder, Parkinson’s disease is now well characterized by an array of non-motor symptoms. These non-motor symptoms range from behavioural and cognitive changes, to autonomic and sensory changes (Chaudhuri and Schapira, 2009; Park and Stacy, 2009). Cortico-striatal circuitry has been the primary anatomical focus of many of the symptoms of Parkinson’s disease. However, the insula is also highly interconnected with the basal ganglia (Chikama et al., 1997; Fudge et al., 2005), and many other cortical regions including the frontal, temporal, parietal, and cingulate cortices (Cauda et al., 2011; Nieuwenhuys, 2012). Thus, the insula is able to interact with multiple brain networks, and is multifaceted in its involvement in a wide range of cognitive, affective, sensory and autonomic processes. Studies investigating brain abnormalities in Parkinson’s disease underlying non-motor symptoms have focused on many of these brain regions, however, the insula is rarely a central focus despite its potential importance in contributing to these symptoms.

According to Braak’s staging hypothesis of Parkinson’s disease progression, alpha-synuclein is highly deposited throughout the insula by stage 5 (Braak et al., 2006) (Fig. 1). Thus, it would not be surprising, that alpha-synuclein could cause alteration in receptor function and thus synaptic activity in these neurons. This could in part, contribute to a number of non-motor symptoms experienced by patients with Parkinson’s disease. Additionally, the degeneration of neurotransmitter systems in Parkinson’s disease could affect the normal modulation of cortical activity in the insula. Degeneration of dopaminergic, cholinergic and serotonergic pathways projecting to the insula in patients with Parkinson’s disease (Halliday et al., 1990) could have drastic effects on the functional integrity of this region. The insula, like other cortical regions, relies on neuromodulation from these neurotransmitter systems for normal function. For example, levels of excitatory glutamate in the insula have been shown to correlate with the awareness of one’s own emotions (Ernst et al., 2013), demonstrating the relationship between levels of neurotransmitter release and function. Finally, this area may be susceptible to structural changes such as grey matter loss in more advanced disease stages, either due to direct involvement of alpha-synuclein pathology or secondary to loss of synaptic input.

Although Parkinson’s disease affects the whole brain, more special attention should be paid to the insula as a region underlying non-motor symptoms in Parkinson’s disease. Here, we will review the potential role of the insula as revealed by neuroimaging studies evaluating various non-motor symptoms of Parkinson’s disease. First, we will review insular involvement in cognitive impairment in Parkinson’s disease. This will lead to a discussion of the role of the insula in behavioural and affective symptoms of Parkinson’s disease, followed by a review of the contribution of the insula to somatosensory symptoms in Parkinson’s disease. Lastly, the potential role of the insula in autonomic dysfunction in Parkinson’s disease will be discussed.

A brief overview of insular anatomy

The insula is tucked beneath the frontal and temporal lobes bilaterally within the brain. The anatomical organization of the insula corresponds to its functional roles and can be divided into anterior and posterior divisions, separated by the central insular sulcus. It is highly interconnected with the basal ganglia in a connectivity gradient from posterior to anterior, with posterior insula projecting to the dorsal/posterior striatum, and anterior insula progressively towards anterior and ventral regions of the striatum (Fig. 2). This organization is highly consistent with the functional roles of both dorsal/posterior insula and striatum in sensorimotor processes, and anterior/ventral regions in cognitive and affective processing (Chikama et al., 1997; Flynn et al., 1999). The insula is also divided into posterior granular and anterior agranular sections with a large transitional dysgranular mid-section (Fig. 3). The posterior division receives convergent spinal, humoral and vagal nerve...
projections carrying visceral and interoceptive information. The connections in the posterior insula to posterior and dorsal basal ganglia, as well as the thalamus support its role in sensorimotor processing. The anterior agranular insula is highly interconnected with a number of cortical regions involved in cognition, decision-making and emotion. It has bidirectional interconnections with the orbitofrontal cortex, amygdala, hippocampus, dorsolateral prefrontal cortex and anterior cingulate cortex (Mesulam and Mufson, 1982a, b; Flynn et al., 1999).

Cognition and the insula in Parkinson’s disease

Accumulating research suggests that the anterior insula plays a central role in directing cognitive processes. It has been shown, often in conjunction with the anterior cingulate cortex, to allow for switching between brain networks required for executive functioning (Seeley et al., 2007; Menon and Uddin, 2010). Additionally, the anterior
insula is highly involved in complex social interactions that require interoception, self-awareness and the incorporation of both emotional and environmental stimuli (Craig, 2009) (Fig. 4). Patients with Parkinson’s disease experience a wide range of cognitive difficulties that may progress to full-blown dementia (Litvan et al., 2012). Cortical regions including the dorsolateral prefrontal cortex, anterior cingulate cortex and ventrolateral prefrontal cortex show abnormal activation in patients with Parkinson’s disease related to executive functioning, and thus are of interest in potentially underlying cognitive changes (Monchi et al., 2004, 2007). In patients with Parkinson’s disease, the insula has been found to have abnormal activation patterns during cognitive tasks (Monchi et al., 2004; Shine et al., 2013), and its dorso-anterior portion is functionally connected with the anterior cingulate cortex and dorsolateral prefrontal cortex, which are consistently involved in cognitive processes (Chang et al., 2013). Few studies have set out to investigate the insula, and its role has not been discussed in the context of contributing to cognitive decline in Parkinson’s disease. Thus, abnormalities in the insula are likely under-reported. It has recently been shown that those patients with mild cognitive impairment also have

Figure 3 Illustration of various classifications of insular subdivisions. (A and C) Cytoarchitectonic maps of the insula; (B) the connectivity gradient in the insula. (D–F) Different functional subdivisions of the insula. The anterior subdivision is involved in cognition, affective and chemosensory processing, whereas the posterior division is involved in somatosensory and autonomic processing. Image from Klein et al. (2013).
deficits in social cognition, whereas those without cognitive impairment, do not (Anderson et al., 2013). Due to the close proximity in anatomical location of cognitive and socio-emotional regions in the anterior insula, it is reasonable that pathological processes affecting the anterior insula could disrupt both cognitive and social function. Now that the cognitive role of the insula is becoming more prevalent in the literature, it will be important to investigate its role in Parkinson’s disease and how its dysfunction could lead to disruptions in cognition and eventually dementia.

The anterior cingulate cortex and insula are functionally and structurally connected, and have recently been described as part of a ‘salience network,’ due to their consistent activation during cognitively demanding tasks, and the ability of this network to switch between brain networks involved in cognition, including the central executive and default-mode networks (Seeley et al., 2007) (Fig. 5). Thus, it is crucial to consider the role of the insula as part of a network interacting with other brain regions. The strong connectivity of these regions in humans is reflected by the presence of unique von Economo neurons, which are large bipolar neurons interconnecting the anterior cingulate cortex and anterior insula in humans and chimpanzees, thought to rapidly transmit information related to cognition and awareness (Allman et al., 2010). Patients with Parkinson’s disease with cognitive deficits not meeting criteria for dementia, are described as having Parkinson’s disease with mild cognitive impairment and are at an increased risk for developing dementia (Caviness et al., 2007). A recent study conducted by our group investigating dopaminergic contributions to Parkinson’s disease with mild cognitive impairment using PET imaging (Christopher et al., 2013), found that these patients have more severe striatal dopamine depletion than both healthy control subjects and cognitively normal patients with Parkinson’s disease. The level of dopamine depletion was correlated with loss of D2 receptor availability in the right anterior insula. Patients with Parkinson’s disease with mild cognitive impairment also showed reduced D2 receptor availability in the bilateral insula compared to healthy controls and cognitively normal patients. Furthermore, the D2 receptor availability in the right anterior insula was directly proportional to executive performance in a neuropsychological test battery (Fig. 6). These findings demonstrate that striatal dopamine depletion, which is a hallmark of Parkinson’s disease, is associated with a loss of dopaminergic modulation in the insula in Parkinson’s disease with mild cognitive impairment, and in turn that insular dopamine modulation is directly related to executive abilities. We concluded that both striatal and insular dopamine dysfunction underlie executive impairment, and that such a loss likely disrupts normal function of the insula as a cognitive hub, and as a key region of the salience network in patients with Parkinson’s disease and mild cognitive impairment.

A recent study investigating potential mechanisms underlying visual misperceptions in Parkinson’s disease found that the inability to activate the anterior insula was related to impaired viewing of bistable images (Shine et al., 2013). The authors concluded that dysfunctional attentional networks involving the insula could

Figure 4 Image adapted from Chang et al. (2013) demonstrating terms most strongly associated with activation in various insular subdivisions (strength of association represented by size and opacity of the word). The dorsal anterior (blue) and ventral anterior (red) insula are most strongly associated with cognitive flexibility and emotion, respectively, whereas the posterior division is involved in pain and somatosensation.
underlie visual misperceptions or hallucinations, which are common problems in Parkinson’s disease, especially but not exclusively related to antiparkinsonian medications. The insula is also highly involved in social behaviour, and thus it seems appropriate that it possesses both cognitive and emotional processing abilities. For example, it is involved in emotional processes such as disgust, which may emanate from social encounters. One study investigating the ability of patients with Parkinson’s disease to recognize facial emotions, found that patients had an impaired ability to recognize disgust on the faces of others (Suzuki et al., 2006). The authors claimed that dysfunction of the insula is a likely reason for this impairment based on previous findings demonstrating that insular lesions do in fact impair the recognition of facial emotions (Calder et al., 2000). This is also in agreement with evidence for dysfunction of the anterior insula in disorders such as autism and schizophrenia, where the ability to perceive and relate to the emotions of others is significantly impaired (Uddin and Menon, 2009; White et al., 2010).

The mid-to-dorsal anterior insula is normally highly functionally connected to the pre-supplementary motor area in healthy people (Chang et al., 2013), which is a brain region crucial for integrating information for the preparation of movements. Thus, relevant information obtained from cognitive processes is made available for selecting actions. The right mid-anterior insula has reduced functional connectivity to the pre-supplementary motor area in patients with Parkinson’s disease compared with healthy controls (Wu et al., 2011). Although this region is involved in motor control, such a loss of connectivity could impact the effective incorporation of higher order cognitive information into the selection of behaviours. Resting state functional connectivity analysis of the anterior insula shows high connectivity with the inferior temporal and anterior cingulate cortex (Cauda et al., 2011), which are also crucial regions for cognitive function. Interestingly, these are some of the first and most affected cortical regions by alpha-synuclein deposition according to Braak’s staging hypothesis (Braak et al., 2006). The insula is not only one of the first cortical regions to be pathologically affected in Parkinson’s disease, but also in other neurodegenerative diseases, including Alzheimer’s disease and frontotemporal dementia (Chu et al., 1997; Braak et al., 2006; Seeley, 2010). In non-parkinsonian patients with amnestic mild cognitive impairment, it was shown that anterior insular connectivity to brain regions, including the inferior frontal gyrus, pre-supplementary motor area, anterior cingulate cortex, inferior parietal cortex, caudate, putamen, thalamus, and hippocampus, was significantly reduced compared to healthy control levels (Xie et al., 2012). Thus cognitive function, including memory, may be reliant on intact functional brain networks including the insula. A more severe loss of insular function may have a profound effect on self-awareness and thus appropriate

Figure 5 Image from Seeley et al. (2007) demonstrating co-activation of the anterior insular cortex and anterior cingulate cortex as part of a salience network. AI, anterior insula; antTHAL, anterior thalamus; dCN, dorsal caudate nucleus; dmTHAL, dorsomedial thalamus; DMPFC, dorsomedial prefrontal cortex; HT, hypothalamus; PAG, periaqueductal gray; Put, putamen; SLEA, sublenticular extended amygdala; SN/VTA, substantia nigra/ventral tegmental area; TP, temporal pole; VLPFC, ventrolateral prefrontal cortex.
behaviour, which is often severely impaired in neurodegenerative
disease. Although not specifically investigated in Parkinson’s disease,
patients with frontotemporal dementia have a loss of von Economo
neurons; the large bipolar neurons interconnecting the anterior
cingulate cortex and insula in humans (Seeley et al., 2006). Pathological
changes in the insula affecting these neurons may have an impact on self-awareness and cognitive function in
Parkinson’s disease. Further investigation into insular pathology
and its impact on cognition in Parkinson’s disease is clearly needed.

The insula and affective and behavioural symptoms

The insula was originally thought of as a limbic cortical structure,
and has a well-established role in processing affect and emotion.
The ventro-anterior portion of the insula is functionally connected
to limbic areas including the amygdala, superior temporal sulcus,
postero-lateral orbitofrontal cortex and the ventral tegmental area
(Chang et al., 2013). It also becomes engaged in situations involving
the evaluation of risk and uncertainty (Paulus et al., 2003;
Rudorf et al., 2012). The insula has been reportedly involved in
contributing to depression, and insular activity may aid in predict-
ing outcomes of depression treatment (Sprengelmeyer et al.,
2011; McGrath et al., 2013). Patients with Parkinson’s disease
experience a wide range of non-motor behavioural symptoms
such as depression, anxiety and fatigue, which could in part be
related to dysfunction of the insular cortex. In a PET imaging study
investigating depression in patients with Parkinson’s disease, it was
found that serotonin 1A receptor availability was reduced in
depressed patients with Parkinson’s disease in the right insula
compared to non-depressed patients with Parkinson’s disease
(Ballanger et al., 2012). Receptor availability was also reduced in
the left hippocampus, left superior temporal cortex and orbitofron-
tal cortex compared with non-depressed patients with Parkinson’s
disease. These changes in depressed patients with Parkinson’s dis-
ease could potentially contribute to limbic dysfunction. Although
not well explored in Parkinson’s disease, the insula is known to be
interconnected with the amygdala, and the level of connectivity is
directly related to trait anxiety (Baur et al., 2013). The amygdala is
also a limbic region highly affected by alpha-synuclein deposition
in Parkinson’s disease (Braak et al., 1994). Thus, the symptoms of
anxiety frequently seen in patients with Parkinson’s disease could
be related to dysfunction of this amygdala-insula pathway. More
research investigating the neural correlates of anxiety in
Parkinson’s disease is needed to determine key brain regions asso-
ciated with this psychiatric symptom.

Central fatigue, another common non-motor symptom in
Parkinson’s disease, affects patients’ ability to sustain mental and
physical tasks. Fatigue is difficult to study in patients with
Parkinson’s disease as its symptoms can overlap with psychiatric
disturbances such as depression (Friedman et al., 2007). However,
it is clear that fatigue occurs in patients with no evidence of psy-
chiatric illness as well. Additionally, mental fatigue, which is char-
acterized by deficits in sustaining attention and vigilance, may be
associated with cognitive impairment (Friedman et al., 2007).
A PET imaging study investigating serotonergic and dopaminergic
function in relation to fatigue in Parkinson’s disease found that
serotonin transporter availability was reduced in the insula (left
and right, whole insula), anterior cingulate cortex, striatum and
thalamus in patients with fatigue (Pavese et al., 2010). The au-
thors also reported reduced ¹⁸F-DOPA uptake in the left caudate
and insula (mid-posterior) of patients with Parkinson’s disease with
fatigue versus those without fatigue. They concluded that insular

Figure 6 Image from Christopher et al. (2013) showing a direct linear relationship between D2 receptor availability and executive
performance in the right anterior insula of patients with Parkinson’s disease with mild cognitive impairment.
dopaminergic and serotonergic dysfunction could contribute to symptoms of fatigue in Parkinson’s disease.

The anterior insula is a key region involved in the experience of empathy. This can be considered an affective function, however ‘perspective-taking’ must also be involved which may require cognitive functions such as attention, working memory and cognitive flexibility in social situations (Leigh et al., 2013). It is well known that patients with Parkinson’s disease have an apathetic disposition, characterized by a dulled sense of emotion, which can have a significant impact on daily life (Pluck and Brown, 2002). In a recent study examining the metabolic basis of apathy in nondemented and non-depressed patients with Parkinson’s disease, it was found that cerebral metabolism measured with PET in the right anterior insula as well as right inferior frontal gyrus, right middle frontal gyrus, and right cuneus, was positively correlated with apathy scores (Robert et al., 2012). A loss of normal metabolic activity in insular neurons in Parkinson’s disease could contribute to the blunting of emotion frequently observed in patients with Parkinson’s disease. High apathy scores have also been shown to correlate with lower grey matter density in the bilateral insula of patients with Parkinson’s disease, as well as the bilateral inferior parietal gyrus, the bilateral inferior frontal gyrus, the right (posterior) cingulate gyrus and the right precuneus (Reijnders et al., 2010). Considering the insula as a central hub for emotional awareness, it is likely that dysfunction of this region would be associated with a lack of motivation in patients with Parkinson’s disease. This is in agreement with studies showing that damage or atrophy in the insula can result in apathy, blunted emotional responses during risky decision-making (Case et al., 2009; Weller et al., 2009), or the finding that patients with Parkinson’s disease have a reduced ability to recognize facial emotions of others (Suzuki et al., 2006).

In addition to experiencing depression or apathy, anywhere from 6–15.5% of patients with Parkinson’s disease develop impulse control disorders and related compulsive disorders such as hobbyism, punding and dopamine dysregulation syndrome, which are typically due to dopaminergic medication (Callesen et al., 2013). Impulse control disorders in Parkinson’s disease have been suggested to be attributable to altered activity of the mesocorticolimbic dopamine system (Steeves et al., 2009; van Eimeren et al., 2009; Ray et al., 2012). In a PET imaging study using a high affinity D2 receptor antagonist radioligand to measure cortical D2 receptor availability, it was found that novelty seeking, a trait associated with impulsive behaviour, was negatively correlated with D2 receptor availability in the insula (Kaasinen et al., 2004). Thus, baseline dopaminergic modulation in the insula may affect the propensity of patients with Parkinson’s disease to behave impulsively in response to medication. In another study investigating impulsivity, patients with Parkinson’s disease with pathological gambling showed significant negative correlations between gambling severity and regional cerebral blood flow in prefrontal, limbic, temporal, and striatal regions as well as the bilateral anterior insular cortices (Cilia et al., 2011). Although a major finding of this study was disconnection of the striatum from the anterior cingulate cortex in Parkinson’s disease gamblers, patients with Parkinson’s disease both with and without pathological gambling also showed a diminished connectivity of the insula to the posterior cingulate gyrus and parahippocampal gyrus, respectively, compared with healthy controls (Cilia et al., 2011). Thus, diminished connectivity in the insula with other key regions involved in evaluating risk and executing behaviours could affect impulse control in Parkinson’s disease. As previously mentioned, patients with Parkinson’s disease often show a blunted emotional response. Consistent with this, is the observation that patients with Parkinson’s disease have increased levels of alexithymia, a condition characterized by difficulty expressing emotions, compared with healthy control subjects (Costa et al., 2010). Interestingly, alexithymia in Parkinson’s disease was recently found to significantly correlate with self-reported impulse control disorders, and patients with alexithymia had significantly higher levels of impulse control disorders than non-alexithymic patients (Goerlich-Dobre et al., 2014). Thus, dysfunction in the insula affecting emotional processing may also increase the likelihood of problems with impulse control in Parkinson’s disease. The normal role of the insula in processing mood states and impulsive behaviours in healthy individuals is not well understood, and therefore more research is needed to better disentangle the role of the insula in affective processes.

**Posterior insula and disruptions in bodily awareness**

Experimental studies in non-human primates have shown that the insular cortex receives afferents from the dorsal thalamus, which processes information from the brainstem and spinal cord (Mufson and Mesulam, 1984; Mesulam and Mufson, 1985). This information is related to conscious awareness of head motion, balance, perception, pain, temperature, gustatory and visceral sensory information. The insula receives afferents from several sensory cortical areas, including somatosensory cortex, somatosensory association areas, primary vestibular areas and auditory association areas (Nieuwenhuys, 2012). The mid to posterior insula has been frequently implicated in the processing of awareness with relation to the position, movement and sensation of the body, and is functionally connected to the supplementary motor area and somatosensory cortex (Chang et al., 2013). This interoceptive information of how the body ‘feels’ is constantly incorporated into cognitive, social and emotional processes in order to execute behaviour (Craig, 2002). Thus, awareness of bodily sensations and cognitive functions are not distinct, but rather are integrated into behaviour through the insula. For example, the posterior insula is thought to play an integral role in distinguishing one’s own body from the bodies of others (Heydrich and Blanke, 2013).

Patients with Parkinson’s disease often experience disturbances in sensory perceptions of the body (Koller, 1984). One crucial function of the posterior insula related to bodily sensation is its involvement in the processing of pain. Awareness of pain is critical, as it allows for rapid action in response to threatening situations. In a study examining pain thresholds in patients with Parkinson’s disease with H2O PET, it was found that patients with Parkinson’s disease OFF medication experience lower pain thresholds,
associated with increased activation in the right insular cortex, as well as prefrontal cortex and anterior cingulate cortex (Brefel-Courbon et al., 2005). However, when ON L-DOPA medication this activation was within the normal range. This established that in patients with Parkinson’s disease, dopamine has a modulating effect on insular activation in response to pain. This may hold true not only for painful stimuli, but the processing of other sensory stimuli that have an impact on behaviour. Additionally, the anterior insula may use contextual information combined with somatosensory information from the posterior insula, producing a subjective experience or perception of events. For example, one study examining how the insula is involved in pain perception, found that anterior insular activity correlated with the significance of a stimulus (i.e. highly threatening versus low threat), and that this was related to the subject’s perception of how painful the stimulus was (Wiech et al., 2010). Abnormal salience processing in the anterior insula could also affect how sensations are perceived in patients with Parkinson’s disease.

Patients with Parkinson’s disease have considerable difficulty in executing coordinated movement. They also have reduced performance on tests of kinaesthesia, which is the ability to perceive the motion and position of the body in space (Jobst et al., 1997). The mid and posterior insula are essential for awareness of bodily movements and thus for coordinated motion. For example, the mid-insula becomes activated during the experience of agency or control over one’s actions (Farrer and Frith, 2002). Patients with Parkinson’s disease show increased gait-induced activation in the right posterior insula (as well as left cingulate and temporal cortices) when walking on a treadmill compared to healthy control subjects (Hanakawa et al., 1999). This increased activation could be due to dysfunctional regulation of cortical activity, or the result of compensatory activation. Activation in the insula associated with bodily awareness may be necessary for coordinating movements effectively. The insula is also thought to be involved in the perception of time, and timing of movements. Patients with Parkinson’s disease’s required to synchronize movements show increased activation in the right insula among other regions compared with healthy control subjects (Cerasa et al., 2006). This increased activation could be related to the greater difficulty they experience in effectively timing synchronized movement, or compensatory activation. Thus, mid and posterior insular cortex serve a crucial role in interoceptive sensation and behaviour, and should be further considered in understanding the complex neurobehavioural disturbances of Parkinson’s disease.

The insula and autonomic dysfunction

In particular, the posterior part of the insula processes visceral and autonomic information. As mentioned previously, this autonomic information from the body is incorporated into cognitive, social and emotional processes, to aid in effective decision-making and behaviour (Beissner et al., 2013). For example, patients with peripheral autonomic denervation have reduced insula activity related to fear conditioning (Critchley et al., 2002). This demonstrates how the insula integrates autonomic information relevant to the current state of the body with environmental cues to guide behaviour. Such autonomic input is crucial for preparation to act in various situations whether they are threatening, challenging or emotionally salient. Thus, the seemingly disparate functions of the insula can be unified into a framework that describes its overall purpose as integration of cognitive, affective and interoceptive information in uncertain conditions to create a state of subjective awareness (Fig. 7). Autonomic functions have been shown to directly relate to emotional states and subjective experience. The constriction of the gut in response to stress or the increase in heart rate when anxious, among other bodily states of arousal, are examples of how autonomic changes in the body directly relate to emotional states, and how these enter conscious awareness (Critchley, 2005). These ‘somatic markers’ as proposed by Damasio and colleagues (1996), are thought to act as ‘gut feelings’ that guide adaptive behaviour. The loss of awareness, or dampening of these feelings that enter subjective awareness could negatively affect behaviour in neurodegenerative disease, such as Parkinson’s disease (Fig. 7). However, there is little evidence from neuroimaging studies of dysfunctional autonomic processing at the cortical level in patients with Parkinson’s disease.

In Parkinson’s disease, the autonomic nervous system is severely affected by Lewy pathology throughout the sympathetic ganglia and parasympathetic nuclei (Wakabayashi and Takahashi, 1997). Pathological changes in the insula could also play a role in autonomic dysfunction, or ‘dysautonomia’ in Parkinson’s disease (Siddiqui et al., 2002). Dysautonomia in Parkinson’s disease can
include bladder disturbances, sweating abnormalities, and orthostatic hypotension. Autonomic dysfunction is typically associated with advanced stages of the disease, although it may also occur in the early disease stages (Bonnet et al., 2012), and has a significant impact on daily life (Magerkurth et al., 2005). The insula is known to be involved in autonomic arousal, including cardiovascular arousal. For example, insula (right in particular) activation correlates with mean arterial blood pressure and heart rate during mental stressor tasks or exercise (Critchley et al., 2000). A post-mortem study in Parkinson’s disease showed that Lewy body densities in the left posterior insular cortex were significantly higher in patients with Parkinson’s disease with orthostatic hypotension than those without orthostatic hypotension. This group difference was not observable in other cortical areas such as the temporal or parietal cortex (Papapetropoulos and Mash, 2007). However, the pathogenesis of orthostatic hypotension is also associated with degeneration of the peripheral autonomic nervous system (Jain and Goldstein, 2012), which may even precede the classical motor symptoms of Parkinson’s disease (Goldstein et al., 2012).

Studies investigating the neural correlates of autonomic dysfunction in Parkinson’s disease are scarce, and thus there is little evidence at the moment for a clear link between dysautonomia and aberrant insula function in Parkinson’s disease. More research is needed to determine the potential contribution of the insula to autonomic symptoms in Parkinson’s disease.

The somatosensory regions for processing olfaction and taste reside in the ventro-anterior insula adjacent to somatosenсорy and viscerosensory cortex from other areas of the body (De Araujo et al., 2003; Ogawa et al., 2005). Although there is little neuroimaging evidence of insular involvement in olfaction or gustation in Parkinson’s disease, it should be noted that a loss of smell and taste, in particular the loss of smell is one of the first and even symptomatic signs of Parkinson’s disease (Doty et al., 1992). This is likely due to the olfactory blub being affected by alpha-synuclein deposition early in the disease process (Hawkes et al., 1997); however, the loss of input to the olfactory and gustatory areas in the insula may also propagate these symptoms and affect chemosensory function in Parkinson’s disease. More work will be needed to elucidate the role of the insular cortex in association with chemosensation in patients with Parkinson’s disease.

Conclusions and future directions

The insula has been under-recognized as a key region involved in the pathogenesis of non-motor symptoms in Parkinson’s disease. There is accumulating evidence that the insula plays a crucial role in cognitive, affective, somatosensory and autonomic processes, and thus abnormalities in the insula found in neuroimaging studies of patients with Parkinson’s disease should be considered and explored in greater detail. The insula is substantially affected by alpha-synuclein deposition in Parkinson’s disease, and shows altered functional connectivity as well as abnormalities in dopaminergic and serotonergic function related to cognitive and affective symptoms. There is evidence that abnormal insular activity may be related to a range of non-motor symptoms, including somatosensory disturbances. Now that the insula is known to be a central hub involved in integrating diverse information for behavioural processes, it should be considered as a region of interest when investigating cognitive and behavioural changes, as well as disruptions in viscerosensory or somatosensory processes in Parkinson’s disease.

Funding

This work was supported by Canadian Institutes of Health Research (MOP 110962). A.P.S. is supported by the Canada Research Chair program. Leigh Christopher is supported by a scholarship from Parkinson’s Society Canada.

References


White TP, Joseph V, Francis ST, Liddle PF. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. Schizophr Res 2010; 123: 105–15.

