Chapter 11
Brain Processing of CT-Targeted Stimulation

Malin Björnsdotter

Abstract CT afferents, together with other types of unmyelinated and thinly myelinated afferents, likely project via the spinothalamic tract to a specific posterior/basal ventral medial nucleus of the thalamus in primates. Functional imaging studies in patients with selective denervation of unmyelinated or myelinated afferents and in healthy subjects suggest that CT-targeted stimulation activates the insular cortex in the hemisphere contralateral to stimulation. This area shows a somatotopical response to CT stimulation, supporting the idea that it is a primary cortical target for CT afferent projections. This chapter reviews findings related to the insular cortex.

Keywords fMRI • MRI • Brain • Insular cortex

The poetic name of the insular cortex (*insula* means island in Latin) stems from its isolated position deep within the Sylvian fissure of the brain, snugly tucked in under the lid formed by the operculum (Fig. 11.1).

As a whole, the insular cortex is associated with an astonishing array of functions, ranging from basic processing of sensory and visceral information (Augustine 1985) to complex processing of emotion and self-awareness (Craig 2009, 2011). The insula is a cytoarchitectural heterogeneous area, however, and it can be divided into distinct regions within the ventrodorsal plane: the granular region in the posterior part to a granular area in the anterior part. The posterior, granular insula (Ig) is the putative primary target for the system of thin afferent fibers—including CT fibers—which project information related to the physiological condition of the body (Craig 2002). This region can be further divided into three distinct cytoarchitectural regions: one dysgranular (Id1), and two granular regions (Ig1 and Ig2) (Fig. 11.2) (Kurth et al. 2010).

The notion that the Ig region receives primary input from thin afferents is supported by a growing body of literature on pain and temperature sensations. Studies

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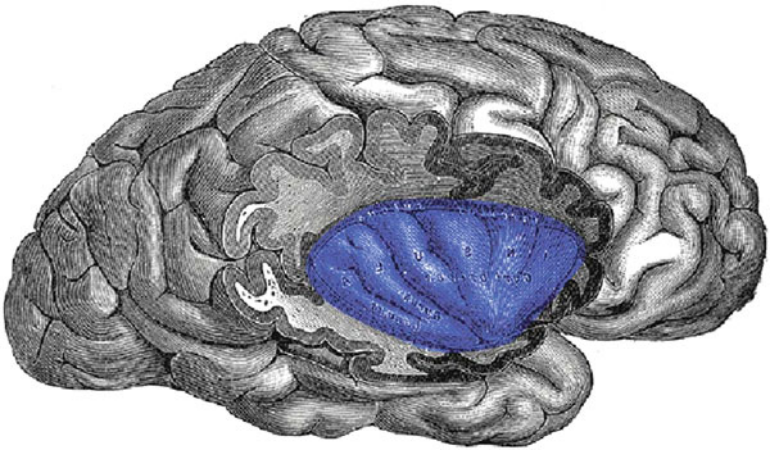

Fig. 11.1 The insular cortex of the human brain, highlighted in *blue*. Adapted from Gray's Anatomy of the Human Body, 1918

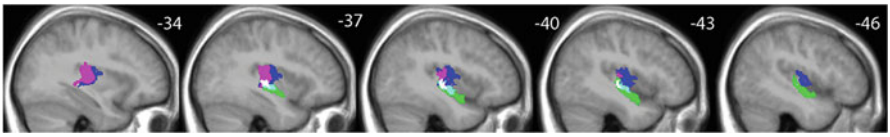

Fig. 11.2 Right hemisphere probabilistic representation of the granular posterior portion of the insular cortex; Id1 (*green*), Ig1 (*violet*), and Ig2 (*blue*). Overlap is indicated in *white* and *turquoise* (Kurth et al. 2010)

in awake humans have found that electrical stimulation of the posterior portion of the insula elicits sensations of temperature changes (warmth and cooling) and pain, mainly on the contralateral side of the body to the stimulated hemisphere (Ostrowsky et al. 2000, 2002; Penfield and Faulk 1955; Stephani et al. 2011). Corroborating the electrophysiological findings, neuroimaging studies have shown that painful stimuli and temperature changes activate the insular cortex in humans (Apkarian et al. 2005; Craig et al. 2000). Interestingly, electrical stimulation in the posterior insular cortex also elicited sensations of less well-defined, innocuous sensations, described as "tickling" (Ostrowsky et al. 2002; Penfield and Faulk 1955). These responses were attributed to the proximity of the insular cortex to the secondary somatosensory cortex (Penfield and Faulk 1955) and the reciprocal connections between posterior insular and somatosensory areas (Stephani et al. 2011). An alternative explanation, however, is that these sensations reflect primary processing of tactile information mediated through CT fibers.

Central projections of CT afferents are notoriously difficult to study since the CT preferred stimuli—slow, soft, and caress-like strokes—also vigorously co-activate thick, myelinated Aβ afferents which activate multiple brain regions (most notably the primary and secondary somatosensory cortices). How can the brain projections

Table 11.1 Somatosensory and insular brain activations during CT-targeted stimuli in neuronopathy patients GL (left forearm) and IW (right forearm) (Olausson et al. 2008)

Region		Patient GL	Patient IW
S1 (arm area)		n.s.	n.s.
S2		n.s.	n.s.
Insula, contralateral	Posterior	5.0 (−38, −14, 8)	4.3 (44, −12, 6)
			3.9 (40, −18, 6)
	Mid/anterior	3.6 (−46, 6, 0)	n.s.
		4.2 (−36, 12, −2)	
		3.9 (−34, 16, 6)	
Insula, ipislateral		4.6 (44, 8, 12)	3.8 (−40, −4, −10)

The table indicates peak *T*-values and associated coordinates in the MNI atlas. *n.s.* nonsignificant

of CT and Aβ input be dissociated? The first answer to this question came in the form of a landmark study by Olausson and colleagues (Olausson et al. 2002). During his research work at McGill University, Olausson came across a unique patient: GL. At the age of 31, GL suffered permanent specific loss of large-diameter myelinated afferents—including Aβ fibers—below the level of the nose. Her unmyelinated and small-diameter myelinated afferents—including CT fibers—were intact, however (Forget and Lamarre 1995). As a consequence, she can readily feel pain and temperature changes but not touch (Olausson et al. 2002, 2008). GL provided a unique opportunity to selectively study the behavioral and brain correlates of CT afferents, unshadowed by Aβ fiber input. Olausson and colleagues examined GL's brain responses to CT stimuli using a combination of psychophysics and functional magnetic resonance imaging (fMRI). During scanning, GL was gently stroked on the left forearm with a soft brush. Analyzing GL's brain responses to stroking, Olausson found that the somatosensory cortices were not activated (Table 11.1). In stark contrast, the same stimuli vigorously activated both the primary and the secondary somatosensory cortices in healthy control volunteers.

Instead, the patient's insular cortex was activated (Fig. 11.3). Similar activations in the insular cortex were found in healthy control volunteers, suggesting that GL's brain responses to CT stimuli were not a specific result of the neuronopathy. Olausson later replicated the findings in a second, similarly deafferented subject (IW), who was stroked on the right forearm (Olausson et al. 2008). Also in IW, the insular, but not somatosensory, cortices were activated (Fig. 11.3, Table 11.1).

The lack of activations in primary and secondary somatosensory cortices suggests that posterior insular processing of touch sensations occurs independently of Aβ afferents, which, in turn, casts doubt on the theory that insular activations are a consequence of connections to somatosensory cortices. Particularly consistent brain activations, across both patients and healthy control volunteers, were found in the posterior Ig2 region of the insular cortex in the hemisphere contralateral to the stimulated limb (Figs. 11.3 and 11.5a, Table 11.1). This finding suggests that the putative primary representation of bodily sensations in the posterior insula also includes CT-mediated information, similar to nociception and thermoception. Moreover, the CT

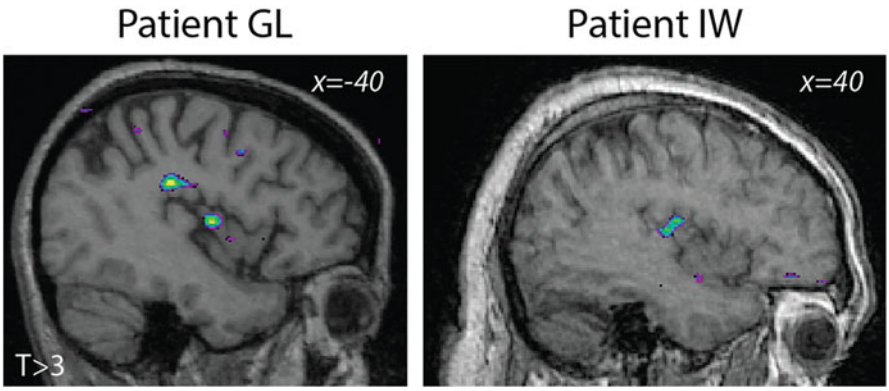

Fig. 11.3 Contralateral insular activations during CT-targeted stimuli in neuronopathy patients GL (*left forearm*) and IW (*right forearm*). Data from (Olausson et al. 2002, 2008)

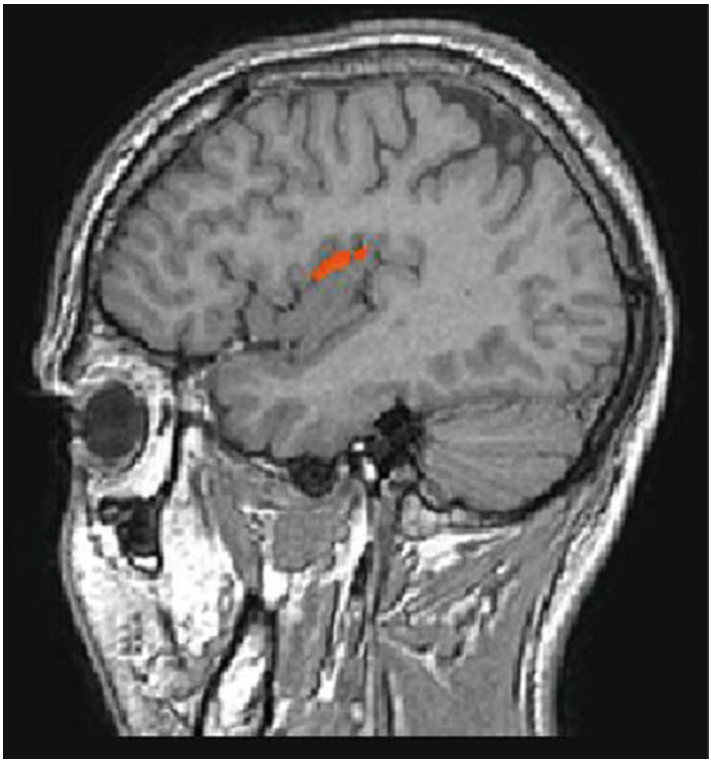

Fig. 11.4 Insular activations to CT-targeted stroking (velocity 3 cm/s) compared to Aβ-targeted stroking (30 cm/s) in the posterior insular cortex contralateral to the stimulated limb. Data from Morrison et al. (2011a)

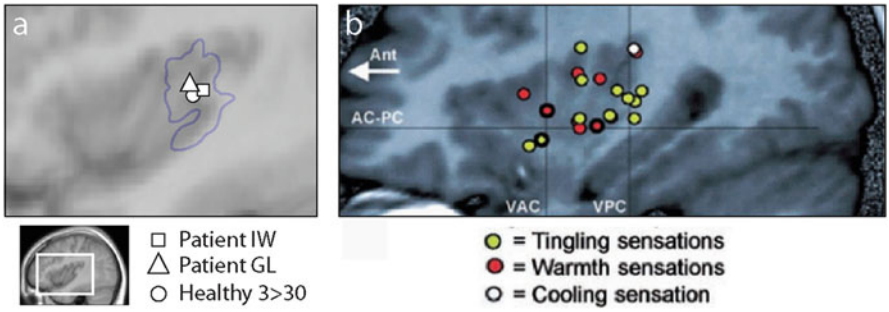

Fig. 11.5 (**a**) Loci of insular responses to CT-targeted stimuli in neuronopathy patients GL (*triangle*) (Olausson et al. 2002) and IW (*square*) (Olausson et al. 2008), and brain responses to 3 cm/s > 30 cm/s stroking in healthy volunteers (*circle*) (Morrison et al. 2011a). The Ig2 region is outlined in *blue*. (**b**) Locations of electrodes that elicited an innocuous tingling sensation shown in *green* (Ostrowsky et al. 2002)

loci correspond well to the locations of electrodes that elicit tingling sensations reported in the electrophysiological studies (Fig. 11.5b), supporting the idea that these sensations may be associated with the CT pathway.

Further support for the idea that the posterior insular cortex is the primary projection site of CT fibers comes from studies that dissociate Aβ and CT input using *velocity control*. A peculiar feature of the CT system is the distinct manner in which the afferent nerve discharge frequency is modulated by the velocity of the stroking stimulus. CT afferents vigorously respond to strokes with a velocity in the range of 1–10 cm/s, and less to slower or faster strokes (Löken et al. 2009). This velocity profile stands in sharp contrast to that of thick afferents, whose discharge frequency increase monotonically with stroking velocity. If the posterior insular cortex represents a primary target for CT input, the brain responses should reflect this velocity modulation. In order to examine this issue, Morrison and colleagues studied brain responses in 14 healthy volunteers to CT optimal slow (3 cm/s) and nonoptimal fast (30 cm/s) stroking by a soft goat hair brush (Morrison et al. 2011a). The results confirmed the hypothesis: the analysis identified a cluster of voxels in the contralateral posterior insular cortex where the 3 cm/s strokes elicited a larger brain response than the 30 cm/s strokes (Fig. 11.4). This cluster was located near the posterior insular cortex activations reported in the neuronopathy patients (x, y, z = 31, −15, 5), also within the granular Ig2 region (Fig. 11.5a). Again, this activation locus corresponded well with the reported locations of electrodes that elicit tingling sensations (Fig. 11.5b).

In a second study, Morrison examined the effects of stroking velocity in the insular cortex in a group of patients with reduced C fiber density. These patients suffer from a heritable disorder associated with a mutation affecting the nerve growth factor beta gene (Morrison et al. 2011b). Affected carriers exhibit reduced density of thin and unmyelinated nerve fibers, including C afferents. If the previously demonstrated insular responses to skin stroking are in fact contingent on CT afferents, decreased C fiber density should lead to selectively reduced activations of the posterior insular cortex. Morrison examined five patients and five gender and age-

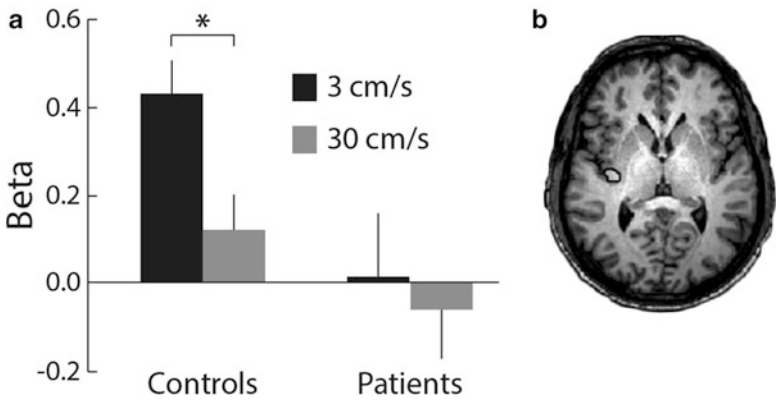

Fig. 11.6 Brain responses to CT-optimal (3 cm/s) and nonoptimal (30 cm/s) stroking in healthy controls and patients with reduced C-fiber density (**a**) in a posterior insular region of interest (**b**)

matched controls using fMRI, and applied brush strokes on the forearm at a CT-optimal stroking velocity (3 cm/s) and at a nonoptimal stroking velocity (30 cm/s). In the healthy control group, the contralateral posterior insular cortex in the healthy participants showed the greatest response to 3 cm/s stroking on the forearm. In patients, however, no significant responses to 3 cm/s stroking were found in the insular cortex. In order to verify the lack of response, a region-of-interest (ROI) mask created from the healthy group's activation cluster, was applied to the patient group's data. Mean brain responses (beta-values) were extracted for each voxel time course. In the patient group, there was no difference between 3 and 30 cm/s (Fig. 11.6). These results suggest a necessary role for CT input in posterior insular modulation to stroking stimulation.

Primary processing regions tend to have well-defined topographies, such as the somatotopy of the primary somatosensory cortex. Supporting the role of the posterior insula as a primary processing region, a growing number of studies of innocuous cooling and painful stimuli demonstrate that the posterior insular cortex is organized in a somatotopic fashion. Neuroimaging has demonstrated that upper body stimuli activate regions anterior to those of the lower body (Baumgärtner et al. 2010; Brooks et al. 2005; Henderson et al. 2007, 2011; Hua et al. 2005) (Fig. 11.7), and this organization has been identified also during electrical stimulation in patients (Mazzola et al. 2009). In order to assess whether CT responses are organized somatotopically, the neuronopathy patient GL was reexamined (Björnsdotter et al. 2009). In this study, soft brush stimuli were applied to the right forearm and thigh of GL and six healthy subjects during fMRI, and brain responses in the contralateral (left) insular cortex were analyzed. Similar to the findings in pain and temperature studies, it was found that forearm and thigh tactile stimulation activated distinctly separate clusters of voxels in the posterior insular cortex in GL (Fig. 11.7). The same organization was consistently found in all healthy subjects with forearm stimuli activating a region anterior to thigh stimulation. Again, the activations were located

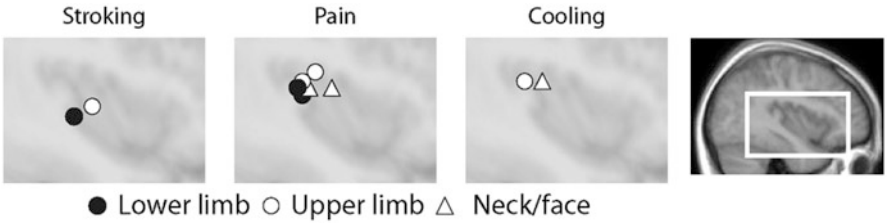

Fig. 11.7 Somatotopic organization with upper body limb stimuli projecting anterior to lower body stimuli in CT-targeted stroking in healthy controls (Björnsdotter et al. 2009), painful stimuli (Mazzola et al. 2009; Brooks et al. 2005), and cooling (Hua et al. 2005). Note that axial and coronal plane coordinates are represented as projections onto the sagittal plane $x = 40$ for display purposes

to the Ig2 region of the insular cortex. This somatotopic projection pattern is consistent with that found in thermosensation and nociception (Fig. 11.7), providing further support for the notion that the posterior insular cortex represents a primary target area for CT input.

Taken together, the studies examined in this chapter provide compelling support for the idea that the posterior insular cortex is the primary cortical target of information projected through CT afferents. Nevertheless, the central projection pathway of CT afferents remains unclear. A recent study suggests that, in rats, CT afferent signals merge with wide dynamic range neurons in the spinal cord (Andrew 2010) and brain responses to CT stimulation are modulated by tactile allodynia (Liljencrantz et al. 2013). Further research efforts are required to elucidate whether the posterior insular cortex contains a CT-selective neural representation, or whether the processing associated with CT-targeted stimuli is a generalized reflection of thin fiber sensations.

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