Isolated Insular Stroke: Clinical Presentation

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Keywords

Insular stroke · Autonomic activation after stroke · Stroke diagnostics · Neurointensive care

Abstract

The symptoms related to insular ischemia have been the object of several studies in patients affected by stroke, although they are often accompanied by other ischemic alteration of adjacent brain structures supplied by the middle cerebral artery (MCA). The insula is vulnerable because of an ischemia due to thromboembolic vascular occlusion of the M1 MCA segment and the 2 main MCA branches (M2), mainly when they abruptly arise from the principal stem at a right angle. This topographical and anatomical peculiarity could enable an embolic formation, especially due to atrial fibrillation (AF), to occlude the transition pathway between M1 and M2, while the proximal origin of vascular supply protects the insula from ischemia due to hemodynamic factors. The aim of the study is to characterize the clinical aspects of acute ischemic strokes as a first event in the insular territory with specific attention to atypical manifestation. We have considered 233 patients with a first event stroke involving the insular territory and 13 cases of isolated insular stroke (IIS), from the stroke registry of the Policlinico "G.Martino", University of Messina, between the February 10, 2014 and

the February 7, 2018. IIS patients showed CT/MRI lesions restricted to the insular region. Exclusion criteria were coexisting neurological diseases, structural brain lesions, extension to the subinsular area >50% of the total infarct volume. We identified 13 IIS patients (mean age 74 years), with an isolated symptom or a combination of typical and atypical aspects. Furthermore, we observed high frequency detection of cardiac disturbances. To our knowledge, just a few previous studies have described IIS; their incidence is still not well defined. IIS manifested with a combination of deficits including motor, somatosensory, speaking, coordination, autonomic and cognitive disturbances. After an ischemic stroke, AF manifestation could follow briefly the major event and its duration could be very short, as an autonomic dysfunction due to an insular infarction. This clinical condition requires a continuous cardiac monitoring for this dangerous occurrence.

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Introduction

The human insular cortex (IC) is a complex structure that has been implicated in a large number of functions and in the pathophysiology of a variety of neurologic disorders [1].

Fig. 1. The approximate position of functional areas and the course of some fiber connections in the insula of the rhesus monkey [1]. AA, agranular anterior zone; GI, GII, primary and secondary gustatory areas; ILC, insular limbic cortex; INTC, insular nociceptive and thermoreceptive cortex; ISAC, insular somatic association cortex; IVSC, insular viscerosensory cortex; OCI, primary olfactory cortex; PIVC, parieto-insular vestibular cortex.

From the cytoarchitectural, connectivity, and functional standpoint, it is subdivided into dorsocaudal and rostroventral zones. The dorsocaudal (granular) zone comprises several areas that receive inputs from different subnuclei of the thalamus that relay gustatory, viscerosensory, somatosensory, pain, and vestibular sensations. The rostroventral (agranular) zone is interconnected with the anterior cingulate cortex and the amygdala and is primarily involved in emotional processing. The terms agranular and granular refer to the absence or presence of an internal granular layer (IV). There is a wide intermediate zone, termed dysgranular because granule cells are rather scarce in layer IV and do not display complete laminar differentiation.

It appears that in monkeys, the superior tier of the insula contains 4 anteroposteriorly arranged primary sensory areas; gustatory, general viscerosensory, somatosensory (pain and temperature), and vestibular.

According to the neuroanatomical studies in rhesus macaques (Fig. 1), the IC:

- receives afferents from the dorsal thalamus (ventral posterior superior nucleus, ventral posterior inferior nucleus, ventromedial posterior nucleus, parvocellular part of the ventral posteromedial nucleus) and from several sensory cortical areas. In particular, the afferents from olfactory prepiriform cortex, the primary and secondary gustatory cortices and the primary in-

sular viscerosensory cortex converge on the agranular anterior zone of the insula, which participates with the caudal orbitofrontal cortex in the formation of an “orbital network”, involved in the analysis and integration of food-related information. Afferents from the primary somatosensory cortex, the somatosensory association areas 5 and 7b, the primary vestibular areas 3a and 2v, as well as from the auditory association areas, surrounding the primary auditory cortex, project to the posterosuperior portion of the insula (parieto-insular vestibular cortex; insular nociceptive and thermoreceptive cortex) and converge on the area which may hence be characterized as the insular somatic association cortex.

- is reciprocally connected with the amygdala as well as with several limbic and association cortical areas. Limbic structures, including the entorhinal (area 28), perirhinal (areas 35, 36), posterior orbitofrontal (areas 13, 14), temporopolar (area 38), and cingulate (areas 23, 24) cortices, as well as the amygdaloid complex, are strongly and reciprocally connected with the antero-basal sector of the insula, the insular limbic cortex. The insular somatic association cortex and the insular limbic cortex represent way stations in a somatolimbic projection, may provide a means for interrelating events in the extrapersonal world with relevant motivational states. Some high-order association areas, including the anterior orbitofrontal cortex (area 11), the prefrontal cortex (areas 45, 46), and the polymodal association cortex occupying the banks of the superior temporal sulcus, are also known to be connected with the insula.
- projects to the supplementary and presupplementary motor areas forming part of the medial premotor cortex, as well as to the ventral and dorsal striatum.
- moreover, there is an abundance of local intrasular connections.

In humans, the posterior insular cortex (PIC), middle insular cortex, and anterior insular cortex (AIC) sectors of the insula represent 3 different stages or levels of integration in a posteriorly-to-anteriorly directed processing stream. Afferents from the solitary nucleus, and from the phylogenetically new pathway from lamina I spinal neurons, converge upon the PIC, where they provide a primary interoceptive representation of the physiological condition of the body. The middle insular cortex is to be considered a polymodal integrative zone, where the interoceptive information from the posterior insula is represented and associated with inputs from multiple other sources. Prominent among these are

higher-order sensory cortices, providing emotionally salient information from the external world, and the cingulate cortex and amygdala, providing homeostatic information related to the current motivational state. The information thus gathered is conveyed to the AIC and there once again integrated with novel types of information from many sources [2–4]. Auditory and language tasks preferentially activate an area in the dorsal part of the anterior insula. Motor tasks involving both the upper and the lower extremity appeared to activate a posterior-anterior insula region, adjacent to the sulcus centralis insulae. Mutschler et al. [5] found the ventral part of the anterior insula to be activated by peripheral physiological changes such as measured by cardiovascular activity or sympathetic skin responses. A special feature of the (AIC) is that its fifth layer contains, in addition to pyramidal neurons, numerous large spindle-shaped cells, termed von Economo neurons. Von Economo neurons are hypothesized to form part of circuits underlying decision making, complex social cognition, and self-awareness [6].

The appearance of symptoms related to insular dysfunction has been the object of several studies in patients affected by stroke, but these symptoms are often intermingled with a variability of concomitant symptoms due to the vastity of the vascular territory usually involved by the stroke. The functional prognosis of isolated insular stroke (IIS) appears to be excellent, considering that IIS are small by definition and that surrounding or distant structures can generally compensate limited insular damage [7].

However, insula stroke is rarely seen without the involvement of other adjacent structures supplied by the middle cerebral artery (MCA): insular involvement is associated with poor functional outcome and neurologic abnormalities [8].

The insula is supplied directly by the proximal portions of the 2 main branches of the MCA (M2), where they abruptly arise from the main stem (M1) at a right angle. This topographical and anatomical characteristic of the insula could enable an embolism, especially an atrial fibrillation (AF), to occlude in the transition region between the M1 and M2. The insula is vulnerable to ischemia due to thromboembolic vascular occlusion of the M1 MCA segment and the superior and inferior MCA trunks, because no possibility exists of pial collateral supply from the anterior or posterior cerebral arteries [9]. However, the proximal origin of vascular supply protects the insula from ischemia due to hemodynamic factors in the absence of thromboembolic oc-

clusion. Insular involvement might be highly associated with the specific pathomechanism of ischemic stroke [8].

The IC plays an important role in the regulation of the autonomic nervous system. Electrical stimulation of the left IC more frequently elicited a small decrease in heart rate (HR) and blood pressure, whereas stimulation of the right IC elicited the opposite effects [10]. This has led to the suggestion that the left IC primarily regulates the parasympathetic and the right IC the sympathetic influence on the heart [11]. This appears to be supported by fMRI studies showing a correlation between left IC activation and high frequency (vagal) modulation of HR variability [12], and lateralization of insular activation during the Valsalva maneuver, cold pressor test, and handgrip maneuver [13]. However, this may be an oversimplification. For example, concomitant fMRI and microelectrode recordings show that resting muscle sympathetic nerve activity coincides with activation of the left IC, whereas skin sympathetic activity coincides with activation of the left posterior and right anterior insula [14].

To isolate insular symptoms it would be interesting to analyze the clinical consequences of the rare ischemic strokes limited to the insula. The aim of the study is to characterize the clinical aspects of acute ischemic strokes as a first event in the insular territory with specific attention to atypical manifestation.

Materials and Methods

We have considered 233 patients with a first event stroke involving the insular territory and 13 cases of IIS, from the stroke registry of the Policlinico “G.Martino”, University of Messina, between the February 10, 2014 and the February 7, 2018. We reviewed medical charts and neuroimaging studies of the last 723 patients of each database with MCA stroke. Those with infarcts predominantly affecting the IC were eligible. IIS patients showed CT/MRI lesions restricted to the insular region. Extension to the adjacent operculae or subinsular area (extreme capsule, claustrum, external capsule) was accepted as long as it accounted for <50% of the total infarct volume. Exclusion criteria were coexisting neurological diseases, structural brain lesions, extension to the subinsular area >50% of the total infarct volume.

Intravenous thrombolysis (IVT) with tissue-type plasminogen activator (rT-PA) was administered to eligible patients, according to Guidelines for Thrombolytic Therapy [15]. Therapeutic approaches included direct mechanical thrombectomy (MT) or bridging therapy with rT-PA plus MT. Collected data included patient demographic and clinical characteristics, time of symptoms onset, initial stroke severity as expressed by the National Institutes of Health Stroke Scale score on admission and discharge, and the modified Ranking Scale on admission and discharge [15].

Results

We identified 13 IIS patients (5 males, 8 females), with a mean age of 74 years (range, 47–90), divided as right IS and left IS depending of the hemisphere involved (Fig. 2–5). IIS patients presented with an isolated symptom or a combination of typical – motor deficits (13/13 – 4 right, 9 left), sensory impairment (6/13 – 2 right, 4 left), speech disorder (11/13 – 3 right, 8 left) – and atypical aspects – hemispatial inattention (2/13 – 2 right), sleepiness (2/13 – 2 right), vestibular-like syndrome (5/13 – 3 left, 2 right), auditory disturbance (1/13 – 1 left), transient dysphagia (3/13 – 3 left), space-time disorientation (1/13 – 1 right), confusion and agitation (1/13 – 1 left), weeping tendency (1/13 – 1 left) and anxiety (1/13 – 1 right), autonomic disturbance (11/13 – 8 left, 3 right; Table 1 and Fig. 6).

Somatosensory manifestations were reported in 13 patients (100%). Symptoms included numbness ($n = 4$) and dysesthesia ($n = 2$). The deficit was contralateral to the lesion in all cases. It affected a hemibody with ($n = 1$) or without facial sparing ($n = 9$), or was limited to facial territory and omolateral arm ($n = 3$).

Aphasia was reported in 6 patients (46%). Non-fluent aphasia with anomia and phonemic paraphasia was the most frequently reported clinical picture ($n = 5$). Wernicke's aphasia ($n = 1$) was also reported.

Dysarthria ($n = 5$, 38%) and a vestibular-like syndrome variably described as vertigo, dizziness, unsteadiness or instability ($n = 5$, 38%) were also frequently reported. Hemispatial inattention ($n = 2$), sleepiness ($n = 2$), auditory disturbance ($n = 1$), transient dysphagia ($n = 3$), space-time disorientation ($n = 1$), confusion and agitation ($n = 1$), weeping tendency ($n = 1$) and anxiety ($n = 1$) were rarely reported.

Dysautonomic disorders were also frequently reported ($n = 11$, 85%), characterized by hypertension bursts ($n = 6$), hypotensive/hypertensive episodes ($n = 4$), and cardiac rhythm disturbances ($n = 9$).

Furthermore, we observed high frequency detection of cardiac involvement ($n = 11$, 85%): history of tachycardia ($n = 1$) or AF (permanent, $n = 2$; paroxistic, $n = 2$), newly detected ($n = 2$) or suspected AF (biatrial enlargement on transthoracic echocardiogram, $n = 2$), atrial flutter ($n = 2$), sinus bradycardia ($n = 1$) or tachycardia ($n = 1$), atrio-ventricular blocks (complete or incomplete left/right branch block, QT prolongation, atrioventricular block, $n = 6$) and an increased ectopic beats ($n = 2$; Fig. 7).

IVT with rT-PA was performed, at the standard dose of 0.9 mg/kg, for 8 patients. Within this group, 2 patients

Fig. 2. Left insular stroke [1].

Fig. 3. Right insular stroke [1].

Fig. 4. Right insular stroke [2].

Fig. 5. Left insular stroke [2].

out of 8 underwent MT in a setting of bridging therapy. Five patients did not receive IVT with rT-PA: within this group, 1 patient underwent direct MT to perform right carotid angioplasty and stenting; 1 patient underwent MT alone because of the presence of early ischemic signs on CT scan; 3 patient did not perform IVT because of rapid regression of symptoms, late hospital arrival (outside time window for IVT) or because of the presence of high microbleed counts on MRI. Table 2 shows the summary results for reperfusion treatments with National Institutes of Health Stroke Scale on admission and discharge and modified Ranking Scale before and after the hospitalization.

Discussion/Conclusion

IIS were described only in few previous studies or case reports and their incidence is not well defined. Due to the confluence of functions in a restricted region, IIS results in multimodal deficits combining in descending order motor and somatosensory, speech or language, vestibular-like, autonomic and cognitive disturbances [7].

Although motor and sensory deficits, aphasia and dysarthria are among the well-known, described symptoms of IS, in accordance with literature, we observed many unusual clinical presentations, such as vestibular-like syndrome, auditory disturbances, hemispatial inattention, cognitive alterations, and autonomic dysfunction.

Neurons in the parieto-insular vestibular cortex respond to vestibular stimuli; further, most of these elements also responded to somatosensory and visual information and were hence, classified as polymodal vestibular units. In humans, a vestibular cortical network with right hemispheric dominance comprises, among many other cortical areas, the PIC as well as the AIC [16]. In contrast to these observations, however, we did not find a side preference for vestibular-like syndrome.

The PIC is involved in auditory processing, such as tuning into novel auditory stimuli and allocating auditory attention [17]. This could explain the singular finding of acute auditory disturbance.

Some patients with hemiplegia after right-sided strokes deny their paralysis (anosognosia for hemiplegia) and are convinced that their paralyzed limbs function normally or they may experience their limb(s) as not belonging to them

Table 1. Clinical presentation in patients with IIS

Patient	Gender	Topography	Typical symptoms	Atypical symptoms
1	63, male	Right	Left hemiparesis, dysarthria	
2	76, female	Left	Right hemiparesis, non-fluent aphasia, right tactile extinction	Vestibularlike syndrome, newly-detected AF, incomplete LBB and hypertensive episode
3	70, male	Left	Right facial and arm weakness, non-fluent aphasia	Transient dysphagia, vestibularlike syndrome, hypotensive/hypertensive episodes
4	68, male	Right	Left hemiplegia, left arm hypoaesthesia, mild dysarthria	Sleepiness, left hemineglect, hypotensive/hypertensive episodes
5	84, male	Right	Left hemiparesis	Sleepiness, space-time disorientation, left hemineglect, vestibularlike syndrome, atypical atrial flutter and hypertensive episode
6	90, female	Left	Right hemiparesis, non-fluent aphasia	Atypical atrial flutter, hypertensive episode and bradycardic episode
7	47, female	Right	Left hemiparesis, right limbs pain, dysarthria	Anxiety, transient dysphagia, vestibularlike syndrome, hypotensive/hypertensive episodes and sinus tachycardia
8	74, female	Left	Right facial and arm weakness, right arm pain	Sinus bradycardia, atrial extrasystole and hypertensive episode
9	85, female	Left	Right hemiparesis, non-fluent aphasia	Transient dysphagia, constipation, newly detected AF, sinus bradycardia with AVB I and RBB, hypertensive episode
10	71, male	Left	Right hemiparesis, non-fluent aphasia	Weeping tendency, ectopic ventricular beats and hypertensive episode
11	69, female	Left	Right facial and arm weakness, dysarthria	Hypertensive episode
12	81, female	Left	Right hemiparesis, right hemihypoaesthesia, fluent aphasia	Confusion, agitation, auditory disturbance, delayed RB conduction
13	88, female	Left	Right limbs weakness, right hemihypoaesthesia, mild dysarthria	Vestibularlike syndrome, RBB and hypotensive/hypertensive episodes

IIS, isolated insular stroke; AF, atrial fibrillation.

and may even attribute them to other persons (somatoparaphrenia). The disturbances are consistently associated with damage to the right insula, suggesting a prominent role of the right insula in our sense of limb ownership as well as in our self-awareness of actions. Hence, Karnath and Baier hypothesized that the right IC forms a central node of the network involved in human body scheme representation [18]. In accordance with this observation, we found 2 cases of left hemineglect in patient with right IIS.

The AIC is involved in a large variety of cognitive control tasks. This insular region forms, together with other cortical regions, among which the anterior cingulate cortex, the presupplementary motor area, the dorsal premo-

tor cortex, the dorsolateral prefrontal cortex, and the posterior parietal cortex, a highly interconnected cognitive control network [19]. The frontoinsula cortex is a cytoarchitecturally distinct anterior subdivision of ventral AI, and right frontoinsula has been proposed as the central node within a large-scale “salience network” that responds to personally significant ambient events. In contrast to the ventral anterior insula, which participates in social-emotional function, the dorsal anterior insula has been strongly linked to cognition [20]. Sterzer et al. [21] demonstrated that gray matter volume in bilateral AIC and left amygdala was significantly reduced in Conduct Disorder patients, compared to healthy control subjects.

Fig. 6. Frequency of typical and atypical symptoms.

Fig. 7. Cardiac involvement in patients with IIS. AF, atrial fibrillation.

Table 2. Summary results for reperfusion treatments with NIHSS on admission and discharge and mRS before and after the hospitalization

Patient	IVT	MT	NIHSS (admission)	NIHSS (discharge)	Premorbid mRS	Discharge mRS
1	Y	Y	5	1	0	1
2	Y	N	11	4	1	3
3	N	Y	9	6	1	4
4	N	Y	16	3	0	3
5	Y	Y	13	2	0	2
6	Y	N	14	12	0	4
7	N	N	4	3	3	4
8	N	N	3	1	1	1
9	Y	N	11	4	3	3
10	Y	N	11	1	1	3
11	Y	N	3	0	0	0
12	N	N	11	1	2	2
13	Y	N	3	1	0	2

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Ranking Scale; IVT, intravenous thrombolysis; MT, mechanical thrombectomy.

According to the authors mentioned, these findings suggest a critical role for the AIC in regulating social behavior. These observations could explain our findings of alterations in space-time orientation, level of consciousness, behavior, mood and stress response.

The insula is shown to play a role in swallowing, due to the evidence that a lesion in the IC produces profound dysphagia. Some studies have revealed the bilateral involvement of the insula, while other researchers have reported the activation of the right insula during swallow. There is also some evidence about the presence of anterior insula engagement in dysphagic patients and the interaction of insula as a modulator of motor function with primary sensory cortex lead to control of swallowing [22]. Swallowing disorder after stroke shows a spontaneous recovery and these observations are in accordance with our findings.

The insula plays a role in autonomic regulation. Electrical stimulation of the insular region in humans may elicit a variety of visceromotor phenomena, including vomiting and other alterations of the gastrointestinal tract, respiratory arrest, as well as changes in cardiac rate and rhythm control, and blood pressure [10, 23].

Central autonomic disorders may manifest with a wide spectrum of cardiac arrhythmias, some of them life-threatening. Sympathetic hyperactivity triggers both supraventricular and ventricular tachycardia; vagal hyperactivity leads to bradyarrhythmias, including AV block, and sympathetic or vagal hyperactivity may lead to AF. Reduced HR variability is a relevant marker of cardiovascular risk, including predisposition toward ventricular arrhythmias in patients with primary cardiac disease. They may reflect abnormalities in forebrain vagal or sympathetic drive, brainstem reflexes, or vagal or sympathetic output [24].

AF detected after acute ischemic stroke may be short-lasting and perhaps a nonrecurrent autonomic and inflammatory epiphenomena of stroke. The autonomic regulation of cardiac rhythm constitutes an integrated relay system. The highest level of control is exerted by the cerebral cortex, particularly the insula. The onset of AF may be associated with an imbalance of sympathetic and parasympathetic activity, a common consequence of insular infarctions. This autonomic imbalance and an interruption in the cerebral regulation of the intrinsic cardiac autonomic system constitute the most likely mechanisms responsible for the autonomic pathway. Insular damage has been associated with newly detected AF, atrioventricular blocks and an increased amount of ectopic beats. Furthermore, insular damage is associated with adverse cardiac outcome, such as sudden cardiac death and congestive heart failure

[25]. Early and accurate identification of stroke patients at high risk for AF is important in selecting candidates for intensive cardiac monitoring such as implantable loop recorders. Larger studies are needed to better define the incidence and clinical presentation in IIS [26].

To our knowledge, just a few previous studies have described IIS; their incidence is still not well defined [7]. IIS manifested with a combination of deficits including motor, somatosensory, speaking, coordination, autonomic and cognitive disturbances. After an ischemic stroke, AF manifestation could follow briefly the major event and its duration could be very short, as an autonomic dysfunction due to an insular infarction. This clinical condition requires a continuous cardiac monitoring for this dangerous occurrence.

Limitations

It is a small study on clinical aspects of IISs from a prospective registry.

Acknowledgment

We acknowledge the territorial emergency medical service, which has contributed in an essential way in carrying out the centralization system.

Statement of Ethics

Subjects (or their parents or guardians) have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Sources

This study did not receive any funding.

Author Contributions

F. Giammello, D.C., C.C., and R.F.M. contributed to the study design. F. Giammello and D.C. performed data collections. F. Granata performed imaging analysis. M.C.F., M.C., P.L.S. supervised the research. F.Gi, F.Grillo, C.C., C.D.A. and R.F.M. wrote the article. A.T. supervised the submission of reviewed manuscript.

References

- 1 Nieuwenhuys R. The myeloarchitectonic studies on the human cerebral cortex of the Vogt-Vogt school, and their significance for the interpretation of functional neuroimaging data. *Brain Struct Funct*. 2013 Mar;218(2):303–52.
- 2 Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009 Jan;10(1):59–70.
- 3 Craig AD. Once an island, now the focus of attention. *Brain Struct Funct*. 2010 Jun;214(5-6):395–6.
- 4 Craig AD. The sentient self. *Brain Struct Funct*. 2010 Jun;214(5-6):563–77.
- 5 Mutschler I, Wieckhorst B, Kowalevski S, Derrix J, Wentlandt J, Schulze-Bonhage A, et al. Functional organization of the human anterior insular cortex. *Neurosci Lett*. 2009 Jun;457(2):66–70.
- 6 Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, et al. The von Economo neurons in frontoinsula and anterior cingulate cortex in great apes and humans. *Brain Struct Funct*. 2010 Jun;214(5-6):495–517.
- 7 Lemieux F, Lanthier S, Chevrier MC, Gioia L, Rouleau I, Cereda C, et al. Insular ischemic stroke: clinical presentation and outcome. *Cerebrovasc Dis Extra*. 2012 Jan;2(1):80–7.
- 8 Fink JN, Selim MH, Kumar S, Voetsch B, Fong WC, Caplan LR. Insular cortex infarction in acute middle cerebral artery territory stroke: predictor of stroke severity and vascular lesion. *Arch Neurol*. 2005 Jul;62(7):1081–5.
- 9 Kang J, Hong JH, Jang MU, Kim BJ, Bae HJ, Han MK. Cardioembolism and Involvement of the Insular Cortex in Patients with Ischemic Stroke. *PLoS One*. 2015 Oct;10(10):e0139540.
- 10 Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. *Neurology*. 1992 Sep;42(9):1727–32.
- 11 Nagai M, Hoshida S, Kario K. The insular cortex and cardiovascular system: a new insight into the brain-heart axis. *J Am Soc Hypertens*. 2010 Jul-Aug;4(4):174–82.
- 12 Napadow V, Dhond R, Conti G, Makris N, Brown EN, Barbieri R. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. *Neuroimage*. 2008 Aug;42(1):169–77.
- 13 Macey PM, Wu P, Kumar R, Ogren JA, Richardson HL, Woo MA, et al. Differential responses of the insular cortex gyri to autonomic challenges. *Auton Neurosci*. 2012 May;168(1-2):72–81.
- 14 Macefield VG, James C, Henderson LA. Identification of sites of sympathetic outflow at rest and during emotional arousal: concurrent recordings of sympathetic nerve activity and fMRI of the brain. *Int J Psychophysiol*. 2013 Sep;89(3):451–9.
- 15 SPREAD – Stroke Prevention and Educational Awareness Diffusion. Ictus cerebrale: Linee guida italiane di prevenzione e trattamento. VIII Edizione; 2015.
- 16 Fasold O, von Brevern M, Kuhberg M, Ploner CJ, Villringer A, Lempert T, et al. Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. *Neuroimage*. 2002 Nov;17(3):1384–93.
- 17 Bamiou DE, Musiek FE, Luxon LM. The insula (Island of Reil) and its role in auditory processing. Literature review. *Brain Res Brain Res Rev*. 2003 May;42(2):143–54.
- 18 Karnath HO, Baier B. Right insula for our sense of limb ownership and self-awareness of actions. *Brain Struct Funct*. 2010 Jun;214(5-6):411–7.
- 19 Cole MW, Schneider W. The cognitive control network: integrated cortical regions with dissociable functions. *Neuroimage*. 2007 Aug;37(1):343–60.
- 20 Lamm C, Singer T. The role of anterior insular cortex in social emotions. *Brain Struct Funct*. 2010 Jun;214(5-6):579–91.
- 21 Sterzer P, Stadler C, Poustka F, Kleinschmidt A. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage*. 2007 Aug;37(1):335–42.
- 22 Dehaghani SE, Yadegari F, Asgari A, Chitsaz A, Karami M. Brain regions involved in swallowing: evidence from stroke patients in a cross-sectional study. *J Res Med Sci*. 2016 Jun;21(1):45.
- 23 Oppenheimer S. Cerebrogenic cardiac arrhythmias: cortical lateralization and clinical significance. *Clin Auton Res*. 2006 Feb;16(1):6–11.
- 24 Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. *Neurology*. 2014 Jul;83(3):261–71.
- 25 Sposato LA, Riccio PM, Hachinski V. Post-stroke atrial fibrillation: Cause or consequence? Critical review of current views. *Neurology*. 2014 Apr;82(13):1180–6.
- 26 Frontzek K, Fluri F, Siemerkus J, Müller B, Gass A, Christ-Crain M, et al. Isolated insular strokes and plasma MR-proANP levels are associated with newly diagnosed atrial fibrillation: a pilot study. *PLoS One*. 2014 Mar;9(3):e92421.