LOCALIZATION OF THE PRIMARY GUSTATORY CORTEX WITHIN THE INSULAR LOBE USING STRUCTURAL WHITE MATTER CONNECTIVITY EVIDENCE AS DETERMINED BY DIFFUSION TENSOR IMAGING.

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by

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LIST OF SYMBOLS

α	Alpha
β	Beta

LIST OF ABBREVIATIONS

MRI	Magnetic Resonance Imaging
DTI	Diffusion Tensor Imaging
MR	Magnetic Resonance
FSL	FMRIB Software Library
FMRIB	Functional Magnetic Resonance Imaging of the Brain
GUI	Graphical User Interface
SIG	Significance
STD. ERROR	Standard Error
mIns	Middle dorsal Insula
rIns	Rostral Insula
rCBF	Regional cerebral blood flow
AN	Anorexia nervosa
PE	Prediction error
Err prob	Error probability

ABSTRAK

PENENTUAN LOKASI KORTEKS GUSTATORI PRIMER DALAM LOBUS INSULA MENURUT KESAMBUNGAN STRUKTUR JISIM PUTIH OTAK MENGGUNAKAN PENGIMEJAN DIFUSI TENSOR

PENGENALAN: Penyetempatan korteks gustatori primer tidak konsisten dalam penyelidikan terdahulu. Kajian semasa bertujuan untuk membahagikan lobus insular kepada subbahagian untuk menyiasat ketersambungan setiap subbahagian ini ke kawasan pemprosesan rasa yang lain di dalam otak.

BAHAN DAN KAEDAH: Data pengimejan berwajaran resapan daripada tiga belas peserta wanita yang sihat diperoleh daripada pangkalan data yang dibina pada tahun 2013. Semua peserta mempunyai persepsi rasa normal seperti yang ditentukan oleh Soal Selidik Rasa & Bau Monell-Jefferson yang diubah suai. Traktografi probabilistik menggunakan Perpustakaan Perisian FMRIB (FSL) dilakukan untuk menentukan kebarangkalian sambungan relatif bagi sebelas bahagian lobus insula untuk menyasarkan kawasan otak yang ditunjukkan dikaitkan dengan pemprosesan rasa, iaitu amygdala, operkulum hadapan dan striatum ventral.

KEPUTUSAN: Bahagian inferior lobus tengah dan bahagian inferio-posterior lobus anterior insula mempunyai kebarangkalian sambungan tertinggi ke kawasan pemprosesan rasa yang disasarkan dalam penyelidikan ini. Lobus posterior insula mempunyai kebarangkalian sambungan paling sedikit kepada semua sasaran seperti yang ditunjukkan dalam penyelidikan terdahulu, manakala operkulum hadapan mempunyai sambungan meluas ke semua lobus insula. Keputusan penyelidikan ini adalah dengan nilai statistika $p<0.05$.

KESIMPULAN: Aspek inferior lobus tengah dan bahagian inferio-posterior lobus anterior insula mempunyai sambungan kebarangkalian tertinggi ke kawasan pemprosesan rasa menjadikannya sangat berkemungkinan menjadi tapak untuk korteks rasa primer.

ABSTRACT

LOCALIZATION OF THE PRIMARY GUSTATORY CORTEX WITHIN THE INSULAR LOBE USING STRUCTURAL WHITE MATTER CONNECTIVITY EVIDENCE AS DETERMINED BY DIFFUSION TENSOR IMAGING

INTRODUCTION: The primary taste cortex localisation has been inconsistent in previous research. The current study aims to divide the insular lobe into subdivisions to determine investigate their individual structural connectivity to taste processing areas of the brain.

MATERIALS AND METHODS: Diffusion-weighted imaging data from thirteen healthy female participants were obtained from a databse built in 2013. All participants had normal taste perception as determined by the modified Monell-Jefferson Taste & Smell Questionnaire. Probabilistic tractography using FMRIB Software Library (FSL) was performed to determine the relative connection probability of eleven divisions of insula lobes to target brain areas shown to be associated with taste processing, namely amygdala, frontal operculum and ventral striatum.

RESULTS: The inferior part of the middle lobe and the inferio-posterior part of the anterior lobe of the insula had the highest connection probability to the areas of taste processing targeted in this research. The posterior lobe of the insula had the least connection probability to all targets as shown in previous research, while the frontal operculum had widespread connection to all lobes of the insula. The results of this research are with the statistical value of $p<0.05$.

CONCLUSION: The inferior aspect of the middle lobe and the inferio-posterior part of the anterior lobe of the insula had the highest probabilistic connection to the areas of taste processing making it highly probable to be the site for primary taste cortex.

1. INTRODUCTION

1.1 Role of the insular lobe

One of the many functions of insula is in taste processing, and the primary taste cortex localisation has been quoted in different areas within the insular lobe. Nakamura et al (2013) localised it to the right middle insula, while Chikazoe et al (2019) took it to be in the anterior and middle insula. Canna et al (2019) extended the primary taste cortex areas to the right middle posterior and left middle insula, as well as bilaterally the anterior insula, middle-posterior insula as well as the inferior insula, while Ianilli et al (2014) included all lobes including the posterior lobe.

This study aims to estimate the most probable location of the primary taste cortex in the insular lobe according to its structural connections. The connections of the insula were determined using the Rolls (2011) Model of taste processing and taking those brain areas outlined by the model as target regions; namely the frontal operculum, striatum and amygdala. The seed regions are areas in the insula that have been named as primary taste cortex.

Anatomy of the insular lobe

Previously, the whole insula was thought to be just the primary taste cortex before more functions were found such as emotions processing, visceral information processing and many more. The oldest study that mentioned the primary taste cortex was a study by Small et al (1997) which reflected the understanding at the time that the insular lobe was considered as a whole as the primary taste cortex. It was only later that the other many and varied functions of the insular lobe was found. Since then, many other studies have been performed but there is still debate as to the location of the primary taste cortex within the insular lobe, with some studies mentioning it in the anterior lobe, others in the middle insula and some included the posterior insula as well.

One reason for this could be that new research (Porcu et al, 2020), corroborated by a few studies such as Canna et al (2019), Ianilli et al (2018), shows that the insular lobe is not organised by distinct taste but rather by the intensity of taste. It is organised by gradient of strongest intensity of taste to lowest, and this has been shown in the study by Canna et al (2019). This could be the reason for the variety of localisation found in earlier studies, or other tastant-dependent characteristics or oral somatosensory stimuli, that it would activate different regions because the tastant characteristics were different. Therefore, having structural connectivity evidence that would not be influenced by tastant intensity as functional magnetic resonance imaging (fMRI) would be, would show the passive connections and this evidence could be used alongside fMRI evidence to reach a better conclusion on the localisation of the primary gustatory cortex.

Spatial organisation

Porcu et al (2020) stated that the insula is organised according to taste category and concentration rather than taste identity, while Rolls (2015) included temperature and texture in the categorization. Another mention of note is the lateralisation of the primary gustatory cortex as mentioned by Prinster (2017) that there is a difference in function between the right and left primary gustatory cortex.

Blurring of borders between insula subdivisions

Cerliani (2012) mentioned that a general consensus on the borders of the insula subregions is still lacking. This can be dated back all the way to Brodmann (1909) in the early 1990s quoting multiple times that the task of dividing the insula into individual fields was met with great difficulties. This gradual transition of the insula as opposed to a sharp transition between lobes could be the reason for the difficulties in localising the primary gustatory cortex up until now.

1.2 Problem Statement & Study Rationale

The localization of the primary taste cortex in the insula is still debatable, with studies localizing it in varied areas within the insula subdivisions. Anatomically, there is blurring of borders within the insula subdivisions that may contribute to the difficulty in coming to a consensus to the localization of the primary gustatory cortex. This study will investigate the structural connectivity of the insular lobe with brain areas identified to be involved in the processing of taste.

This is also the first study that will map the connection probabilities between subdivisions of the insula and the target regions related to food processing using diffusion magnetic resonance imaging (dMRI) in the Malaysian youth population. It may also serve as a guide for brain connectivity in the said regions as comparison to the diseased brain in future.

1.3 Research Questions

i) How to subdivide the insula to investigate its structural connectivity to other taste processing areas in the brain

ii) What are the insular locations most connected to other brain areas involved in taste processing

1.4 Study Objectives

1.4.1 General Objective

This study aims to localize the primary gustatory cortex within the insula using dMRI and probabilistic tractography.

1.4.2 Specific Objectives

The specific objectives of the study are:

1) To divide the insula into small subdivisions based on previous literature findings.
2) To track the connectivity and compare the connection of the superior and inferior halves of the insula with brain areas related to food processing
3) To track the connectivity and compare the connection of the subdivisions of the anterior, middle and posterior lobes of the insula with brain areas related to food processing
4) To track the connectivity and compare the connection of the subdivisions of the middle lobe of the insula with brain areas related to food processing

2. LITERATURE REVIEW

2.1 Insula

In a study by Avery et al. (2020) looking at enjoyable and unenjoyable taste representation areas in the brain, they found that the way it was processed, there was no specificity of area to one taste, rather that the primary taste cortex was activated by all tastes. However, they also found that distinct tastes could be identified within some regions, namely the mid-insula, striatum, amygdala and operculo-frontal cortex cortex. From these findings, they suggest that there is a population code of distribution in taste quality representation, and not topographical in the representation. The hedonistic and repulsive aspects of food are processed in the ventral striatum, operculo-frontal cortex and amygdala, and the distribution in these regions also appears to be by population code.

Using insights from this study, the brain areas under interest for the current study can be determined with more focus on the operculo-frontal cortex, ventral striatum, amygdala and insula. There is a contradiction in this study which identifies the bilateral dorsal mid-insula as the primary taste cortex, while in Rolls (2011) the anterior insula was cited to be the location of this cortex.

Another study by Rodriguez et al. (2019) found a mediation effect of food cravings by visceral adiposity levels. The functional connectivity of two insular regions were correlated against visceral fat levels; the middle-dorsal insula (mIns) which codes for homeostatic changes and the rostral insula (rIns) which processes food properties representation. This insular network has been associated with visceral fat influencing food cravings. With greater visceral adiposity, reduced connectivity was found in the mIns network, involving the hypothalamus and the bed nucleus of the stria terminalis; a reduced connectivity in this network has been linked with greater food cravings. Increased connectivity was found in the networks involving the mIns and the middle frontal gyri, mIns with the right intraparietal cortex, and rIns with the right amygdala. The conclusion drawn is that visceral fat disrupts the processing of homeostatic signals in the insula which has an effect of boosting food cravings.

From this study, the relevance of the rostral insula and the middle-dorsal insula to food cravings, mediated among other things by visceral fat, can be a useful insight in seeing the areas of the insula showing functions in the taste processing network.

An interesting study by Pujol et al. (2018) recorded the sequence of brain events and their locations that occur in response to food that is perceived to be disgusting. This involved the insula, amygdala and hippocampus which are areas coding for the emotion of disgust, as well as the hypothalamus for the regulation of food intake.

From this study, it can be seen that these areas will be connected to the insula for the emotion of disgust in reaction to disgusting food, and the resultant regulation of food intake.

Another study, by Pak et al (2018) using Positron Emission Tomography found that in obese subjects there was greater regional cerebral blood flow (rCBF) in the insular lobe. This study is another study showing that there are adaptive changes in the insular lobe where the primary taste cortex lies, that occur from obesity.

A study by Guido et al (2018) investigated the insular lobe in its role in adult and adolescent anorexia nervosa (AN). Looking at the brain reward learning in response to taste, they found that white matter connectivity strength between the insula and operculo-frontal cortex was positively correlated with dopamine-related prediction error (PE) response. A larger left medial operculo-frontal gyrus was also observed in subjects recovered from AN, as well as in adult bulimia nervosa. From this study, the operculo-frontal gyrus can be seen as a region of interest for the taste processing network.

2.2 Other taste processing areas: amygdala, ventral striatum and frontal operculum

Amygdala, “almond” in Greek, comes from the shape of the brain structure. Part of the limbic system, its function is primarily involved in emotions such as fear and reward.

An interesting theory about the amygdala is that instead of being a functional or structural unit, it consists simply of regions that belong to other regions or systems of the brain. The visual, auditory, somatosensory, olfactory, and taste sensory systems all have inputs to the amygdala (LeDoux, 2007) and the amygdala has outputs to both the subcortical and cortical brain areas. .

While the nucleus accumbens of the ventral striatum makes the decision of reward vs effort, the amygdala is necessary for the representation of value that is required for reward-based decision-making (Benarroch, 2015).

The ventral striatum consists of the nucleus accumbens and olfactory tubercle (Chen et al., 2020) . Part of the limbic system, it is important in the circuitry of goal-directed behaviours, sensitisation and affect (Carlezon & Wise, 1996; Ito et al., 2004).. Weighing the reward against the effort required, the ventral striatum gives an integrated estimate of utility for a given action (Haber, 2011). The ventral striatum supports the invigoration of behaviour, through reinforcement learning (Mannella et al., 2013).

Forming a lid over the insular cortex, the frontal operculum is the cortical structure that blocks it from external view. It is directly adjacent to the insular lobe and the surrounding circular sulcus. Its function depends on the location of the segment. The frontal operculum has roles in the prefrontal association cortex, thought, cognition, and planning behaviour. The most famous function of the frontal operculum may be that the left frontal operculum is part of the location of Broca's aphasia. However, another big function of the area is the pathway of taste processing (Damasio, H. (1998).

2.3 Rolls Processing Pathway

The model of taste processing in the brain used for this study starts in the primary taste cortex in the anterior insula, where only taste is processed and reward is not yet given a value. This process is independent of hunger or reward and pleasantness (Rolls, 2011). The next synapse from here is in the frontal operculum, where aspects of reward are integrated to give a value representation (Cannaet al, 2019; Ianilli et al, 2014, & Chikazoe et al, 2019). When it comes to reward from food, it is not only the taste, but would also include processing of visual stimuli, scent, and texture. These aspects of reward are integrated with projections coming from the amygdala and hippocampus, as well as other regions, for emotion as well as the control of termination of food intake (Rolls, 2015). Decisions for reward-related behaviour are processed in the decision-making networks with the ventral striatum being a key region (Carlezon and Wise, 1996; Ito et al, 2004).

2.4 Other roles of the insular lobe

The functions of the insular lobe include sensory processing, representations of feelings and emotions, autonomic and motor control, risk prediction, decision-making, bodily- and self-awareness, empathy, conscious desires, cravings, addiction, and neuropsychiatric disorders (schizophrenia, panic, and more) (Gogolla, 2017) It is also involved in the salience network (attention-cognition) as well as taste perception and pain processing(Uddin et al., 2017). The functional connections of the insular lobe include the amygdala-insular interaction for object recognition memory, as well as connections in pathways for nociceptive and visceral sensory input, as well as many others including the food reward network (Bermudez-Rattoni F, 2014).

Rewarding aspects of food include the positive and negative emotions: hedonistic and revolting responses to food(Rolls, 2008). This would include the feeling of disgust which the insular lobe plays an important role in representing, for food that is perceived as disgusting, and positive feelings for food that is perceived as rewarding (Gogolla, 2017).

2.5 Diffusion MRI

Diffusion MRI is a magnetic resonance technique used to look at axonal white matter organisation in the brain (Cheng & Calhiun 2021). Diffusion weighted imaging (DWI) is a technique of using anisotropy, the Brownian movement of water molecules through the path of least resistance along the axons.

Probabilistic tractography is a fibre reconstruction method for analysing data collected by DWI (Rosen & Halgren, 2020). The main parameter is Mean Diffusivity (MD); the average magnitude of molecular displacement by diffusion. The higher the MD value, the more isotropic the medium.