Histological age related changes in the cingulate cortex of male rabbits

Thesis
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Mohamed Esmat Elnaggar

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List of Abbreviations

ACC	:	Anterior Cingulate cortex.
AD	:	Alzheimer's disease
Aβ	:	β-Amyloid.
APP	:	Amyloid Precursor Protein
CC	:	Cingulate Cortex
CMSR	:	Caudo Medial Subregion
fMRI	:	Functional magnetic resonance imaging
GM	:	Grey Matter
MCC	:	Mid Cingulate Cortex
MTI	:	Magnetization transfer imaging
NFP	:	Neurofilament Protein
NO	:	Nitric oxide
PCC	:	Posterior Cingulate cortex.
PET	:	Positron emission tomography
PND	:	Postnatal day
RSC	:	Retrosplenial Cortices
SD	:	Standard deviation
SPs	:	Senile Plaques
WM	:	White Matter

Introduction

The importance of the cerebral cortex in various motor and cognitive functions has drawn scientists' attention to the study of its age-related modifications in the last few decades. Various changes develop with age in the nervous system of man and animals. Lesions such senile plaques, cerebral β-amyloid angiopathy, neurofibrillary tangles, corpora amylacea and mineralization appear with advancing age in the human brain but are not specific to the human brain. In the brains of aged dogs, horses and rats similar changes have been reported frequently (**Uchida et al., 1995).**

Biological, epidemiological, and demographic data have generated a number of theories that attempt to identify a cause or process to explain aging and its inevitable consequence, death. However, in recent years, the search for a single cause of aging, such as a single gene or the decline of a key body system, has been replaced by the view of aging as an extremely complex, multifactor process. Several processes may interact simultaneously and may operate at many levels of functional organization (**Weinert and Timiras, 2003)**.

During normal aging humans exhibit some cognitive decline, but it is difficult to determine the underlying causes of this decline, because information about cognitive status is rarely

available and preservation of the brain is usually inadequate for detailed cytological examination **(Peters, 2002).**

Age-related DNA damage has been regarded as one of the possible explanations of aging, and these age-related changes have been associated with lifestyle variables (**Soares et al., 2015).**

Aging is characterized by an increasing morbidity and functional decline that eventually results in the death of an organism. Aging is the largest risk factor for numerous human diseases, and understanding the aging process may thereby facilitate the development of new treatments for age-associated diseases (**Mitchell et al., 2015).**

Although the impact of aging on the function of the central nervous system is known, only a limited amount of information is available about accompanying changes affecting the cellular composition of the brain and spinal cord **(Fu et al., 2015).**

The anterior cingulate cortex (ACC) is thought to be the neuroanatomical interface between emotion and cognition. Because effective emotion-cognition interactions are essential to optimal decision making, clarifying how the functionality of the ACC changes in older age using functional imaging holds great promise for ultimately understanding what contributes to the psychological changes occurring in late life **(Vaidya et al., 2007).**

The cingulate cortex comprises a number of structurally and functionally distinct areas that mediate aspects of attention, emotional regulation, and the integration of cognitive and emotional processes, in studies of healthy aging, the cingulate cortex has often shown vulnerability to gray matter loss **(Mann et al., 2011).**

Aim of the study

Few literatures described the detailed histological age related changes in the cingulate cortex so; the aim of this work is to investigate the histological age related changes in the cingulate cortex of male rabbits that would help in treatment of emotional and cognitive age related disorders.

Review of Literature

Development of Cingulate Cortex :

In general, the primary structures of the human limbic system include the hypothalamus, amygdala, hippocampus, septal nuclei, and cingulate gyrus; structures which are directly interconnected by massive axonal pathways. At 13 weeks, the entire inner limbic arch of the hippocampal formation is visible on the medial surface of the cerebral hemisphere. The hippocampal sulcus extends from frontal lobe to temporal lobe. At 16 weeks, the outer neocortical limbic arch of the subcallosal area, cingulate gyrus, and parahippocampus gyrus is present. Growth of the corpus callosum is associated with reduction in size of the hippocampal formation in the frontal lobe. The sulcus of the corpus callosum is the remnant of the anterior part of the hippocampal sulcus. At 18 weeks, growth of the parahippocampal gyrus begins to conceal the hippocampal formation. The supracallosal gyrus (indusiumgriseum), hidden from view by the corpus callosum, and the paraterminal gyrus are remnants of the previously larger hippocampal formation **(Kier et al., 1995).**

Anatomical and Functional Aspects Of Cingulate Cortex :

Human cingulate cortex:

The cingulate gyrus is the most prominent cortical feature on the medial surface of the human brain.It extends from the lamina

terminalis rostral to the anterior commissure, around the genu of the corpus callosum, over the body of the callosum, and just ventral to the splenium.The cingulate gyrus has a major role in most theories of emotion.Although it forms a single and continuous structure, the cingulate gyrus is structurally and functionally heterogeneous **(Vogt et al., 1992).**

The cingulate gyrus is the area that shows the most consistent pain-evoked changes in synaptic activity related to regional cerebral blood flow as measured by either positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) **(Derbyshire et al., 1997).**

The five layered of the human cingulate gyrus sits atop the corpus callosum and can be broadly divided into two segments. The anterior cingulate ACC (areas 24, 25, and 33) is concerned with vocalizing, emotional, and motoric functioning involving the hands and regulating autonomic and endocrine activities; and the posterior cingulate PCC (area 23) is involved in visual-spatial and tactile analysis as well as motor output and memory (**Joseph, 2000)**.

The structural and functional organization of the human cingulate cortex is an on-going focus. Recently, a four-region neurobiological model was proposed based on structural, circuitry, and functional imaging observations. It encompasses the

anterior cingulate, midcingulate, posterior cingulate, and retrosplenial cortices (ACC, MCC, PCC, and RSC, respectively **(Palomero-Gallagher et al., 2009).**

The cingulate gyrus may be divided rostrocaudally into several cytoarchitectonically discrete areas. These are the prelimbic (area 32) and infralimbic (area 25) cortices, the anterior cingulate cortex (areas 23 and 24) and part of the posterior cingulate or retrosplenial cortex (area 29). Through this system, afferents from widespread areas of association cortex converge upon the medial temporal lobe and hippocampal formation. (**Standring, 2008 and Kobayashi, 2011).**

Human functional imaging and neurocytology have produced important revisions to the organization of the cingulate gyrus and demonstrate four structure/function regions: anterior, midcingulate (MCC), posterior (PCC), and retrosplenial **(Hoffstaedter et al., 2012).**

The humancingulate cortex is a part of the brain situated in the medial aspect of the cerebral cortex. The cingulate cortex includes the cortex of the cingulate gyrus, which lies immediately above the corpus callosum, and the continuation of this in the cingulate sulcus. The cingulate cortex is usually considered as a part of the limbic lobe. It receives inputs from the thalamus and the neocortex, and projects to the entorhinal cortex via

the cingulum. It is an integral part of the limbic system, which is involved with emotion formation and processing, learning and memory (**Kozlovskiy et al., 2013).**

Amiezand Petrides (2014) examined the anatomo-functional organization of the cingulate motor areas in the human brain and revealed the existence of three somatotopically organized motor areas along the banks of the cingulate sulcus.

Vogt and Vogt (2004) studied the human cingulate cortex and demonstrated that anterior cingulate cortex (ACC) is not a single structural entity because amygdala and parietal projections into this region distinguished between its rostral and caudal parts. The amygdala has widespread connections throughout the cerebral cortexincluding primary and secondary visual areas; the primary distribution of this input on the medial surface is to areas 25 and 32 and rostral area 24. There is little input to the midcingulate region and none to posterior cingulate and retrosplenial cortices. In contrast, the parietal projection is massive throughout posterior cingulate cortex and midcingulate cortexbut does not appreciably extend into the perigenual part of ACC.

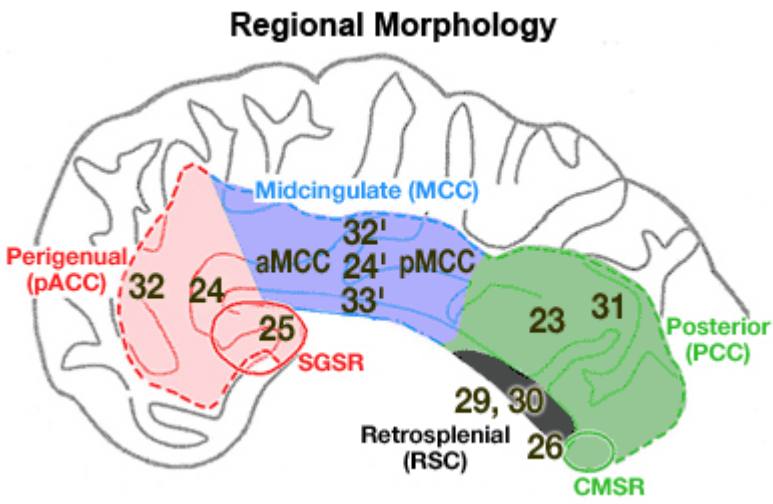

Figure 1: Four region neurobiological model of human cingulate cortex.A. pACC is comprised of areas; 33, 24, and 32 and includes a subgenual subregion 25.MCC includes areas 33', 24', 24d, and 32', the PCC is areas 23 and 31 and the caudomedialsubregion (CMSR), and the RSC is areas 29 and 30 **(After Vogt and Vogt, 2004)**.

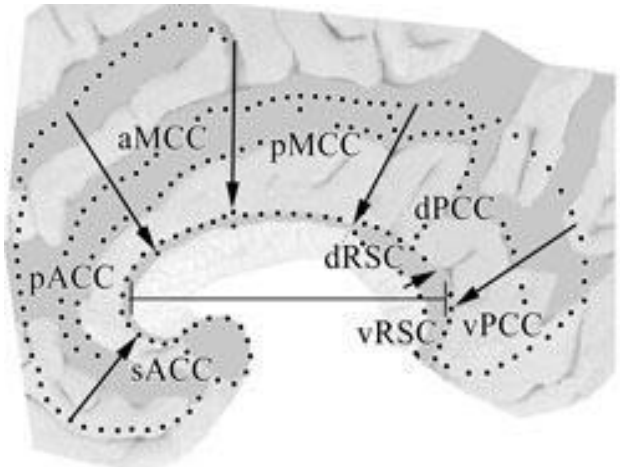

Figure 2: Cytoarchitectural bases of cingulate gyrus regions **(After Vogt and Vogt, 2004).**