

INTRODUCTION

The thalassemia syndromes and the structural hemoglobin variants (e.g. HbS in sickle cell disease) are considered the two major categories of hemoglobinopathies, which is now considered to be the commonest recessive monogenic disorders all over the world with about 7% carrier rate (**Weatherall, 2004; De Sanctis et al., 2017**). In Egypt, B-thalassemia is also considered the most common chronic hemolytic anemia, with a carrier rate varying from 5.3 to $\geq 9\%$ (**Shawky and Kamal, 2012**). Good control of anemia to hemoglobin at a level of (10–12 g/dl.) is achieved by cyclic transfusions of blood. The body also responds by increasing the intestinal iron absorption. These factors together with chronic hemolysis and apoptosis of the erythroid precursors lead eventually to iron overload (**Rund and Rachmilewitz, 2005**).

Elalfy et al. showed that patients with Beta-thalassemia had poorer cognitive functions in comparison to control subjects. Therefore, more researches are still needed to search for the causes of such neurological abnormalities. One of the major culprits is the secondary iron overload occurring in such group of patients (**Elalfy et al., 2017**). Furthermore, cerebrovascular accidents are serious complications in sickle cell disease (SCD) patients which can be the cause of neurocognitive impairments (**Brown et al., 2000; Helton et al., 2014**). However, there were some evidences that even in the

absence of overt cerebral strokes or parenchymal abnormalities in neurologically intact SCD patients; neurocognitive dysfunction could occur (*Vichinsky et al., 2010*).

Elevated iron in the brain has a neurotoxic effect through the formation of reactive oxygen species (ROS) which are a source of oxidative stress that initiates apoptotic signal pathways (*Hare et al., 2013*). Ferritin and hemosiderin are present in sufficient quantities to affect MR contrast in the human brain (*Schenck, 2003*). At least one third of the non-heme iron in the brain was in the form of ferritin with transferrin concentrations are at least 10 times lower than ferritin (*Conner et al., 1990*).

MRI is a reliable, safe, and non-invasive method for early detection of iron overload in many organs including the liver and heart and in therapeutic monitoring of the effect of chelation therapy. Studies have shown a good correlation between liver iron measured using MRI-T2* and that measured by liver biopsy (*Farhangi et al., 2017*). In MRI T2 weighted images using long echo times, regions with high iron deposition show marked loss of signal (hypointensity) due to decreased T2 transverse relaxation time caused by the induced microscopic magnetic fields surrounding the iron deposits (*Schenck, 2003*). T2* is calculated by fitting the single exponential terms to the signal decay curves of the respective multiecho data. R2* values are calculated as $R2^* = 1/T2^*$, so high R2* values indicate high iron deposition (*Blasco et al., 2014*).

AIM OF THE WORK

Up till now, it has not been known whether or not the brain is a target site for (abnormal) iron accumulation in beta-thalassemia or sickle cell disease patients. The current study will assess brain iron content (using $R2^*$ values) in the caudate and thalamic regions through quantitative brain MRI study in B-Thalassemia and SCD patients in comparison to age and sex-matched healthy controls. Also, evaluation of the association with the liver and heart iron concentrations will be done.

Chapter (1)

GROSS AND MRI ANATOMY OF THE BRAIN

The adult human brain weighs about 1336 grams (in males), and 1198 grams (in female) (*Hartmann et al., 1994*), with estimated volume of around 1260 cm³ in men and 1130 cm³ in women yet with individual variations (*Cosgrove et al., 2007*).

The brain (Fig.1) consists of: The cerebrum (cerebral hemispheres and diencephalon), the brainstem (midbrain, pons, and medulla), and the cerebellum. It is covered by three connective tissue membranes, the meninges and surrounded by cerebrospinal fluid (CSF) that supports and protects it from trauma. Another classification is that the brain could be classified into six postembryonic divisions: telencephalon, diencephalon, mesencephalon, pons, medulla oblongata, and cerebellum (*Gould, 2013*).

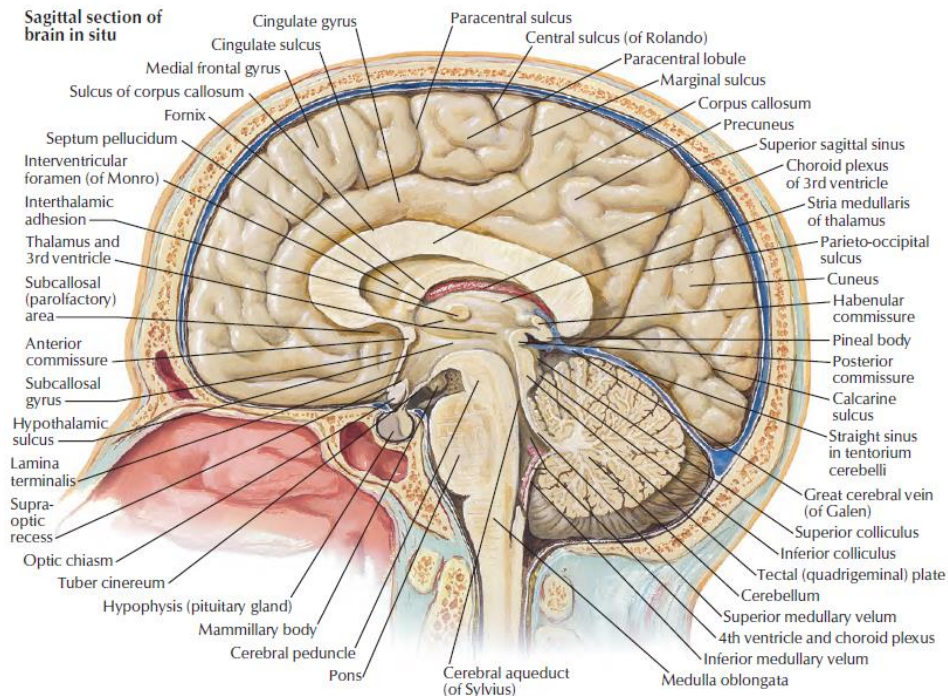


Figure 1: Anatomy of the sagittal section of the brain (*Netter, 2014*).

1- The cerebral hemispheres:

The cerebral hemispheres (Fig.2&3) are of nearly equal size, separated by a median deep cleft named the (Great longitudinal (interhemispheric) fissure) where the falx cerebri lies within and they are linked together by commissural white fibers. Each consists of outer cortical grey matter overlying the white matter with the lateral ventricles forming a cavity within each hemisphere (*Harnsberger et al., 2006*).

The superlateral surface of each cerebral hemisphere has two main deep sulci: The lateral sulcus (sylvian fissure) separating the frontal and temporal lobes, and the central sulcus

(of Rolando), which extends from the lateral sulcus upwards to the superior border of the hemisphere separating the frontal and parietal lobes. The medial surface has the parieto-occipital sulcus which separates the parietal and the occipital lobes yet with no complete sulcal separation of the parietal, temporal and occipital lobes on the lateral surface of each hemisphere (**Ryan et al., 2011**).

Each hemisphere is divided into *four* main lobes: the frontal, the parietal, the temporal, and the occipital lobes, yet in some other sources, three other lobes are included which are a central lobe, a limbic lobe, and an insular lobe. The central lobe comprises the precentral gyrus and the postcentral gyrus and is included as a separate lobe as it forms a distinct functional role (**Ribas, 2010; Frigeri et al., 2015**).

- **Insular lobe** (Insula of Reil): This is the cortex buried in the floor of the lateral sulcus and crossed by branches of the middle cerebral artery. Its function is still unknown yet the area closest to the sensory cortex may be related to taste. The operculum is defined as the parts of the frontal, parietal and temporal lobes overlying the insula (**Ryan et al., 2011**)
- **Limbic lobe (Fig.4&5)**: A C-shaped group of structures present on the medial surface of each cerebral hemisphere surrounding the corpus callosum and the lateral aspect of the midbrain.

Includes the following structures:

- (1) Paraterminal gyrus and subcallosal area.
- (2) Cingulate gyrus.
- (3) Parahippocampal gyrus.
- (4) Hippocampal formation (*Gould, 2013*)

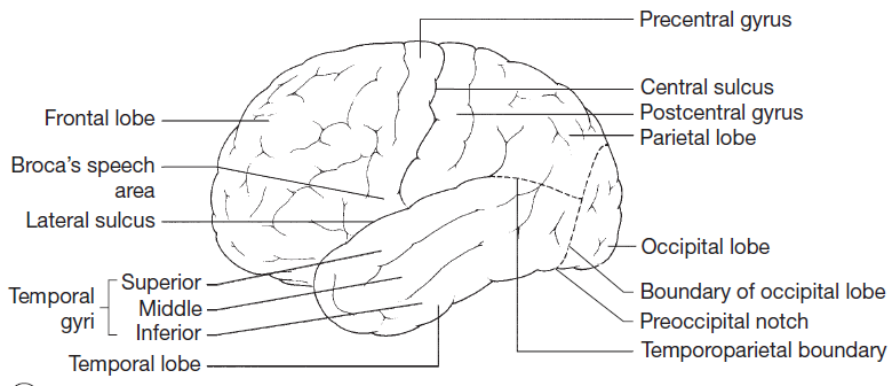


Figure 2: Cerebral hemisphere lobes (lateral surface)
(*Ryan et al., 2011*).

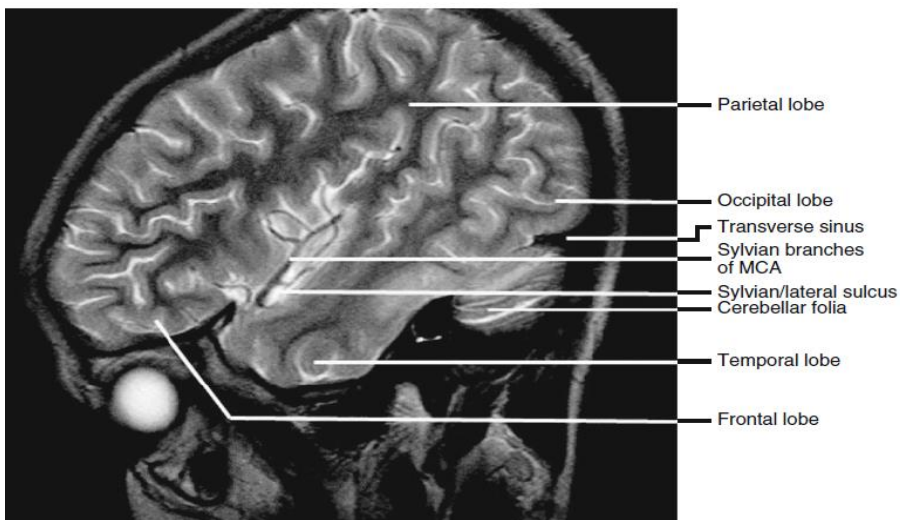


Figure 3: Sagittal T2 at the level of the Sylvian fissure
(*Andronikou, 2012*).

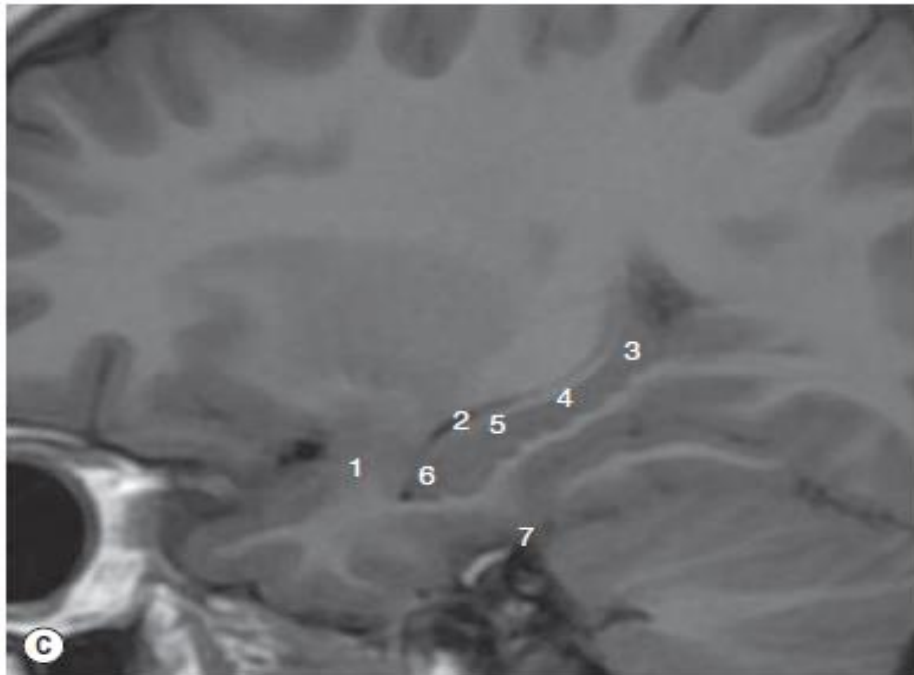


Figure 4: Parasagittal MRI showing hippocampus; 1.Amygdala 2.Temporal horn of lateral ventricle 3.Hippocampal tail 4.Hippocampal body 5.Fimbria of hippocampus 6.Hippocampal head 7.Parahippocampal gyrus (*Ryan et al., 2011*).

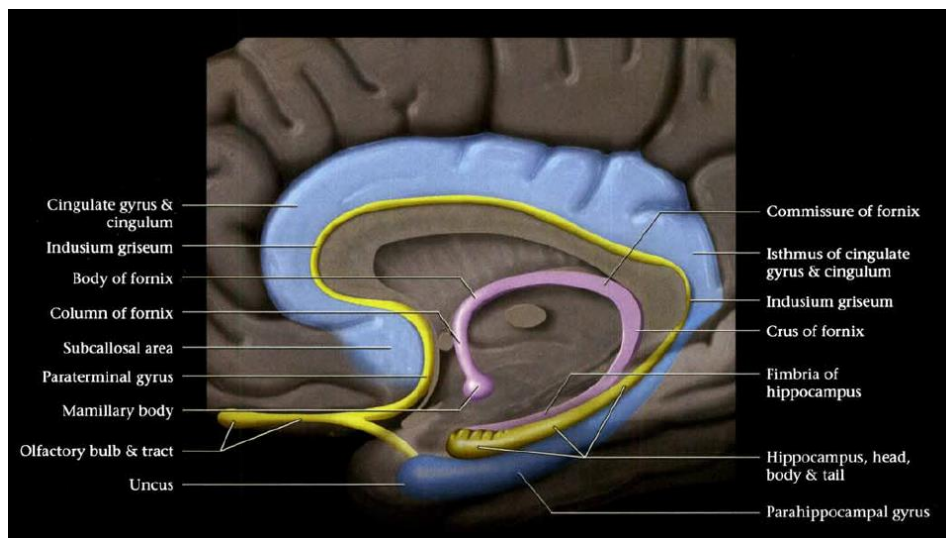


Figure 5: Sagittal diagram of the limbic system (*Harnsberger et al., 2006*).

Brain Lobes' Functions:

The frontal lobe: It contains the primary motor cortex, premotor cortex and prefrontal area.

- The **primary motor cortex** and premotor cortex controls the voluntary movements, the posteroinferior part of the premotor area on the dominant hemisphere controls the motor aspects of speech and is called Broca's speech area.
- **Prefrontal cortex** is found anterior to the motor and premotor cortex and it is involved with intellectual, emotional and autonomic activities (*Harnsberger et al., 2006; Ryan et al., 2011*).

The parietal lobe: It contains areas with known functions: the primary sensory cortex and the parietal association cortex (*Ryan et al., 2011*).

- **The primary somatosensory cortex** is found on the postcentral gyrus, its main function is controlling the somatic sensations of the contralateral body, where the face, tongue and lips are represented on the inferior surface, the trunk and upper limb superolaterally and lower limb on the medial aspect (*Harnsberger et al., 2006*).
- **Parietal association cortex** is posterior to the sensory cortex, involved with recognition and integration of sensory stimuli (*Ryan et al., 2011*).

The temporal lobe: It contains the following gyri:

- **Transverse temporal gyri of Heschl:** found within the lateral sulcus containing the **primary auditory areas** of the cerebral cortex (areas 41 and 42) (*Gould, 2013*).
- **Superior temporal gyrus:** associated with auditory functions and contains the **Wernicke speech area** in the dominant hemisphere (area 22) (*Gould, 2013*).

The Occipital lobe: It contains areas with specific functions including **the visual cortex** and **the occipital association cortex**.

- The **Visual cortex** is the area surrounding the calcarine sulcus (a deep sulcus running anteriorly on the medial surface from the occipital pole) receiving visual stimuli from the opposite half field of sight.
- The **Occipital association cortex** lies anterior to the visual cortex and is important in the recognition and integration of visual stimuli.

(*Ryan et al., 2011*)

2- Basal Ganglion:

This subcortical grey matter includes (Fig.6):

- The corpus striatum, the caudate and lentiform nuclei;
- The amygdaloid body; and
- The claustrum.

Strands of grey matter connect the head of the caudate nucleus with the putamen of the lentiform nucleus through the anterior limb of the internal capsule, that's why it has striated appearance and therefore it is named as (corpus striatum). It is considered as a part of the extrapyramidal system and has a role in the voluntary motor activity (*Ryan et al., 2011*).

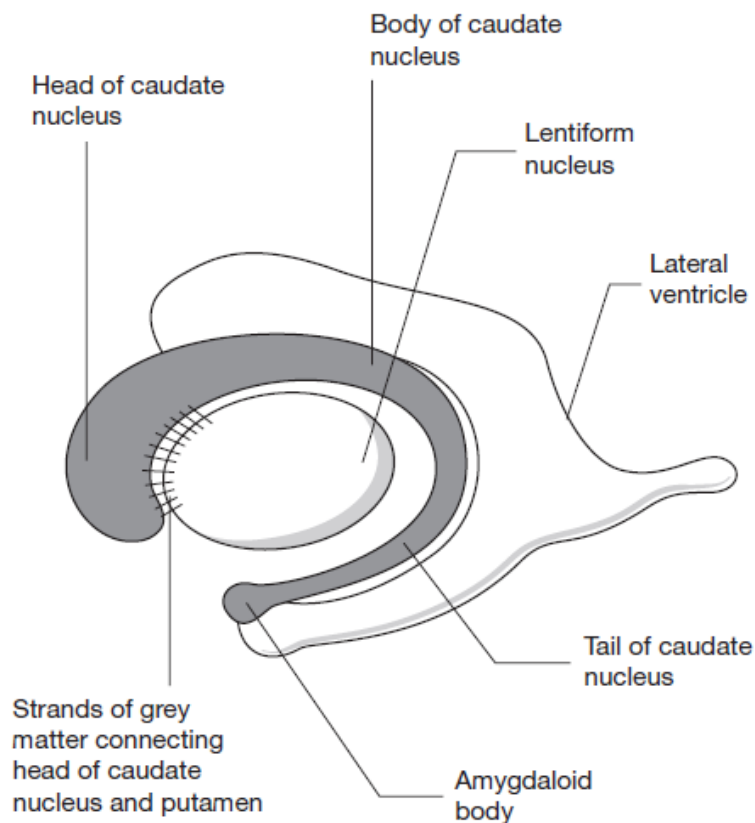


Figure 6: Basal ganglia structures (*Ryan et al., 2011*).

Morphological MRI Features of B.G.:

A- Lentiform nucleus:

- It looks like a biconcave lens (Fig.7) and is made up of a larger lateral putamen and a smaller medial globus pallidus. The internal capsule separates it from the head of the caudate medially and from the thalamus posteriorly. The external capsule is the thin layer of white matter on its lateral surface.

B- Caudate nucleus

- This nucleus consists of head, body and tail (Fig. 8, 9&10). It is highly curved and lies within the concavity of the lateral ventricle with its head projects into the floor of the anterior horn and its body lies along the body of the lateral ventricle and its tail lies in the roof of the inferior horn of this ventricle and ends in the amygdaloid nucleus

C-Clastrum:

- It is a thin sheet of grey matter lying between 2 thin layers of white matter: the external capsule medially and the extreme capsule laterally just deep to the insula.

(Ryan et al., 2011)

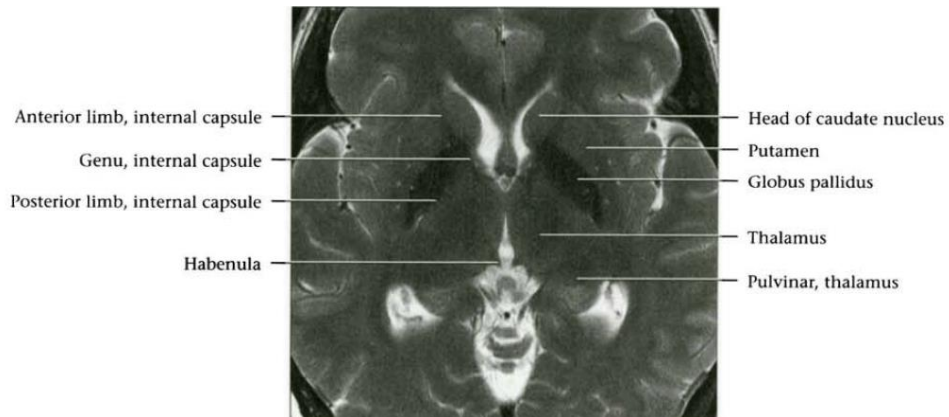


Figure 7: Axial MRI T2 image through basal ganglia & thalamus (*Harnsberger et al., 2006*).

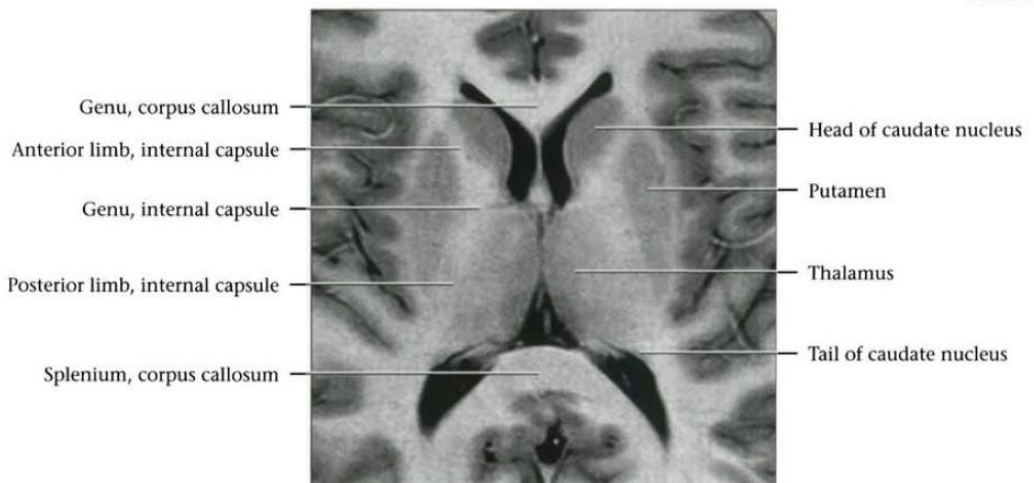


Figure 8: Axial T1 image through basal ganglia at level of genu & splenium of corpus callosum. Head & tail of caudate nucleus are seen as caudate curves around lateral ventricle (*Harnsberger et al., 2006*).



Figure 9: Axial T1 image at a higher-level shows body of caudate as it runs parallels to the lateral ventricles (*Harnsberger et al., 2006*).

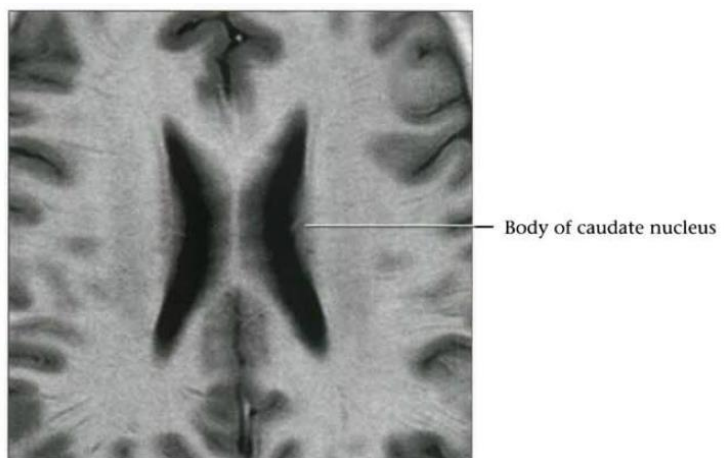


Figure 10: Axial T1 image at level of centrum semiovale shows body of caudate as it wraps around lateral ventricle (*Harnsberger et al., 2006*).

Basal Ganglion's Functions:

Studies show that the basal ganglion and its related nuclei (e.g. substantia nigra, subthalamic nucleus) plays an important role in the control of the motor body functions, also

they have many roles in executive, emotional, motivational, cognitive functions and in behaviour control.

The striatum, through the thalamus, connects the cortical regions of the brain to the prefrontal, premotor and motor area of the frontal lobes. Such circuits play important and substantial roles in attention, learning and potentiating behaviour-guiding rules.

Affection of the basal ganglion leads to many disorders, **Abulia** is one of commonest basal ganglionic disorders which lead to apathy with loss of initiative and of spontaneous thought and emotional responses. **Dystonia** is another disorder which causes affection of the motor functions and behavioural changes (*Herrero et al., 2002; Lanciego et al., 2012*).

3- Diencephalon:

- Located between the telencephalon and mesencephalon and between the interventricular foramina and the posterior commissure.
- It consists of the epithalamus, thalamus, hypothalamus, subthalamus, and the third ventricle and its associated structures (*Gould, 2013*).