● REVIEW

Neuroimaging characterization of recovery of impaired consciousness in patients with disorders of consciousness

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Abstract

Elucidation of critical brain areas or structures that are responsible for recovery of impaired consciousness in patients with disorders of consciousness is important because it can provide information that is useful when developing therapeutic strategies for neurorehabilitation or neurointervention in patients with disorders of consciousness. In this review, studies that have demonstrated brain changes during recovery of impaired consciousness were reviewed. These studies used positron emission tomography, electroencephalography/transcranial magnetic stimulation, diffusion tensor tractography, and diffusion tensor tractography/electroencephalography. The majority of these studies reported on the importance of supratentorial areas or structures in the recovery of impaired consciousness. The important brain areas or structures that were identified were the prefrontal cortex, basal forebrain, anterior cingulate cortex, and parietal cortex. These results have a clinically important implication that these brain areas or structures can be target areas for neurorehabilitation or neurointervention in patients with disorders of consciousness. However, most of studies were case reports; therefore, further original studies involving larger numbers of patients with disorders of consciousness are warranted. In addition, more detailed information on the brain areas or structures that are relevant to the recovery of impaired consciousness is needed.

Key Words: *consciousness; vegetative state; minimally conscious state; ascending reticular activating system; diffusion tensor imaging; neuroimaging; neural regeneration; review*

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Introduction

Consciousness is mainly controlled by actions of the ascending reticular activating system (Paus, 2000; Zeman, 2001). Impaired consciousness is caused by various brain pathologies including stroke, hypoxic-ischemic brain injury, and traumatic brain injury (Eapen et al., 2017). Among the various areas or structures of the brain, including the ascending reticular activating system, elucidation of the critical brain areas or structures that are responsible for recovery of impaired consciousness in patients with disorders of consciousness is important because it can provide information that is useful in developing prognoses or neurorehabilitation or neurointervention therapeutic strategies for patients with disorders of consciousness (Ragazzoni et al., 2017; Vanhoecke and Hariz, 2017). Many researchers have tried to elucidate the critical brain areas or structures in patients with disorders of consciousness using various neuroimaging techniques (Laureys et al., 1999, 2000; Boly et al., 2004, 2011; Giacino et al., 2004; Smith et al., 2004; Schnakers et al., 2008; Pollonini et al., 2010; Fernandez-Espejo et al., 2011; Lehembre et al., 2012; Rosanova et al., 2012; Kotchoubey et al., 2013; Bonfiglio et al., 2014; Holler et al., 2014; Bender et al., 2015; Jang and Lee, 2015; Qin et al., 2015; Stender et al., 2015; Jang et al., 2015, 2016a, b, c, 2017; Zou et al., 2017; Tan et al., 2018). However, the majority of those studies have focused on the difference between the vegetative state and the minimally conscious state. Fewer studies have demonstrated changes in the brain during recovery of impaired consciousness in patients with disorders of consciousness (Laureys et al., 2000; Rosanova et al., 2012; Jang et al., 2015, 2016a, b, c, 2017; Jang and Lee, 2015; Zou et al., 2017; Tan et al., 2018). In addition, the majority of the aforementioned studies have focused on individual patients rather than on original studies that involved a large number of patients.

Early studies on brain areas or structures that are relevant to the recovery of impaired consciousness have used positron emission tomography (PET) or electroencephalography (EEG) combined with transcranial magnetic stimulation (TMS) (Laureys et al., 1999, 2000; Boly et al., 2004; Schnakers et al., 2008; Pollonini et al., 2010; Boly et al., 2011; Lehembre et al., 2012; Rosanova et al., 2012; Kotchoubey et al., 2013; Bonfiglio et al., 2014; Holler et al., 2014; Qin et al., 2015; Stender et al., 2015). However, such evaluation tools are limited in their capacity to demonstrate the structural characteristics of the ascending reticular activating system, which is the main brain structure relevant to consciousness. By contrast, diffusion tensor tractography (DTT), which is reconstructed from diffusion tensor imaging data, has enabled three-dimensional evaluation of the ascending reticular activating system (Edlow et al., 2012). In addition, detailed estimation of the entire ascending reticular activating system, *via* segmentation of the ascending reticular activating system based on specific portions of the brain, has been made possible by applying DTT, for example, the lower dorsal ascending reticular activating system (the pontine reticular formation is connected to the intralaminar thalamic nuclei), the lower ventral ascending reticular activating system (the pontine reticular formation is connected to the hypothalamus), and the upper ascending reticular activating system (the intralaminar thalamic nuclei is connected to the cerebral cortex) have been reconstructed *via* DTT (Yeo et al., 2013; Jang and Kwon, 2015; Jang and Kwak, 2017). Several studies have used DTT to demonstrate structural changes in the ascending reticular activating system during recovery of impaired consciousness in patients with disorders of consciousness (Jang et al., 2015, 2016a, b, c; Jang and Lee, 2015, 2017; Zou et al., 2017; Tan et al., 2018).

In this review, neuroimaging studies that have demonstrated changes in the brain during recovery of impaired consciousness in patients with disorders of consciousness are reviewed. This review suggests a hypothesis that specific brain areas or structure is related to recovery of impaired consciousness. Relevant studies reported between 1966 and 2018 were identified by accessing electronic databases (PubMed, Google Scholar, and MEDLINE). In those database searches, the following keywords were used: disorders of consciousness, consciousness, ascending reticular activating system, diffusion tensor imaging, DTT, PET, functional MRI (fMRI), TMS, EEG, vegetative state, minimally conscious state, unresponsive wakefulness syndrome, and recovery of consciousness. This review is limited to studies of humans with disorders of consciousness and the relevant studies were selected according to the flow diagram presented in **Figure 1**. As a result of these searches, 11 studies (Laureys et al., 1999, 2000; Rosanova et al., 2012; Jang et al., 2015, 2016a, b, c; Jang and Lee, 2015, 2017; Zou et al., 2017; Tan et al., 2018) were selected for review and are discussed below.

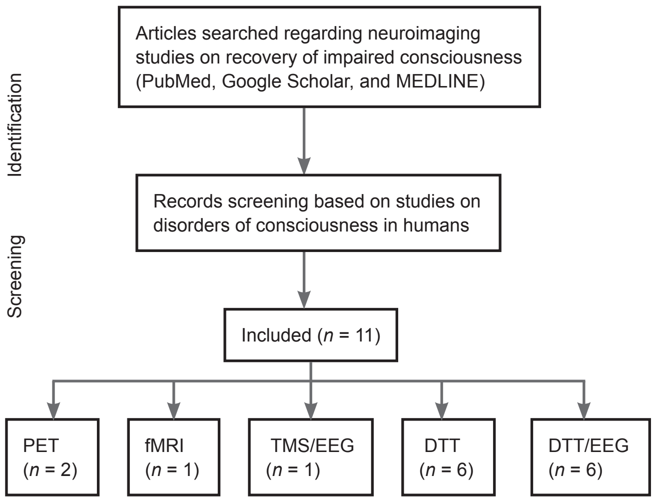

Figure 1 Flow diagram of study selection.
PET: Positron emission tomography; fMRI: functional magnetic resonance imaging: TMS; transcranial magnetic stimulation; EEG: electroencephalography; DTT; diffusion tensor tractography.

Review

Eleven studies (Laureys et al., 1999, 2000; Rosanova et al., 2012; Jang et al., 2015, 2016a, b, c; Jang and Lee, 2015, 2017; Zou et al., 2017; Tan et al., 2018) demonstrated changes in the brain during recovery of impaired consciousness. These studies used PET (two studies), fMRI (one study), TMS/EEG (one study), DTT (six studies), and DTT/EEG (one study) to describe the changes. These studies are summarized in **Table 1** and are reviewed in the following.

PET

In 1999, by applying fluorodeoxyglucose PET, Laureys et al. (2019) reported a change in the cerebral glucose metabolic rate during recovery of impaired consciousness in a patient with disorders of consciousness following CO intoxication. Fluorodeoxyglucose PET was performed twice, first during the patient's vegetative state (15 days after admission) and second after the patient recovered to consciousness (37 days after admission). During the vegetative state, the cerebral glucose metabolic rate decreased in the left and right superior parietal lobules, the left inferior parietal lobule, the precuneus, the left superior occipital gyrus, the superior and middle temporal gyri, and the premotor, postcentral, and precentral cortices. The patient revealed an attention deficit with moderate impairment of short-term memory at 1 month after admission and a spastic gait, slurred speech, and minor short-term memory disturbance at 1 year after onset. After recovery of consciousness at 37 days after admission, metabolic impairment was confined to the left and right precentral and postcentral gyri and the premotor cortex, with resolution of the metabolic decrement in the posterior associative cortices. As a result, the authors concluded that the posterior associative cortices had a critical role in recovery of impaired consciousness in this patient (Laureys et al., 1999).

Subsequently, Laureys et al. (2000) demonstrated a change in regional cerebral blood flow using $H2^{15}O$ PET during recovery of impaired consciousness in a patient with disorders of consciousness (the disease entity was not documented in the paper). They assessed the functional connectivity between the intralaminar thalamic nuclei and the cerebral cortex during the patient's vegetative state and after recovery of consciousness (the precise state of consciousness of the patient after recovery was not described in the paper). When the patient was in a vegetative state, Laureys et al. observed that the functional connectivities between the intralaminar thalamic nuclei and the right prefrontal (Brodmann's areas 10, 9, and 8) and anterior cingulate (area 24/32) cortices were lower than those in healthy controls, whereas these decrements were normalized when the patient recovered from impaired consciousness. Consequently, the authors suggested that restoration of consciousness appeared to be paralleled by the resumption of the functional relationships between the thalamus and the aforementioned associative cortices. Based on those observations, the thalamocortical connections were deemed to have an important role in the maintenance of consciousness in human brain.

fMRI

In 2017, Zou et al. analyzed resting state fMRI using whole brain voxel-wise amplitude of low-frequency fluctuation to measure the fluctuation strength of local spontaneous activity in 23 acquired brain injury patients (8 patients: fully preserved consciouness state, 9 patients: minimally conscious state, 4 patients: unresponsive wakefulness syndrome/vegetative state, and 2 patients: coma state) and 30 control subjects. The first scan was conducted at average 81.1 days after onset, and a time gap between the two scans at average 75.8 days after onset. The level of consciousness was assessed using the Glasgow Coma Scale (GCS) and Coma Recovery Scale-Revised (CRSR) scale on both fMRI scan days. Results showed that the interaction effect in the precuneus was driven by restored low-frequency fluctuation in the acquired brain injury group without significant change in the control group. The decreased low-frequency fluctuation of the precuneus in the acquired brain injury group was increased to a similar level to the control group at the second scan, suggesting that the local neuronal activity in the precuneus in acquired brain injury patients recovered normal. The average longitudinal changes in low-frequency fluctuation in the presumes showed positive correlations with improvements in both the GCS and CRSR scores. As a result, the authors concluded that the resting-state local neuronal activity in the precuneus could be useful for the guidance and development of rehabilitative therapy.

TMS with EEG

In 2012, using TMS combined with EEG, Rosanova et al. estimated the levels of cortical effective connectivity (a key requirement for consciousness is that multiple, specialized cortical areas can engage in rapid causal interactions) in three patients who showed recovery of impaired consciousness. The three patients (two patients: stroke; one patient: traumatic brain injury) revealed recovery of impaired consciousness from a vegetative state to a functionally communicable state (able to obey motor commands) through a minimally conscious state. Using three sessions of TMS/EEG in the three patients, they observed that TMS triggered a complex pattern of activation that sequentially involved a large set of cortical areas (*i.e.*, effective connectivity) and could occur at an early stage before reliable communication was established. On the other hand, the two patients who remained in the vegetative state showed either a local simple activation wave or no response. As a result, they suggested that measurement of cortical effective connectivity using TMS/EEG can be an effective way to detect and track recovery of consciousness in patients who are unable to exchange information with the external environment following disorders of consciousness.

DTT

In 2015, Jang et al. reported recovery of an injured lower dorsal ascending reticular activating system in a patient with traumatic brain injury. The patient suffered the traumatic brain injury by falling while riding a horse and underwent decompressive craniectomy and removal of a subdural hematoma on the right fronto-temporo-parietal lobe. At 4 months

Table 1 Neuroimaging studies that have demonstrated changes in the brain during recovery of impaired consciousness in patients with disorders of consciousness

Neuroimaging technique	Authors	Patient number	Disease	Consciousness state	Brain areas related to recovery of impaired consciousness
PET	Laureys et al. (1999)	1	CO intoxication	Vegetative → normal	Posterior associative cortices (parieto-temporo-occipital)
	Laureys et al. (2000)	1	Unknown	Vegetative → not described	Thalamocortical connectivity (prefrontal & anterior cingulate)
fMRI	Zou et al. (2017)	23	Acquired brain injury		Precuneus
TMS/EEG	Rosanova et al. (2012)	3	Stroke (2) TBI (1)	Vegetative → communicable	Cortical effective connectivity
DTT	Jang et al. (2015)	1	TBI	MCS → communicable	Lower dorsal ARAS
	Jang & Lee (2015)	1	HI-BI	PVS → MCS	Lower dorsal ARA Upper ARAS (prefrontal & basal forebrain)
	Jang et al. (2016c)	1	HI-BI	MCS → normal	Lower dorsal & ventral ARAS Upper ARAS (prefrontal & basal forebrain)
	Jang et al. (2016b)	1	Stroke	PVS → MCS	Upper ARAS (prefrontal & thalamus)
	Jang et al. (2016a)	1	TBI HI-BI	Vegetative → MCS	Upper ARAS (hypothalamus, basal forebrain, prefrontal, anterior cingulate & parietal)
	Jang & Lee (2017)	1	Stroke	Vegetative → normal	Lower dorsal & ventral ARAS Upper ARAS (prefrontal & basal forebrain)
DTT/EEG	Tan et al. (2018)	1	TBI	Vegetative → MCS	Temporoparietal junction area

PET: Positron emission tomography; fMRI: functional MRI; TMS/EEG: transcranial magnetic stimulation/electroencephalography; TBI: traumatic brain injury; DTT: diffusion tensor tractography; MCS: minimally conscious state; ARAS: ascending reticular activating system; HI-BI: hypoxic-ischemic brain injury; PVS: persistent vegetative state.

from onset, he was in a minimally conscious state with a GCS score of 7 (eye opening: 3, verbal response: 1, and motor response: 3) (Teasdale and Jennett, 1974; Giacino et al., 2002). At 40 months after onset, the patient recovered to a communicable state with a GCS score of 15 (full score). A 4-month DTT of the patient showed injury of the lower dorsal ascending reticular activating system when compared with that in normal subjects; however, on a 40-month DTT, the once-injured lower dorsal ascending reticular activating system had recovered to a state similar to that of normal subjects. As a result, the authors demonstrated recovery of an injured lower dorsal ascending reticular activating system concurrent with recovery of impaired consciousness (Jang et al., 2015).

During the same year, Jang and Lee (2015) demonstrated recovery of the lower dorsal ascending reticular activating system, as well as recovery of the upper ascending reticular activating system in a patient who recovered from impaired consciousness following hypoxic-ischemic brain injury. The patient was diagnosed as hypoxic-ischemic brain injury following cardiac and respiratory arrest due to epiglottitis. At 7 months after onset, the patient exhibited a persistent vegetative state with a GCS score of 6 (eye opening: 2, best verbal response: 1, and best motor response: 3) (Teasdale and Jennett, 1974; Multi-Society Task Force on PVS, 1994). She underwent comprehensive rehabilitation, including drugs for recovery of impaired consciousness (ropinirole and bromocriptine) for 4 years after onset. At 4 years after onset, her impaired consciousness had recovered to a minimally conscious state with a GCS score of 12 (eye opening: 4, best verbal response: 2, and best motor response: 6) (Teasdale and Jennett, 1974; Giacino et al., 2002). At 7 months after onset, DTT revealed that both the upper and right lower dorsal ascending reticular activating system were injured when compared with those in normal controls. However, on DTT at 4 years after onset, these injuries were no longer detected and the ascending reticular activating system appeared to have recovered to a normal state. In particular, compared to the 7-month DTT, there was increased neural connectivity to both the basal forebrain and prefrontal cortex observed on the 4-year DTT. The authors suggested that the lower dorsal and upper ascending reticular activating system changes were related to the recovery of impaired consciousness in this patient (Jang and Lee, 2015).

In 2016, Jang et al. reported on a patient who showed recovery of impaired consciousness and injured ascending reticular activating system over a period of 3 weeks in the early stage of hypoxic-ischemic brain injury. The patient had suffered cardiac arrest induced by acute coronary syndrome and was transferred to the emergency room of a local medical center. When the patient started rehabilitation at 2 weeks after onset, he exhibited a minimally conscious state with a GCS score of 8 and a CRSR score of 8 (Teasdale and Jennett, 1974; Giacino et al., 2004; Jang and Kwak, 2017). He underwent comprehensive rehabilitation including drugs for recovery of impaired consciousness (modafinil, levodopa, ropinirole, amantadine, zolpidem, and donepezil) (Georgiopoulos et al., 2010; Schiff, 2010; Ciurleo et al., 2013; Noormandi et al., 2017). He recovered well and rapidly, and his consciousness recovered to full scores on the GCS (15) and CRSR (23) at 5 weeks after onset. On DTT at 5 weeks after onset, the left lower dorsal ascending reticular activating system and the right lower ventral ascending reticular activating system showed recovery compared with those on 2-week DTT. Regarding the upper ascending reticular activating system, the neural connectivity to the basal forebrain and prefrontal cortex in both hemispheres on 5-week DTT had increased compared to that observed on 2-week DTT. As a result, consciousness and injury recoveries in the injured lower dorsal, lower ventral, and upper ascending reticular activating systems were demonstrated to occur during a 3-week period in the early stage of hypoxic-ischemic brain injury in this patient (Jang et al., 2016c).

During the same year, Jang et al. reported on a stroke patient with changes in the ascending reticular activating system that were concurrent with recovery from a persistent vegetative state to a minimally conscious state (Jang et al., 2016b). The patient underwent computed tomography-guided stereotactic drainage three times for management of spontaneous intracerebral and intraventricular hemorrhage. At 4 months after onset, the patient showed impaired consciousness (persistent vegetative state) with a GCS score of 6 and a CRSR score of 2 (Teasdale and Jennett, 1974; Multi-Society Task Force on PVS, 1994; Giacino et al., 2004). He underwent comprehensive rehabilitation including drugs for recovery of impaired consciousness (modafinil, methylphenidate, amantadine, levodopa, zolpidem, and baclofen) (Georgiopoulos et al., 2010; Schiff, 2010; Ciurleo et al., 2013; Noormandi et al., 2017). His consciousness recovered to a minimally conscious state at 10 months after onset with test results revealing a GCS score of 11 and a CRSR score of 20 (Teasdale and Jennett, 1974; Giacino et al., 2002, 2004). Compared to their status on 4-month DTT, the DTT results at 10 months after onset revealed increased neural connectivity of the thalamic intralaminar nucleus to the cerebral cortex in both prefrontal cortices, as well as improved connectivity in the right thalamus. However, on 10-month DTT, there was no significant change in the lower dorsal ascending reticular activating system. The authors suggested that the prefrontal cortex and thalamus, which showed increased neural connectivity, appeared to be related to the patient's recovery from a persistent vegetative state to a minimally conscious state (Jang et al., 2016b).

Also in 2016, Jang et al. demonstrated changes in the ascending reticular activating system that were concurrent with the recovery from a vegetative state to a minimally conscious state in a patient with traumatic brain injury (Jang et al., 2016a). While a passenger in a vehicle suffered a traumatic brain injury during a collision with a truck. At the time, he underwent cardiopulmonary resuscitation for approximately 10 minutes due to immediate cardiac arrest after the head trauma. At 10 months after onset, the patient exhibited a vegetative state with a CRSR score of 7 (Teasdale and Jennett, 1974; Multi-Society Task Force on PVS, 1994; Giacino et al., 2004) and underwent a ventriculo-peritoneal shunt operation for hydrocephalus. After the shunt operation, he underwent comprehensive rehabilitation including drugs for recovery of impaired consciousness (modafinil, methylphenidate, ropinirole, and baclofen) (Georgiopoulos et al., 2010; Schiff, 2010; Ciurleo et al., 2013; Noormandi et al., 2017). At 2 weeks after the operation, his GCS score indicated recovery to a minimally conscious state with a GCS score of 11 and a CRSR score of 15 (Teasdale and Jennett, 1974; Giacino et al., 2002, 2004). At 8 weeks post-operation, his consciousness improved, with a GCS score of 12 and a CRSR score of 17 (Teasdale and Jennett, 1974; Giacino et al., 2002; Giacino et al., 2004). As a result, he was able to control head movements for approximately 1 minute in a sitting position and to track his eyes intermittently in response to a verbal command at 8 weeks post-operation. Serial post-operation DTT results showed increased neural connectivities to the hypothalamus, basal forebrain, prefrontal cortex, anterior cingulate cortex, and parietal cortex in both hemispheres compared to the connectivities observed on the pre-operation DTT. The authors concluded that connectivity recovery in these areas might have contributed to the recovery of impaired consciousness in this patient (Jang et al., 2016a).

Recently, Jang and Lee (2017) reported on a stroke patient who showed recovery of consciousness concurrent with recovery of an ascending reticular activating system with multiple injuries (Jang and Lee, 2016). The patient was diagnosed as spontaneous intraventricular hemorrhage and intracerebral hemorrhage in the left basal ganglia, and he underwent frontal extraventricular drainage in both hemispheres. At 1 month after onset, when starting rehabilitation, he exhibited a vegetative state with a GCS score of 9 and a CRSR score of 5 (Teasdale and Jennett, 1974; Multi-Society Task Force on PVS, 1994; Giacino et al., 2004). He underwent comprehensive rehabilitation with drugs for recovery of impaired consciousness (pramipexole, ropinirole, amantadine, and levodopa) (Georgiopoulos et al., 2010; Schiff, 2010; Ciurleo et al., 2013; Noormandi et al., 2017). At 7 months after onset, his test scores indicated he had recovered to a communicable state, exhibiting a GCS full score (15) and a CRSR score of 22 (Teasdale and Jennett, 1974; Giacino et al., 2004). The patient's 7-month DTT results revealed recovery of the injured lower dorsal and ventral ascending reticular activating system; moreover, the neural connectivity of the upper ascending reticular activating system to the right prefrontal cortex and basal forebrain had increased compared with that on the DTT results obtained at 1 month after onset. As a result, the authors concluded that recovery of the multiple injuries in the ascending reticular activating system was related to the concurrent recovery of impaired consciousness in this patient (Jang and Lee, 2016).

DTT with EEG

Recently, Tan et al. (2018) reported on a patient with traumatic brain injury due to a traffic accident who recovered from a vegetative state to a minimally conscious state. At 1.5 months after onset, the patient showed a vegetative state with a CRSR score of 4. Sleep spindle wave was not found on 24-hour dynamic EEG. With the conservative management, the patient recovered consciousness to a minimally conscious state: at 5 months after onset, the patient's CRSR score had recovered to 16 and 24-hour dynamic EEG revealed obvious sleep stages and spindle waves. In connectometry analysis of diffusion tensor imaging data, the number of fibers with increased density and magnitude was greatest in the temporoparietal junction at the minimally conscious state compared with the vegetative state, which was coincided with the active areas observed on 24-hour EEG recordings. In addition, analysis of different fibers across the brain showing at least a 10% increase in density showed that altered white matter connections were located within or across visual-related areas and auditory cortex.

Conclusions

Most of the studies reported the importance of supratentorial areas or structures for recovery of impaired consciousness. The described specific brain areas or structures can be summarized as follows: the prefrontal cortex, the basal forebrain, the anterior cingulate cortex, and the parietal cortex (**Figure 2**). Among these areas, results associated with the prefrontal cortex, which has been reported most commonly as an area critical for consciousness, appear to support the results of studies demonstrating the importance of the prefrontal lobe in distinguishing between the vegetative state and the minimally conscious state (Boly et al., 2004, 2011; Holler et al., 2014; Stender et al., 2015). These results have a clinically important implication that the results of the studies reviewed herein indicate that the above-mentioned brain areas or structures could be target areas for neurorehabilitation or neurointervention in patients with disorders of consciousness (Ragazzoni et al., 2017; Vanhoecke and Hariz, 2017). However, most studies were case reports; therefore, further original studies involving a larger number of patients with disorders of consciousness are warranted. In addition, there is a need for more detailed information on the areas or structures of the brain that are critical or relevant to the recovery of impaired consciousness. Further studies which elucidate the critical areas discriminating vegetative, minimally conscious, confusional, and normal conscious states are also needed.

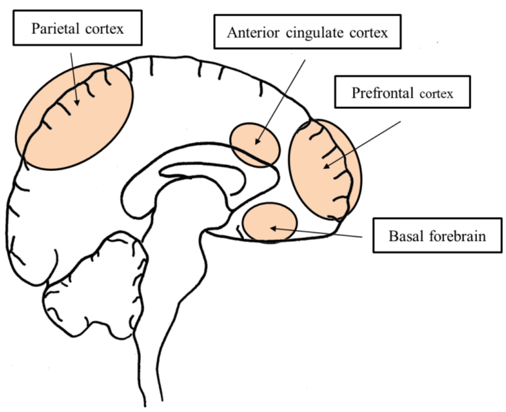

Figure 2 Cartoon line diagram about brain areas or structures for recovery of impaired consciousness.

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