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CASE STUDY

Cognitive dysfunction in basal ganglia and thalamic stroke patients: A case study approach

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Abstract

BACKGROUND: Cerebrovascular stroke presents a wide range of cognitive features. The cortical strokes are widely associated with higher-order cognitive dysfunctions, while the subcortical strokes are reported to result in a more homogeneous profile of executive dysfunctions. Now a growing body of evidence indicates complex functional impairment for insults in the subcortical systems such as basal ganglia (BG) and thalamus as well but more systematic reporting is awaiting.
AIMS: The aim of our study was to identify the nature of cognitive dysfunctions if any in BG and Thalamic insults.
METHODS AND MATERIAL: From a pool of 12 patients with BG stroke, 7 patients were selected for the present study. Amongst them 4 patients had predominantly unilateral putaminal lesions with and without associated unilateral thalamic lesions and 2 patients had bilateral BG and thalamic lesions and 1 bilateral putaminal lesion extending to the left caudate nucleus. Their level of cognitive functioning was evaluated using neuropsychological tests such as Digit span tests, the Random 'A' letter test, Serial Subtraction test and the Block design test.
RESULTS: The findings revealed attentional and working memory impairment in BG stroke with associated thalamic strokes. The tasks of concept attainment were adversely affected in BG stroke with or without thalamic insults, indicating the necessity of BG and thalamic mediation in complex task.
CONCLUSION: A specific pattern of cognitive impairment is evident in BG and thalamic stroke implicating their role in higher cognitive functions.

Introduction

Post-stroke cognitive impairment is the result of loss of functional connectivity between different areas of the brain. Clinically, cerebrovascular stroke presents a wide range of cognitive features that often involves difficulties in attention, working memory, executive functions and visuospatial processing (Lo *et al.* 2019).

While cortical strokes are mostly associated with deficits in cognitive processes of executive functions, abstract reasoning, language and memory (Nys *et al.* 2007), the subcortical post stroke cognitive impairment (PSCI) presents more homogenous cognitive profile characterized by executive dysfunction and less severe memory impairment (Andrade *et al.* 2012). During the initial investigation phase for this study, the second author and the third author observed in-house patients with subcortical strokes presenting complex cognitive features unlike suggested in the existing literature. Although a few recent studies on basal ganglia and thalamic lesions have reported complex functional impairments not constrained to just local functional abnormalities (Yao *et al.* 2020; Temel *et al.* 2021); more systematic reporting is still awaiting. Moreover, the role of the cortico-striato-thalamo-cortico circuit is known to be a key component in many different cognitive processes (Alexander *et al.* 1986; Grahn *et al.* 2009; Stocco *et al.* 2010) that range from attention (Ravizza & Ivry 2001), perception (Prat *et al.* 2007), memory (Packard *et al.* 1989), to higher order cognitive functions, such as, planning (Anderson *et al.* 2005) and mathematical problem solving (Stocco & Anderson 2008). The models of the subcortical systems, such as BG and thalamus that represent them just as conduits of the bidirectional flow of neural signals between cortical and subcortical structures, are now being pushed aside revealing a more complex contribution of these systems for cognition. Both the BG and thalamus are heterogeneous structures with multiple nuclei each with different anatomical connectivity and functional properties. Much of the cognitive functionality, however, has been attributed to the activity changes in the caudate nucleus of BG and ventral anterior nucleus of thalamus (VA) (Zhang *et al.* 2020). The putamen, on the other hand, has been ascribed the motor functionality aspect though a growing body of evidence suggests its role in cognition as well (Ell *et al.* 2011).

The need for more systematic research for further understanding of the pattern of cognitive dysfunctions in striatal lesions prompted us to study a series of 7 selected patients with BG, mostly putaminal lesions, with and without associated bilateral or unilateral thalamic lesions, to identify their independent contribution to the cognitive impairment, with the vision to develop an accurate understanding of their roles in the cognitive network.

Methods

Participants

The patients, previously neurologically normal, who suffered an ischemic infarction of the BG, were selected for the purpose of this study following ethical processes of research. The diagnosis was made by neurologists, in a clinic of Neurology Department, in a Government Hospital in Kolkata. Of a pool of 12 patients investigated, seven patients (6 males and 1 female) between 33 and 65 years were included in this study.

Patients(right-handed) suffering from unilateral or a bilateral BG lesion due to ischemic stroke sparing the cerebral cortex, were included in the study.

Patients with a history of any prior stroke, head injury, Central Nervous System infection, pre-stroke dementia or any other psychiatric disorder and with other severe post-stroke symptoms were excluded from the study.

Informed consent was taken from each participant before final inclusion.

Assessment tools

The following tools were used for initial assessment

1. Information schedule
2. Edinburgh handedness Inventory (Oldfield 1971) - This is a self-administering screening test to assess handedness, a prerequisite for neuropsychological assessment.
3. Brief mental status examination form (Mayer-Gross *et al.* 1960)
4. Neuroimaging- MRI and/or CT scan

Neuropsychological measures

The following tests were used as Neuropsychological measures

1. **Digit span test** (Wechsler 2008) – The items of this task have been taken from Wechsler Adult Intelligence Scale- IV(WAIS-IV). The Digit span test comprises of two different tests, Digits Forward and Digits Backward. Both tests consist of pairs of random numbers in increasing sequence length.
   - Digit Span Forward (DF) - In this task, the digits are to be repeated in the same order as read out by the examiner. It measures the efficiency of attention i.e. freedom from distractibility (Lezak *et al.* 2004, pg-353) and hence assesses the selectivity aspect of attention.
   - Digit Span Backward (DB) - In this task, digits are to be repeated in the reverse order by the participants. This is a working memory task involving double tracking where both the memory and the reversing operations must proceed simultaneously (Lezak *et al.* 2004, pg-360). This task demands spatial repositioning of the digit sequence hence requiring the simultaneous online processing of both verbal and visual information.

Tab. 1. Characteristics and Neuroimaging findings of the patients

Case No.	Age	Sex* M/F	Detailed Neuroimaging findings (site of lesion)
1	36	M	Right Putamen, centrum semiovale, posterior limb of internal capsule and right periventricular region.
2	33	F	Right Putamen, posterior limb of internal capsule and right periventricular area
3	58	M	Left Putamen, left thalamus, left posterior limb of internal capsule, adjoining areas of globus pallidus externa,
4	50	M	Left putamen, external capsule and left periventricular region.
5	62	M	Bilateral basal ganglia and bilateral thalamus
6	65	M	Bilateral basal ganglia and bilateral thalamus
7	54	M	Bilateral Putamen and left caudate

*M=Male; F= Female

2. **Random 'A' Letter Test (ARLT)** (Nasreddine 2005) – This test was taken from Montreal Cognitive Assessment test. It consists of a series of random letters among which a target letter appears with "greater than random" frequency (Strub & Black 1995). The task was administered in the auditory modality by reading out the letters. The task of the participant is to tap when the target letter is presented. The test demands selection of task-relevant information and suppression of task-irrelevant information. It evaluates the response inhibitory capacity of the participant. Scoring in this test is done in terms of errors (Lezak *et al.* 2004).
   i. Omission error – Failure to indicate when the target letter has been presented
   ii. Commission error – Indication made when a non-target letter has been presented
   iii. Perseveration error – continuation of commission error for a long period, failing to suppress response to task irrelevant information.
3. **Serial Subtraction (SS)** (Nasreddine 2005) – The task requires continuous subtraction of a specific number (40–3) in a consecutive sequence in a reverse order up to 5 steps. It evaluates the ability to maintain task relevant activity over a period of time and also requires continuous self-monitoring (Lezak *et al.* 2004).
4. **Block Design (BD)** (Wechsler 2008) – This task has been taken from WAIS IV. It involves the construction of a two-dimensional design with three dimensional blocks. This task demands visuo-spatial concept attainment, planning and problem solving (Lezak *et al.* 2004).

Procedure

Patients with primary lesion in BG as revealed on neuroimaging findings, diagnosed by the neurologist and fulfilled the inclusion and exclusion criteria, were taken up in this study. After screening for handedness using Edinburgh Handedness inventory, a detailed case history was taken, which was followed by neuropsychological testing, using the respective standard procedure of administration. The overall assessment took around one and a half hours. In between the assessment, rest was provided for five minutes every thirty minutes to reduce the fatigue effect and as required by the patient. The testing was done in a single structured room.

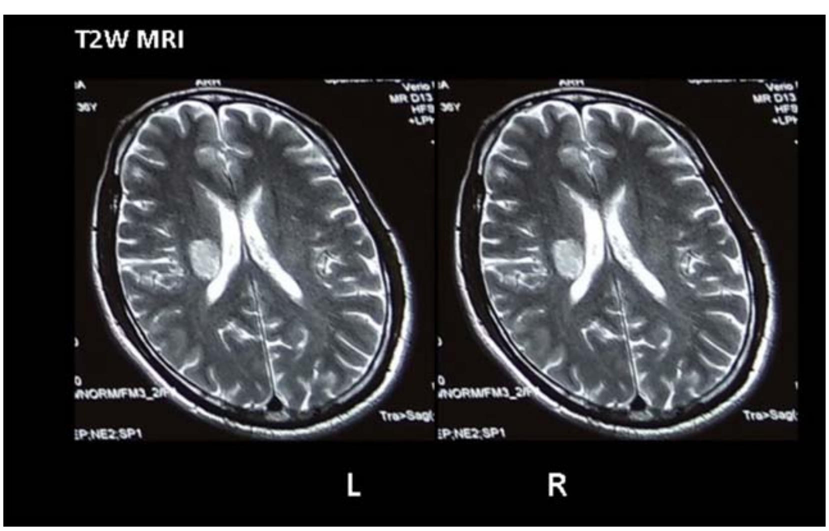

Fig. 1A. A T2 Weighted Magnetic resonance image of a 36 year old man with a right putaminal infarct extending to the right periventricular region. L=left hemisphere; R= right hemisphere

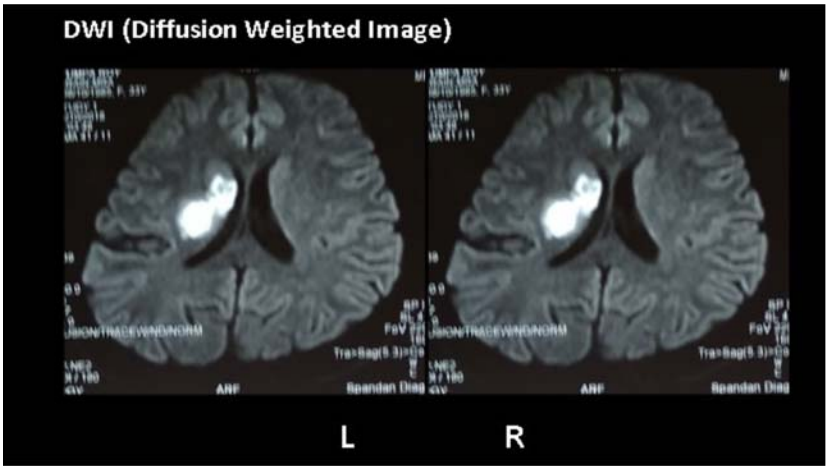

Fig. 1B. A Diffusion Weighted Magnetic resonance image of a 33 year old woman with a right putaminal infarct extending to the right periventricular region. L=left hemisphere; R= right hemisphere

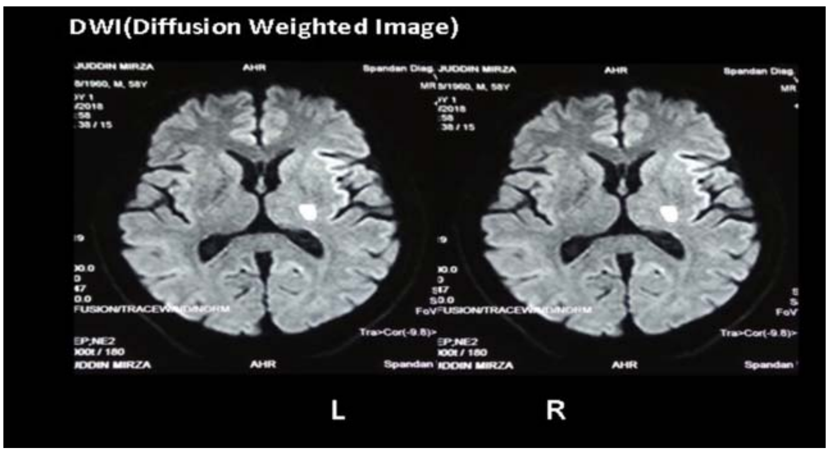

Fig. 1C. A Diffusion Weighted Magnetic resonance image of a 58 year old man with a left putaminal infarct extending to the left thalamus region left posterior limb of internal capsule, adjoining areas of globus pallidus externa. L=left hemisphere; R= right hemisphere

Results

Of seven patients with BG stroke (6 males and 1 female) and mean age of 51.1 years (range 33-65 years), two patients had infarcts in the right putamen with associated infarcts in right periventricular areas, internal capsule and centrum semiovale [patient 1, Fig 1A and patient 2, Fig 1B]. Two patients showed infarcts in the left putamen that extended to the thalamus in one case [patient 3, Fig 1C] and left periventricular region in the other [patient 4, Fig.1D]. The radiological findings suggested infarcts in bilateral basal ganglia extending to bilateral thalamus in two cases [patient 5 and 6], and bilateral putaminal lesion with an affected left caudate and bilateral periventricular region in one [patient 7, Fig 1E].

Table 1 displays the demographic details and the anatomical locations of lesions of the study participants.

Findings of the neuropsychological tests

Cognitive functioning of the patients was assessed in the domains of attention, working memory and visuospatial ability. Attention was assessed using Digit span forward (DF) test and random 'A' Letter test (ARLT). Working memory was assessed using the Digit span backwards (DB) test and Serial Subtraction (SS) test. The visuospatial ability was measured using the Block Design (BD) test.

The findings from the tests are graphically illustrated in figure 2.

Performance in DF task, Random "A" letter test (ALRT) and Digit backward test (DB)was found to be most impaired in bilateral basal ganglia and thalamic lesion (patient 5 and 6).

Performance on Serial subtraction test (SS) was most impaired in patients with bilateral BG with or without an affected thalamus (patient- 5 and 6, patient 7, Fig 1E)

Performance in Block design test (BD) was found to be most impaired in case of bilateral basal ganglia lesions with (Patient 5 and 6) or without affected thalamus (patient-7, Fig- 1E) and in case of left putaminal lesion with an associated left thalamic insult (Patient 3, Fig 1C).

Discussion

This study demonstrates a definite pattern in cognitive dysfunction that results from the specific impact of unilateral and bilateral BG and thalamic insults.

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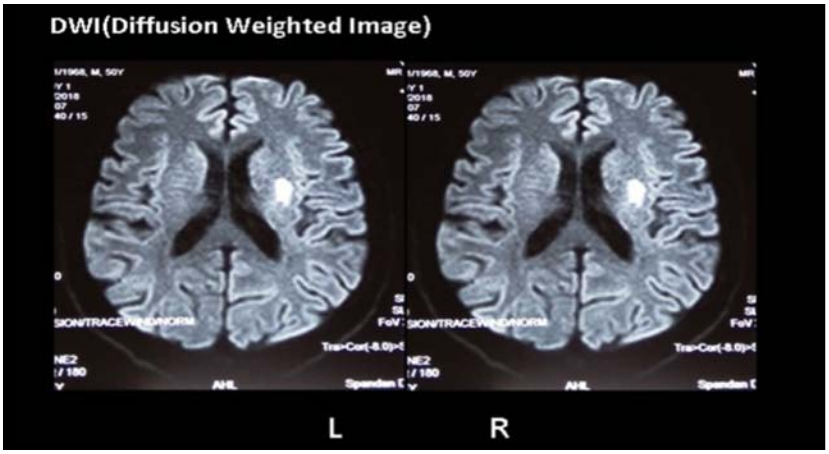


Fig. 1D. A Diffusion Weighted Magnetic resonance image of a 50 year old man with a left putaminal infarct extending to the left periventricular region. L=left hemisphere; R= right hemisphere

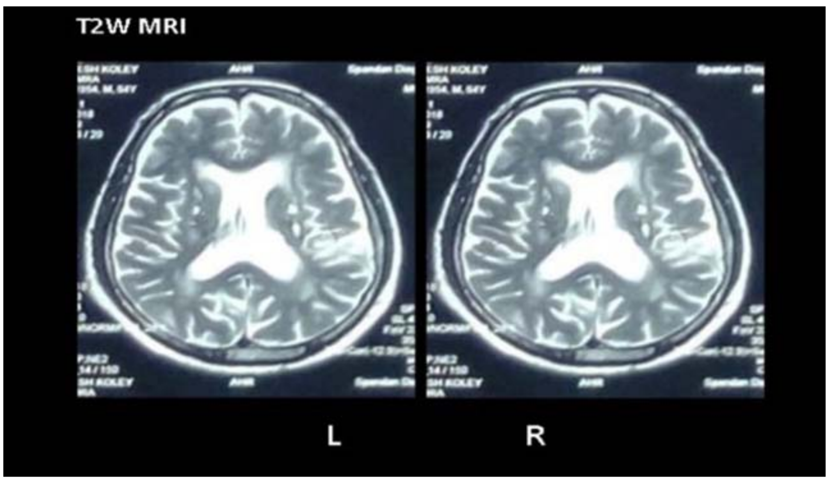
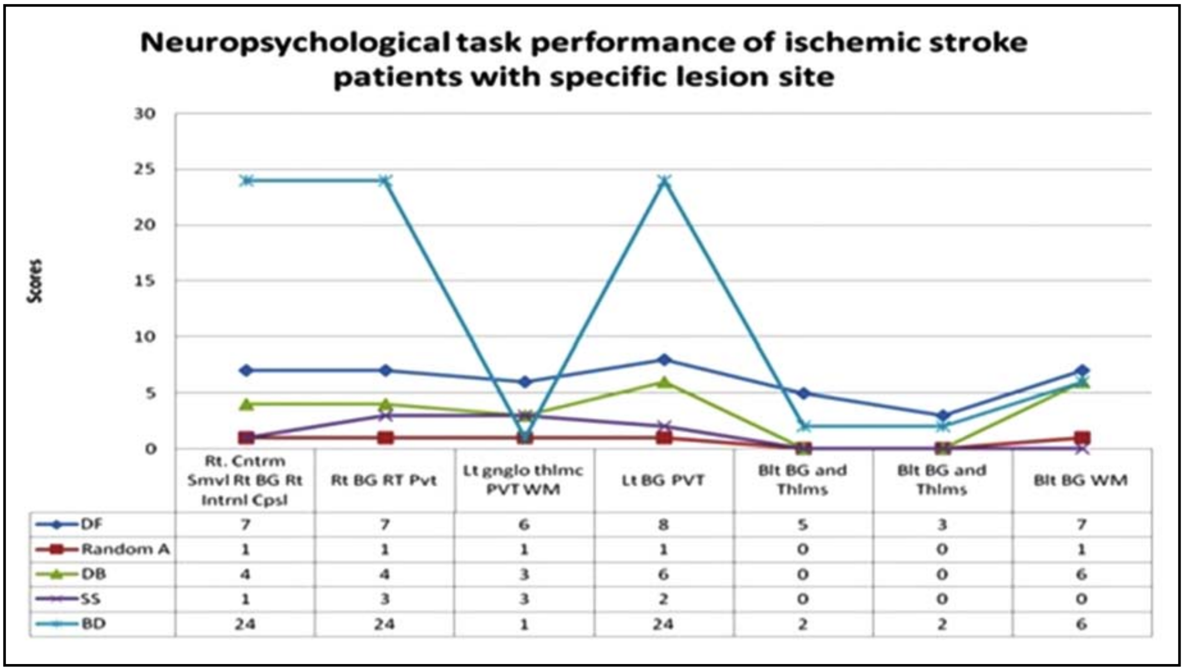


Fig. 1E. A Diffusion Weighted Magnetic resonance image of a 54 year old man with a bilateral basal ganglia infarct L=left hemisphere; R= right hemisphere

In DF, three patients with only unilateral putaminal lesion (patient-1; Fig. 1A, patient-2; Fig. 1B and patient-4; Fig. 1D); one (patient-3; Fig. 1C) with unilateral putaminal lesion along with unilateral thalamic lesion and one (patient-7; Fig. 1E) with bilateral putaminal lesion extending to left caudate, sparing the thalamus, performed within average. However, impairment in DF performance in bilateral BG lesions when extended to the bilateral thalamus (patient 5 and 6), signify the thalamus is crucial for optimal registration of information and BG not being an essential substrate.

The results of ARLT, another attentional task, showed a similar pattern. Bilateral BG with bilateral thalamic lesions (patient 5 and 6) impaired the task performance. In all the other cases with unilateral putaminal lesions, where thalamus is spared, the patients completed the task with a single omission only. In ARLT, where an individual has to identify the target (letter A) and discriminate between the target from the non-target distracters (other letters), it is evident that the role of thalamus is crucial. Moreover, only omission errors in putaminal and thalamic lesions implicate their role in attentional dysfunction. As no commission error is apparent, behavioural disinhibition is indicated neither in putaminal nor in thalamic lesions. Thalamus plays a critical role in the attentional network as it controls the monitoring of sensory information (Koch 1987; Ahissar 1997) and mediates the interaction between attention and arousal (Sherman & Koch 1986; Portas *et al.* 1998). Previous investigations have reported the role of corticothalamic feedback loop in the modulation of the cortical expression of attention (La Berge & Brown 1989; Sherman 2001; Sillito & Jones 2002).

In a similar vein, DB task, which is a reversed digit span task, shows performance at the deficit level in case of right putaminal lesion (patient-1; Fig. 1A and patient -2; Fig 1B) and left putaminal lesion with affected thalamus (patient-3; Fig 1C). Bilateral BG and left putaminal lesion, with spared thalamus (patient-7; Fig. 1E and patient-4; Fig. 1D) showed performance within average. Like DF and ARLT, performance on DB also reflects that the thalamus is an essential component for optimal level of performance on attention task. DF with the task demand of registration of information, and ARLT and DB tasks, with working memory load both demand thalamic participation. The function of thalamus as a selective gated relay of multimodal sensory information via the frontal systems makes it likely to be involved in a volitional selective engagement process like working memory (Nadeau 2008).



	Rt. Cntrm Smvl Rt BG Rt Intrnl Cpsl	Rt BG RT Pvt	Lt gnglo thlmc PVT WM	Lt BG PVT	Blt BG and Thlms	Blt BG and Thlms	Blt BG WM
DF	7	7	6	8	5	3	7
Random A	1	1	1	1	0	0	1
DB	4	4	3	6	0	0	6
SS	1	3	3	2	0	0	0
BD	24	24	1	24	2	2	6

Fig. 2. A graphical presentation of the Neuropsychological findings. Rt- Right hemisphere;Lt-Left hemisphere; cntrm smvl-centrum semiovale; BG- Basal Ganglia; Intrnl Cpsl- Internal Capsule; PVT- Periventricular; WM- White matter; BLT- Bilateral; gnglothlmc- Gangliothalamic; thlms- Thalamus.

SS task that requires continuous computation of basic mathematical skills on mental plane with a greater demand on the cognitive control (Bristow *et al.* 2016), is much affected with bilateral BG lesion (patient-5,6 and patient-7; Fig. 1E) than the unilateral one. The active maintenance of the goal-relevant information, its updating and necessary cognitive switching of mental operations require modulation of the dopamine-sensitive basal ganglia that moderates the functioning between the prefrontal cortex and posterior cortex (Schouwenburg *et al.* 2010) Hence, this task is highly sensitive to BG damage, unlike the DB task.

Impairment in BD task is observed in left putaminal lesion with associated thalamic lesion (patient 3; Fig 1C), in bilateral BG lesions with thalamic lesion (patient 5 and 6) and in bilateral BG lesions without an affected thalamus (patient 7; Fig 1E). This finding indicates the critical role of both the basal ganglia and the thalamus in the completion of the BD task. With increased task demand for visuospatial concept attainment, the involvement of cortico-striatal-thalamo-cortical loop is crucial (Schendan 2009). The main task demand of BD is visuospatial ability along with planning. The impairment in BD performance reveals that BG along with thalamus has a role to play in planning and in visuospatial processing. Our findings uphold the previous observations of spatial impairment and executive dysfunction in thalamic lesion (Ouhaz *et al.* 2018; Wolff & Vann 2019).

This widespread pattern of cognitive deficits resulting from BG and thalamic insults provides evidence for the substantial involvement of BG and thalamus in many neuronal pathways connecting cortical and subcortical brain areas responsible for various cognitive functions.

Conclusion

The findings from our study suggest that both BG and thalamic insult result in impairment of higher cognitive functions such as working memory, attention and visuospatial ability implicating its crucial role in these functions. Our findings further emphasize the idea that thalamus is more than a passive gateway for sensory signals and plays a crucial role in cognitive functions. Mediation of BG is a necessary condition in higher order cognitive function of concept attainment as in serial subtraction and block design tasks. Further studies are required with a larger sample to help us to extrapolate our findings.

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Declaration of competing interest

All authors declare no conflicts of interest.

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