

1 **Neuropsychological evidence of multi-domain network hubs in the human thalamus**

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32

33 **Abstract**

34

35 Hubs in the human brain support behaviors that arise from brain network interactions.
36 Previous studies have identified hub regions in the human thalamus that are connected
37 with multiple functional networks. However, the behavioral significance of thalamic
38 hubs has yet to be established. Our framework predicts that thalamic subregions with
39 strong hub properties are broadly involved in functions across multiple cognitive
40 domains. To test this prediction, we studied human patients with focal thalamic lesions
41 in conjunction with network analyses of the human thalamocortical functional
42 connectome. In support of our prediction, lesions to thalamic subregions with stronger
43 hub properties were associated with widespread deficits in executive, language, and
44 memory functions, whereas lesions to thalamic subregions with weaker hub properties
45 were associated with more limited deficits. These results highlight how a large-scale
46 network model can broaden our understanding of thalamic function for human
47 cognition.

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50 **Keywords**

51 Thalamus, hub, functional connectivity, memory, executive function, language.

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55 **Introduction**

56
57 Hubs are highly connected network components crucial for network functions. In the
58 human brain, hubs are thought to facilitate communication between information-
59 processing systems, and support cognitive functions that likely arise from brain-wide
60 network interactions (Bertolero et al., 2015; Gratton et al., 2018; van den Heuvel and
61 Sporns, 2013). Prior studies have identified hubs in frontoparietal association cortices
62 that have extensive connections with distributed brain regions (Goldman-Rakic, 1988;
63 Hagmann et al., 2008; Power et al., 2013). These frontoparietal hubs are behaviorally
64 significant. For example, the connectivity pattern of cortical hubs correlates with
65 behavioral task performance (Bertolero et al., 2018; Cole et al., 2013), and focal damage
66 to cortical hubs is associated with behavior across cognitive domains (Reber et al., 2021;
67 Warren et al., 2014).

68
69 The human thalamus also possesses hub-like network properties (Cole et al., 2010;
70 Hwang et al., 2017). The thalamus consists of different constituent subregions, each with
71 a unique functional, anatomical, and connectivity profile (Sherman and Guillery, 2013).
72 Many thalamic subregions exhibit “many-to-one” and “one-to-many” connectivity
73 motifs—a subregion receives converging projections from multiple cortical regions, and
74 simultaneously projects to multiple cortical regions (Giguere and Goldman-Rakic, 1988;
75 Guillery and Sherman, 2002; Selemon and Goldman-Rakic, 1988). This connectivity
76 motif is a hallmark characteristic of higher-order thalamic nuclei (i.e., the mediodorsal
77 nucleus), and can be supported by a specific group of thalamocortical projection cells,
78 the “Matrix” cells (Jones, 2009). Matrix cells have a diffuse and distributed projection
79 pattern; they innervate the superficial layers of multiple cortical regions, crossing
80 receptive fields and functional boundaries. Consistent with these anatomical features,
81 formal network analyses have found “connector hubs” in the human thalamus.
82 Thalamic connector hubs have strong functional connectivity with multiple cortical
83 networks (Greene et al., 2020; Hwang et al., 2017), and each network can be associated
84 with a distinct set of cognitive functions (Bertolero et al., 2015; Crossley et al., 2013; Yeo
85 et al., 2015). This connectivity architecture suggests that a thalamic hub participates in

86 functions that involve multiple networks and might contribute to many different
87 cognitive functions.

88

89 However, the behavioral significance of this important network position of the
90 thalamus has yet to be established. Large-scale meta-analyses of functional
91 neuroimaging research, primarily functional magnetic resonance imaging (fMRI)
92 studies, have found that tasks from many different cognitive domains (e.g., executive
93 function, memory, perception) are associated with increased activity in overlapping
94 thalamic subregions (Hwang et al., 2017; Yeo et al., 2015). Functional neuroimaging
95 findings are nevertheless correlational, because increased brain activity in response to a
96 particular behavior is not evidence that this brain region is necessary for the studied
97 behavior (Sutterer and Tranel, 2017). The lesion method, studying patients with focal
98 damage to the thalamus, can provide a stronger test of whether thalamic hubs are
99 necessary for human cognition.

100

101 Based on the prominent hub property of the thalamus, we hypothesize that thalamic
102 hubs are involved in multi-domain processing involving multiple functional systems
103 and contribute to behavior across multiple cognitive domains. To test this hypothesis,
104 we combined neuropsychological evaluations from patients with focal thalamic lesions
105 with network analyses of the human thalamocortical functional connectome. To
106 evaluate behavior across cognitive domains, we analyzed neuropsychological tests that
107 assess executive, language, memory, learning, visuospatial, and construction functions.
108 To evaluate the hub properties of different thalamic subregions, we used two different
109 measures: first, a well-established graph-theoretic metric, participation coefficient (PC),
110 and second, the estimated density of matrix projection cells. PC estimates the
111 distribution of coupling between a brain region with multiple brain systems in the
112 functional connectome (Power et al., 2013; Warren et al., 2014). Hub regions with higher
113 PC values are thought to participate in processes recruiting multiple functional
114 networks (Shine et al., 2016). Matrix cells in the thalamus diffusely project to multiple
115 brain regions, and thus thalamic hub regions should have a higher density of matrix
116 cells. We predict that patients with focal lesions to thalamic subregions with high PC
117 values and high density of matrix cells will exhibit more extensive impairment across

118 cognitive domains. In contrast, lesions to thalamic subregions with lower PC values and
119 lower density of matrix cells will exhibit more limited impairment.

120

121

122 **Results**

123

124 We identified 20 patients (ages 18–70, 13 males) with focal lesions restricted to the
125 thalamus, and 42 comparison patients (ages 19–77 years, 21 males) with lesions that
126 spared the thalamus (Figure 1A). All patients were drawn from the Iowa Neurological
127 Patient Registry. The registry contains data from patients with focal, stable brain lesions
128 who have undergone neuropsychological assessment and brain imaging at least three
129 months after lesion onset. Comparison patients had lesions that spared the thalamus,
130 but were similar in size to those found in thalamic patients ($\leq 5088 \text{ mm}^3$, size of the
131 largest observed thalamic lesion). Lesion sizes were not significantly different between
132 groups (thalamus group: mean = 1364 mm^3 , SD = 1212 mm^3 ; comparison group: mean =
133 1321 mm^3 , SD = 729 mm^3 ; group difference in lesion size, $p = 0.38$). There were no
134 significant group differences in age, full scale IQ, verbal IQ, and performance IQ
135 between thalamus patients and comparison patients (Supplementary Table 1).

136

137 We predicted that lesions to hub regions in the thalamus will affect behavior across
138 different cognitive domains. To test the behavioral relevance of the thalamic hubs, we
139 first compared neuropsychological outcomes between the thalamus and comparison
140 patients. The goal of this comparison was to determine whether lesions of the thalamus
141 were associated with cognitive impairment, beyond any nonspecific lesion effects. We
142 analyzed outcome data from several neuropsychological tests, assessing functions from
143 the following domains: (1) executive function using the Trail Making Test Part B (TMT
144 Part B); (2) verbal naming using the Boston Naming Test (BNT); (3) verbal fluency using
145 the Controlled Oral Word Association Test (COWA); (4) immediate learning using the
146 first trial test score from the Rey Auditory-Verbal Learning Test (RAVLT); (5) total
147 learning by summing scores from RAVLT, trials one through five; (6) long-term
148 memory recall using the RAVLT 30-minute delayed recall score; (7) long-term memory
149 recognition using the RAVLT 30-minute delayed recognition score; (8) visuospatial

150 memory using the Rey Complex Figure delayed recall score; (9) psychomotor function
151 using the Trail Making Test Part A (TMT Part A); and (10) construction using the Rey
152 Complex Figure copy test. We grouped these tests into the executive (TMT part B),
153 verbal (COWA and BNT), memory (RAVLT delayed recall and delayed recognition),
154 learning (RAVLT immediate learning and total learning), psychomotor (TMT part A)
155 and visuospatial (Complex Figure tests) domains (Lezak et al., 2012). To adjust for
156 demographic factors such as age and years of education, all test scores were
157 transformed to z-scores using published population norms. Statistical significance of
158 between group comparisons was assessed with the randomized permutation tests
159 unless otherwise noted.

160
161 We found that patients with thalamic lesions performed significantly worse than
162 comparison patients on the following tests: TMT Part B (thalamus patients: mean = 1.97,
163 SD = 2.96; comparison patients: mean = 0.21, SD = 1.70; $p = 0.0012$); BNT (thalamus
164 patients: mean = -0.25, SD = 0.73; comparison patients: mean = 0.43, SD = 0.81; $p =$
165 0.0043); RAVLT delayed recall (thalamus patients: mean = -0.7, SD = 1.27; comparison
166 patients: mean = 0.36, SD = 1.06; $p = 0.0019$); and RAVLT delayed recognition (thalamus
167 patients: mean = -1.26, SD = 2.67; comparison patients: mean = 0.18, SD = 0.87; $p =$
168 0.003). The COWA test did not show statistically significant difference after correcting
169 for multiple comparisons (thalamus patients: mean = -0.41, SD = 1.27; comparison
170 patients: mean = 0.42, SD = 1.05; $p = 0.013$). Notably, each test had at least one thalamus
171 patient that performed worse than 95% of the normative population (z -score < -1.645).
172 These results suggest that thalamic lesions were associated with more severe behavioral
173 impairments in executive, verbal, and memory functions relative to comparison patients
174 that had damage outside of the thalamus.

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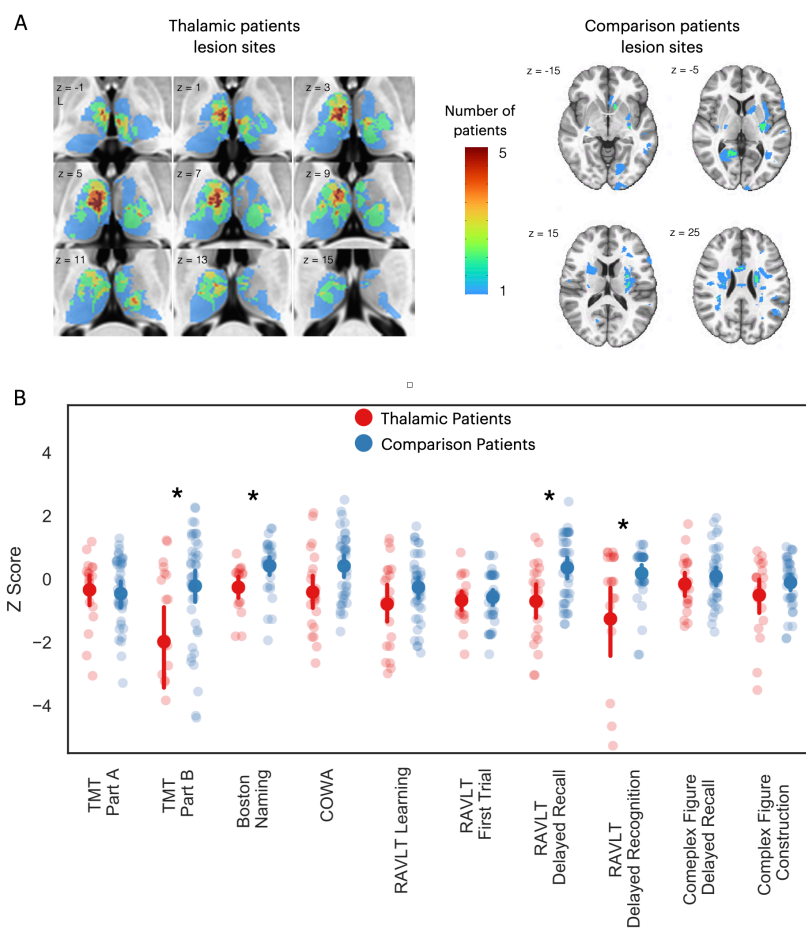


Figure 1. Thalamic patients performed significantly worse on multiple neuropsychological tests compared to comparison patients. (A) Overlap of lesions in patients with thalamic lesions and comparison patients with cortical lesions. (B) Neuropsychological test scores from patients with thalamic lesions and comparison patients. All test scores transformed to z-score using published population norm. Negative z-scores indicate more severe impairment. For each plot, the solid dot depicts the mean, and the bar depicts the 95% bootstrapped confidence interval.

* Indicates corrected $p < .05$.
TMT: Trail Making Test;
COWA: Controlled Word Association; RAVLT: Rey's Auditory Verbal Learning Task.

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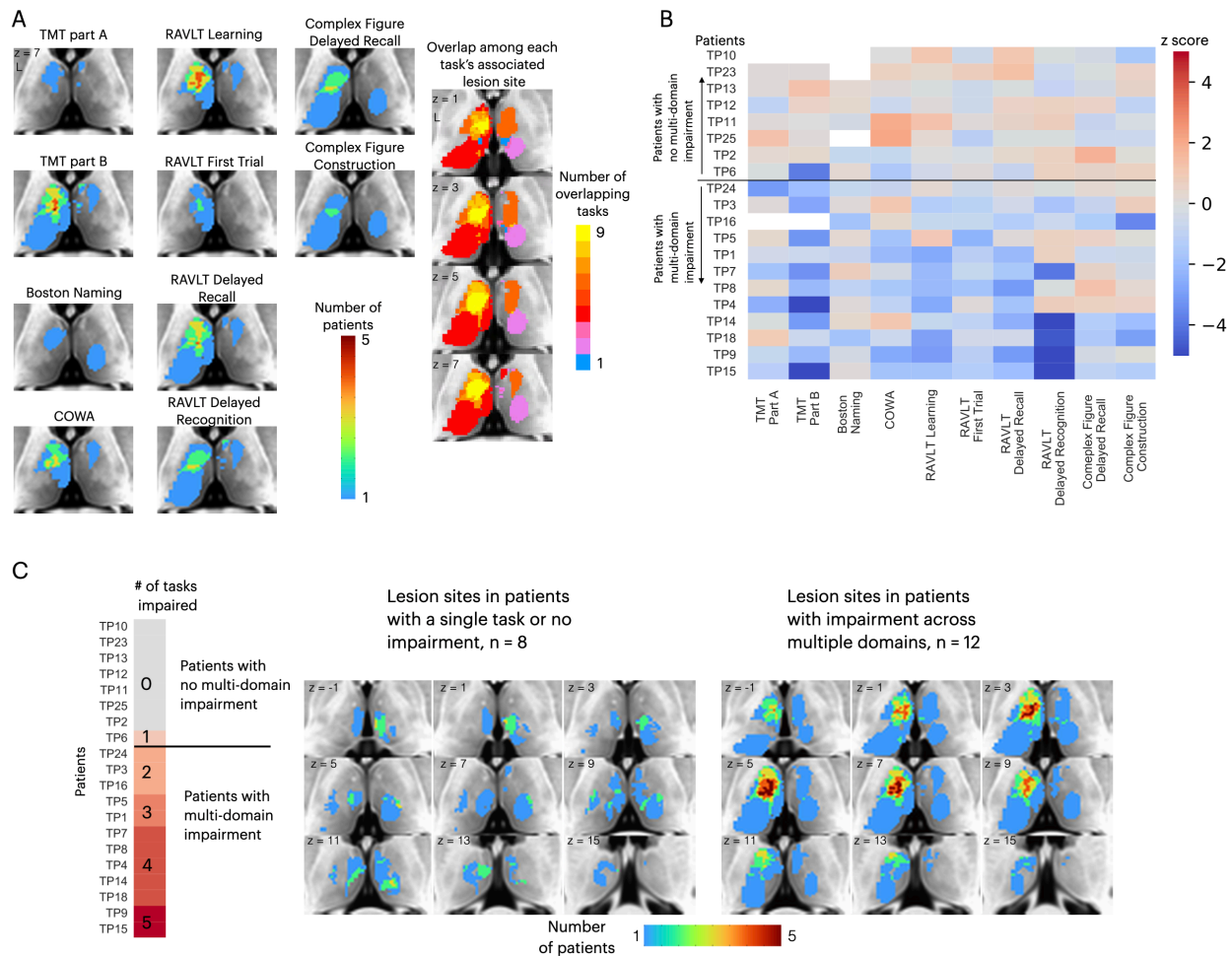
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181 There are two potential models of thalamocortical connectivity that could explain the
182 observed behavioral impairments. First, each cognitive domain is associated with a
183 distinct thalamocortical system, thus different task impairments are associated with
184 segregated lesion sites within the thalamus. Alternatively, thalamic hubs are involved
185 in many cognitive processes across domains through their widespread connectivity
186 with multiple systems, and thus lesions to a critical hub region could be associated with
187 widespread impairment. The first explanation predicts little to no lesion overlap among
188 different impaired tasks, whereas the second model predicts a high degree of lesion
189 overlap among the impaired tasks. To discern between these two possibilities, we first
190 examined lesion sites associated with impaired performance separately for each task

191 (Figure 2A, left panel). Notably, we found an overlapping lesion site in the left anterior-
192 medio-dorsal thalamus that is associated with impairment across different cognitive
193 domains (Figure 2A, right panel). This result suggests that a patient with a focal
194 thalamic lesion to this multi-domain lesion site could exhibit behavioral impairment
195 across cognitive domains.

196
197 We plotted the degree of impairment (expressed by z-score) across all tasks and
198 cognitive domains separately for each patient (Figure 2B), and found that in 12 out of 20
199 patients, significant impairment ($z < -1.645$) was reported in more than two cognitive
200 domains. We then examined whether patients with behavioral impairments across
201 multiple domains had lesions to this identified overlapping site (Figure 2C). We found
202 that in the 12 patients that exhibited impairment across multiple domains, there was
203 indeed an overlapping lesion site in the left anterior-medio-dorsal thalamus. This
204 overlapping site was notably absent in the eight patients that exhibited either no
205 behavioral impairment or impairment in one single task (Figure 2C, left panel). This
206 pattern was also observed when examining lesion sites from individual patients, as
207 individual patients with impairments across multiple domains had lesions that
208 overlapped with this left anterior-medio-dorsal thalamic region (Supplementary Figure
209 1).



210

Figure 2. Lesions associated with impaired performance on tasks across multiple cognitive domains. (A) Left panel: overlap of lesion masks from subjects with impaired test performance on each task. Impaired task performance defined as $z < -1.645$ (95 percentile in z distribution). Right panel: overlap of lesion sites associated with impairment on each individual task (summing each individual task's lesion map from the left panel). (B) Table showing each thalamus patient's task performance on 10 different neuropsychology tests. For all tasks, negative z -scores indicate more pronounced impairment. Both TMT Part A and Part B scores were inverted to match the directionality of other tests. (C) Left panel: classifying thalamic patients into groups that exhibit impairment in one versus multiple tasks across cognitive domains. Right panel: Lesion sites in patients with or without impairment across multiple tasks.

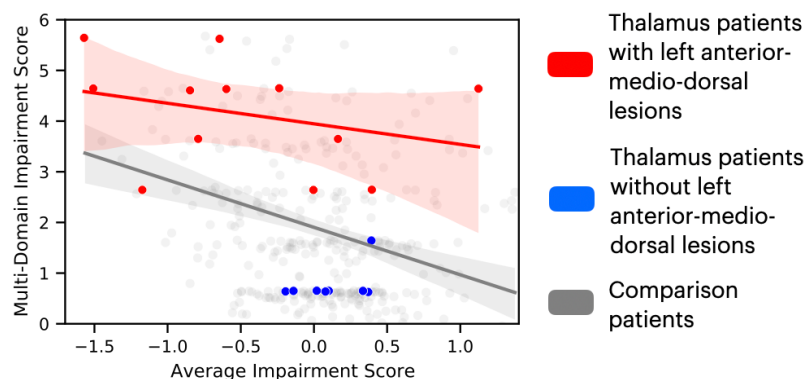
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213 We further tested whether lesions to the left anterior-medio-dorsal thalamus were
 214 associated with broad impairment across more cognitive domains rather than being
 215 driven by more severe deficits in a limited number of domains. For this purpose, we
 216 included an expanded group of 320 comparison patients from the Iowa Neurological

217 Patients Registry (ages 19–81 years, 163 males; for lesion coverage see Supplementary
218 Figure 2). Unlike the first group of comparison patients (Figure 1), these comparison
219 patients were not matched with the thalamus patients on the lesion size, but on the
220 averaged severity of behavioral deficits averaged across all 10 neuropsychology tests.
221 We predicted that when matched on the severity of behavioral deficit, patients with
222 lesions that overlapped with the left anterior-medio-dorsal thalamus would exhibit
223 impairments on more cognitive domains, whereas comparison patients will exhibit
224 more circumscribed deficits in fewer cognitive domains. To test this prediction, we first
225 calculated an “average impairment score” by averaging the normalized z-scores across
226 all 10 neuropsychological tests, and a “multi-domain impairment score” by summing
227 the number of tests with significant behavioral deficits (defined as $z < 1.645$). Both
228 scores regressed out the variance associated with differences in lesion size. We then fit
229 separate linear regression models for thalamus patients and a group of 320 comparison
230 patients that had average impairment scores similar to thalamus patients (maximum =
231 1.39, minimum = -1.59). We found that 11 out of 12 thalamus patients with lesions that
232 overlapped with the left anterior-medio-dorsal thalamus (Figure 2C) exhibited higher
233 multi-domain impairment score when compared to comparison patients (Figure 3). This
234 suggests that lesions to the left anterior-medio-dorsal thalamus are not merely
235 associated with more severe behavioral impairment, but also associated with
236 impairment across multiple cognitive domains to a greater extent than would be
237 expected from lesions in other brain regions.

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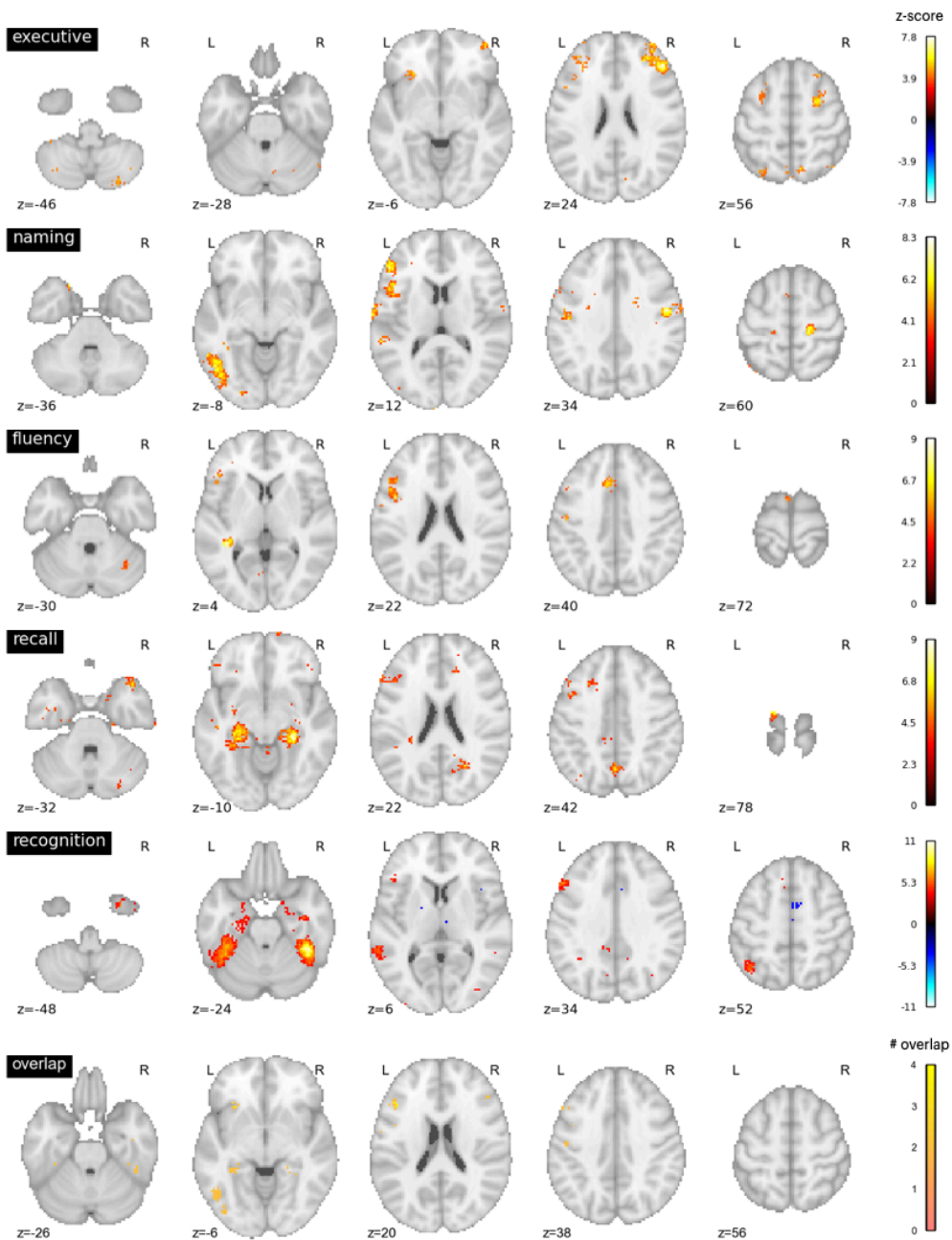
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Figure 3. Comparing the degree of average behavioral impairment (x axis) and multi-domain behavioral impairment (y axis) between thalamus patients and comparison patients. More negative average impairment score represents more severe behavioral impairment. Higher multi-domain impairment score indicate more cognitive domains were affected. Individual dots represent individual patients. Solid lines indicate fitted regression lines for each patient group, shaded are represents 95% confidence interval.

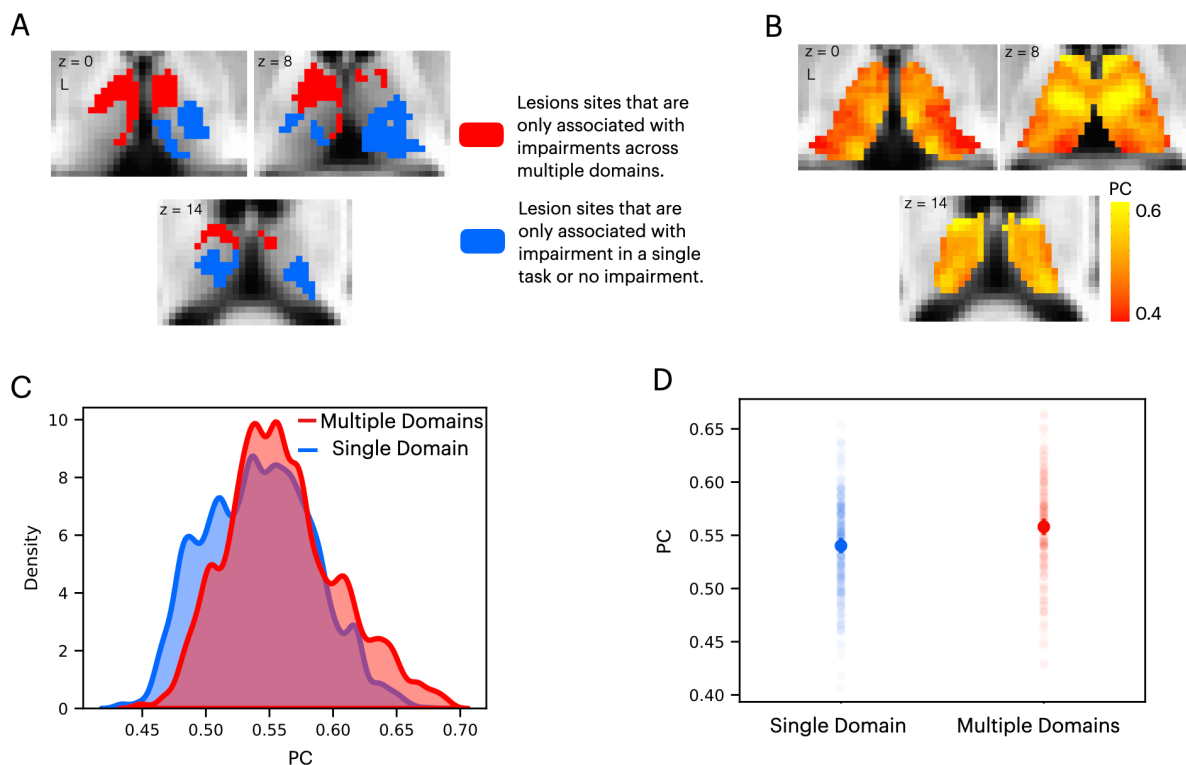
243 Because it is possible that impairment across cognitive domains was driven by larger
244 lesions that damaged many functionally-specialized subregions in the thalamus, we
245 tested whether there was a significant association between lesion size and the extent of
246 behavioral impairment. We found that there was no significant correlation between
247 lesion volume and number of cognitive domains impaired ($r(19) = 0.21$, $p = 0.36$).
248 Furthermore, patients with impairment in more than two cognitive domains did not
249 have larger lesions when compared to patients with impairment in less than two
250 cognitive domains (randomized permutation test $p = 0.42$).

251
252 We further evaluated the brain activity maps likely associated with the putative
253 cognitive processes assessed by each of the neuropsychological tests we assessed.
254 Specifically, we utilized the Neurosynth database (Yarkoni et al., 2011), which contains
255 activation loci from thousands of published fMRI studies, to perform automatic meta-
256 analyses and identify brain regions likely recruited for each task. We queried the
257 following terms: “executive function”, “recall”, “recognition”, “fluency”, “naming”. We
258 found that these terms were associated with distinct brain activity maps with minimal
259 overlap (Figure 4). Maps for terms “naming” and “fluency” overlapped in the left
260 frontal cortex, maps for “recall” and “recognition” overlapped in temporal cortices, and
261 all four maps overlapped in a small region (three 2 mm^3 voxels) in the left inferior
262 frontal gyrus.



263

Figure 4. Neurosynth metanalyses. Top four rows: brain regions associated with putative cognitive processes assessed by the TMT Part B, BNT, COWA, RAVLT delayed recall, and RAVLT delayed recognition tests. Color bar represents the strength of association in z-score. Bottom row: overlap between the top four maps. Maps for “naming” and “fluency” overlapped in the left frontal cortex, maps for “recall” and “recognition” overlapped in temporal cortices. All four maps overlapped with 6 voxels in the left middle frontal gyrus.



264

Figure 5. Lesions to thalamic regions with strong hub property are associated with behavioral impairment across cognitive domains. (A) Thalamic lesion sites associated with multitask impairment are located in the anterior-medio-dorsal thalamus. (B) Right panel: left medial and anterior thalamus is associated with prominent hub property (measured by participation coefficient [PC]). (C) Kernel density plot of voxel-wise PC values from lesion sites associated with multiple domain and single domain impairment. Voxel-wise PC values were significantly higher for multi-domain lesion sites. The y-axis was scaled so area under the curve is summated to one. (D) In a group of 235 subjects, PC values were significantly higher in multi-domain versus single domain lesion sites. Each data dot indicates PC value from one normative subject.

265

266

267 We performed additional analyses to contrast the hub properties between thalamic
268 lesion sites that were only observed in patients that exhibited impairment across
269 multiple domains, versus lesion sites only observed in patients that exhibited no
270 behavioral impairment or impairment in a single domain (Figure 5A). Lesion sites that
271 overlapped between patients that exhibited multi-domain impairment and patients
272 with no behavioral impairment were excluded. Our prediction was that lesions to
273 thalamic regions exhibiting prominent hub properties—as measured with PC—will
274 have an association with widespread negative behavioral outcomes across multiple

275 domains. In contrast, lesions to thalamic regions with lower hub properties will have
276 less widespread association. We calculated the PC value for each thalamic voxel using a
277 large normative thalamocortical functional connectome dataset (Hwang et al., 2017).
278 The purpose was to estimate hub properties of thalamic subregions in the healthy
279 population, and use this result to estimate hub properties of the lesion sites. Briefly, for
280 each normative subject, we calculated thalamocortical functional connectivity between
281 thalamic voxels and 400 cortical regions of interests (ROI), spanning seven canonical
282 cortical networks (Schaefer et al., 2018). We did not calculate functional connectivity
283 between thalamic voxels. Voxel-wise PC values were calculated for each subject, and
284 averaged across subjects. A high PC value indicates that a hub region has distributed
285 connectivity with multiple cortical networks. We found that when averaged across
286 normative subjects, the anterior, medial, and dorsal thalamus exhibit strong connector
287 hub properties (Figure 5B). We then compared the distribution of voxel-wise PC values
288 between the multi-domain and single-domain lesion sites using the Komogorov-
289 Smirnov test, and found that thalamic voxels in the multi-domain lesion sites had on
290 average higher PC values compared to those in the single domain lesion sites (Figure
291 5C). The voxel-wise PC values were significantly higher in the multi-domain sites
292 compared to the single-domain sites (Kolmogorov-Smirnov $d = 0.16$, $p < 0.001$;
293 replication dataset: Kolmogorov-Smirnov $d = 0.11$, $p < 0.001$). We then statistically
294 compared PC values between multi-domain and single-domain sites across normative
295 subjects, and found that the multi-domain sites exhibited significantly higher PC values
296 (Figure 5D, $t(234) = 6.472$, $p < 0.001$; replication dataset: $t(61) = 3.21$, $p = 0.002$),
297 confirming our central prediction.

298
299 This finding suggests that lesion sites associated with impairment across cognitive
300 domains have a diverse functional relationship with distributed systems involved in
301 different cognitive functions. Thus, we mapped the cortical functional networks that
302 show strong functional connectivity with voxels within the multi-domain lesion site.
303 For every thalamic voxel, we calculated its average functional connectivity with seven
304 cortical functional networks (Schaefer et al., 2018), including the visual, somatomotor
305 (SM), limbic, dorsal attention (DA), cingulo-opercular (CO), frontoparietal (FP), and
306 default mode (DMN) networks. We then divided the functional connectivity estimates
307 of each network by the total summated functional connectivity strength of each voxel.

308 The purpose of this procedure was to derive a functional connectivity weight ratio
309 estimate to assess the network selectivity of each voxel. If a voxel only interacts with a
310 specific network, the majority of its functional connectivity strength should be devoted
311 to that network, resulting in a high functional connectivity weight ratio, whereas
312 connectivity with other networks should be considerably lower. In contrast, if a voxel is
313 broadly interacting with multiple functional networks, then it should exhibit
314 overlapping functional connectivity weight ratios for those networks. Consistent with
315 the high PC values we observed, we found that thalamic voxels in the multi-domain
316 lesion sites exhibit a diffuse functional connectivity relationship with cortical functional
317 networks that are predominately located in heteromodal association areas, including
318 the FP, DMN, limbic, and CO networks (Figure 6A). The centroids of functional
319 connectivity weights were between 0.15–0.3 for these networks, and lower (close to 0)
320 for the visual, SM, and DA networks.

321
322 We repeated the functional connectivity weight ratio analysis to assess functional
323 connectivity between thalamic voxels and cortical regions identified via the Neurosynth
324 meta-analyses (Figure 4). Specifically, we calculated the functional connectivity between
325 each thalamic voxel and cortical voxels associated with each queried term (“executive”,
326 “naming”, “fluency”, “recall”, “recognition”), then divided the averaged functional
327 connectivity estimates of each term by the total summated functional connectivity
328 strength of each voxel. The purpose was to determine whether there are voxels only
329 selectively interacting with brain regions associated with specific cognitive processes.
330 We also found a distributed thalamocortical functional connectivity relationship with
331 brain regions associated with these putative cognitive processes (Figure 6B). Higher
332 functional connectivity weight ratios were found for regions implicated in “executive”
333 and “fluency”, and lower ratio for “naming”, “recall” and “recognition”. Notably, we
334 did not observe a pattern that would indicate strong functional specificity, as the
335 highest observed weight ratio was less than 37 percent. This result suggests that the
336 thalamic hub region is not selectively interacting with a specific cortical system, instead
337 it diffusely interacts with distinct brain regions associated with these varied cognitive
338 processes.

339

340 The thalamus is also known to have dozens of constituent nuclei that can be defined
341 using chemoarchitectural and cytoarchitectural properties. We further examined which
342 thalamic nuclei overlapped with the multi-domain lesion sites, by calculating the
343 percentage of lesioned voxels within the multi-domain lesion sites for each thalamic
344 nucleus. Thalamic nuclei were defined using a published atlas derived from
345 postmortem human brains (Krauth et al., 2010). We found that the multi-domain lesion
346 sites overlap with several higher-order thalamic nuclei, including the anterior nucleus
347 (AN), the mediodorsal nucleus (MD), the ventromedial nucleus (VN), the intralaminar
348 nucleus (IL), as well as other nuclei, including the ventro anterior (VA) and the
349 ventrolateral (VL) nuclei (Figure 6C).

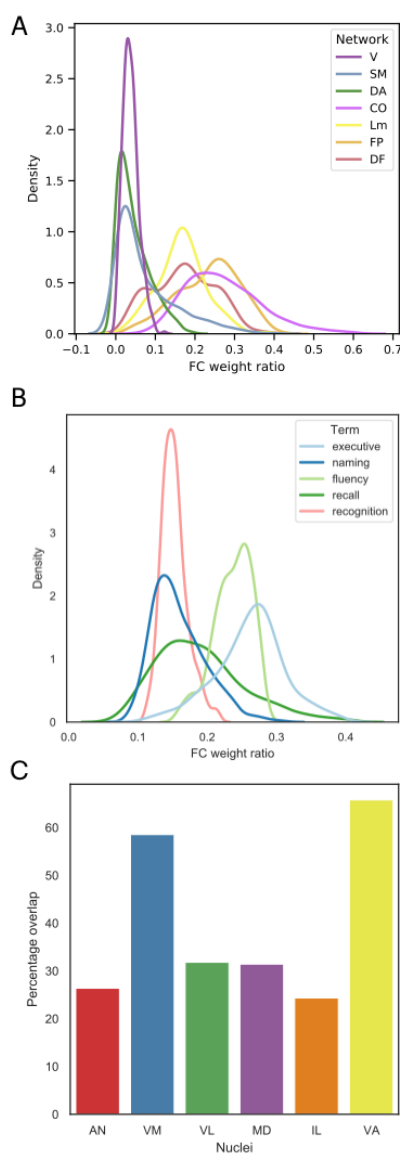
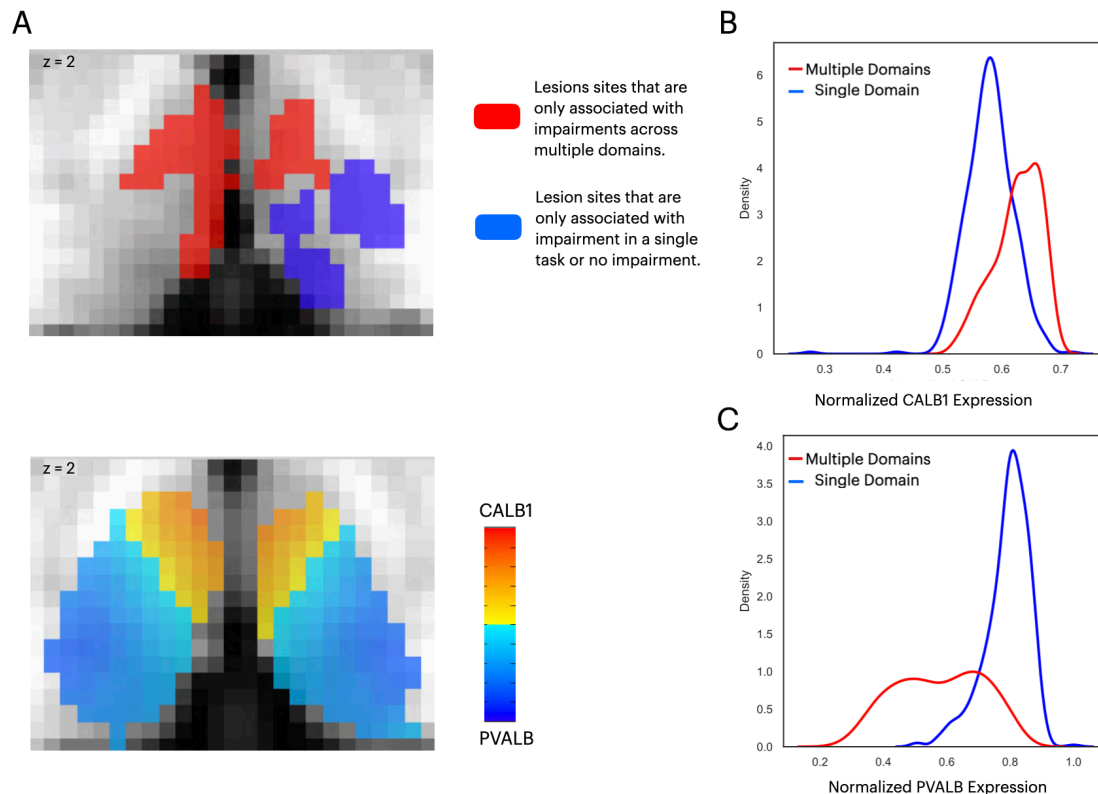


Figure 6. (A) Voxel-wise kernel density plot of thalamocortical functional connectivity weight for each cortical network. Voxels in the multi-domain lesion site exhibit stronger functional connectivity with the cingulo-opercular (CO), limbic (Lm), fronto-parietal (FP), and default mode (DMN) networks. Weaker connectivity with visual (V), somatomotor (SM), and dorsal attention (DA) networks. (B) Voxel-wise kernel density plot of thalamocortical functional connectivity weight with cortical regions identified via Neurosynth meta-analyses. For both (A) and (B), higher weight ratio indicates functional specificity, suggesting that voxel is selectively interacting with a specific cortical system. (C) The multi-domain lesion site overlaps with higher-order thalamic nuclei, including the anterior (AN), ventromedial (VM), mediodorsal (MD), intra-laminar (IL), ventro-anterior (VA), and ventrolateral (VL) nuclei.

351 Thalamic subdivisions are comprised of a mixture of “Core” and “Matrix”
352 thalamocortical projections cells, and each type has a different projection pattern to the
353 cortex (Jones, 2009, 2001). Calbindin-rich matrix cells project diffusively to the
354 superficial layers of the cerebral cortex, unconstrained by functional borders between
355 cortical regions. In contrast, parvalbulmin-rich core cells send topographic specific
356 projections to the middle layers of the cerebral cortex. The distributed projection pattern
357 of matrix cells is conceptually analogues to the inter-network connectivity property of
358 connector hubs. Therefore, we further predicted that the multi-domain lesion sites
359 would contain relatively higher concentrations of matrix cells when compared to the
360 single-domain lesion sites. To test this prediction, we examined data from the Allen
361 Human Brain Atlas that estimated the brain-wide expression of calbindin and
362 parvalbulmin proteins, CALB1 and PVALB, respectively (Gryglewski et al., 2018). This
363 allowed us to estimate the relative density of matrix and core cells in each thalamic
364 voxel (Müller et al., 2020). We found that CALB1 were more strongly expressed in the
365 anterior-medio-dorsal thalamus (Figure 7A), suggesting that multi-domain lesion sites
366 likely contain higher densities of matrix projection cells. We then compared the
367 distribution of voxel-wise CALB1 expression between the multi-domain and single-
368 domain lesion sites using the Komogorov-Smirnov test, and found that thalamic voxels
369 in the multi-domain lesion sites had on average higher CALB1 expression when
370 compared to those in the single domain lesion sites (Figure 7B; Kolmogorov-Smirnov d
371 = 0.483, $p < 0.001$). This suggests that the multi-domain lesion sites had more matrix
372 cells when compared to the single-domain lesion sites. In contrast, thalamic voxels in
373 the single-domain lesion sites had on average higher PVALB expression compared to
374 those in the multi-domain lesion sites (Figure 7C; Kolmogorov-Smirnov $d = 0.482$, $p <$
375 0.001), suggesting relatively higher concentrations of core cells in the single-domain
376 lesion sites.
377



378

379

380 Figure 7. (A) The anterior-medial thalamus had a relative higher expression of CALB1
381 (lower panel), which overlapped with the multi-domain lesion sites (upper panel).
382 Color intensity in the lower panel denotes the relative expression of CALB1 and
383 PVALB in different thalamic voxels (Jones, 2009; 2001). (B) Voxel-wise kernel density
384 plot of normalized CALB1 expression level for the multi-domain versus the single-
385 domain lesion sites. (C) Voxel-wise kernel density plot of normalized PVALB
386 expression level for the multi-domain versus the single-domain lesion sites.

385

386

387

388 Discussion

389

390 Prior studies that examined the network organization of the human brain have
391 consistently identified the thalamus as a prominent hub. Within the thalamus there are
392 regional differences in relative hubness, with the anterior, medial, and dorsal thalamus
393 found to exhibit the strongest hub property and broadly connected with distributed
394 functional networks (Cole et al., 2010; Hwang et al., 2017). This connectivity architecture
395 likely allows the thalamus to flexibly participate in functions that support cognition

396 across multiple domains. Findings from the current study provide empirical evidence
397 that confirms the behavioral significance of this network architecture.

398
399 The lesion method is well suited for determining the relationship between thalamic
400 hubs and cognition. Lesioning a hub region should weaken network interactions across
401 multiple systems, and have a widespread influence on behavior across cognitive
402 domains. In contrast, lesioning a thalamic subregion with a specific cognitive function
403 should have a more limited effect. Past studies have found that lesions to the human
404 thalamus are associated with a wide range of cognitive impairments, including
405 executive dysfunction (Hwang et al., 2020; Liebermann et al., 2013), amnesia (Graff-
406 Radford et al., 1990; Pergola et al., 2016; von Cramon et al., 1985), aphasia (Crosson et
407 al., 1986; Graff-Radford et al., 1984), and attention deficits (de Bourbon-Teles et al., 2014;
408 Snow et al., 2009). However, it is not clear whether deficits reported in prior studies
409 each localize to distinct thalamic regions, or whether a restricted lesion to a hub region
410 can be associated with widespread effects. Our findings help to answer this question.

411
412 Specifically, we found significant impairment on the TMT Part B, RAVLT, and BNT
413 tests in patients with lesions to an overlapping region in the left anterior-medio-dorsal
414 thalamus. Of note, basic perceptual and motor functions in thalamic patients were
415 comparable to comparison patients, given that we did not find a significant difference
416 in the TMT Part A and Rey Complex Figure construction test. Thus, the impairment we
417 observed is related to higher-order cognitive processes related to language, memory,
418 and executive functions. How can a thalamic subregion be simultaneously associated
419 with executive, language, and memory functions? Our framework suggests that each of
420 these cognitive domains is associated with a different brain system, and these brain
421 systems have converging connectivity with the multi-domain lesion site that we
422 identified. In support, we found that this lesion site exhibited a strong connector hub
423 property, with a diverse functional connectivity relationship with multiple cortical
424 networks. Importantly, the connector hub property of this multi-domain lesion site was
425 greater than lesion sites that were associated with more limited impairment, again
426 confirming the behavioral relevance of network hubs.

427

428 We suspect that the left thalamus is involved because language-related functions are
429 more lateralized to the left hemisphere, and cognitive performance using standard
430 neuropsychological tests tends to be left-lateralized (Bowren et al., 2020). Successful
431 performance on the delayed recall and delayed recognition tests likely requires a long-
432 term memory system within which the anterior thalamus is a pivotal component,
433 interlinking the hippocampal and cortical systems (Aggleton et al., 2010). Prior studies
434 on lesion symptom mapping have found that TMT and language-related tasks are
435 associated with medial frontal, lateral frontal, and temporal cortices (Baldo et al., 2013;
436 Gläscher et al., 2012). These brain regions likely overlap with the FP, CO, and DF
437 networks that we found to have strong functional connectivity with the multi-domain
438 lesion site. Furthermore, these cortical regions are known to receive anatomical
439 projections from the anterior and mediodorsal nuclei, which we also found to overlap
440 with the identified lesion site (Barbas et al., 1991; Giguere and Goldman-Rakic, 1988;
441 Selemon and Goldman-Rakic, 1988). In addition to the anterior and mediodorsal nuclei,
442 the multi-domain lesion sites also overlapped with the intralaminar and ventromedial
443 nuclei. These thalamic nuclei are known to have higher densities of matrix projection
444 cells (Jones, 2009). Matrix cells broadly project to multiple cortical regions crossing
445 receptive fields and functional boundaries (Jones, 2001), an anatomical feature that is
446 consistent with the network properties of thalamic connector hubs.

447
448 How do thalamic connector hubs support cognitive functions across these diverse
449 domains? Studies on brain network organization may offer some insights. For example,
450 brain functions engage functional segregation, where segregated systems can perform
451 specialized functions without interference, and functional integration, where outputs
452 from specialized systems can be integrated between domains via connector hubs that
453 interlink distributed systems (Bertolero et al., 2015; Cohen and D'Esposito, 2016; Shine
454 et al., 2016). This modular-like organization balances segregated and integrated
455 processes and can be reliably observed in the human brain (Meunier et al., 2010; Sporns
456 and Betzel, 2016). Furthermore, an optimal modular structure has been found to
457 correlate with behavioral performance on tasks across multiple domains (Bertolero et
458 al., 2018), and lesions to connector hubs, including the thalamus, have been shown to
459 disrupt modular organization more so than other non-hub lesions (Gratton et al., 2012;
460 Hwang et al., 2017). Therefore, lesions to thalamic hubs may disrupt the optimal

461 organization of multiple systems via its widespread thalamocortical connectivity, and
462 affect both functional segregation and integration. This disruption will not be limited to
463 one system, a prediction that is consistent with our finding. Thus, one hypothetical
464 function of thalamic connector hubs is to maintain a cognitively optimal architecture
465 across multiple functional systems to support diverse cognitive processes.

466
467 Another explanation of thalamic lesions associated with behavioral impairment on
468 multiple tasks is that thalamic lesions are associated with distal disruptions
469 (“diaschisis”; Sutterer and Tranel, 2017, Von Monakow, 1911) of cortical systems
470 involved in control functions that impact behavior across multiple cognitive domains.
471 For example, we found that the multi-domain lesion site has strong functional
472 connectivity with FP and CO networks, which are cortical networks hypothesized to be
473 involved in domain general processes such as maintaining task-relevant information,
474 guiding relevant sensory inputs toward the correct behavioral output, and adjusting
475 behavior when errors are made (Dosenbach et al., 2008; Gratton et al., 2018). It is also
476 possible that thalamic lesions disrupt processing in a hypothetical supraordinate,
477 domain-general cortical system, known as the “Multi-Demand System” (Cole et al.,
478 2013; Duncan, 2010). The multi-demand system consists of a set of medial frontal, lateral
479 frontal, and posterior parietal regions do not have clear functional specializations, but
480 are instead broadly tuned to implement operations that might be required to perform
481 the different neuropsychological tests that we utilized. This system spatially overlaps
482 with the CO and FP networks (Gratton et al., 2018), and a prior study found strong
483 functional connectivity between this multi-domain system with the anterior and dorsal
484 thalamus (Assem et al., 2020), which overlaps with the multi-domain lesion site that we
485 identified. Thus, lesions to thalamic hubs may disrupt functions associated with the CO
486 and FP networks, or the multi-demand system, which in term affect functions that are
487 necessary for cognition across domains.

488
489 One caveat of our study is we might have missed other multi-domain lesion sites. For
490 example, the posterior thalamus could be involved in integrating visual and
491 visuospatial attention functions (Greene et al., 2020), but we did not have adequate
492 lesion coverage to test this. It is possible that each of these neuropsychological tasks
493 recruits a distinct, parallel thalamocortical circuitry (Alexander et al., 1986), and that

494 larger lesions can cover many small specialized subregions in the thalamus, thus
495 affecting behavior across cognitive domains. Results from ours and previous studies do
496 not support for this explanation. First, lesion size did not correlate with the degree of
497 multi-domain impairment. Second, we observed multi-domain impairment in several
498 patients with restricted lesions to the left anterior-medio-dorsal thalamus. Third,
499 previous large-scale meta-analyses of fMRI research have found that multiple tasks
500 increased activity in overlapping thalamic subregions, but not segregated thalamic
501 subregions (Hwang et al., 2017; Yeo et al., 2015). Fourth, our functional connectivity
502 weight ratio analysis also showed that most, if not all voxels in the multi-domain lesion
503 site have a broad functional connectivity relationship with multiple cortical networks.
504 Finally, Neurosynth queries showed that cognitive processes putatively involved in the
505 impaired neuropsychological tests each associated different sets of spatially segregated
506 brain regions. In other words, the multi-domain lesion site does not appear to have
507 strong functional specificity. Thus, while it is possible that the lesion method does not
508 have the resolution and anatomical specificity to detect lesions that cover many small,
509 spatially-restricted, functionally-specific thalamic subregions, our results do not
510 support this interpretation. Instead, the cross-domain impairment that we observed
511 were likely associated with lesions to thalamic hubs that have a converging relationship
512 with multiple systems.

513
514 To conclude, the principal contribution of our study is to demonstrate the behavioral
515 significance of thalamic hubs. We found that a thalamic hub in the left anterior-medio-
516 dorsal thalamus is critical for memory, executive, and language-related functions. This
517 significant behavioral profile supports the prominent network position of the thalamic
518 hub. These findings lead to the question: what is the function that is implemented by a
519 thalamic hub that allows it to be broadly involved in cognition? Our findings constrain
520 the possible answers—it must be processes that are not specific to a single cognitive
521 function but can be generalized across domains. As discussed above, one possibility is
522 that thalamic hubs maintain an optimal functional network structure, to promote both
523 segregated and integrated functions, which are domain-general network processes that
524 support cognition across multiple domains.

525

526

527 **Methods**

528

529 *Subjects*

530

531 We studied 382 neurological patients (mean age = 52.51, age range = 18–81 years, SD =
532 14.05 years, 193 males). These participants were selected from the Iowa Neurological
533 Patient Registry, and had focal lesions caused by ischemic stroke, hemorrhagic stroke,
534 or benign tumor resection. Patients with learning disabilities, substance abuse, or
535 premorbid personality disorders were excluded from the study. Neuropsychological
536 assessment was conducted at least three months post-lesion onset. We first identified 20
537 patients with lesions restricted in the thalamus caused by ischemic or hemorrhagic
538 stroke (age = 18-70 years, mean = 55.8 years, SD = 13.94 years, 13 males). In addition to
539 patients with focal lesions within the thalamus, we included comparison patients that
540 had lesions outside of the thalamus, in an attempt to control for lesion effects not
541 specific to the thalamus. Given that lesion size correlates with behavioral impairment
542 (Reber et al., 2021), we first tried to minimize any bias that could be introduced by
543 different lesion sizes between the two patient groups. Thus, the first group of 42
544 comparison patients had lesion sizes that were equal to or smaller than the largest
545 lesion size we observed in the thalamus group (ages 19–77 years, mean = 54.25 years,
546 SD = 12.19 years, 21 males). We further included an expanded group of comparison
547 patients with 320 patients (ages 19-81, mean = 52.34 years, SD = 14.3 years, 163 males).
548 The expanded comparison patients had lesions outside the thalamus, not matched in
549 lesion size but the overall averaged severity of behavioral deficit with the thalamus
550 patients. Demographic data for all patients are presented in Supplementary Table 1. All
551 participants gave written informed consent, and the study was approved by the
552 University of Iowa Institutional Review Board.

553

554

555 *Neuropsychological Assessment*

556

557 A set of standardized neuropsychological tests was used to assess neuropsychological
558 outcomes. To account for age-related effects, all test scores were converted to age-
559 adjusted z-scores using the mean and standard deviation from published population

560 normative data. We determined the behavioral domain that each test assessed, as
561 described in *Neuropsychological Assessment* (Lezak et al., 2012). We compared test
562 outcomes between thalamus and comparison patients using the non-parametric
563 randomized permutation test. Each test creates an empirical null distribution of no
564 group difference between patients by randomly permuting group membership
565 (thalamus or comparison patients) of each test score while keeping the number of
566 patients in each group constant. We reported significant results after correcting for
567 multiple comparisons using the Bonferroni correction (10 neuropsychological tests, $p <$
568 0.005).

569
570 We used TMT Part B test scores to assess executive function. Stimuli in TMT Part B
571 consist of both numbers and letters scattered on a page, and patients are asked to use a
572 pencil to connect circles between them, in an alternating sequence (i.e., 1-A-2-B-3-C,
573 etc.) as quickly as possible. TMT Part B is considered to be a test of control-related
574 functions that include working memory and cognitive flexibility (Crowe, 1998; Kortte et
575 al., 2002). In contrast, TMT Part A is an easier test, which requires patients to use a
576 pencil to connect 25 circled numbers in numeric order as quickly as possible. Part A is
577 thought to test psychomotor functions (Bowie and Harvey, 2006).

578
579 The Boston Naming and COWA tests were used to assess verbal naming and verbal
580 fluency functions. The Boston Naming Test consists of 60 line drawings depicting
581 objects for subjects to name (Tombaugh and Hubley, 1997). COWA presents a set of
582 letters; subjects are then asked to say as many words as they can think of that begin
583 with a given letter (Ruff et al., 1996).

584
585 Various components from RAVLT were used to assess learning and memory functions
586 (Vakil and Blachstein, 1993). Subjects were presented with a 15-word list and then asked
587 to repeat as many words as they could over five recall trials. They were then given a
588 delayed recognition and a delayed recall test after a 30-minute delay. Delayed recall and
589 delayed recognition test scores were calculated using correct recalls/recognitions minus
590 the number of false recalls/recognitions. We did not administer the “Trial B”
591 interference procedure. We assessed the immediate learning capacity from the score of
592 the first trial (RAVLT first trial, also known as immediate recall), the cumulative of

593 learning outcome (summing the scores across the five trials; RAVLT learning), and
594 long-term verbal memory (RAVLT delayed recall and RAVLT delayed recognition).

595

596 We used the Rey-Osterrieth Complex Figure Test to assess visuospatial memory and
597 construction (Fastenau et al., 1999). The Rey-Osterrieth figure was presented, and
598 subjects were asked to copy the figure onto a blank paper (the copy trial). After a 30-
599 minute delay, subjects were asked to recall and draw the figure from memory (the
600 delayed recall trial). We did not administer the immediate recall test. A standardized
601 scoring system was used to assess the accuracy of a subject's copy and recall
602 performances (Meyers and Meyers, 1995).

603

604

605 *Anatomical analysis of lesion location*

606

607 The anatomic location and spatial extent of each lesion was determined using available
608 T1, T2, and computed tomography data. Because all patients were selected from the
609 Iowa Neurological Patient Registry, which has been continuously enrolling patients for
610 decades, imaging data were acquired using a variety of sequences. For T1 and T2 data,
611 most images were acquired with $0.9375 \times 0.9375 \times 1.5 \text{ mm}^3$ or $1 \times 1 \times 1 \text{ mm}^3$ resolution;
612 for computed tomography data, data were acquired with $0.94 \times 0.94 \text{ mm}^2$ in-plane
613 resolution, with slice thickness ranging from 2 to 5 mm. All lesions were manually
614 traced by trained technicians and reviewed by a board-certified neurologist (co-author
615 A.D.B.), who was blinded to neuropsychological outcome results. Lesion masks were
616 transformed to the Montreal Neurological Institute (MNI) International Consortium for
617 Brain Mapping (ICBM) 152 Nonlinear Asymmetrical template, version 2009c, using a
618 procedure that we reported previously (Hwang et al., 2020). Briefly, we used a high-
619 deformation, non-linear, enantiomorphic, registration procedure from the Advanced
620 Normalization Tools (Avants et al., 2009; Brett et al., 2001; Nachev et al., 2008). This
621 high-deformation, non-linear registration procedure allows local deformation to
622 account for differences in size and shape between brain structures. We used
623 enantiomorphic normalization to insert voxel intensities from the non-damaged
624 homologue of the lesion site in place of the manually-defined lesion mask to improve
625 transformation accuracy. After transformation, lesion masks went through a second

626 round of manual editing as needed, to ensure that the anatomical borders of the lesion
627 were accurately represented on the template atlas. The Morel atlas was used determine
628 the location of different thalamic nuclei (Krauth et al., 2010). This atlas identifies human
629 thalamic nuclei based on cyto- and myelo-architecture information in stained slices
630 from five postmortem human brains, and further transformed to the template space.

631
632

633 *Functional connectivity and network hub analyses*

634

635 The normative functional connectome dataset consisted of resting-state fMRI data from
636 235 subjects (mean age = 21.7 years, SD = 2.87 years, age range =19–27, 131 males). Data
637 from these subjects were acquired as part of the Brain Genomics Superstruct Project
638 (Holmes et al., 2015), which we have previously used to map the hub properties of the
639 thalamus (Hwang et al., 2017). For each normative subject, two six-minute runs of fMRI
640 data were collected using a gradient-echo echo-planar imaging sequence (repetition
641 time [TR] = 3000 ms, echo time [TE] = 30 ms, flip angle = 85 degrees, 3 mm³ isotropic
642 voxels with 47 axial slices). We replicated our results using 62 subjects from an
643 independent dataset from the Nathan Kline Institute-Rockland Sample (Nooner et al.,
644 2012). For the replication dataset, nine minutes and 35 seconds of resting-state fMRI
645 data were collected for each subject using with the following parameters: TR = 1400 ms,
646 TE = 30 ms, multiband factor = 4, flip angle = 65 degrees, 2 mm³ isotropic voxels with 64
647 axial slices.

648

649 To prepare fMRI data for connectivity and network analyses, brain images were
650 segmented into different tissue classes (white matter (WM), gray matter (GM), and
651 cerebrospinal fluid (CSF)) using FSL's FAST software which helps co-registering
652 functional and anatomical data using boundary-based registration algorithm. We used
653 rigid body motion correction to correct for head motion. T1 data were then spatially
654 normalized to the MNI-152 space using the same high-deformation, non-linear function
655 from the Advanced Normalization Tools that we used to transform lesion masks into
656 the MNI space. We performed anatomical CompCor nuisance regression to further
657 reduce non-neural noise (Behzadi et al., 2007). The close physical proximity between the
658 thalamus and high-noise regions, such as the ventricles, could result in blurring the

659 fMRI signal. To minimize this confound we further regressed out the mean signals from
660 CSF, WM, and GM that were within five voxels (10 mm) from the thalamus.
661 Importantly, no spatial smoothing was performed. After regression, data were
662 bandpass filtered (0.009–0.08 Hz).

663
664 Following preprocessing, mean resting state fMRI time-series were extracted from 400
665 cortical ROIs (Schaefer et al., 2018) and concatenated across runs for subjects. To
666 localize the thalamus, the Morel atlas (Krauth et al., 2010) was used to define its spatial
667 extent (2227 2-mm³ voxels included in the atlas, registered to the MNI template). We
668 used Pearson correlation to estimate thalamocortical functional connectivity. Note that
669 no correlations were calculated between thalamic voxels. This procedure resulted in a
670 2227 (thalamus voxel) x 400 cortical ROI matrix. To estimate the connector hub property
671 of each thalamus voxel, we calculated its participation coefficient value across a range
672 of density thresholds of this thalamocortical matrix (density = 0.01–0.05), and averaged
673 across thresholds. The PC value of thalamus voxel *i* is defined as:

$$674 \quad PC = 1 - \sum_{s=1}^{N_M} \left(\frac{K_{is}}{K_i} \right)^2,$$

675 where K_i is the sum of total functional connectivity weight for voxel *i*, K_{is} is the sum of
676 functional connectivity weight between voxel *i* and the cortical network *s*, and N_M is
677 the total number of networks. To perform this calculation, we assigned the 400 cortical
678 ROIs to seven cortical functional networks including FP, DF, CO, DA, limbic, SM and
679 visual networks (Schaefer et al., 2018; Yeo et al., 2011). If a thalamic voxel acts as a
680 connector hub for cortical functional networks, it should exhibit functional connectivity
681 uniformly distributed with cortical networks, and its PC value will be close to 1;
682 otherwise, if its functional connectivity is concentrated within a specific cortical
683 network, its PC value will be close to 0 (Gratton et al., 2012; Guimerà and Nunes
684 Amaral, 2005).

685
686 *Neurosynth meta-analyses*

687
688 We used the Neurosynth database (Yarkoni et al., 2011) to identify brain regions
689 associated with putative cognitive processes that are assessed by the TMT Part B, BNT,
690 COWA, RAVLT delayed recall, and RAVLT delayed recognition tests. Neurosynth

691 performs automated meta-analyses on a large fMRI corpus, with more than 14000 fMRI
692 studies included in the database. We queried the following terms, “executive” (for
693 TMT Part B), “naming” (for BNT), “fluency” (for COWA), “recall” (for RAVLT delayed
694 recall), and “recognition” (for RAVLT delayed recognition). Neurosynth then
695 performed an association test for each term, to identify voxels more consistently
696 reported in fMRI studies that contained the queried term than studies that didn’t
697 contain the term. The resulting maps depicts putative brain systems whose activities are
698 associated with the searched term.

699

700 *Estimating the density of Matrix cells*

701

702 Procedures used to estimate the densities of matrix and core projection cells were
703 previously published (Müller et al., 2020). Briefly, we obtained spatial maps (in MNI-
704 152 space) of mRNA expression levels for PVALB and CALB1 proteins provided by the
705 Allen Human Brain Atlas (Gryglewski et al., 2018). These proteins have been previously
706 shown to delineate matrix and core thalamic projection cells (Jones and Hendry, 1989).
707 Voxel-wise mRNA levels were first normalized and transformed into z-scores across all
708 voxels within the thalamus, and the voxel-wise distributions of these normalized values
709 were compared between lesion sites. A difference score was also calculated to identify
710 thalamic voxels with higher densities of matrix cells.

711

712

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716 **Code and data availability statement**

717 Functional connectivity analyses utilized publicly available datasets (Holmes et al.,
718 2015; Nooner et al., 2012). Code and de-identified neuropsychological assessment
719 outcome data can be accessed at <https://github.com/kaihwang/LTH>.

720

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724

725 **References**

726

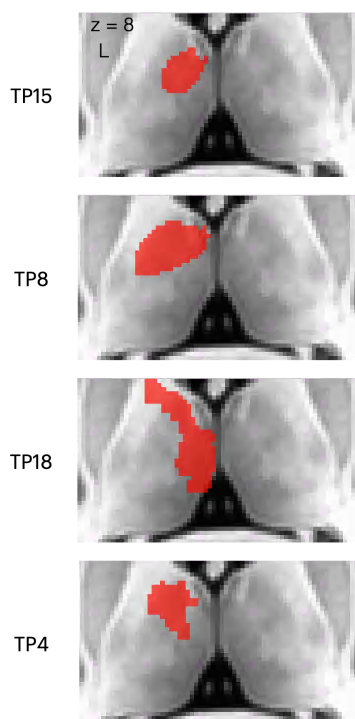
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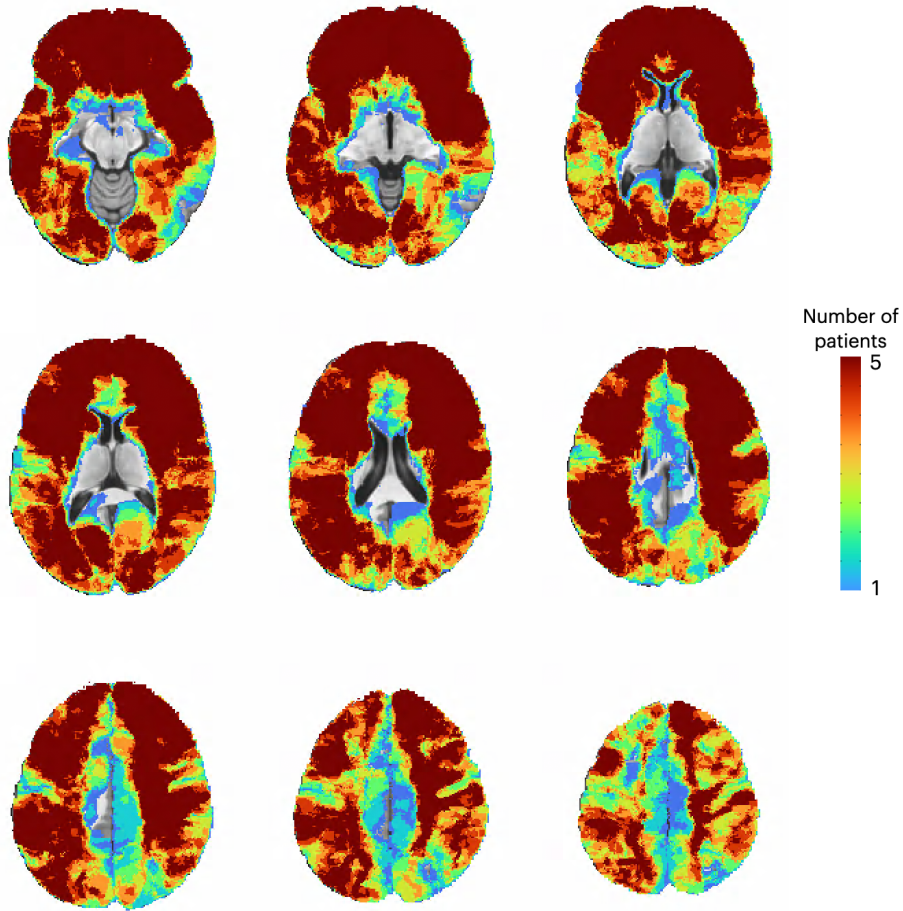
915 Supplementary Info



Supplementary Figure 1. Lesion sites of four example patients' that exhibited behavioral impairments ($Z < -1.645$) on 2 or more cognitive domains. Patient TP15 and TP4 had impairment on executive, language, and memory functions. TP8 and TP18 had impairment on language and memory functions.

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Supplementary Figure 2. Lesion sites 348 comparison patients.