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Postmortem structural studies of the thalamus in schizophrenia

Karl-Anton Dorph-Petersen[a,b,c,*] and **David A. Lewis**[c]

[a]Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[b]Centre for Stochastic Geometry and Advanced Bioimaging, Aarhus University, Aarhus, Denmark

[c]Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

In this review, we seek to answer the following question: Do findings in the current literature support the idea that thalamo-cortical dysfunction in schizophrenia is due to structural abnormalities in the thalamus? We base our review on the existing literature of design-unbiased stereological studies of the postmortem thalamus from subjects with schizophrenia. Thus, all reported results are based upon the use of unbiased principles of sampling to determine volume and/or total cell numbers of thalamus or its constituent nuclei. We found 28 such papers covering 26 studies. In a series of tables we list all positive and negative findings from the total thalamus, the mediodorsal, pulvinar and anterior nuclei, as well as less frequently studied thalamic regions. Only four studies examined the entire thalamus and the results were inconsistent. We found largely consistent evidence for structural changes (reduced volume and cell numbers) in the pulvinar located in the posterior thalamus. In contrast, findings in the mediodorsal thalamic nucleus are inconsistent, with the largest and most recent studies generally failing to support earlier reports of a lower number of neurons in schizophrenia. Thus, the current findings of stereological studies of the thalamus in schizophrenia support the idea that thalamo-cortical dysfunction in schizophrenia might be attributable, at least in part, to structural alterations in the pulvinar that could impair thalamic inputs to higher order cortical association areas in the frontal and parietal lobes. However, more studies are needed before robust conclusions can be drawn.

Keywords

Cell number; Postmortem; Schizophrenia; Stereology; Thalamus

[*]Corresponding author at: Translational Neuropsychiatry Unit, Aarhus University Hospital, Risskov, Skovagervej 2, DK-8240 Risskov, Denmark. karl-anton@dorph-petersen.dk (K.-A. Dorph-Petersen).

Contributors

Karl-Anton Dorph-Petersen and David A. Lewis planned the review together. Karl-Anton Dorph-Petersen managed the literature searches. Karl-Anton Dorph-Petersen and David A. Lewis wrote the first draft of the manuscript together. Both authors contributed to and have approved the final manuscript.

Conflict of interests

David A. Lewis currently receives investigator-initiated research support from Pfizer and in 2013 to 2015 served as a consultant in the areas of target identification and validation and new compound development to Autifony, Bristol-Myers Squibb, Concert Pharmaceuticals, and Sunovion. Karl-Anton Dorph-Petersen declares that he has no conflicts of interest.

1. Introduction

The thalamus is a bilateral dove-egg-sized structure located deep in each cerebral hemisphere just lateral to the third ventricle. The thalamus functions as a relay station for sensory input to the cerebral cortex, and represents a key node in distributed neuronal circuits involving various regions of the cerebral cortex, striatum and cerebellum. The thalamus is subdivided into numerous nuclei reflecting the functional and structural parcellation of the cerebral cortex. Thus, some nuclei such as the lateral and medial geniculate bodies are nodes in basic sensory pathways controlling perceptual input to the primary visual and auditory sensory areas of the cortex, respectively. In contrast, other nuclei, such as the mediodorsal nucleus and the pulvinar, participate in thalamo-cortical circuits integrating the activity of association cortical areas in the frontal and parietal lobes involved in complex sensory and cognitive functions (Jones, 2007).

Schizophrenia is characterized by disturbances in both perceptual processing (e.g., hallucinations) and cognitive functions (e.g. impaired working memory and reduced processing speed) which likely reflect alterations in thalamo-cortical circuitry (Lewis and Sweet, 2009). Thus, the thalamus, the cortex, or both areas could be sites of pathology in schizophrenia. In this review we seek, using the current literature, to address the following question: Could thalamo-cortical dysfunction in schizophrenia be due to structural abnormalities in the thalamus?

In vivo imaging studies of subjects with schizophrenia have found evidence of smaller thalamic volumes bilaterally (Shepherd et al., 2012; Haijma et al., 2013; van Erp et al., 2016a, 2016b). Especially, midline thalamic structures (including the mediodorsal nucleus) have been reported to be robustly smaller (Shepherd et al., 2012). Subjects with first-episode schizophrenia, including those who are antipsychotic naïve, seem to show a larger volume reduction or greater effect size of the volume reduction compared to subjects with chronic schizophrenia (Shepherd et al., 2012; Haijma et al., 2013). However, current imaging methods do not have the capacity to resolve more detailed cellular structures. Thus, histological studies at the light microscopic level are needed for detailed assessment of the structural changes that could serve as basis for the observed thalamic volume reductions in individuals with schizophrenia. Consequently, in this article we focus on postmortem studies of the thalamus in schizophrenia.

1.1. The importance of stereology in postmortem structural studies

Due to the absence of gross pathological alterations in schizophrenia, the ability to detect potentially small, but functionally significant, differences in structural or cellular features in the illness requires the use of very robust, accurate and precise methods. Design-unbiased stereological methods, which utilize principles of random sampling, fulfill these requirements and are currently considered the gold standard for structural microscopy studies. These stereological methods provide the means to overcome confounds from sampling biases present in traditional non-random sampling of sections as well as methodological issues such as tissue shrinkage (Boyce et al., 2010). By systematic, uniformly random sampling of a well-defined reference volume, accurate and precise estimates of a range of structural parameters can be generated. These parameters include

total regional volume, total cell number of various cell types, mean cell size, total length of capillaries, etc. (Howard and Reed, 2005; West, 2012). For further details of these methods and the rationale for their use in schizophrenia research, see our previous review of the use of stereology in studies of postmortem brains from subjects with schizophrenia (Dorph-Petersen and Lewis, 2011).

Given the importance of design-unbiased stereological methods, in this review we consider only postmortem studies of the thalamus that employed these approaches. Especially, we required the complete region of interest to be included and sampled systematic, uniformly randomly leading to accurate estimates of total volume and/or total cell numbers. Studies only reporting cell densities are omitted as number of cells per volume (or 2D cross-sectional area) are very difficult to interpret as it is not clear whether any differences in such a ratio represent a change in numerator (cell number) or denominator (total tissue volume) or both. Also, we required full adherence to the unbiased principles of sampling for all results reported here. Thus, as an example, we here report the neuron number estimates but not the neuronal soma volume estimates from our study of the mediodorsal nucleus in schizophrenia (Dorph-Petersen et al., 2004), as the latter estimates did not fulfill the requirement of randomly rotated sections to ensure unbiasedness. Likewise, we exclude cell number estimates based upon cell counts without guard zones needed to eliminate the confounding of neurons lost when tissue sections are cut. It is important to note that some of the included studies provided very limited details regarding the stereological methods employed; however, these (Mileaf and Byne, 2012; Young et al., 2008) were included as the terminology used suggested that they met our criteria.

1.2. Literature study

We updated our previous literature search of postmortem stereology studies by new searches conducted in January 2016—see Dorph-Petersen & Lewis (2011) for methodological details. In total, we found 27 papers covering 25 robust stereological studies of the thalamus in schizophrenia. One additional study (Young et al., 2008) was pointed out to us by one of the peer reviewers. The 26 studies are based upon tissue samples from approximately 162 subjects with schizophrenia, 127 control subject, and 42 subjects with other psychiatric disease such as major depression or bipolar disorder. The brain samples, some of which are used by several groups across multiple papers, originate from 11 brain banks (Table 1).

We have tabulated the main study parameters and findings in Tables 2–6. However, because some studies report only summary data of a larger base cohort of which not all subjects were used, we cannot provide full details on demographics, but have reported these data as completely as possible from the published papers. Especially, the reader should notice that seven studies (Byne et al., 2008; Chana et al., 2008; Mileaf and Byne, 2012; Selemon and Begovic, 2007; Young et al., 2004, 2007, 2008) are based upon subsets drawn from the same sample made available by The Stanley Foundation Neuropathology Consortium (Torrey et al., 2000). The full sample consists of tissue from a total of 60 subjects—15 from each of four diagnostic groups: schizophrenia, control, major depression, and bipolar disorder. Thus, even though these studies are made by independent groups the results cannot be said to be

completely independent as they are based upon various samples of the same tissue from the same subjects.

2. Postmortem thalamic findings in schizophrenia based upon robust design-unbiased stereological methods

In the following, we review the findings of robust stereological studies of the whole thalamus and each of the three major thalamic nuclei most frequently studied in schizophrenia: the mediodorsal nucleus, the pulvinar, and the anterior nucleus. Finally, we summarize results from the few studies of other thalamic nuclei.

2.1. Whole thalamus

Four stereological studies have assessed the total volume of the thalamus in schizophrenia (Table 2). Of these studies, only one found a significant reduction in total thalamic volume in individuals with schizophrenia.

Byne et al. (2002) investigated the right thalamus in 14 subjects with schizophrenia and eight control subjects. However, seven of the 22 subjects had Alzheimer's type pathology. Excluding these subjects the material consisted of 10 subjects with schizophrenia and 5 control subjects for which no significant difference in mean total thalamic volume was observed.

Cullen et al. (2003) studied both right and left thalamus in 21 subjects with schizophrenia and 27 control subjects, and did not observe any significant group differences in mean thalamic volume.

Danos et al. (2003) examined the right and left thalamus in 12 subjects with schizophrenia and 13 control subjects. This study found a significant reduction of the total thalamic volume in schizophrenia in both left (16.4%, $P = 0.003$) and right (15.2%, $P = 0.006$) hemispheres.

Young et al. (2008) explored right or left thalamus in 12 subjects with schizophrenia, 15 control subjects, 14 subjects with major depression, and 13 subjects with bipolar disorder. The study did not find any significant differences in mean thalamic volume for the schizophrenia group.

Comparisons of the demographics of the subjects in these four studies do not reveal any clear differences between the single positive and the three negative studies.

2.2. Mediodorsal nucleus

The mediodorsal nucleus (MD), a large association nucleus of the thalamus, is the major source of thalamic input to the prefrontal cortex and therefore an obvious target for studies of schizophrenia. Indeed, the MD is the most studied thalamic region in postmortem stereology studies of schizophrenia with a total of 15 studies of this nucleus (Table 3). Pakkenberg (1990) found a substantial smaller volume (26.4%) and fewer neurons (40.3%), astrocytes (43.7%) and oligodendrocytes (44.7%) of the MD in patients with chronic

schizophrenia hospitalized for many years. Portions of these data were initially published in two preceding methods papers (Pakkenberg and Gundersen, 1988; Pakkenberg and Gundersen, 1989). The differences were present in subjects treated with, as well as those who had not received, antipsychotic medications (Pakkenberg, 1992) and were more pronounced in leucotomized subjects (Pakkenberg, 1993). Twelve subsequent stereological studies of the MD were conducted by a number of labs (Table 3). Of these 12 studies, three reported a smaller (9–24%) volume of the MD (Young et al., 2000; Byne et al., 2002; Danos et al., 2003) and two studies reported fewer (27–35%) neurons (Popken et al., 2000; Young et al., 2000).

In contrast, the most recent eight studies (Chana et al., 2008; Cullen et al., 2003; Damgaard Nielsen et al., 2008; Danos et al., 2005; Dorph-Petersen et al., 2004; Kreczmanski et al., 2007, 2009; Young et al., 2004), based upon larger groups of subject from multiple independent brain banks, failed to detect any significant differences in MD volume or neuron number between schizophrenia and comparison subjects. Noticeably, these negative studies include a report from Pakkenberg's group (Damgaard Nielsen et al., 2008).

A few studies examined MD subregions (Popken et al., 2000; Byne et al., 2002; Damgaard Nielsen et al., 2008). However, the findings are not fully consistent, with one study finding fewer neurons in the parvocellular and densocellular regions in schizophrenia (Popken et al., 2000), a second finding a smaller volume only of the parvocellular region in schizophrenia (Byne et al., 2002) and the third study finding no differences between schizophrenia and control subjects (Damgaard Nielsen et al., 2008).

2.3. Pulvinar

The pulvinar is the largest thalamic association nucleus, is located posterior in thalamus, receives input from the superior colliculus, and is widely interconnected with a number of cerebral areas such as prefrontal cortex, somatosensory cortex, multimodal sensory association areas in temporal and parietal lobes, visual cortical areas, insula, the cingulate gyrus, and amygdala. Especially, the pulvinar is a key node in the visual attention network (Benarroch, 2015). Six stereological studies have investigated the pulvinar in schizophrenia (Table 4). Five of these studies reported a smaller (19–22%) volume in schizophrenia subjects (Byne et al., 2002, 2007; Danos et al., 2003; Highley et al., 2003; Mileaf and Byne, 2012) and one study did not find any differences (Young et al., 2007). Interestingly, the material of this negative study was reanalyzed by Mileaf & Byne (2012) who found a significant smaller neuron number in schizophrenia selectively in the medial pulvinar of the right thalamus. Likewise, the study by Highley et al. (2003) found 14% and 26% smaller volumes of the right medial and right lateral pulvinar, respectively, and a 24% smaller neuron number of the right lateral pulvinar.

It should be noted that the material description of the two initial studies by Byne et al. (2002, 2007) only list summary statistics. Thus, it is not known to what degree these two studies overlap in the subjects studied and to what degree they can be said to be statistically independent.

2.4. Anterior nucleus

The anterior nucleus is located at the rostral tip of the thalamus, is interconnected with the mammillary bodies, anterior cingulate cortex, subiculum, and retrosplenial cortex, and is an important node in the hippocampal system for episodic memory (Child and Benarroch, 2013). The anterior nucleus has been the subject of six stereological schizophrenia studies (Table 5). Young et al. (2000) found 16% fewer neurons in the left anteroventral-anteromedial nucleus in subjects with schizophrenia. However, all subsequent studies have failed to detect any significant differences. Of these, the three studies by Byne et al. (2002, 2006, 2008), as well at the single study by Dixon and Harper (2004), robustly estimated the reference volume which did not differ between subject groups. Also, Young et al. (2004) in a newer and larger set of subjects did not detect group differences in either volume or neuron number of the anterior nucleus.

2.5. Other thalamic nuclei

Six stereological studies have looked at various other thalamic nuclei in schizophrenia (Table 6). Of these, only one study found changes in relation to schizophrenia: Danos et al. (2002) studied both left and right ventral lateral posterior nucleus, a motoric relay, and found a 25% smaller volume and 27% fewer neurons in the nucleus of the left thalamus.

Popken et al. (2000) studied the left ventral posterior medial nucleus and found no group differences in volume or neuron number.

Two studies of the volume of the centeromedian nucleus by the same group of researchers (Byne et al., 2002, 2008), but in different subject cohorts, did not find any changes in relation to schizophrenia.

Likewise, two studies by two different groups of authors (Selemon and Begovic, 2007; Dorph-Petersen et al., 2009) of the subregions of the lateral geniculate nucleus (LGN) did not reveal any changes in volume, neuron or glial cell numbers associated with schizophrenia.

3. Conclusion/summary

Since the initial findings of a substantial smaller volume and neuron number in the mediodorsal thalamus in schizophrenia by Pakkenberg in the early 1990’s, multiple other stereological studies of the thalamus in schizophrenia have examined tissue from a large number of subjects. However, despite the initial promising findings, the more recent studies have found less substantial structural changes—if any—in the mediodorsal thalamus in schizophrenia. Similarly, five of six studies of the anterior nucleus have been negative. In contrast, five of six studies of the pulvinar have found reductions of volume and/or neuron number in schizophrenia. Furthermore, targeted reassessment of sections from the only negative study found a smaller neuron number in the right medial pulvinar.

Looking at the rest of the thalamus, so far no conclusive pattern has emerged. However, only a few studies have been conducted in each of these regions. Also, a number of thalamic nuclei have not yet been assessed in schizophrenia using stereological methods.

The consistent findings of a smaller pulvinar in schizophrenia is interesting given that this nucleus is a key node in the visual attention network and intimately interconnected with visual cortical regions. Intriguingly, the only stereological postmortem study of the primary visual cortex in schizophrenia found a 22% smaller volume and 25% fewer neurons in the primary visual cortex in subjects with schizophrenia (Dorph-Petersen et al., 2007). However, currently, no stereological study has investigated the pulvinar and the primary visual cortex in the same subjects with schizophrenia. Therefore, it is presently unknown to what degree these two reported schizophrenia related reductions are correlated at the level of the individual subjects. It is also important to note that the pulvinar projects to the prefrontal cortex. Thus, the in vivo evidence of thalamo-prefrontal dysfunction in schizophrenia might reflect, at least in part, the structural alterations in the pulvinar.

In light of the initial strong findings in the mediodorsal nucleus by Pakkenberg and others, it is puzzling why these findings of smaller size and fewer neurons and glial cells in subjects with schizophrenia have not been replicated in subsequent investigations. The initial studies (Byne et al., 2002; Pakkenberg, 1990, 1992, 1993; Popken et al., 2000; Young et al., 2000) do suggest that at least some subjects with schizophrenia might have a substantially smaller mediodorsal thalamic nucleus compared to unaffected comparison subjects, as the measures in individual subjects showed almost no overlap between subject groups in some studies. However, in contrast, some of the more recent studies showed measures in individual subjects where no subjects with schizophrenia reached values below the range of the comparison subjects (Cullen et al., 2003; Dorph-Petersen et al., 2004; Young et al., 2004). These differences in findings might be related to the use in the initial Pakkenberg studies of a relatively homogenous group of Danish patients who had all been hospitalized for a long time, whereas the more recent studies have been conducted in more heterogeneous samples of subjects living in society and receiving newer antipsychotic medications. However, whether such differences account for the discrepancy in findings cannot be determined at present. Intriguingly, the age of the studied subjects seems to influence the outcome of MD studies in schizophrenia with group differences more likely to be present in studies based upon older cohorts. Thus, summing across all 15 results in Table 3, studies based upon older cohorts (i.e., mean subject ages greater than approximately 60 years) have 6 positive vs. 2 negative results, whereas studies based upon younger cohorts (i.e., mean subject ages approximately 40–60 years) have 1 positive vs. 6 negative results. This pattern is significantly different from chance ($P = 0.041$, Fishers Exact test, two-sided). Therefore, it is possible that the observed reductions of the MD volume and cell number become more distinct with age.

Interestingly, looking across all the results in the Tables 2–6, the positive findings predominate in studies using tissue samples from brain banks that acquired samples from psychiatric hospitals (Table 1), whereas negative findings dominate the studies using tissue samples from brain banks that acquired community-based samples. Summing across all 37 results in Tables 2–6, studies using hospital-acquired samples have 10 positive vs. 6 negative results whereas studies using community-based samples have 5 positive vs. 16 negative results. This pattern is significantly different from chance ($P = 0.023$, Fishers Exact test, two-sided).

This difference in outcomes might be due to any of number of potential differences between individuals with schizophrenia who were chronically hospitalized versus those living in the community. For example, subjects from hospital-acquired samples are more likely to have 1) a better documented clinical history (due to the availability of detailed medical records), 2) fewer comorbidities such as drug and alcohol abuse, 3) very low frequency of suicide, gunshots and accidents as cause of death (although they are more likely to have died of causes associated with agonal state events that can alter tissue integrity), and 4) greater homogeneity diagnostically. Furthermore, relative to subjects from hospital-acquired samples, subjects in community-acquired samples are 1) more likely to have a less severe form of the illness, 2) more likely to have been responsive to treatment, and 3) in general be more diagnostically heterogeneous.

It is also important to note that most of the hospital-based brain banks are European (one British, two German, two Danish, one American). Thus, greater genetic homogeneity may also be a factor compared to the community-acquired American and Australian brain banks that likely include individuals with greater genetic diversity.

Furthermore, the positive studies involved subjects from brain bank 3 who died between 1986–1993, subjects from brain bank 4 (used by Pakkenberg) who died between 1965–1987, and the 8 un-medicated cases from brain bank 5 who died between 1945–1949. Thus, it cannot be excluded that changes in unknown but potentially important demographic parameters (e.g. nutrition, smoking habits, educational level, etc.) over time contribute to the differences in outcomes between the early and later studies.

In the light of the discussion of the MD studies, subject ages could have a general effect on the outcomes of studies of the thalamus. However, summing across all 37 results in Tables 2–6, studies based upon older cohorts (mean subject ages greater than approximately 60 years) have 10 positive vs. 8 negative results whereas studies based upon younger cohorts (mean subject ages approximately 40–60 years) have 5 positive vs. 14 negative results. This general pattern does not significantly differ from chance although a trend towards significance can be observed with more positive studies in older cohorts ($P = 0.10$, Fishers Exact test, two-sided). Thus, more studies are needed to determine if age in general influences the frequency and/or severity of thalamic pathology in schizophrenia.

In general, differences in sex ratio or hemisphere do not seem to have influenced the results. For example, one of the three studies based upon exclusively males (Young et al., 2000) found a smaller mediodorsal nucleus with fewer neurons in subjects with schizophrenia whereas the other two (based upon a different cohort) did not detect any differences (Kreczmanski et al., 2007; Kreczmanski et al., 2009) between subject groups. Likewise, studies of either left (Pakkenberg, 1990) or right (Byne et al., 2002) mediodorsal nucleus reported positive findings whereas most, but not all, of the newer negative studies included tissue samples from both hemispheres. However, it should be noted that studies of the pulvinar suggest a tendency for reductions in the right hemisphere.

In concert, these factors suggest that studies of larger subject cohorts (including both chronically-hospitalized and community-living subjects with schizophrenia) assessing

multiple nuclei (including but not restricted to the mediodorsal nucleus and the pulvinar) are needed. Such studies might reveal subtypes of schizophrenia, or the influence of factors frequently comorbid with schizophrenia, that may correlate with a specific pattern of thalamic pathology. In this light, it is of concern that only a few stereological studies of the thalamus have recently been performed. Thus, we only found one study newer than 2009 (Mileaf and Byne, 2012)—the only new study since our previous review of stereology in schizophrenia (Dorph-Petersen and Lewis, 2011). In this context, it should also be mentioned that stereological estimates of cell numbers are substantially more robust than volume estimates which are sensitive to shrinkage that may or may not be the same across diagnostic groups, age, etc. (Boyce et al., 2010; Dorph-Petersen et al., 2001). Unfortunately, only 19 of the 37 results in Tables 2–6 provide cell number estimates. Thus, more studies of thalamic cell numbers are warranted, especially for the pulvinar where only two of the positive studies investigated neuron numbers.

Another potential concern is the substantial cross-study differences in the reported volumes and absolute neuron numbers for individual thalamic nuclei—see e.g. Fig. 11 in (Dorph-Petersen et al., 2004) and discussion in (Dorph-Petersen et al., 2009). Such cross-study differences have also been observed in stereological studies of other brain regions such as the hippocampus (Korbo et al., 2004; West, 1993). Due to the mathematically unbiased nature of the stereological methods employed, such differences likely reflect one or more the following possible differences between studies: 1) the delineation or definition of the regions of interest, 2) identification of the cells within, 3) definitions of top and bottom of sections, 4) technical factors that affect tissue shrinkage, 5) the variable impact of neurons lost during tissue sectioning, 6) errors in the implementation or calculation of the stereological estimates, and 7) differences in study populations. Although a more detailed consideration of this topic is beyond the scope of the current paper, it is important to note that most of these factors (in an otherwise well-executed stereological study) would be unlikely to affect cross-group comparisons within a given study.

Finally, it is unclear why in vivo imaging studies more consistently show reduced thalamic volume bilaterally and in the midline area of the thalamus in schizophrenia than the structural postmortem studies. In general, imaging studies have larger cohorts and thus greater statistical power. Subjects in imaging studies might be less affected by comorbid factors than subjects in postmortem studies, making disease-related differences more easily detected by neuroimaging. On the other hand, it is unclear to what degree the observed changes in in vivo imaging studies reflect non-structural factors (e.g., fluid displacements in the brain) that do not confound postmortem studies (Weinberger and Radulescu, 2016).

In summary, the most robust evidence for structural changes of the thalamus in schizophrenia indicates a reduction in volume and cell numbers in the pulvinar. In contrast, findings in the best studied thalamic nucleus, the mediodorsal nucleus, are inconsistent and require further investigation in new subject cohorts. Thus, the current findings of stereological studies of thalamus in schizophrenia support the idea that thalamo-cortical dysfunction in schizophrenia might be attributable, at least in part, to structural alterations in the thalamus.

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Table 1

Brain collections providing tissue samples for stereological studies of the thalamus in schizophrenia.

Brain bank number	Name	Comments
1	Mount Sinai/Bronx VA Schizophrenia Brain Bank, USA	Community sample. 80 μm frozen sections.
2	Runwell Hospital, Essex; Royal Victoria Hospital, Belfast; and Radcliffe Infirmary, Oxford; UK	Hospital sample. 25 μm paraffin sections.
3	New Magdeburg Brain Collection, Germany	Psychiatric hospital sample. 20 μm paraffin sections.
4	Sct. Hans Psychiatric Hospital, Roskilde, Denmark	Psychiatric hospital sample. Long-time hospitalized patients. Thick (40 μm) and thin (4 μm) paraffin sections.
5	The Brain Collection, Risskov, Denmark	Psychiatric hospital sample. Old collection of 9479 brains from psychiatric patients including chronically-hospitalized and untreated subjects with schizophrenia. Fixed tissue blocks.
6	Brain Tissue Repository of the Center for Neuroscience, University of California, Davis, USA	Community sample. 50 μm frozen sections.
7	Terrell State Hospital, and the Waco VA Medical Center, USA	Psychiatric hospital sample. 60 μm frozen sections
8	The Stanley Foundation Neuropathology Consortium, USA	Community sample. Thalamus cohort: 15 schizophrenia, 15 controls, 15 major depression, 15 bipolar. 60 μm frozen sections from deparaffinated paraffin blocs.
9	Allegheny County Coroner's Office, Pittsburgh, USA	Community sample. 80 μm frozen sections.
10	Morphological Brain Research Unit, University of Wuerzburg, Germany	Psychiatric hospital sample. Chronically-hospitalized patients. Large whole-hemisphere 600–700 μm thick frozen sections.
11	New South Wales Tissue Resource Centre, Australia	Community sample. 50 μm frozen sections.

Table 2

Stereological estimates in postmortem schizophrenia studies of **the whole thalamus**.

Authors (year)	Brain bank[a]	Region	Schiz/Cont/Other[b]	Mean age (years)	Estimates[c]	Reported significant schiz. related diff.[d]
Byne et al. (2002)	1	Right thalamus	4M6F/4M1F[e]	66.6/75.0	V	No difference
Cullen et al. (2003)	2	Right and left thalamus	11M10F/14M13F	68/71	V	No difference
Danos et al. (2003)	3	Right and left thalamus	7M5F/9M4F	50.7/51.6	V	**Decreased V: 16% left, 15% right**
Young et al. (2008)	8	Right or[f] left thalamus	8M4F/9M6F/8M6F/8M5F[g]	44.3/48.1/45.2/43.7[h]	V	No difference

Positive findings in bold.

[a] Brain bank according to Table 1.

[b] Number of males (M) and females (F) in each diagnostic group: Schizophrenia (Schiz), Control (Cont) group, Other diagnostic group(s).

[c] Abbreviations: V volume.

[d] Statistically significant differences for the schizophrenia group. Abbreviations as in “Estimates” column.

[e] “Restricted” subject groups without Alzheimer’s type pathology. The results listed are for these subjects without Alzheimer’s type pathology. Full subject sample: 14 Schiz, 8 Cont.

[f] Schiz 7R5L; Cont 8R7L; Major Depression (MDD) 9R5L; Bipolar Disorder (BPD) 6R7L.

[g] Groups: Schiz, Cont, MDD, BPD.

[h] Mean ages for full study sample of 12 Schiz, 15 Cont, 14 MDD, and 13 BPD.

Table 3

Stereological estimates in postmortem schizophrenia studies of **the mediodorsal nucleus**.

Author(s) (year)	Brain bank(s)[a]	Region(s)	Schiz/Cont/Other[b]	Mean age (years)	Estimates[c]	Reported significant schiz. related diff.[d]
Pakkenberg (1990)	4	Left mediodorsal n.	8M4F/6M6F	62.8/62.3	V, N(neu, astro, oligo), Nv(neu, astro, oligo)	**Decreased V 26%, N(neu 40%, astro 44%, oligo 45%), N_V(neu) 22%**
Pakkenberg (1992)	4,5	Right and/or[e] left mediodorsal n.	3M5F + 8M4F/3M5F + 6M5F[f]	58 + 63/59 + 60[g]	V	**Decreased V (untreated 31% and treated 22%)**
Pakkenberg (1993)	4	Left mediodorsal n.	4M4F[h] + 8M4F/6M6F	69.0[h] + 62.8/62.3	V, N(neu, astro, oligo), NV(neu, astro, oligo)	**Decreased V[i] 26% (20%), N(neu[i], 40% (19%), astro 44%, oligo 45%), N_V(neu) 23%**
Popken et al. (2000)	6	Left mediodorsal n. (MD) incl. parvocellular (P), densocellular (D), magnocellular (M) subregions	5M1F/5M1F	66.0/64.0	V, N(neu), NV(neu)	**Decreased N: MD 27%, *P* 31%, D 25%**
Young et al. (2000)	7[j]	Left mediodorsal n.	8M/8M	65.4/64.9	V, N(neu), NV(neu)	**Decreased V 24%, N 35%**
Byne et al. (2002)	1	Right mediodorsal n. (MD) incl. parvocellular (P), magnocellular (M), and caudodorsal (CD) subregions	4M6F/4M1F[k]	66.6/75.0	V	**Decreased V: MD 15%, P 13%**
Cullen et al. (2003)	2	Right and left mediodorsal n.	11M10F/14M13F	68/71	V, N(neu)	No differences
Danos et al. (2003)	3	Right and left mediodorsal n.	7M5F/9M4F	50.7/51.6	V	**Decreased V (left side only) 9%**
Dorph-Petersen et al. (2004)	9	Left mediodorsal n.	7M4F/6M3F/8M4F[l]	48.1/53.9/50.8[l]	V, N(neu type 1 & 2)	No differences
Young et al. (2004)	8	Right or[m] left mediodorsal n.	7M3F1?/7M4F/6M5F1?/6M5F1?[m]	45.8/49.2/46.1/40.3[n]	V, N(neu), N_V(neu)	No differences
Danos et al. (2005)	3	Right and left mediodorsal n.	10M10F/10M8F	52.9/52.6	V	No differences
Kreczmanski et al. (2007)	10	Right and left mediodorsal n.	13M/13M	51.5/51.9	V, N(neu), NV(neu)	No differences
Chana et al. (2008)	8	Right or[o] left mediodorsal n.	8M5F1?/9M6F/8M5F1?/9M6F[o]	44.2/48.1/46.4/42.3[p]	V, N(glia), NV(glia)	No differences

Author(s) (year)	Brain bank(s)[a]	Region(s)	Schiz/Cont/Other[b]	Mean age (years)	Estimates[c]	Reported significant schiz. related diff.[d]
Damgaard Nielsen et al. (2008)	4	Right or[q] left mediodorsal n. incl. magnocellular, parvocellular, and densocellular subregions.	5M4F/3M5F	68.8/68.5	V, N(neu type 1 & 2, glia)	No differences
Kreczmanski et al. (2009)	10	Right and[r] left mediodorsal n.	13M/11M	51.5/55.7	L(µvsl), L_V(µvsl), L_N(µvsl/neu)	No differences

Positive findings in bold.

[a] Brain bank(s) according to Table 1.

[b] Number of males (M) and females (F) in each diagnostic group: Schizophrenia (Schiz), Control (Cont) group, Other diagnostic group(s). Subgroups within same category are separated by "+" sign.

[c] Abbreviations: V volume; N number; N_V numerical density; L length; L_V length density; L_N mean length per cell; neu neuron; astro astrocyte; oligo oligodendrocyte; µvsl microvessel.

[d] Statistically significant differences for the schizophrenia group. Abbreviations as in "Region(s)" and "Estimates" columns.

[e] Untreated Schiz vs. Cont study: Schiz 3R2L3B, Cont 3?5B. Right/left study: Schiz 12B, Cont 11B. R right, L left, B bilateral.

[f] Study groups: 8 Untreated Schiz, 12 Schiz, 8 Cont for untreated Schiz, 11 Cont for Schiz. 5 Cont subjects are included in both control groups and thus listed twice here.

[g] Mean ages for the four study groups: 8 Untreated Schiz, 12 Schiz, 8 Cont for untreated Schiz, 11 Cont for Schiz. 5 Cont subjects are included in both control groups.

[h] Group of leucotomized subjects with schizophrenia.

[i] Further decreased in the leucotomized schizophrenia group. Percent changes are Schiz vs. Cont and (Leucotomized Schiz vs. Schiz).

[j] All of the tissue samples from schizophrenia subjects were obtained from Texas Psychiatric Hospitals and one control subject was obtained from the Stanley Foundation; the latter was not included in the 60 brains from The Stanley Foundation Neuropathology Consortium (Dr. Keith Young, personal communication).

[k] "Restricted" subject groups without Alzheimer's type pathology. The results listed are for these subjects without Alzheimer's type pathology. Full subject sample: 14 Schiz, 8 Cont.

[l] Mood disorder group.

[m] Schiz 3R7L1?; Cont 5R6L; Major Depression (MDD) 5R6L1?; Bipolar Disorder (BPD) 6R5L1?. One Schiz, one MDD, and one BPD excluded without details from the full study sample of 12 Schiz, 11 Cont, 13 MDD, and 13 BPD. Thus, side and sex not reported for 3 subjects.

[n] Mean ages for full study sample of 12 Schiz, 11 Cont, 13 MDD, and 13 BPD.

[o] Schiz 5R8L1?; Cont 7R8L; MDD 6R9L; BPD 7R6L1?. One Schiz and one BPD excluded without details from the base sample of 15 Schiz, 15 Cont, 15 MDD, and 15 BPD. Thus, side and sex not reported for two subjects.

[p] Mean ages for base sample of 15 Schiz, 15 Cont, 15 MDD, and 15 BPD.

[q] Schiz 7R2L, Cont 7R1L.

$r_{\text{Schiz 1L12B, Cont 2L9B.}}$

Table 4

Stereological estimates in postmortem schizophrenia studies of **the pulvinar**.

Authors (year)	Brain bank[a]	Region(s)	Schiz/Cont/Other[b]	Mean age (years)	Estimates[c]	Reported significant schiz. related diff.[d]
Byne et al. (2002)	1	Right pulvinar	4M6F/4M1F[e]	66.6/75.0	V	**Decreased V21%**
Danos et al. (2003)	3	Right and left medial pulvinar	7M5F/7M2F2?[f]	50.7/51.6[g]	V	**Decreased V 20% left, 22% right**
Highley et al. (2003)	2	Right and left medial (MP) and lateral (LP) pulvinar	12M7F4?/12M10F3?[h]	62–73/67–73[i]	V, N(neu)	**Right side only: Decreased V: MP 14%, LP 26% & N: LP 24%**
Byne et al. (2007)	1	Right pulvinar (P) incl. medial (M) and inferior/lateral (IL) parts	8M5F/7M3F	66.6/72.5	V	**Decreased V: P 19%, M 24%**
Young et al. (2007)	8	Right or[j] left pulvinar	6M3F3?/9M6F/5M2F4?/5M2F4?[j]	44.2/48.1/46.4/42.3[k]	V, N(neu)	No differences
Mileaf & Byne (2012)	8	Right or[l] left medial pulvinar	7M2F/7M5F	44/46	N(neu, oligo)	**Right side only: Decreased N(neu)? %**[m]

Positive findings in bold.

[a] Brain bank according to Table 1.

[b] Number of males (M) and females (F) in each diagnostic group: Schizophrenia (Schiz), Control (Cont) group, Other diagnostic group(s).

[c] Abbreviations: V volume; N number; neu neuron; oligo oligodendrocyte.

[d] Statistically significant differences for the schizophrenia group. Abbreviations as in “Region(s)” and “Estimates” columns.

[e] “Restricted” subject groups without Alzheimer’s type pathology. The results listed are for these subjects without Alzheimer’s type pathology. Full subject sample: 14 Schiz, 8 Cont.

[f] Two Cont excluded without details from the full study sample of 12 Schiz and 13 Cont. Thus, sex not reported for two subjects.

[g] Mean ages for the full study sample of 12 Schiz and 13 Cont.

[h] Base sample of 16M11F Schiz and 15M13F Cont reported with summary statistic in paper. Used sample: 21-23 Schiz and 21-25 Cont per side, per estimate, without further details. I.e. exact number, sex and age of subjects for each estimate not reported in the paper. Inferred numbers of males and females for max sample of 23 Schiz and 25 Cont listed here.

[i] Mean ages for base sample of 27 Schiz and 28 Cont.

[j] Schiz 3R6L3?; Cont 7R8L; Major Depression (MDD) 2R5L4?; Bipolar Disorder (BPD) 4R3L4?. Three Schiz, four MDD, and four BPD excluded without details from the base sample of 15 Schiz, 15 Cont, 15 MDD, and 15 BPD. Thus, side and sex not reported for 11 subjects. R right, L left.

[k] Mean ages for base sample of 15 Schiz, 15 Cont, 15 MDD, and 15 BPD.

[l] Schiz 6R3L; Cont 7R5L.

[m] Right and left combined: N(neu) 14% decrease but not statistically significant. N(neu) for right side significant smaller but difference not reported.

Table 5

Stereological estimates in postmortem schizophrenia studies of **the anterior nucleus**.

Authors (year)	Brain bank(s)[a]	Region(s)	Schiz/Cont/Other[b]	Mean age (years)	Estimates[c]	Reported significant schiz. related diff.[d]
Young et al. (2000)	7[e]	Left anteroventral-anteromedial n.	8M/8M	65.4/64.9	V, N(neu), Nv(neu)	**Decreased N 16%**
Byne et al. (2002)	1	Right anterior n.	4M6F/4M1F[f]	66.6/75.0	V	No differences
Dixon & Harper (2004)	11	Right (& left)[g] anterior thalamic complex	5M1F/5M1F	47/51	V	No differences
Young et al. (2004)	8	Right or[h] left anteroventral-anteromedial n.	8M4F/7M4F/7M6F/7M6F[i]	45.8/49.2/46.1/40.3[i]	V, N(neu), NV(neu)	No differences
Byne et al. (2006)	1	Right anterior principal n.	14M9F/8M4F	67.7/73.2	V	No differences
Byne et al. (2008)	8	Right or[j] left anterior principal n.	9M5F/8M6F/7M6F/9M6F[i]	43.3/48.6/46.8/42.3[i]	V	No differences

Positive findings in bold.

[a] Brain bank(s) according to Table 1.

[b] Number of males (M) and females (F) in each diagnostic group: Schizophrenia (Schiz), Control (Cont) group, Other diagnostic group(s).

[c] Abbreviations: V volume; N number; N_V numerical density; neu neuron.

[d] Statistically significant differences for the schizophrenia group. Abbreviations as in "Estimates" column.

[e] All of the tissue samples from schizophrenia subjects were obtained from Texas Psychiatric Hospitals and one control subject was obtained from the Stanley Foundation; the latter was not included in the 60 brains from The Stanley Foundation Neuropathology Consortium (Dr. Keith Young, personal communication).

[f] "Restricted" subject groups without Alzheimer's type pathology. The results listed are for these subjects without Alzheimer's type pathology. Full subject sample: 14 Schiz, 8 Cont.

[g] Schiz 6R; Cont 4R2L. R right, L left.

[h] Schiz 4R8L; Cont 5R6L; Major Depression (MDD) 6R7L; Bipolar Disorder (BPD) 7R6L.

[i] Groups: Schiz, Cont, MDD, BPD.

[j] Schiz 6R8L; Cont 6R8L; MDD 6R7L; BPD 8R7L.

Table 6

Stereological estimates in postmortem schizophrenia studies of **other thalamic nuclei**.

Authors (year)	Brain bank[a]	Region(s)	Schiz/Cont/Other[b]	Mean age (years)	Estimates[c]	Reported significant schiz. related diff.[d]
Popken et al. (2000)	6	Left: ventral posterior medial n.	5M1F/5M1F	66.0/64.0	V, N(neu), Nv(neu)	No differences
Danos et al. (2002)	3	Right and left ventral lateral posterior n.	5M3F/5M3F	52.3/55.4	V, N(neu), N_V(neu)	**Left side only: Decreased V 25% & N 27%**
Byne et al. (2002)	1	Right centeromedian n.	4M6F/4M1F[e]	66.6/75.0	V	No differences
Byne et al. (2008)	8	Right or[f] left centeromedian n.	7M3F2?/8M6F/7M6F/8M5F1?[f]	43.3/48.6/46.8/42.3[g]	V	No differences
Selemon & Begovic (2007)	8	Right or[h] left lateral geniculate n.: magnocellular, and parvocellular layers	9M6F/9M6F	44.5/48.1	V, N(neu, glia)	No differences
Dorph-Petersen et al. (2009)	9	Left: lateral geniculate n. (LGN) incl. magno - (M) and parvo - (P) cellular laminae and interlaminar regions (I)	6M3F/5M2F/8M5F[i]	44.8/50.6/53.3[i]	V: LGN, M, P, I; N(neu): LGN, M, P	No differences

Positive findings in bold.

[a] Brain bank according to Table 1.

[b] Number of males (M) and females (F) in each diagnostic group: Schizophrenia (Schiz), Control (Cont) group, Other diagnostic group(s).

[c] Abbreviations: V volume; N number; N_V numerical density; neu neuron. Regions are abbreviated as in the "Region(s)" column.

[d] Statistically significant differences for the schizophrenia group. Abbreviations as in "Estimates" column.

[e] "Restricted" subject groups without Alzheimer's type pathology. The results listed are for these subjects without Alzheimer's type pathology. Full subject sample: 14 Schiz, 8 Cont.

[f] Schiz 4R6L2?; Cont 6R8L; Major Depression (MDD) 6R7L; Bipolar Disorder (BPD) 7R6L1?. Two Schiz & one BPD excluded without details from the full study sample of 14 Schiz, 14 Cont, 13 MDD, and 15 BPD. Thus, side and sex not reported for three subjects. R right, L left.

[g] Mean ages for the full study sample of 14 + 14 + 13 + 15 subjects.

[h] Schiz 9R6L; Cont 8R7L.

[i] Mood disorder group.