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Structural brain abnormalities in genetic generalized epilepsies: A systematic review and meta-analysis

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Supporting Appendices Include: Meta-analyses Statistics and Forest Plots, Data Extraction Table, Study Quality Rating Table and Brain Region Extraction Table

Abstract

Objective: According to the International League Against Epilepsy definition (ILAE), no structural abnormalities are present in a standard brain MRI in genetic generalized epilepsy patients (GGE). However, recent studies raise contradictory evidence with increasing use of quantitative MRI techniques.

Methods: Following PRISMA guidelines, a systematic, quantitative review was conducted using 28 peer-reviewed, case-control studies published after 1989. Furthermore, a meta-analysis with random-effect model revealed differences in structural brain abnormalities between GGE patients and controls.

Results: Significant structural differences between GGE and healthy controls were observed with volume reductions in whole brain, thalamus, putamen, caudate, pallidum and supplementary motor area. Furthermore, grey matter volume reduction in the right and left hemispheres, thalamus, insula, and surface area reduction in the caudal anterior cingulate cortex were revealed, along with grey matter increase in the medial frontal gyrus.

Significance: Due to methodological differences, findings should be interpreted with caution. Nevertheless, contrary to the ILAE definition it would appear that structural brain abnormalities may be present in GGE patients. Findings are consistent with hypothesis regarding the underlying involvement of the thalamo-cortical networks in the generation of generalized spike-wave discharges but structural abnormalities appear to extend outside these regions to potentially involve attention and other cognitive domains.

Keywords: Structural brain abnormalities, Genetic generalized epilepsy, Idiopathic Generalised Epilepsy, systematic review, meta-analysis.

1. Introduction

Genetic generalized epilepsy (GGE) encompasses several electro-clinical syndromes diagnosed and classified according to clinical features and EEG characteristics with no clear underlying cause apart from a presumed genetic predisposition[1]. The syndromes are defined by an age-related onset and specific clinical features[2]. The defining electroencephalographic characteristic of GGE is typical generalized, bisynchronous and symmetric activity with spike-wave or polyspike-wave discharges[3,4]. GGE constitutes 15-20% of all epilepsies[5]. The most common electro-clinical syndromes recognized by the International League Against Epilepsy (ILAE) are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and generalized tonic-clonic seizures alone (GTCSA)[2,6]. Although the term 'genetic' has only recently been introduced by the ILAE as a replacement term for 'idiopathic' [7,8] and both terms were used when conducting this systematic review to ensure comprehensive retention of all the research on the topic, we will only use the newer GGE term in this paper.

According to the current ILAE definition, GGE patients are required to be intellectually unimpaired with standard magnetic resonance imaging (MRI) brain showing no abnormalities (ILAE, 1989). However, with the increasing use of more quantitative MRI studies structural brain abnormalities in cortical and subcortical regions have sometimes been revealed when comparing patients with healthy controls. A previous review concerning structural and functional abnormalities in GGE patients compared to healthy controls revealed differences in brain shape[9]. Magnetic resonance imaging studies involving the structural abnormalities of the thalamus are inconclusive. The majority of studies report decreases of thalamic volumes in GGE[10,11,12]. Some studies also report increased volumes[12,13] or no difference in thalamic volumes in GGE patients[9,14,15]. Furthermore, increases[16] and decreases[11] of frontal cortical grey matter in GGE are reported.

The most common GGE syndrome, JME has been the subject of intensive research in recent years[17]. Again, reviews looking at neuroimaging studies conducted in JME cohorts report inconsistent findings. Thalamic abnormalities showed either increased or decreased thalamic volume, grey matter volume or grey matter concentration[18,19,20,21,22] Overall frontal lobe structural and functional changes are seen in JME affecting orbitofrontal, mesial areas and the supplementary motor areas (SMA). Diffusion tensor imaging (DTI) showed altered connectivity of the SMA to prefrontal and fronto-polar areas[23,24,25]. Another region showing altered structural connectivity and altered volume was the corpus callosum. Volume alterations were especially prominent in the rostrum and rostral body[26].

Diversity of results could be partially due to methodological variability[21,22]. Some studies measure grey matter volume while others measure grey matter concentration. Furthermore, small sample size reported from many studies could also have an impact on the results. Due to these inconsistencies in the literature, no clear picture can be formed of the structural abnormalities in GGE patients.

To our knowledge, no systematic review or meta-analyses of the current literature has been conducted to this date. In this review we aim to address the following questions:

1. Are there structural abnormalities in GGE patients in comparison to healthy controls?
2. If structural abnormalities are present in GGE patients is there a consistent topological pattern?

2. Methods

2.1 Protocol registration

The systematic review was conducted using the PRISMA guidelines[27]. The protocol was registered with the international Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42015027195).

2.2 Eligibility criteria

Publications prior to 1989 were excluded to limit the diagnostic impact of epilepsy seizure and syndrome classification prior to the 1989 ILAE revisions. Titles and abstracts were screened to identify relevant articles. Reference lists of selected articles were also searched for additional studies. Articles had to meet the following inclusion criteria (a) research published in a peer reviewed journal (b) case-control, human, cohort and case-series studies (c) all studies should include GGE consisting of one or a group of mixed sub-syndromes recognised by the ILAE and a healthy control group (d) outcomes include structural imaging results.

Articles were excluded if they met the following criteria (a) non-English articles (b) articles published before 1989 (c) full-text article was not available (d) animal studies (e) single case-reports or case-series with no control group (f) control groups consisting of focal epilepsy patients (g) GGE patients with coexisting brain pathology (h) epilepsy sample includes GGE patients but no separate analyses were conducted for GGE, for example, focal epilepsy and GGE patients were analysed together (i) no precise descriptive statistics where

given for example, only illustrative figures, no exact p-values or t-values or when insufficient participant numbers could be included.

2.3 Information sources

A keyword search was conducted using electronic databases. The search was applied to Medline, PsychInfo and Embase with a final list of full text articles updated on the 11th of November 2016.

2.4 Search

The following search terms were used in all 3 databases.

(i) (idiopathic adj2 generali*ed adj2 epileps*).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw, tc, id, tm]

(ii) (structural and brain and abnormal* and magnetic resonance imaging).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tn, dm, mf, dv, kw, tc, id, tm]

(iii) (i) and (ii)

(iv) (genetic adj2 generali*ed adj2 epileps*).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, tn, dm, mf, dv, kw, tc, id, tm]

(v) (structural and brain and abnormal* and magnetic resonance imaging).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, tn, dm, mf, dv, kw, tc, id, tm]

(vi) (iv) and (v)

2.5 Data collection, data items

Based on the Cochrane public health data extraction template[28], a data extraction sheet was developed (Appendix 3). Pilot testing was conducted on 15 randomly selected articles and the sheet was adjusted accordingly. The included descriptive data items were the following (a) sample sizes, (b) gender, (c) age, (d) age of epilepsy onset, (e) duration of epilepsy, (f) Usage of ILAE classification, (g) GGE syndrome, (h) EEG used, (i) anti-epileptic drug used, (j) recruitment method, (k) imaging methods, (l) analysis and software used, (m) exclusion or inclusion criteria, (n) outcome brain regions. When data items were not reported we listed this item for that particular article as not specified. Data summaries were calculated whenever possible in IBM SPSS statistics 21. A second data collection sheet was developed to list all the brain regions reported in all the articles (Appendix 4).

2.6 Summary measures and synthesis of results

The program Comprehensive Meta-analysis (CMA)[29] version 3 was used to conduct meta-analyses using a random-effect model. An analysis could only be conducted when 2 or more studies involving the same measurement in the same region were available, for example, studies measuring volume in the frontal lobe cannot be synthesized with studies measuring grey matter volume in the frontal lobe. Only studies including exact descriptive data were included in the meta-analysis, for example, means and standard deviation, exact t-test and p-values. CMA displays a forest plot for each analysis and calculates Cohen's d for all studies. A Cohen's d of 0.2 is considered small, 0.5 medium and 0.8 large effects[30].

2.7 Risk of bias

To assess quality between studies, a risk of bias rating was developed based on a modified version of the STROBE guidelines for reporting observational studies[31] (Appendix 2). Three criteria were established for assessing risk of study-level bias. The first aspect is 'representative sampling' consisting of the following questions (a) did researchers sample participants randomly or consecutively? (b) are control and case groups demographically matched (same age and gender)? (c) did researchers use the ILAE syndrome classification, if yes, what year?

The second aspect is 'appropriate variables measured' consisting of the following questions (a) is the measurement instrument (MRI/DTI) administered in both case and control group? (b) Was an EEG diagnostic of GGE made? (c) did researchers report factors that may have an impact on structural brain abnormalities, for example, anti-epileptic drug (AED), disease duration, seizure freedom, age of disease onset, seizure type, neurological illness, exclusion criteria?

The last aspect is 'comprehensiveness of reporting' consisting of the following (a) did the researchers report study outcomes for all planned analyses, regardless of significance, and (b) did researchers report factors that may have an impact on structural brain abnormalities. The risk of bias of 5 articles was also checked by two authors (SN & SB). The inter-rater reliability was 97%.

3. Results

3.1 Study selection

The keyword searches of Medline, Embase and PsychInfo databases resulted in a total of 93 articles. When 35 duplicates were removed, 58 studies remained. Of these, 25 were excluded after screening the titles and abstracts leaving 33 studies that were further assessed for eligibility. Another 12 studies were excluded because no full-text was available, no separate analyses were present or they were review papers. In total the keyword search alone resulted in 21 full text articles. Furthermore, a reference search resulted in 31 more articles that could be included. The full text of 52 studies that resulted from both keyword and reference search articles were examined in more detail. When two or more studies were available with the same outcome measurement in the same region, the studies were included. In total 28 studies could be included for a meta-analysis (Figure 1).

3.2 Study characteristics

Median age of GGE patients over all studies included in the meta-analyses was 28 years (range 9-39). Median age of onset was 14 years (range 7-16). Four studies did not report specific age of onset. Mean duration of disease was 12 years (range 2-23) with 11 studies not specifying duration of disease. Healthy controls had a median age of 29 (range 9-35). Three studies not specify healthy control age. Twenty-five studies conducted an EEG in both patients and control group. In 17 out of 28 studies, it was specified the ILAE was used to diagnose the patients, with 11 studies using ILAE from 1989, one study used the ILAE from 2001 and five studies did not specify the date of the ILAE.

Studies varied in GGE subgroups that were recruited. Two studies reported using an GGE group without specifying a specific subtype. Twenty-two studies recruited JME patients, 11 GTCSA patients, one absence epilepsy (AE) patients, six JAE patients, four CAE patients and one study recruited unspecified GGE patients. Furthermore, some heterogeneity was found concerning the magnetic field strength of the MRI used. Sixteen studies used 1.5T, three used 2T, eight used 3T with six studies also using DTI. Twenty-one studies reported that patients used anti-epileptic drugs and the majority also reported the kind of anti-epileptic drug used.

3.3 Synthesis of results

A meta-analysis using a random effects model was conducted to synthesize the available data. Number of studies (n), Cohen's d, the confidence interval of the effect size (CI), the p-

value, heterogeneity statistics (I^2, Q) and the between-study variance (T^2) was summarized for each analysis. Due to a limited number of studies and multiple observed abnormal brain regions, analyses were only able to be performed for GGE without distinguishing between syndromes. A summary of the findings is presented in the results section Table 1 along with the most important forest plots. All remaining supporting meta-analysis information and forest plots can be found in Appendix 1.

3.3.1 Brain volume and thickness

The meta-analysis of whole brain volume revealed a significant volume reduction in GGE patients compared to healthy controls (Figure 2: n = 6 studies; Cohen's d = -0.55; 95% Confidence Interval [CI] = -0.86 to -0.25; p-value = < 0.001; I^2 = 8.51%; Q = 12.52; T^2 = 0.11). In the small sample of relevance studies, no significant difference was found for whole brain grey matter volume (Supporting Figure 1: n = 2; Cohen's d = -0.50; 95% CI = -1.20 to 0.19; p-value = 0.16; I^2 = no difference; Q = 2.81; T^2 = 0.17) or white matter volume (Supporting Figure 2: n = 2; Cohen's d = -0.28; 95% CI = -0.67 to 0.11; p-value = 0.16; I^2 = no difference; Q = 0.83; T^2 = <0.001). Two studies report left and right hemisphere grey matter volume separately. Analysis revealed that there is a significant reduction in grey matter volume for left (Supporting Figure 3: n = 2; Cohen's d = -0.59; 95% CI = -0.91 to -0.26, p-value = <0.001; I^2 = no difference; Q = <0.001; T^2 = <0.001) and right hemisphere (Supporting Figure 4: n = 2; Cohen's d = -0.59; 95% CI = -0.91 to -0.26; p-value = <0.001; I^2 = no difference; Q = <0.001; T^2 = <0.001). Analyses of cortical thickness revealed no significant difference between groups for left (Supporting Figure 5: n = 2 ; Cohen's d = -0.11; 95% CI = -0.71 to 0.49; p-value = 0.74; I^2 = 1%; Q = 2.14; T^2 = 0.10) and right hemisphere (Supporting Figure 6: n = 3, Cohen's d = 0.95; 95% CI = -1.67 to 3.56; p-value = 0.48; I^2 = 26.85%; Q = 92.72; T^2 = 5.19).

3.3.2 Thalamus

Significant reductions in thalamic volume were found between GGE and healthy control groups for left (Figure 3: n = 5; Cohen's d = -0.69; 95% CI = -0.07 to -0.32; p-value = < 0.001; I^2 = 10.04%; Q = 10.69; T^2 = 0,12) and right thalamus (Figure 4: n = 5; Cohen's d = -0.54; 95% CI = -0.95 to -0.12; p-value = 0.01; I^2 = 14.02%; Q = 15.44; T^2 = 0.19). No significant effect was found for total thalamic volume (Supporting Figure 7: n = 4; Cohen's d = -0.43; 95% CI = -1.26 to 0.41; p-value = 0.31; I^2: = no difference; Q = 35.33; T^2 = 0.66). Some studies used a thalamus to whole brain ratio so a separate analysis was conducted for

these studies and significant reductions were found for the left thalamus to whole brain ratio (Supporting Figure 8: n = 2; Cohen's d = -1.07; 95% CI = -2.09 to -0.04; p-value = 0.04; I^2 = no difference; Q = 2.72; T^2 = 0.35) but not for the right (Supporting Figure 9: n = 2; Cohen's d = -1.08; 95% CI: -2.28 to 0.12; p-value = 0.08; I^2 = no difference; Q = 3.64; T^2 = 0.54) or total thalamic volume to whole brain ratio (Supporting Figure 10: n = 3; Cohen's d = -0.73; 95% CI = -1.54 to 0.08; p-value = 0.08; I^2 = 10.60; Q = 6.91; T^2 = 0.36). The analyses also demonstrated that grey matter thalamic volume analysis was significantly reduced in GGE patients compared to healthy controls for the left (Supporting Figure 11: n = 4; Cohen's d = -0.81; 95% CI = -1.05 to -0.57; p-value = < 0.001; I^2 = no difference; Q = 0.82; T^2 = <0.001) and the right (Supporting Figure 12: n = 2; Cohen's d = -0.75; 95% CI = -1.11 to -0.39; p-value = <0.001; I^2 = no difference; Q = 0.083; T^2 = <0.001). Analysing the fractional anisotropy of the right thalamus revealed no significant effect between both groups (Supporting Figure 13: n = 2; Cohen's d = -0.24; 95% CI = -1.02 to 0.54; p-value = 0.54; I^2 = no difference; Q = 1.78; T^2 = 0.14).

3.3.3 Putamen, Pallidum, Caudate

Three different analyses were used for the putamen. Firstly analysis of putamen volumes demonstrated a significant reduction for GGE patients (Figure 5: n = 2; Cohen's d = -1.56; 95% CI = -2.03 to -1.09; p-value = <0.001; I^2 = no difference; Q = 0.43; T^2 = <0.001). Secondly, analysis of putamen volume to whole brain volume ratio's revealed a significant reduction in left (Supporting Figure 14: n = 2; Cohen's d = -1.45; 95% CI = -2.09 to -0.81; p-value = < 0.001; I^2 = no difference; Q = 0.74; T^2 = <0.001) and right (Supporting Figure 15: n = 2; Cohen's d = -1.72; 95% CI = -2.38 to -1.05; p-value = < 0.001; I^2 = no difference; Q = 0.50; T^2 = <0.001). Putamen fractional anisotropy analysis revealed no significant effects between both groups for left (Supporting Figure 16: n = 2; Cohen's d = 0.54; 95% CI = -0.08 to 1.17; p-value = 0.09; I^2 = no difference; Q = 1.38; T^2 = 0.06) and right (Supporting Figure 17: n = 2; Cohen's d = 0.26; 95% CI = -0.35 to 0.86; p-value = 0.41; I^2 = no difference; Q = 1.24; T^2 = 0.04).

Analysis involving ratios of volume of selected regions to whole brain volumes for the caudate revealed significant reduction for left (Supporting Figure 18: n = 2; Cohen's d = -0.75; 95% CI = -1.34 to -0.17; p-value = 0.01; I^2 = no difference; Q = 0.08; T^2 = <0.001), right (Supporting Figure 19: n = 2; Cohen's d = -0.95; 95% CI = -1.55 to -0.35; p-value = 0.002; I^2 = no difference; Q = 0.49; T^2 = <0.001) and total ratios (Supporting Figure 20: n =

3; Cohen's d = -0.90; 95% CI = -1.31 to -0.49; p-value = <0.001; I^2 = no difference; Q = 0.11; T^2 = <0.001). Furthermore, analysis also revealed significant reductions for the left (Supporting Figure 21: n = 2; Cohen's d = -1.24; 95% CI = -1.87 to -0.62; p-value = <0.001; I^2 = no difference; Q = 0.78; T^2 = <0.001) but not for the right pallidum (Supporting Figure 22: n = 2; Cohen's d = -0.99; 95% CI = -3.02 to 1.02; p-value = 0.33; I^2 = no difference; Q = 9.72; T^2 = 1.90).

3.3.4 Amygdala, Hippocampus

Meta-analysis concerning the volume of the hippocampus indicates a significant reduction for GGE patients (Figure 6: n = 4; Cohen's d = -0.26; 95% CI = -0.49 to -0.02; p-value = 0.03; I^2 = no difference; Q = 2.28; T^2 = <0.001). Secondly amygdala volume did not show any significant effect between both groups (Supporting Figure 23: n = 3; Cohen's d = -0.15; 95% CI = -0.46 to 0.16; p-value = 0.34; I^2 = no difference; Q = 0.64; T^2 = <0.001).

3.3.5 Medial frontal gyrus, SMA, Insula and Caudal anterior cingulate cortex

Significant increase in grey matter volume for GGE patients in comparison to healthy controls was found for the right medial frontal gyrus (Supporting Figure 24: n = 3; Cohen's d = 0.68; 95% CI = 0.41 to 0.95; p-value = <0.001; I^2 = no difference; Q = 0.27; T^2 = <0.001). Moreover, significant reductions in grey matter volume were revealed for left (Supporting Figure 25: n = 3; Cohen's d = -0.65; 95% CI = -0.92 to -0.38; p-value = < 0.001; I^2 = no difference; Q = 0.59; T^2 = <0.001) and right insula (Supporting Figure 26: n = 3; Cohen's d = -0.66; 95% CI = -0.93 to -0.39; p-value = <0.001; I^2 = no difference; Q = 0.72; T^2 = <0.001). Fractional anisotropy analysis for the supplementary motor area revealed significant reductions in GGE patients (Supporting Figure 27: n = 2; Cohen's d =-0.83; 95% CI = -1.24 to -0.41; p-value = <0.001; I^2 = no difference; Q = 0.29; T^2 = <0.001). Secondly, fractional anisotropy analysis for the corpus callosum revealed no significant effect between groups (Supporting Figure 28: n = 2; Cohen's d = 2.82; 95% CI = -4.33 to 9.97; p-value = 0.44; I^2 = no difference; Q = 116.77; T^2 = 26.23). Last, the caudal anterior cingulate cortex surface area was significantly reduced in GGE patients compared to healthy control (Supporting Figure 29: n = 2; Cohen's d =-0.76; 95% CI = -1.27 to -0.24; p-value = <0.001; I^2 = 50.48; Q = 2.02; T^2= 0.07).

3.4 Risk of Bias

In Table 2 a summary of the assessment of risk of bias can be found. Sampling methods were a potential source of bias with almost half of the studies inadequately described. In 17 of the 28 studies included in the meta-analysis, authors did not report how they sampled their participants. Furthermore, in 13 out of 28 studies, researchers did not report if the cases were properly matched to controls concerning age and gender. In 10 out of the 28 studies, researchers did not report using ILAE criteria to classify their epilepsy patients. In more than half of the papers there was incomplete description of factors that potentially could influence brain abnormalities in GGE. In addition, study differences in magnetic field strength, varying age ranges, disease duration and anti-epileptic drug treatment were potential sources of bias. Due to the small number of studies and heterogeneity of methodological quality in many studies, therefore results should be interpreted with caution.

4. Discussion

According to current ILAE syndrome definition, a routine MRI of GGE patients and matched healthy controls should not show any differences (ILAE 1989). In contrast, recent research has increasingly suggested significant structural abnormalities in GGE compared to healthy controls when quantitative MRI techniques are employed. The current meta-analysis attempts to evaluate these reported structural abnormalities in GGE and evaluate the significance of these differences. Based on our analyses patients with GGE appear to have a reduced overall brain volume and reduced grey matter volume with preservation of white matter volume and cortical thickness. Regional reduction in both thalamic volume and thalamic grey matter volume was observed but not thalamic fractional anisotropy.

Furthermore, other focal changes are observed, with overall putamen volume but not fractional anisotropy reduced in GGE patients. Caudate, pallidum and hippocampal volumes are also reduced but not for the amygdala. Grey matter volume for the insula was reduced but medial frontal gyrus volume was increased in GGE compared to healthy controls. Fractional anisotropy for supplementary motor area was also reduced for GGE. Caution is recommended as these findings could potentially be influenced by publication bias, methodological differences between the studies and poor statistical reporting.

4.1 Hemispheric volume

Previous research by Lawson et al[32] suggests that patients with childhood absence epilepsy show a smaller brain volume compared to healthy controls. Our meta-analysis

reports data in agreement with this previous research. To date, few causal studies have explored this observation. If Lawson et al[32] proposition that the brains of people with childhood absence epilepsy is abnormal before or at the onset of their seizures is true and the duration of seizures or even medication are possible explanatory factors, causality of these brain reductions will require longitudinal incident cohorts to definitively explore these observations.

4.2 Thalamo-cortical circuits

EEG research has focused on the origin of the generalized spike-wave discharges as it remains a core sign of GGE. Many studies support the cortico-reticular theory proposed by Gloor[33] which indicates that these generalized spike-wave discharges could be generated by an interplay between the thalamus and a hyper-exitable cortex. More recent EEG-fMRI studies indicated that there is activation in the thalamus[34,35,36,37,38], cerebellum[35,38] and frontal cortex[31,32,35] associated with generalized spike-wave discharges. Functional connectivity studies also confirm the importance of the thalamus and the cortex in GGE pathology. Recent studies have revealed altered thalamo-cortical functional connectivity, especially in the circuits of the frontal cortex[39], putamen, amygdala[40] and SMA[24] in GGE patients compared to healthy controls.

Furthermore, a study conducted with healthy subjects, indicated that there was a clear network connectivity between the basal ganglia and the cerebral cortex[41]. Because the basal ganglia nuclei are shown to be involved in movement disturbances, it is believed that decreased activity of these nuclei could modulate generalized spike-wave discharges through circuits involving the thalamus and cerebral cortex[42,43]. Moreover, a recent resting-state fMRI study involving the basal ganglia network indicated that GGE patients showed significantly more integration within the basal ganglia network except the cerebellum and the supplementary motor area. In patients with inter-ictal epileptic discharges during imaging acquisition, researchers found increased functional connectivity in the caudate nucleus and the putamen and decreases in the cerebellum and supplementary motor area [43].

In summary, it is possible that an altered thalamo-cortical functional connectivity network involving the supplementary motor area, frontal cortex and basal ganglia is involved in GGE pathology. The findings of our meta-analysis indicates structural abnormalities in the thalamus, hemispheres, frontal lobe, putamen, caudate, pallidum and supplementary motor area correspond well with previous findings of functional studies and support this thalamo-

cortical circuit involvement in GGE pathology even more. It is striking that many of these regions are involved in motor activity. This could be explained by the dominant weighting of patients with typical generalized tonic-clonic seizures like JAE, GTCSA and especially JME which is of predominant interest in reported studies. Although our findings are in agreement with previous research meaning that the evidence for the involvement of the thalamo-cortical circuits is enhanced, the causality of these structural and functional findings remain unclear.

4.3 Neurocognitive findings and networks

According to the ILAE, no neurocognitive deficits should be present in GGE patients, but recent research revealed the opposite. Significant neuropsychological deficits in GGE patients were revealed in a recent meta-analysis conducted by Loughman et al[44]. This analysis indicated that GGE patients score significantly lower for processing speed, acquired knowledge, fluid reasoning, working memory and long-term memory retrieval compared to healthy controls. The latter two findings were confirmed in a recent prospective, mixed cohort of treated patients GGE patients[45]. These results are partially supported by our meta-analysis findings. First, research indicates that the hippocampus is an important structure for long-term memory retrieval[46]. A decrease in hippocampal volume is associated with reductions in episodic long-term memory[47,48]. Finding structural abnormalities in hippocampal volume might explain the finding that GGE patients show long-term memory deficits.

Secondly, as previously mentioned, GGE patients show a lower general intelligence compared with healthy controls. This inference is based on meta-analytic and prospective study evidence of reduction specifically in Full-Scale Intelligence (FSIQ) scores as well as reductions in most of the component factor scores that contribute to FSIQ or alternative general intelligence composite scores[44,45]. While it is possible that tertiary referral bias magnifies the impression of disability, similar deficits are observed in more representative community based studies as well[44,45]. There are two assumptions that may explain the lower general intelligence score in GGE patients. It is believed that there is an association between the decrease in widespread cortical thickness of regions in the frontal, temporal, parietal and extra-striate occipital cortex and a decrease in general intelligence[49,50,51]. Following the hypothesis of Tosun et al[52] that lower intelligence in patients with complex partial seizures is related to regional cortical thinning, a decrease of general intelligence in GGE patients could possibly be associated with a decrease in whole brain cortical thickness. However, our meta-

analysis did not support this assumption although insufficient cortical thickness data was reported in the studies reviewed. An alternative argument could be that the disruption of sustained attention could be associated with a lower general intelligence. Schweizer et al[53] and Stankov et al[54] revealed that sustained attention is substantially correlated with intelligence. Previous research indicated that GGE patients perform poorly on sustained attention tasks[55,56]. When this hypothesis was analysed in an fMRI study it became clear that there was disruption of the attention network in GGE. Based on images, the attention regions of interest were the insula, medial frontal, prefrontal and anterior cingulate cortex[56,57]. In our meta-analysis we demonstrated grey matter volume abnormalities in GGE patients for the insula and medial frontal gyrus. It is possible that structural brain abnormalities in insular and medial frontal gyrus grey matter volume contribute to these deficits in attention networks and in this way also influence lower general intelligence scores.

4.4 Default mode network

Resting state fMRI (rsfMRI) is a method of functional brain imaging that can be used to evaluate regional interactions observed through changes in blood flow in the brain which creates what is referred to as a blood-oxygen-level dependent (BOLD) signal that can be measured using functional magnetic resonance imaging (fMRI). Using this technique of resting state fMRI, the regional network defined as the 'default mode network' has been observed comprising several areas of the cortex that are most active when a person is not performing a goal directed task[58]. These resting state fMRI studies have defined the default mode network by widespread activation in the frontal and temporal lobes but also in the cerebellum, hippocampus, caudate and putamen[58]. Several studies have demonstrated altered resting state functional connectivity within the default mode network in GGE patients compared to healthy controls and it could be argued that this altered default mode network could contribute to the GGE pathology[59,60,61]. In agreement with previous research, our meta-analyses in GGE findings indicate structural abnormalities in parts of the default mode network. Volume reduction in the putamen, caudate and hippocampus may contribute to the default mode network alterations.

5. Limitations

One of the main limitations of this meta-analysis was the incomplete measurement and reporting of descriptive data enabling interpretation of quality in the studies reviewed. In addition, the non-systematic standardised reporting and observation of multiple abnormal

regions suggests potential different partitioning of imaging data may have lead to Type I errors in multiple comparisons. In addition, this non-standardised approach made it difficult to compare identical brain regions estimated by different methods, for example, reported volume of the anterior thalamus could not be analysed with the total thalamic volume, so making more robust analysis difficult. Furthermore, heterogeneity in MRI acquisition, clinical factors (syndromic difference, disease duration, age at imaging, medication use etc.) could potentially influence structural abnormalities reported. Small sample sizes and lack of control groups also likely contribute to the effects observed. This makes it impossible to exclude methodological variability influencing our findings. Future research in GGE would benefit from standardised acquisition and reporting of MRI findings making the data readily accessible for other researchers for future analysis.

6. Future directions

This review and meta-analysis was conducted to systematically capture the structural abnormalities in GGE patients published to date. Although considerable research has been published, only a small amount of data could be included in this meta-analysis. Future research should focus on reporting data and methodology in a more standardised way. Furthermore, making the data accessible for other researchers would be beneficial for future meta-analysis. Describing sample features with more precision, recruiting drug free incident disease and tighter age-matching of controls could reduce the risk of bias. It is clear that much GGE research needs to be done to link functional and structural studies. It is also critical for future research to find the associations between the functional and structural abnormalities and the neuropsychological deficits in GGE patients.

7. Conclusions

The current ILAE classification of Genetic Generalised Epilepsy requires no structural abnormalities on routine neuroimaging. Although studies are limited, this meta-analyses suggests the assumption of normal imaging may not hold with more detailed analyses using current brain MRI sequences. While potential risk of bias and heterogeneity was present in a number of analyses, medium to large effect sizes were observed in structural brain regions in GGE patients compared to healthy controls. Consistent with the growing literature on thalamo-cortical networks, default mode network and neurocognitive studies in GGE, alterations in frontal, thalamic areas, basal ganglia, corpus callosum, hippocampus, insula and overall brain volumes were revealed. Future research in larger samples, with

appropriate controls and standardised methods are needed to confirm and clarify the nature and functional expression of these abnormalities in patients with GGE.

8. Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors have no conflicts of interest

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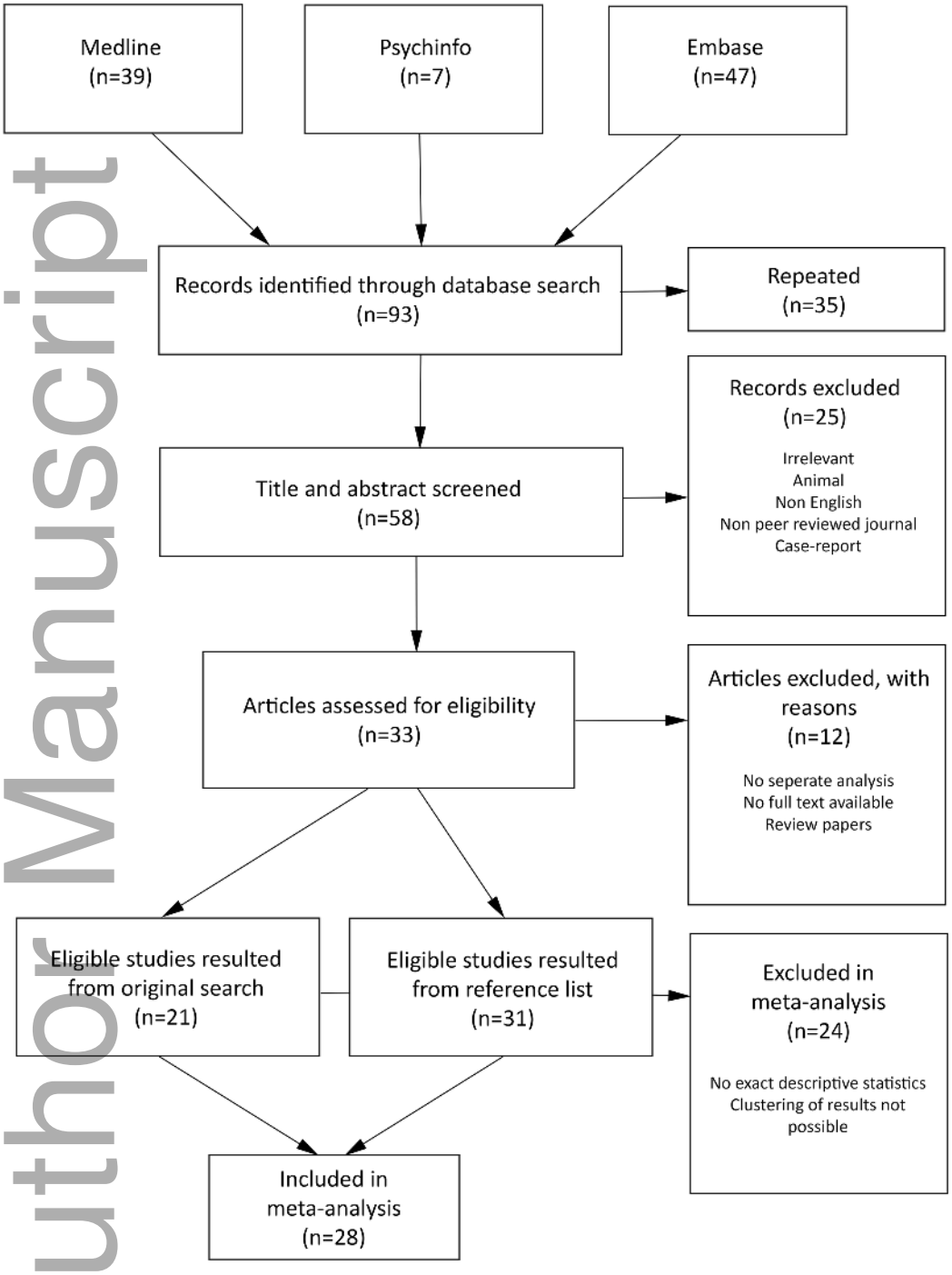
Brain region	Measurement	Location	effect
Hemispheres	Volume	Total	**IGE<HC**
	Grey matter volume	Left	**IGE<HC**
		Right	**IGE<HC**
		Total	IGE=HC
	White matter volume	Total	IGE=HC
	Cortical thickness	Left	IGE=HC
		Right	IGE=HC
Thalamus	Volume	Left	**IGE<HC**
		Right	**IGE<HC**
		Total	IGE=HC
	Volume of interest to whole brain volume	Left	**IGE<HC**
		Right	IGE=HC
		Total	IGE=HC
	Grey matter volume	Left	**IGE<HC**
		Right	**IGE<HC**
	Fractional anisotropy	Right	IGE=HC
Putamen	Volume	Total	**IGE<HC**
	Volume of interest to whole brain volume	Left	**IGE<HC**
		Right	**IGE<HC**
	Fractional anisotropy	Left	IGE=HC
		Right	IGE=HC
Caudate	Volume of interest to whole brain volume	Left	**IGE<HC**
		Right	**IGE<HC**

		Total	**IGE<HC**
Pallidum	Volume of interest to whole brain volume	Left	**IGE<HC**
		Right	**IGE<HC**
Amygdala	Volume	Total	IGE=HC
Hippocampus	Volume	Total	**IGE<HC**
Medial Frontal Gyrus	Grey matter volume	/	**IGE>HC**
Insula	Grey matter volume	Left	**IGE<HC**
		Right	**IGE<HC**
Supplementary motor area	Fractional anisotropy	Total	**IGE<HC**
Corpus Callosum	Fractional anisotropy	Total	IGE=HC
Caudal anterior cingulate cortex surface area.	Surface area	Total	**IGE < HC**

Representative sampling	**Yes**	**Unclear**	**No**	**Not complete**
Random or consecutive sampling	10	17	1	NA
Case-control matching	15	11	2	NA
ILAE criteria	17	11	0	NA
Appropriateness of measurement variables				
Both case and control measurements	27	1	0	NA
IGE diagnosis by EEG	25	3	0	NA
Structural imaging confounders reported	11	NA	NA	17
Comprehensiveness of reporting				
All study analysis reported irrespective of significance	28	0	0	NA



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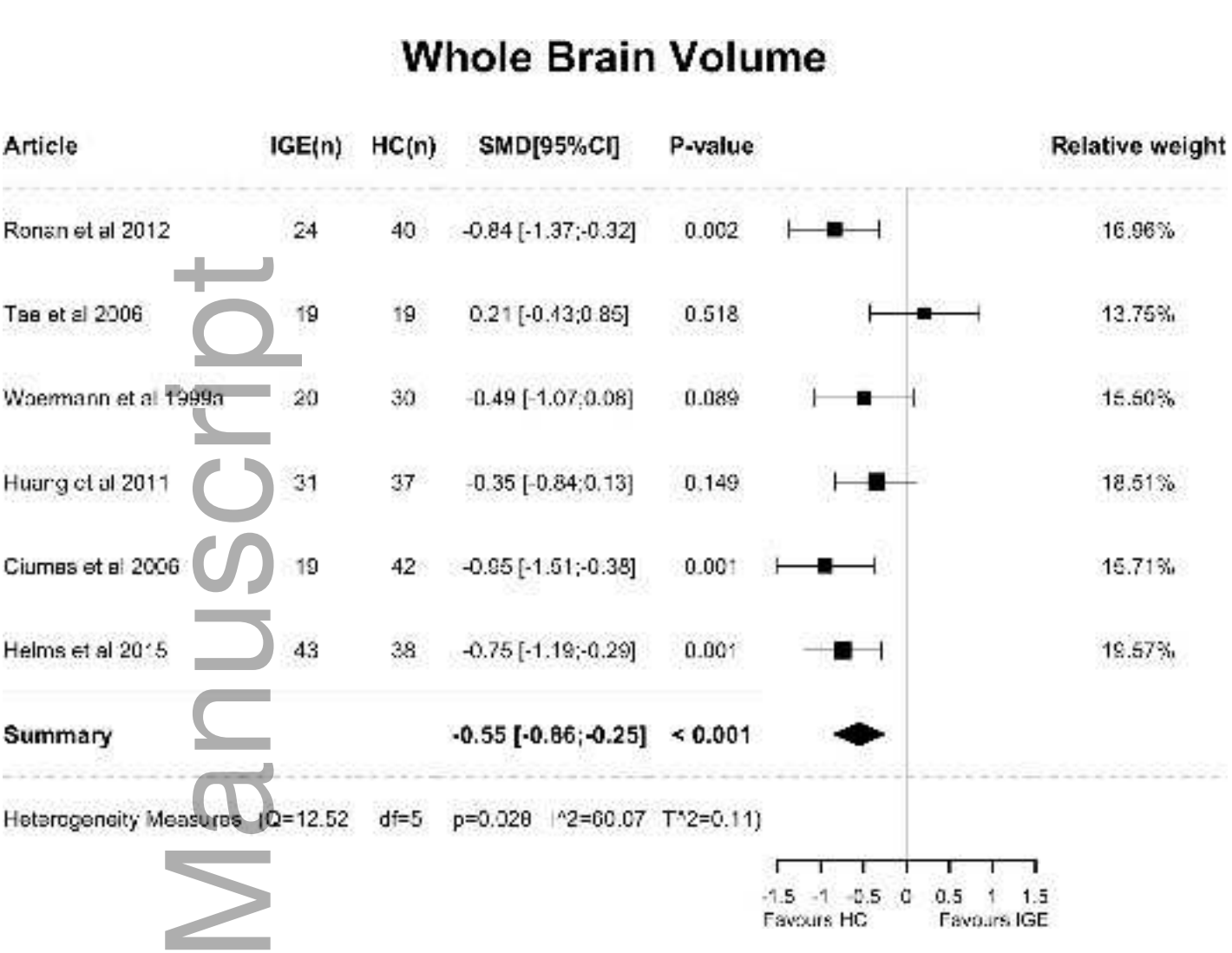

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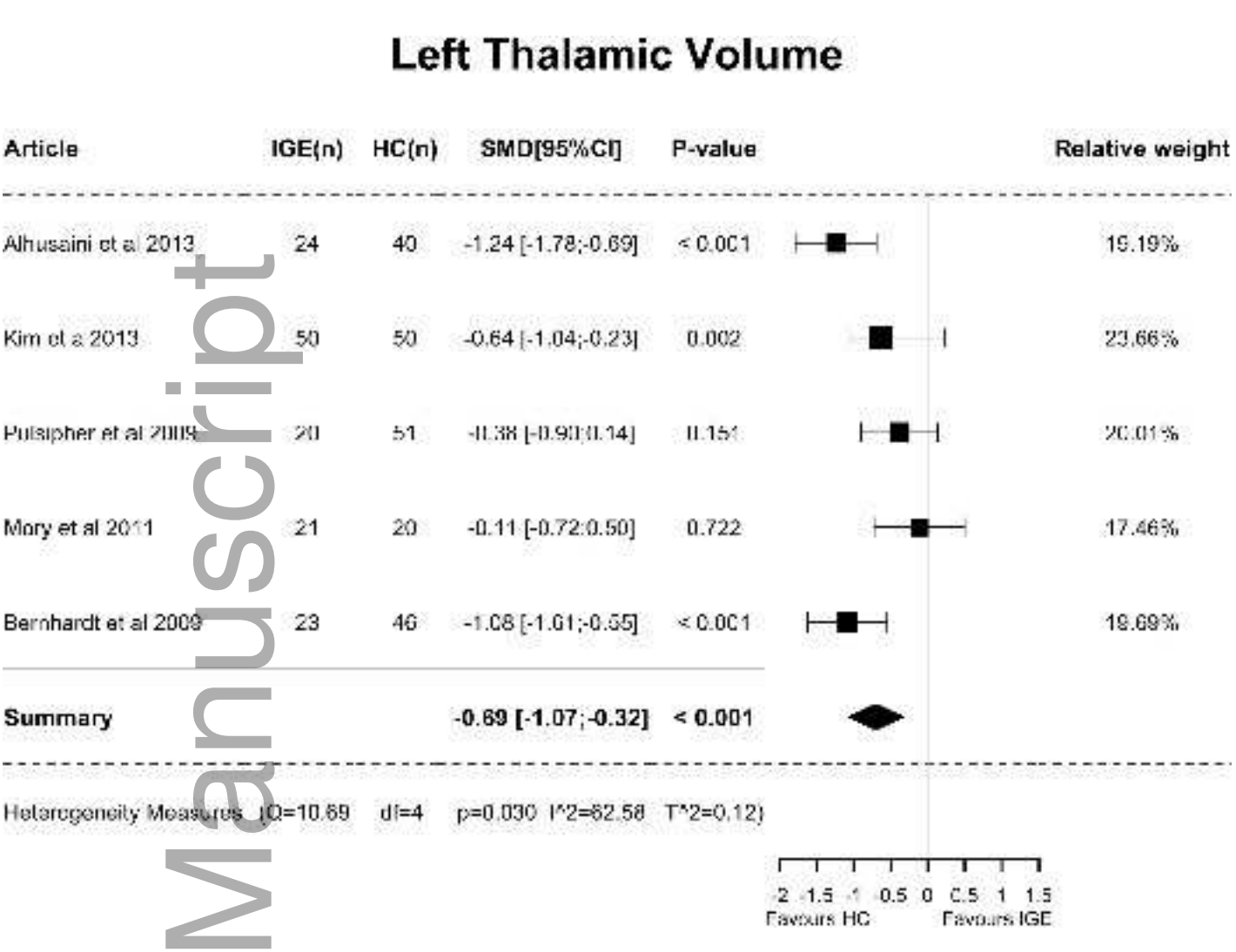

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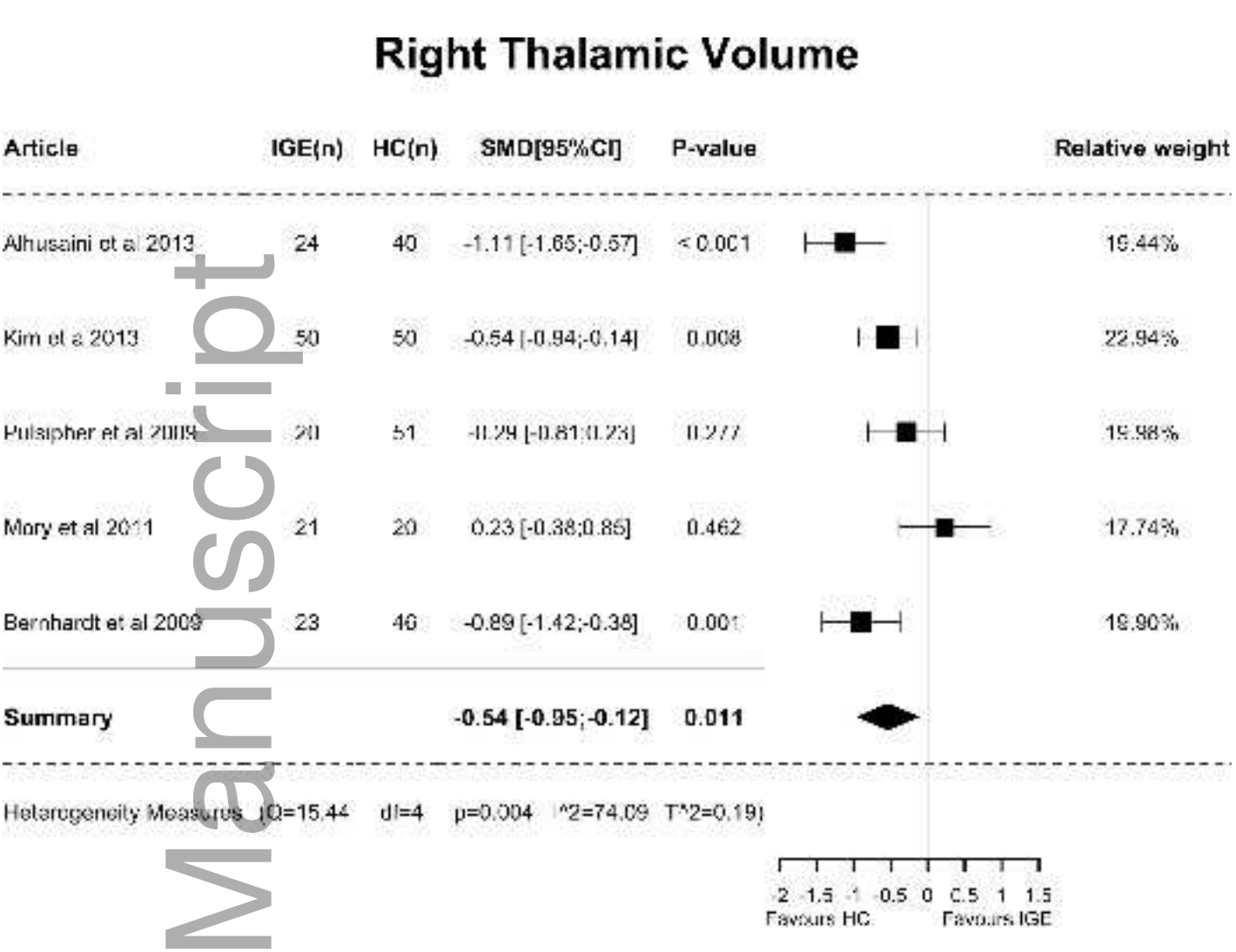

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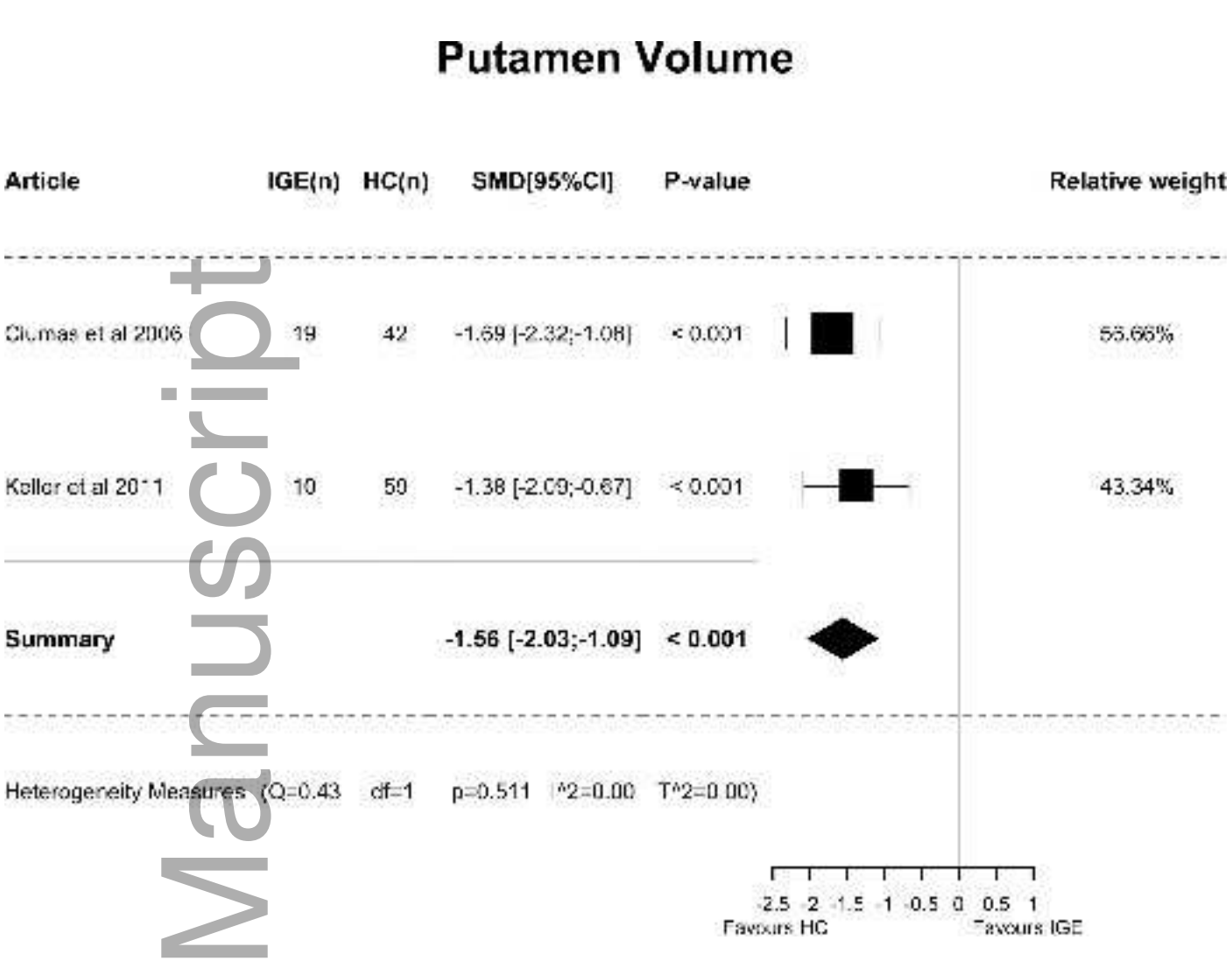

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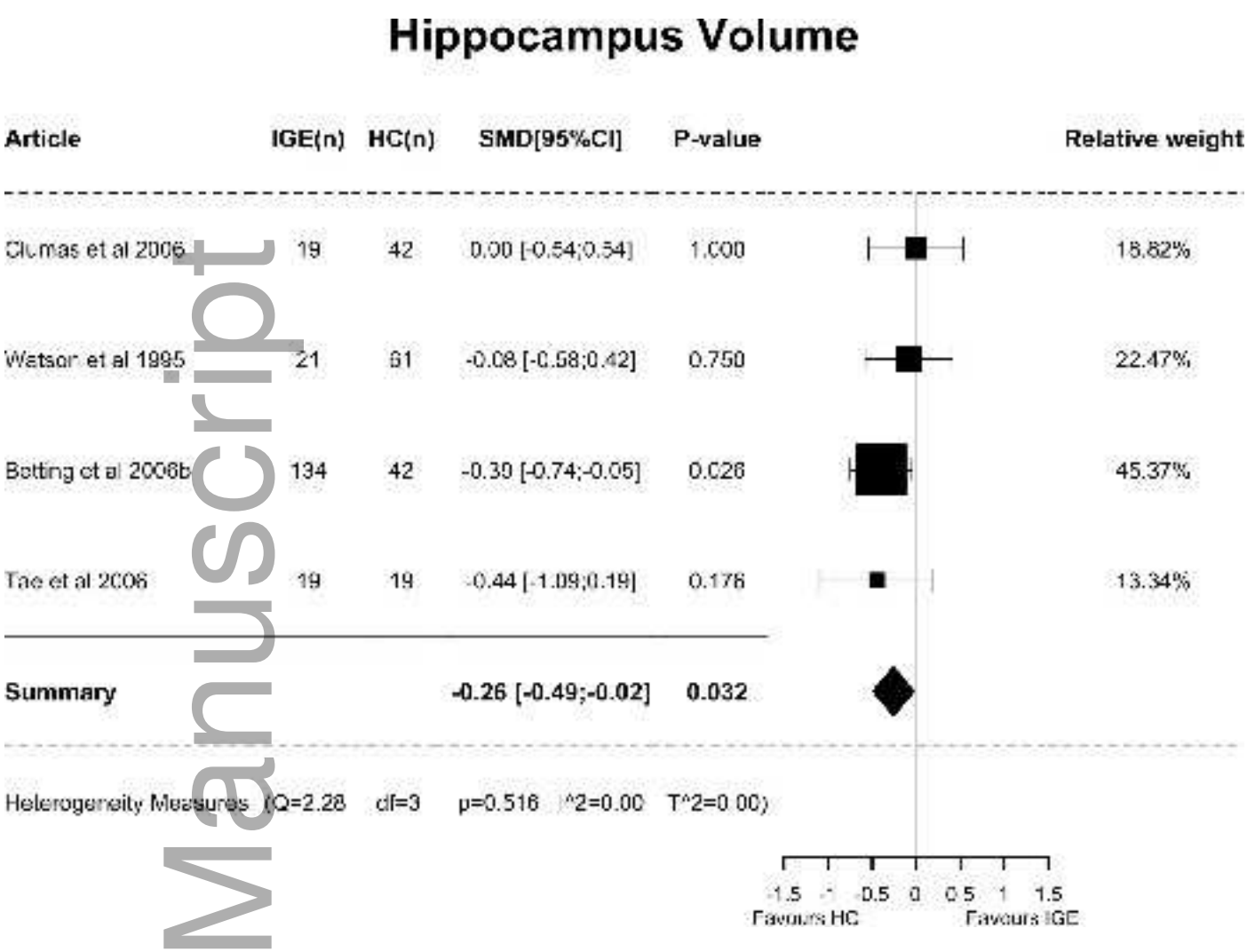

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