Abstract

Repetitive negative thinking (RNT) is a cognitive process characterised by intrusive, repetitive, and difficult-to-disengage-from negative thoughts. Heightened RNT levels are prevalent across clinical disorders and have been associated with ill-health (e.g. cardiovascular disease), even at lower, non-clinical levels. Identifying the neuroanatomical correlates of RNT could help characterise structural alterations that transcend diagnostic boundaries and further understanding of the pathogenesis of clinical disorders. We therefore conducted a systematic review to investigate associations between RNT and brain morphology. Following title/abstract and full-text screening, 24 studies were included. We found evidence that RNT severity is associated with grey and white matter volumes/microstructure, particularly in the dorsolateral prefrontal cortex, anterior cingulate cortex and superior longitudinal fasciculus, regions heavily implicated in cognitive control, and emotional processing and regulation. However, inconsistent associations, potentially due to the heterogeneity of included studies (e.g. methodological differences, type of RNT assessed), preclude specific conclusions being reached regarding any one region's association with RNT. Further, given the defuse nature of thoughts, it may be that RNT is associated with distributed brain regions operating within large-scale networks, rather than with a single structure. High quality longitudinal studies, investigating structural networks, are required to confirm the neuroanatomical basis of RNT and elucidate the direction of relationships.

Key words

Worry; Rumination; Perseverative cognition; Gray matter; White matter; MRI

1. Introduction

Repetitive negative thinking (RNT) is a cognitive process characterised by persistent negative and self-relevant thoughts that are difficult to disengage from (Harvey et al., 2004). It encompasses both worry (future-directed negative thoughts) and rumination (past-directed [e.g. depression-related, anger-related] negative thoughts) and describes the thought process rather than its time orientation or content. Heightened levels of RNT are observed across clinical disorders and are thought to contribute to the development, maintenance and reoccurrence of psychopathologies, such as anxiety and depression (Kaplan et al., 2018; Watkins, 2008). Correspondingly, RNT has been conceptualised as a transdiagnostic process that is prevalent across a wide spectrum of clinical disorders (Harvey et al., 2004; McEvoy et al., 2013). Further, as RNT describes a dimensional rather than categorical process, it is also present in non-clinical populations, albeit to a lesser extent (Ehring & Watkins, 2008). Even at lower, non-clinical levels RNT has been associated with ill-health including increased physiological stress responses (e.g. higher blood pressure, increased cortisol secretion), poor sleep and cognitive decline (Clancy et al., 2016; Marchant et al., 2020; Ottaviani et al., 2016). However, despite the increasingly recognised relevance of RNT to physical and mental health, the anatomical correlates of RNT have not been robustly examined.

Studies investigating the anatomical and functional correlates of RNT have largely focussed on brain regions commonly associated with depression and anxiety, such as regions belonging to the default mode network (e.g. medial prefrontal cortex, posterior cingulate cortex and angular gyrus), the amygdala and hippocampus (Bora et al., 2012; Etkin & Wager, 2007; Kolesar et al., 2019). However, disparate methodologies and the propensity for studies to consider worry and rumination as separate factors, rather than as a single transdiagnostic factor (i.e. RNT), have resulted in inconsistent and incommensurable findings. In an attempt

to overcome these limitations and identify the functional correlates of RNT, Makovac and colleagues (2020) pooled functional neuroimaging investigations of worry and rumination for meta-analysis. Their analysis of 43 studies revealed that RNT involves engagement of prefrontal, insula and cingulate regions (Makovac et al., 2020). The authors propose that the interactions between these regions may underlie the characteristic conjunction of negative and self-relevant thoughts with (aberrant) cognitive control and heightened physiological arousal (Makovac et al., 2020). This meta-analysis contributes important knowledge about the brain regions involved in the *process* (i.e. neural mechanisms) of RNT, however, the long-term grey and white matter alterations that may either antecede RNT or occur as a result of prolonged engagement in RNT remain unknown. Identifying both the functional and structural correlates of RNT has the potential to increase our understanding of the underlying pathophysiology of RNT, which may ultimately manifest in clinical benefits. Further, ascertaining the neuroanatomical correlates of RNT could help characterise structural alterations that transcend diagnostic boundaries and advance our understanding of the pathogenesis of clinical disorders. We therefore conducted a systematic review of structural neuroimaging studies which investigated associations between RNT and regional grey and white matter correlates.

2. Methods

The systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009) and was registered on PROSPERO (CRD42018116615).

2.1. Literature search

Four search strategies were employed to collate relevant articles. First, seven databases (Embase, Medline, PsycInfo, PsycBooks, PubMed, Scopus and Web of Science) were

searched through to February 2020. Second, the reference lists of existing RNT-related systematic reviews and articles were examined for relevant primary studies. Third, as unpublished research may systematically differ from published research, searches to identify unpublished 'grey' literature were conducted on ClinicalTrials.gov, Open Grey, ProQuest and PsycExtra (Hedges & Cooper, 2009). Fourth, the first 300 papers on Google Scholar were searched, as per guidance (Haddaway et al., 2015).

2.2. Search strategy

For a complete overview of the search strategy see Appendix A. Briefly, the search strategy consisted of two components related to RNT (i.e. worry and rumination) and neuroimaging modalities, respectively. Search terms were marginally edited for different databases to account for the requirements of different search engines, and in databases which allowed, appropriate MeSH terms were included to supplement the existing search strategy. No limits were placed on country, language or date of publication. Animal studies were removed safely following Cochrane guidelines (Lefebvre et al., 2011).

2.3. Selection criteria

Covidence was used to facilitate screening (Veritas Health Innovation). Two researchers independently screened titles and abstracts, followed by full texts against eligibility criteria to identify relevant articles. Cases of disagreement were resolved through discussions with a third reviewer. Inter-rater agreement was assessed via Cohen's kappa coefficient (κ) and percentage agreement.

Eligibility criteria were: (i) adults (mean age of $\geq$ 18 years), (ii) non-clinical populations or clinical populations identified by Harvey et al., (2004) to engage in RNT (i.e. panic disorder

with and without agoraphobia, social phobia, post-traumatic stress disorder, unipolar depression, bipolar depression and psychotic disorder) who received a diagnosis according to internationally recognised criteria (e.g. International Classification of Diseases). To align with recent research (e.g. Ottaviani et al., 2016), eligible clinical populations were broadened to include all types of anxiety and depressive disorders. Furthermore, (iii) studies including participants with comorbidities (physical or psychological) were eligible, with the caveat that the comorbidity was not the reason for recruitment.

Additional eligibility criteria included: (iv) use of a state or trait questionnaire to assess RNT, (v) an analysis (correlation or equivalent) between RNT and a neurobiological measure, and (vi) studies that were either experimental, quasi-experimental or observational. Interventional studies were also eligible, but only if pre-treatment associations were reported. Authors of eligible studies were contacted if articles were unobtainable or additional information was required.

In light of a recent comprehensive systematic review and meta-analysis of the functional basis of RNT (Makovac et al., 2020), only studies investigating the structural correlates of RNT were included in this current review.

2.4. Data extraction

A standardised form was developed to extract the following information from eligible studies: (i) authors and year of publication; (ii) characteristics of study sample; (iii) imaging modality; (iv) type and measure of RNT; (v) technical details relating to imaging; (vi) covariates; and (vii) brief summary of results. Data extraction was completed independently by two researchers and forms reviewed for any discrepancies.

3. Results

3.1. Study selection

After removal of duplicates, title/abstract screening and full-text review, a total of 18 articles investigating the association between RNT and brain morphology were included (Figure 1). Inter-rater reliability was almost perfect at both stages of review (title/abstract: $\kappa = .840$ [95% CI, 0.80 to 0.90], $p < .001$, 98.27%; full-text: $\kappa = .872$ [95% CI, 0.77 to 0.92], $p < .001$, 94.31%).

3.2. Study characteristics

The 18 articles reported findings from 24 studies, of which 17 (71%) investigated grey matter (8 whole brain, 9 region of interest [ROI]) and 7 (29%) investigated white matter (4 whole brain, 3 ROI). In total, 9 (38%) studies assessed worry severity and 15 (62%) assessed rumination severity. The majority of studies assessed trait RNT (N = 22 [92%]). Further, the choice of scales used to assess RNT was relatively homogenous across studies, with the Penn State Worry Questionnaire (N = 8) and the Rumination Response Scale (Total score: N = 7; Brooding sub-scale score: N = 2) most frequently utilised. It should be noted that three studies reported data from overlapping participants (Hilbert and colleagues [2015] investigated grey and white matter correlates in the same participants, and Wang and colleagues [2015] and Qiao and colleagues [2013] appear to include participants from the same large cohort study).

3.3. Participant characteristics

The mean age of participants ranged from 19.9 to 68.7 years (median 32.6 years). The proportion of female participants ranged from 38% to 100% (median proportion female was

62%). Nine studies (38%) recruited participants from non-clinical populations, 8 studies (33%) recruited participants from clinical populations and the remainder (29%) recruited participants from both non-clinical and clinical populations.

The characteristics of the included studies are provided in Table 1 and their results summarised in Table 2. Below we summarise study results organised according to whether investigations were conducted in grey or white matter, and the brain regions implicated. In a sub-group analysis we investigated whether the two major components of RNT (i.e. worry and rumination) have distinct and/or overlapping neuroanatomical correlates. No consistent or systematic differences emerged, therefore results are not differentiated and are discussed in relation to RNT.

3.4. Grey matter

Associations between RNT severity and grey matter volume were most frequently reported in prefrontal brain regions. Larger bilateral dorsolateral prefrontal cortex (DLPFC) volume was associated with RNT severity in three independent non-clinical populations (Sin et al., 2018; Wang et al., 2015). However, in a clinical population, RNT severity was associated with smaller bilateral DLPFC volume (Wang et al., 2015). Consistent with these divergent associations, RNT severity was associated with larger left ventral lateral prefrontal cortex (VLPFC) volume in a non-clinical population (Qiao et al., 2013) and smaller right VLPFC cortical volume in a clinical population (Lener et al., 2016). The latter association remained when a sample of non-clinical participants were also included in the analysis (a within group analysis in the non-clinical population was not conducted).

RNT severity was also associated with grey matter volumes in other prefrontal regions, albeit less consistently. In two studies which included non-clinical populations, one reported larger left medial frontal gyrus volume (Wang et al., 2018), while the other observed smaller bilateral inferior frontal gyrus volume (Kuhn et al., 2012). Aligning with the latter finding, in a mixed clinical/non-clinical population, higher RNT levels were associated with smaller right supplementary motor cortex and right paracentral lobule volumes, however, associations were not upheld in subsequent within group analyses (Hilbert et al., 2015). In a separate mixed clinical/non-clinical population, RNT severity was associated with lower grey matter mean diffusivity (i.e. greater structural integrity) in the left orbital frontal cortex (OFC; Andreescu et al., 2011). Aligning with this finding, in another mixed clinical/non-clinical population RNT severity was related to larger bilateral medial OFC volume (Mohlman et al., 2009). However, in subsequent within group analyses RNT severity was only associated with larger left mOFC volume in the clinical population. Likewise, Schienle and colleagues (2011) investigated associations in clinical and non-clinical populations separately but only observed an association between RNT severity and larger bilateral dorsal medial prefrontal cortex volume in the clinical population.

Cingulate regions, particularly the anterior cingulate cortex (ACC), were also frequently associated with RNT. In two non-clinical populations opposing associations were observed; Kühn and colleagues (2012) reported smaller bilateral mid cingulate cortex and left ACC volumes, while Sin and colleagues (2018) reported larger bilateral ACC volume. In the latter study, analyses were also conducted following participant assignment to either a low or high RNT group (Sin et al., 2018). The high RNT group (with RNT levels akin to clinical populations) had larger bilateral ACC volumes compared to the low RNT group. Supporting this distinction between clinical and non-clinical RNT levels, Schienle and colleagues (2011)

observed a positive association between bilateral ACC volume and RNT severity in a clinical population, but found no association in a non-clinical population with low levels of RNT. In a study that included a mixed clinical/non-clinical population, RNT severity was associated with smaller left rostral ACC cortical thickness but lower mean diffusivity (i.e. less microstructural damage) in the left ACC, thus demonstrating discrepant results between grey matter macro- and microstructural changes in the ACC (Andreescu et al., 2011). Similarly, in another mixed clinical/non-clinical population, but not in subsequent within group analyses, an association was observed between RNT severity and smaller left middle cingulate gyrus volume (Hilbert et al., 2015).

Seven studies also reported associations between RNT severity and temporal grey matter regions. In non-clinical populations, RNT severity was associated with smaller left hippocampal volume (Ismaylova et al., 2018), and greater bilateral parahippocampal gyrus (PHG) volume (Wang et al., 2015). Based on their findings, Wang and colleagues (2015) then selected the PHG as a ROI in two independent populations (clinical and non-clinical), and confirmed the positive association between RNT severity and bilateral PHG volume in the non-clinical population only. RNT severity has also been associated with greater right superior temporal gyrus (STG) volume in a clinical population (Machino et al., 2014). However, in a mixed clinical/non-clinical population RNT severity was associated with smaller left STG volume (Kim et al., 2019). This association extended bilaterally in the non-clinical population only. In another mixed clinical/non-clinical population, RNT severity was associated with smaller cortical thickness in the left transverse temporal gyri and left fusiform gyri (Jin et al., 2019). However, despite a relatively large sample (n = 216) subsequent within group analyses were not conducted.

RNT has also been associated with subcortical brain regions. Specifically, in a mixed clinical/non-clinical population, but not in subsequent within group analyses, RNT severity was associated with larger grey matter volumes in regions which comprise the basal ganglia (i.e. the right striatum, left caudate nucleus and right putamen; Hilbert et al., 2015). However, in a separate mixed clinical/non-clinical population, RNT severity was associated with greater grey matter mean diffusivity (i.e. worse structural integrity) in the right putamen (Andreescu et al., 2011).

3.5 White matter

Zuo and colleagues (2012) investigated associations between RNT severity and white matter microstructure in both a clinical and a non-clinical population. They found that RNT severity was associated with white matter microstructure alterations (i.e. lower fractional anisotropy [FA], which is often considered a marker of worse integrity) in the left centre portion of the superior longitudinal fasiculus (SLF) and neighbouring motor fibres in the clinical population only (Zuo et al., 2012). Using the same methodology (i.e. Tract-Based Spatial Statistics [TBSS]) Pisner and colleagues (2019) also reported white matter microstructure alterations in the right SLF in two independent clinical populations. In these two populations, tractography, a technique which offers greater specificity for labelling white matter pathways than TBSS, confirmed the associations with the right SLF, in particular the portion of the SLF connecting the middle/superior temporal gyrus with ipsilateral precentral/cingulo-opercular areas (Pisner et al., 2019). Consistent with these findings, in another clinical sample, RNT severity was associated with reduced axial diffusivity (i.e. worse axon and myelin sheath integrity) in the left inferior frontal-occipital fasciculus (IFOF), a white matter tract that shares many connections with the SLF (Bergamino et al., 2017). Only one study reported a positive

association between RNT severity and white matter integrity; this association was observed in the right amygdala in a clinical population (Zhang et al., 2013).

In the only volumetric investigation of white matter, Hilbert and colleagues (2015) reported a negative association between RNT severity and white matter volumes in the left DLPFC, right precentral lobe and right cerebellum in a mixed clinical/non-clinical sample. Subsequent within-group analyses, however, revealed distinct associations; RNT severity was associated with reduced white matter volume in the bilateral cerebellum, right superior temporal lobe, left hippocampus, and left parahippocampal cortex in the non-clinical population, and with increased white matter volume in the left middle occipital lobe in the clinical population.

4. Discussion

The purpose of this systematic review was to synthesize empirical investigations of the neuroanatomical correlates of RNT, which were operationalised in original studies as worry or rumination. Across 24 studies, which used a variety of morphological neuroimaging techniques, we found diverse and disparate evidence for associations between RNT and regional structures. Although we were unable to reach specific conclusions about any one key region, associations between RNT and grey matter volume in prefrontal and cingulate regions, and altered white matter microstructure in the SLF were frequently reported.

Prefrontal regions play a central role in cognitive control (e.g. self-referential processing) and the regulation of mood related behaviours (Dixon et al., 2017). For example, in clinical disorders characterised by emotion dysregulation (e.g. major depressive disorder, generalised anxiety disorder), meta-analyses have consistently reported structural and functional alterations in prefrontal regions (e.g. Bora et al., 2012; Li et al., 2020; Zhao et al., 2014).

Furthermore, research has implicated these alterations in the pathogenesis of emotional dysregulation and the onset of clinical disorders (e.g. Bora et al., 2012; Etkin & Wager, 2007; Koenigs & Grafman, 2009). Aligning with this literature, engagement of prefrontal regions (together with the insula and cingulate) has recently been coupled with RNT (Makovac et al., 2020). In the current review, RNT was frequently associated with structural alterations in prefrontal regions (e.g. DLPFC, VLPFC, frontal gyrus, inferior frontal gyrus, mOFC and dorsal medial prefrontal cortex). As also evident in studies that have investigated the functional correlates of RNT, multiple brain areas were identified (largely comprised of prefrontal regions), with intra-regional associations seldomly replicated across studies. RNT involves an array of cognitive processes (e.g. self-referencing, past/future-projection, perseveration), therefore, an alteration in anatomical structure or function of an area that subtends any one of these processes may be associated with engagement in RNT, as was observed here. In support of this interpretation, evidence suggests that different rumination types (which likely involve specific cognitive and emotional processes) may have distinct neural correlates (Mandell et al., 2014).

In the current review, associations between RNT and the DLPFC were reported most frequently (in 25% of potential studies) and consistently (positive associations in 100% [N = 3] of non-clinical populations and a negative correlation in 100% [N =1] of clinical populations). The DLPFC is largely involved in the regulation of effortful cognitive operations and executive control. However, cognitive control functions mediated by the DLPFC may also pertain to emotion, specifically the regulation of negative emotion through reappraisal and suppression strategies (Koenigs & Grafman, 2009). Associations between RNT severity and larger bilateral DLPFC volumes in non-clinical populations suggest that it may be a reliable structural correlate of RNT in the absence of pathological levels (Sin et al.,

2018; Wang et al., 2015). However, in a clinical population RNT severity was associated with smaller DLPFC volume (Wang et al., 2015). The latter finding, which aligns with literature reporting smaller DLPFC volume across clinical disorders, suggests associations between RNT and DLPFC volume may depend upon RNT severity. Similarly, we observed the same pattern of divergent results between RNT severity and VLPFC volume (Lener et al., 2016; Qiao et al., 2013) – a region closely coupled with the DLPFC. Taken together the results are consistent with findings from the cognitive literature, which suggest that while pathological levels of negative cognitive processes are associated with maladaptive outcomes, moderate levels (in some circumstances) may beneficial (e.g. Eysenck et al., 2007).

Four studies also identified RNT relationships with ACC volume. Two studies reported larger volumes (Schienle et al., 2011; Sin et al., 2018) and two reported smaller volumes (Andreescu et al., 2011; Kuhn et al., 2012). Akin with prefrontal regions, the ACC is also heavily involved in emotional processing, cognitive control and the regulation of autonomic arousal (Bush et al., 2000; Carnevali et al., 2018), with reductions in ACC volume reported in clinical disorders characterised by heightened RNT levels (e.g. Bora et al., 2012; Du et al., 2012; Lai, 2013; Shang et al., 2014). Recently, ACC activation was found to distinguish between RNT in clinical and non-clinical populations (Makovac et al., 2020), however, in the current review this distinction was not observed on a structural level. The reason for these heterogenous findings are not apparent, however, previous discrepant results (e.g. with regard to larger vs smaller regional grey matter volumes) have been attributed to factors such as different comorbidity constellations, medication usage and illness duration (Bora et al., 2012). Therefore, whilst RNT was frequently associated with the ACC, meaningful interpretation is hampered by the inconsistency of the direction of associations. Further

studies are required to investigate the influences that may modulate the RNT-ACC relationship.

The amygdala has a close functional relationship with both the DLPFC and ACC, and is heavily involved in the visceral and behavioural expressions of emotion (Salzman & Fusi, 2010). This involvement likely underlies the reasoning behind the amygdala being chosen as a ROI in 50% of studies that conducted ROI analyses. However, despite being the most commonly chosen ROI, RNT severity was only associated with amygdala alterations in one (4%) study, which reported increased FA in the white matter of the amygdala (Zhang et al., 2013). Aligning with these (null) findings, analyses of functional neuroimaging investigations of RNT also found little evidence for the involvement of the amygdala (Makovac et al., 2020). Therefore, although the amygdala is heavily involved in emotion regulation and meta-analyses have highlighted amygdala structural and functional abnormalities in clinical populations (e.g. Bora et al., 2012), current evidence does not support its involvement in RNT.

A more consistent picture emerged from the studies that examined RNT relationships with white matter microstructure. Specifically, in three independent studies which used whole brain analysis techniques to investigate associations in clinical populations, RNT severity was associated with lower white matter FA in the SLF – a pivotal bidirectional white matter tract connecting large parts of the frontal cortex with parietal, temporal and limbic circuits (Pisner et al., 2019; Zuo et al., 2012). Findings observed here align with a meta-analysis reporting decreased FA values in the SLF in clinical populations (e.g. major depressive disorder) compared to non-clinical populations, and also with more severe symptoms and longer illness duration (Murphy & Frodl, 2011). Furthermore, the SLF and IFOF (a white

matter tract that was also associated with RNT severity [Bergamino et al., 2017]) have been identified as transdiagnostic white matter biomarkers across emotional disorders (Jenkins et al., 2016). Tying these findings to the grey matter results, the SLF and IFOF have strong connections with the prefrontal cortex, thus degradation of these white matter tracts would inevitably vitiate the prefrontal cortex's mediating role in negative self-referential regulation. Studies investigating both grey matter volume and white matter microstructure within the same models are required to elucidate the relationship between grey and white matter and RNT severity.

It is important to emphasise that RNT was also associated with other brain regions, spanning cortical and subcortical areas. Associations with these regions, however, were reported less frequently and consistently. Diverging and inconsistent results could reflect biological variables (e.g. percentage of females – females report higher RNT levels and there is emerging evidence for sex-dependent neuroanatomical correlates (Carlson et al., 2015)), and/or psychopathological factors (e.g. medication effects –antidepressant treatment can facilitate the generation of new neurons (Micheli et al., 2018)). Further, methodological differences (e.g. image acquisition parameters, post-acquisition processing) are also likely to contribute to inconsistencies. Indeed, in several studies results varied depending on whether RNT was treated as a continuous or dichotomous variable and the post-acquisition processing technique utilised (e.g. Pisner et al., 2019; Sin et al., 2018) . Finally, ROI analyses were conducted in 50% of studies, and may have inflated the significance of certain brain regions (Müller et al., 2018). However, due to inconsistent reporting and study heterogeneity, we were unable to assess the potential influence of these factors.

Despite study inconsistencies, associations between RNT severity and brain morphology were frequently reported in young (non-clinical) adults. These findings likely indicate brain developmental differences rather than atrophy. Only two studies included in the review involved older adults. Despite both including similar populations (mixed clinical/non-clinical), one reported positive associations between RNT severity and regional grey matter volumes (e.g. bilateral mOFC), and the other a negative association with cortical thickness in the left rostral ACC (Andreescu et al., 2011; Mohlman et al., 2009). As RNT has recently been associated with markers of Alzheimer's disease, an age-related disease, it is imperative that more research is conducted in older adults (Marchant et al., 2020).

RNT encompasses a wide range of higher order processes that include emotional and cognitive control. It is unlikely that a single structure would capture all these behaviours, rather RNT may be mediated by distributed brain regions operating within a large-scale network(s). Indeed, the default mode network (DMN), a network of brain areas that form an integrated system for self-referential activities, was recently implicated in the neural conceptualisation of RNT (Makovac et al., 2020). Whilst in the current review associations were consistently observed between RNT and the SLF (a white matter tract which connects key brain regions in the DMN), associations were not observed with core brain regions belonging to the DMN (i.e. medial prefrontal cortex, posterior cingulate cortex and angular gyrus). Future studies utilising brain structural connectivity techniques (e.g. He et al., 2007) are needed to help elucidate whether RNT is associated with anatomic connectivity in large-scale networks.

The mechanisms underpinning associations between RNT and brain morphology have received little attention. However, we might appeal to theories like the Perseverative

Cognition Hypothesis, which holds that engagement in RNT can lead to a prolonged stress response (e.g. chronic activation of the hypothalamic pituitary adrenal system; Brosschot et al., 2006). Heightened exposure to increased cortisol has the potential to negatively affect both grey matter structure and myelination patterns (Echouffo-Tcheugui et al., 2018), and thus may underlie the association between RNT severity and smaller volumes/altered white matter microstructure observed in some regions. However, a heightened stress response has also been associated with increased inflammation, which can lead to expansion of brain regions (Szymkowicz et al., 2016), and may therefore also explain why in some instances RNT is associated with larger grey matter volumes. An alternative explanation may reflect chronic activation related to reduced functioning efficiency (Sin et al., 2018). For example, among individuals with elevated RNT levels, certain regions may be recruited to greater extents to compensate for inefficiencies. Greater engagement (i.e. 'overload state' function) may gradually cause a use-dependent increase in regional volume (Wang et al., 2015). However, failure to engage in effective compensatory processes, may result in greater affective dysregulation (i.e. 'paralysis state' function) and more negative affective states, coupled with reduced volume, as generally observed in clinical disorders (Sin et al., 2018). Longitudinal investigations that track patients from disease onset and prospective studies of healthy adults and individuals at-risk for clinical disorders are needed to help elucidate the underpinning mechanism(s) that may underlie the associations between RNT and brain morphometry.

4.1. Limitations

This review is subject to several limitations. Guidelines suggest that at least 20 studies using whole-brain analysis techniques are needed for a meta-analysis to achieve sufficient power to detect moderate effects (Eickhoff et al., 2009). Only twelve studies included in the current

review conducted whole-brain analyses; a meta-analysis was therefore not appropriate. However, given the heterogeneity observed from the narrative synthesis, it is unlikely that a meta-analysis would have aided interpretation of findings.

It is important to also critically consider the studies included in this review, and the implications that this nascent evidence base has for future research. The cross-sectional design of the studies means that causal relationships cannot be established. Furthermore, although structural imaging studies are not susceptible to experimental or design flexibility, analytical heterogeneity plays a major role (i.e. causing larger differences in the results of individual studies than could be expected to occur from chance alone). Studies often performed a large number of correlations between multiple measures and various brain regions without correcting for multiple comparisons, thus increasing the risk of false positive results and potentially biasing findings both within and across studies. A substantial number of studies also treated clinical and non-clinical populations as a homogenous group (i.e. conducting analyses in mixed clinical/non-clinical samples). Whilst combining clinical and non-clinical populations increases power to detect effects, especially in the presence of small samples sizes, opposing associations between RNT and brain structures were reported in many studies that conducted within group analyses. Additionally, only four (17%) studies adjusted for levels/presence of anxiety or depression in their analyses. Whilst RNT severity and symptoms of anxiety and depression are highly correlated (McEvoy et al., 2019), evidence suggests that RNT is a distinct construct and may therefore have a unique neuroanatomical basis. For example, in a study which assessed both RNT and clinical severity (i.e. levels of anxiety/depression and illness duration), RNT was uniquely associated with mOFC volume (Mohlman et al., 2009). Additional studies controlling for confounding

variables, such as anxiety and depression, are needed help to discern the underlying neuroanatomical basis of RNT.

4.2. Conclusion

In summary, we found evidence that RNT severity is associated with brain morphometry. Associations with the DLPFC, ACC and SLF were reported most frequently. Inconsistent associations prevent us from reaching specific conclusions about any one region's association with RNT, and may point towards a more distributed underlying structural architecture. Future studies investigating grey and white matter correlates of both subcomponents of RNT have the potential to advance our understanding of the structural network of RNT and allow any associations unique to either worry or rumination to be revealed.

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Figure 1 PRISMA flow diagram outlining the systematic review process.

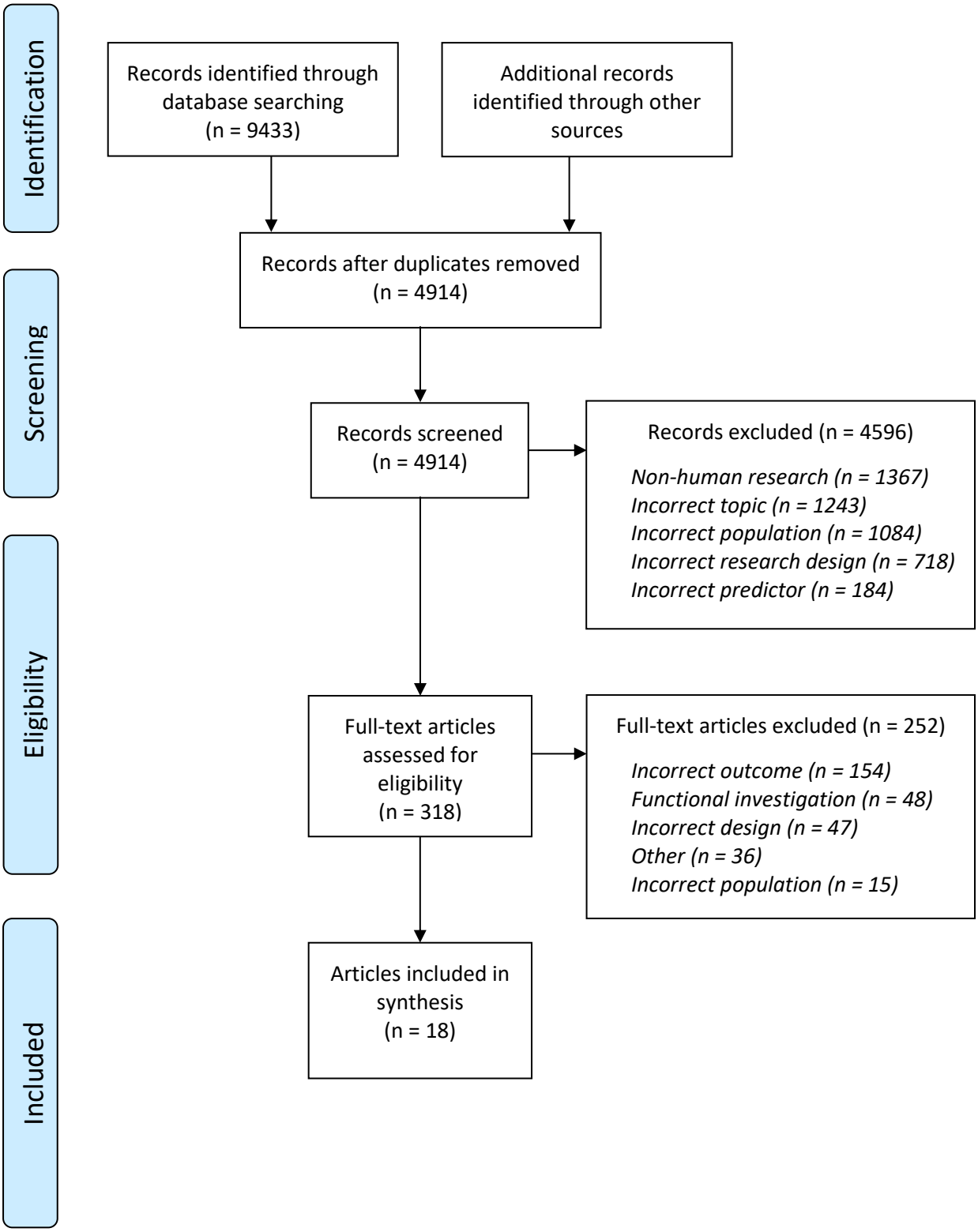

Table 1 Overview of studies included in the systematic review.

Author, year	Population	Sample size	Age (SD)	Females (%)	RNT type (measure)	Scanner/ FWHM	Covariates[†]	Statistical analysis: p-value correction
Grey Matter – whole brain								
Andreescu et al., 2011	Mixed clinical (GAD) & non-clinical	59	68.73 (7.20)	61.02	Worry (PSWQ)	nr/nr	Age	Correlation: p<.05 FDR corr.
Hilbert et al., 2015	Total	43	32.79 (9.05)	76.74	Worry (PSWQ)	3T/8mm	Age, tTV	Regression: p<.001 uncorr. & p<.05 FWE corr.
	Clinical (GAD)	19	33.47 (8.90)	84.21				
	Non-clinical	24	32.25 (9.33)	70.83				
Ismaylova et al., 2018	Non-clinical	42	33.95 (1.15)	54.76	Rumination (modified-RRS)	3T/8mm	-	Regression: p<.001 uncorr. & p<.05 FWE corr.
Jin et al., 2019	Mixed clinical (PTSD) & non-clinical	216	45.67 (13.45)	66.67	Rumination (RRS)	1.5T/nr	Age	Partial correlation: p<.05 corr. (1000 bootstrapped samples)
Kühn et al., 2012	Non-clinical	38	21.30 (nr)	73.68	Rumination (RRS)	3T/12mm	Age, sex, tBV, BDI	Correlation: p<.05 FWE corr.
Lener et al., 2016	Mixed clinical (MDD) & non-clinical	86	39.50 (12.07)	52.33	Worry (VAS-worry)	3T/nr	-	Correlation: p<.05 FDR corr.

	Clinical (MDD)	57	40.27 (12.28)	50.88				
Machino et al., 2014	Clinical (TRD)	29	39.57 (8.29)	44.83	Rumination (RSQ)	1.5T/8mm	Age, sex, medication load score, tBV	Regression: p<.001 uncorr.
Wang et al., 2015	Non-clinical	306	19.92 (1.22)	52.29	Rumination (SRRS)	3T/10mm	Age, sex, tGMV	Regression: p<.05 FWE corr.
Grey Matter – region of interest								
Kim et al., 2019	Total	68	30.00 (7.16)	45.59	Rumination (RRS)	3T/nr	Age, sex, education, antipsychotic dosage, status of medication use, duration of illness, TIV, voxel size	Partial correlation: p<0.05 corr. (bootstrapping with 5000 replications)
	Clinical (FEP)	34	28.35 (7.26)	52.94				
	Non-clinical	34	31.65 (6.76)	38.24			Age, sex, education, TIV, voxel size	
Mohlman et al., 2009	Total	30	67.87 (5.39)	50.00	Worry (PSWQ)	1.5T/nr	Age, hypertension,	Partial correlation: p<.005 *bonf* corr.
	Clinical (GAD)	15	67.39 (5.42)	40.00				
	Non-clinical	15	67.50 (4.94)	60.00				

							presence of GAD, WBV	Regression: *p*<.05 uncorr.
Qiao et al., 2013	Non-clinical	235	20.16 (1.35)	55.32	Rumination (RRS-10)	3T/10mm	Age, sex, general intelligence, tGMV	Partial correlation: *p*<.001 uncorr.
Schienle et al., 2011	Clinical (GAD)	16	22.90 (4.10)	100.00	Worry (PSWQ)	3T/12mm	tGMV	Correlation: *p*<.05 FWE corr.
	Non-clinical	15	23.7 (3.70)	100.00				
Sin et al., 2018	Non-clinical	30	31.77 (6.84)	63.33	Rumination (RRS-brooding)	3T/8mm	Age, sex, TIV, RRS-reflection	Regression: *p*<.001 uncorr. & *p*<.05 FWE corr.
Wang et al., 2015	Clinical (MDD)	60	36.07 (11.57)	71.67	Rumination (SRRS)	3T/10mm	Age, sex, education, tGMV	Partial correlation: *p*<.05 FWE corr.
	Non-clinical	63	32.40 (11.95)	50.79				
Wang et al., 2018	Non-clinical	82	21.03 (1.90)	60.98	Rumination (ARS)	3T/10mm	Age, sex, tGMV	Regression: *p*<.05 cluster level corr.
White Matter – whole brain								
Bergamino et al., 2017	Clinical (MDD)	26	37.00 (11.00)	100.00	Worry (PSWQ)	3T/nr	-	Regression: *p*<.05 FWE corr.
Hilbert et al., 2015	Total	43	32.79 (9.05)	76.74	Worry (PSWQ)	3T/8mm	Age, tTV	
	Clinical (GAD)	19	33.47 (8.90)	84.21				

	Non-clinical	24	32.25 (9.33)	70.83				Regression: p<.001 uncorr. & p<.05 FWE corr.
Pisner et al., 2019	Clinical (MDD)	51	28.71 (9.76)	56.86	Rumination (RRS-brooding)	3T/6mm	Age, sex	Regression: p<.05 FWE corr. for TBSS analyses / p<.01 FDR corr. & *bonf* corr. for tractography analyses
		46	31.02 (6.07)	67.38				
	White Matter – region of interest							
Zhang et al., 2013	Clinical (GAD)	16	30.38 (8.35)	43.75	Worry (PSWQ)	1.5T/6mm	-	Correlation: p<.05 svc corr.
Zuo et al., 2012	Clinical (MDD)	16	37.00 (9.40)	81.25	Rumination (RRS-21-total)	1.5T/nr	Age, sex, HAM-D	Correlation: p<.05 uncorr. & p<.0125 *bonf* corr.
					Rumination (RRS-21-brooding)			
	Non-clinical	19	36.60 (7.7)	63.16	Rumination (RRS-21- total)			
					Rumination (RRS-21-brooding)			

† The highest level of covariates included in analyses.

Abbreviations: ARS, Anger Rumination Scale; BDI, Becks Depression Inventory; *bonf*, Bonferroni; corr., correction; FDR, false discovery rate; FEP; first episode psychosis; FWE, familiar wise error; FWHM, full width half maximum; GAD, generalised anxiety disorder; HAM-D, Hamilton Depression Rating Scale; HC, healthy control; MDD, major depressive disorder; nc, not clear; nr, not reported; PSWQ, Penn State Worry Questionnaire; PTSD, post-traumatic stress disorder; RNT, repetitive negative thinking; RRS, Rumination Response Scale; RRS-10, Rumination Response Scale 10-item; RRS-21, Rumination Response Scale 21-item; RSQ, Response Style Questionnaire; SD, standard deviation; SRRS, Short Ruminative Responses Scale; svc, small volume correction; tBV, total brain volume; tGMV, total grey mater volume; TIV, total intercranial volume; tTV, total tissue volume; TRD, treatment resistant depression; uncorr., uncorrected; VAS-worry, Visual Analogue Scale-Worry; WBV, whole brain volume.

Table 2 Summary of main results from included studies.

Author, year	**Brain analysis methods**	**Regions of interest**	**Population**	**Brief summary of main findings in relation to RNT severity**[†] *(*corrected for multiple comparisons - regions surviving correction are in **bold**)*
Grey Matter – whole brain				
Andreescu et al., 2011	GM: MD & CT	-	Mixed clinical (GAD)/non-clinical	*Reduced MD in left OFC (r = -0.38) & left ACC (r = -0.36). Increased MD in right putamen (r = 0.35). Reduced CT in left rostral ACC (r = -0.30).
Hilbert et al., 2015	GM: VBM	-	Total	*Increased GMV in **right striatum**, left caudate nucleus & right putamen. Reduced GMV in **right SMA**, left MCC & right paracentral lobule.
			Clinical (GAD)	*No associations.
			Non-clinical	*No associations.
Ismaylova et al., 2018	GM: VBM	-	Non-clinical	*Reduced GMV in left hippocampus (r = -0.58).
Jin et al., 2019	GM: SBM	-	Mixed clinical (PTSD)/non-clinical	*Reduced CT in **left fusiform gyrus** (r = -0.16) & **left transverse temporal gyri** (r = -0.20).
Kühn et al., 2012	GM: VBM	-	Non-clinical	*Reduced GMV in **bilateral IFG**, **left ACC** & **bilateral mCC**.

Lener et al., 2016	GM: CV	-	Mixed clinical (MDD)/non-clinical	*Reduced CV in **right VLPFC** (r = -0.43).
			Clinical (MDD)	*Reduced CV in **right VLPFC** (r = -0.39).
Machino et al., 2014	GM: VBM	-	Clinical (TRD)	Increased GMV in right STG (r = 0.55).
Wang et al., 2015	GM: VBM	-	Non-clinical	*Increased GMV in **bilateral DLPFC** & **bilateral PHG**.
Grey Matter – region of interest				
Kim et al., 2019	GM: VBM	Bilateral: amygdala, hippocampus, STG & left hippocampal gyrus	Total	*Reduced GMV: **left STG** (r = -0.37).
			Clinical (FEP)	*No association.
			Non-clinical	*Reduced GMV in **left STG** (r = -0.51) & **right STG** (r =-0.42).
Mohlman et al., 2009	GM: VBM	Bilateral: amygdala, DLPFC, mOFC	Total	*Increased GMV in left mOFC (r = 0.58), right mOFC (r = 0.55). mOFC also a significant predictor of worry in regression model.
			Clinical (GAD)	*Increased GMV in left mOFC (r = 0.87).
			Non-clinical	*No associations.
Qiao et al., 2013	GM: VBM	Left VLPFC	Non-clinical	Increased GMV in left VLPFC (r = 0.23).
	GM: VBM		Clinical (GAD)	*Increased GMV in **bilateral ACC** & **bilateral DMPFC**.

Schienle et al., 2010		Bilateral: ACC, amygdala, DMPFC, insula, VLPFC, VMPFC	Non-clinical	*No associations.
Sin et al., 2018	GM: VBM	Bilateral: ACC, DLPFC	Non-clinical	*Increased GMV in **bilateral ACC** & **bilateral DLPFC**.
Wang et al., 2015	GM: VBM	Bilateral: DLPFC, PHG	Clinical (MDD)	*Reduced GMV in **bilateral DLPFC** (r = -0.31).
			Non-clinical	*Increased GMV in **bilateral DLPFC** (r = 0.24) & **bilateral PHG** (r = 0.26).
Wang et al., 2018	GM: VBM	Bilateral: amygdala, PFC, thalamus	Non-clinical	*Increased GMV in **left MFG** (r = 0.49).
White Matter – whole brain				
Bergamino et al., 2017	WM: AD	-	Clinical (MDD)	*Reduced AD in **left IFOF** (r = -0.88 to -0.92)¶
Hilbert et al., 2015	WM: VBM	-	Total	*Reduced WMV in left DLPFC, right cerebellum & right precentral lobe.
			Clinical (GAD)	*Increased WMV in **left middle occipital lobe**.
			Non-clinical	*Reduced WMV in right superior temporal lobe, left hippocampus, bilateral cerebellum & left parahippocampal cortex.

Pisner et al., 2019	WM: FA	-	Clinical (MDD)	*Reduced FA in large clusters of the **right SLF** (SLF, parietal & temporal parts) & smaller clusters of the **cingulum**, **right posterior corpus callosum** & **corticospinal tract** when using TBSS. Reduced FA: **right SLF-T** when using tractography (survived *bonf* corr. but not FDR corr.)
			Clinical (MDD)	*Reduced FA in large clusters of the **right SLF** (SLF, parietal & temporal parts) & smaller clusters of the **cingulum**, **right posterior corpus callosum** & **corticospinal tract** when using TBSS. Reduced FA in **right SLF-T** when using tractography (survived *bonf* corr. but not FDR corr.)
White Matter – region of interest				
Zhang et al., 2013	WM: FA	Bilateral: amygdala, caudal ACC/mCC & ventral ACC	Clinical (GAD)	*Increased FA in **right amygdala** (r = 0.65).
Zuo et al., 2012	WM: FA	Left centre portion of the SLF & premotor area	Clinical (MDD)	*Reduced FA in **left centre portion of the SLF** (RRS-total: r = -0.70 & RRS-brooding: r = -0.48 [association with RRS-brooding did not survive correction]).
			Non-clinical	*No associations.

† Results have been summarised following the highest level of correction and when available correlation coefficients have been reported.

¶ Results varied depending on which skeletonized voxel-wise analysis approach and fitting procedure was used.

Abbreviations: ACC, anterior cingulate cortex; AD, axial diffusivity; CT, cortical thickness; CV, Cortical volume; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsal medial prefrontal cortex; FA, fractional anisotropy; FEP, first episode psychosis; GAD, generalised anxiety disorder; GM, grey matter; GMV, grey matter volume; HC, healthy control; IFG, inferior frontal gyrus; IFOF, inferior frontal-occipital fasiculus; mCC, mid cingulate cortex; MCC, middle cingulate gyrus; MD, mean diffusivity; MDD, major depressive disorder; mOFC, medial orbital frontal cortex; MFG, medial frontal gyrus; PFC, prefrontal cortex; PHG, para-hippocampal gyrus; PTSD, post-traumatic stress disorder; SLF, superior longitudinal fasciculus; SBM, surface-based morphometry; SMA, supplementary motor area; STG, superior temporal gyrus; TRD, treatment resistant depression; VBM, voxel-based morphometry; VLPFC, ventral lateral prefrontal cortex; VMPFC, ventral medial prefrontal cortex; WM, white matter; WMV, white matter volume.

Appendix A Overview of search terms.

	Search terms[†]
RNT	"reflective thinking" OR "perseverative thinking" OR "intrusive thinking" OR "negative thinking" OR "self referential thinking" OR "obsess* thinking" OR "reflective thought*" OR "perseverative thought*" OR "repetitive thought*" OR "repetitive thinking" OR "intrusive thought*" OR "negative thought*" OR "self referential thought*" OR "stressful thought*" OR "stressful thinking" OR "obsess* thought*" OR "perseverative cognition" OR brood* OR ruminat* OR worr* OR "unconscious stress*" OR "anticipat* stress*" OR "implicit stress*" OR "cognitive intrusion" OR "repetitive negative thinking" OR "repetitive negative thought*" OR "recurrent thinking". *ti, ab, id.*
Neuroimaging	connectivity OR MRSI OR "H MRS" OR spectroscopy OR DTI OR "diffusion tensor imag*" OR PWI or "perfusion weighted imag*" OR PET OR "positron emission tomography" OR SPECT OR "single photon emission computerised tomography" OR "functional magnetic resonance" OR fMRI OR MRI OR "magnetic resonance imaging" OR sMRI OR MRS OR "single photon emission computerized tomography" OR metabol* OR "nuclear magnetic resonance" OR NMR OR neuroimag* OR "brain imag*". *ti, ab, id.*

[†] Search terms were marginally edited for each database to account for specific requirements of different databases.

Abbreviations: ab = abstract; id = key concepts; RNT = repetitive negative thinking; ti = title; * = truncation wildcard (i.e. finds all terms beginning with this string of text).