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REVIEW

Structural changes in the hippocampus as a biomarker for cognitive improvements in neuropsychiatric disorders: A systematic review

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Abstract
Cognitive impairments are a core feature of several neuropsychiatric disorders. A common biomarker for pro-cognitive effects may provide a much-needed tool to select amongst candidate treatments targeting cognition. The hippocampus is a promising biomarker for target-engagement due to the illness-associated morphological hippocampal changes across unipolar disorder (UD), bipolar disorder (BD) and schizophrenia (SCZ). Following the PRISMA guidelines, we searched PubMed and Embase, for clinical trials targeting cognition across neuropsychiatric disorders, with longitudinal structural magnetic resonance imaging (MRI) measures of the hippocampus. Five randomized and three open-label trials were included. Hippocampal volume increases were associated with treatment-related cognitive improvement following treatment with erythropoietin across UD, BD and SCZ, lithium treatment in BD and aerobic exercise in SCZ. Conversely, an exercise intervention in UD showed no effect on hippocampal volume

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or cognition. Together, these observations point to hippocampal volume change as a putative biomarker-model for cognitive improvement. Future cognition trials are encouraged to include MRI assessments pre- and post-treatment to assess the validity of hippocampal changes as a biomarker for pro-cognitive effects.

1. Introduction

Cognitive impairment is a core feature across neuropsychiatric disorders, including unipolar disorder (UD), bipolar disorder (BD), and schizophrenia (SCZ) (Bortolato et al., 2015; Fioravanti et al., 2012; Lam et al., 2014). The impairments affect several cognitive domains, including attention, learning and memory, and executive functioning in moderate to severe degree (Fioravanti et al., 2012; Porter et al., 2015; Van Rheenen et al., 2017). Importantly, the cognitive impairments persist after clinical remission (Bora et al., 2013; Jensen et al., 2016; Palazzo et al., 2017) and contribute to socio-occupational disability (Bowie and Harvey, 2006; McIntyre et al., 2013; Tse et al., 2014), which constitute the largest socio-economic burden of these disorders (Olesen et al., 2012; Wu et al., 2005). Therefore, cognitive impairment has recently become an important treatment target in neuropsychiatric disorders (Gold, 2004; Kaser et al., 2017; Miskowiak et al., 2017). However, except for cognitive remediation to treat cognitive impairment in patients with SCZ, a clinical treatment with replicable effects to treat cognitive deficits is currently not available (Miskowiak et al., 2016a, 2016b; Ramsay and MacDonald, 2015; Sole et al., 2017; Vreeker et al., 2015). One of the reasons why clinically-available treatments are lacking, is that the mechanisms by which neuro-circuitry target engagement occurs to produce pro-cognitive effects are poorly understood. A neural biomarker for cognitive improvement may provide a crucial way to select amongst candidate treatments targeting cognition across neuropsychiatric disorders.

The hippocampus is a promising neurocircuitry biomarker for cognitive impairment and improvement of cognition, because of its critical role in memory and learning (Sweatt, 2004) and hippocampal volume reduction reported mood disorders and SCZ (Antoniades et al., 2018; Chepenik et al., 2012; Videbech and Ravnkilde, 2004). It has been suggested that volumetric hippocampal changes in these disorders reflect reduced neuroplasticity and neurogenesis (Carvalho et al., 2014; Miskowiak et al., 2015; Pajonk et al., 2010), which may be common downstream effects of abnormally elevated levels of cortisol and cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1) (Alfarez et al., 2008; Czeh and Lucassen, 2007; Dienes et al., 2013; Hageman et al., 2008; Hurley and Tizabi, 2013; Khairova et al., 2009; Young et al., 2001). Conversely, treatment-related *increases* in hippocampal volume are thought to result from enhanced neuroplasticity including hippocampal neurogenesis, synapse formation, and neuronal process outgrowth produced by the prevention of microgliosis and injury-related cortical loss (Miskowiak et al., 2015; Wustenberg et al., 2011; Yucel et al., 2007). Although notably, a recent human study suggests that neurogenesis in the dentate gyrus declines rapidly following birth and is rare from 7 years of age (Sorrells et al., 2018). Further, hippocampal volume increase could be due to other mechanisms such as dendritic sprouting or enhanced hippocampal brain-derived neurotrophic factor (BDNF) (Miskowiak et al., 2015). Given the common hippocampal volume decrease in neuropsychiatric disorders and underlying putative deficits in neuroplasticity, the hippocampus seems to be a promising candidate neurocircuitry target for treatments addressing cognitive impairment. The common hippocampal volume decrease in neuropsychiatric disorders and underlying putative deficits in neuroplasticity, the hippocampus seems to be a promising candidate neurocircuitry target for treatments addressing cognitive impairment.

The present systematic review aims to investigate whether structural changes in the hippocampus is a common neurocircuitry biomarker for cognitive improvements across mood disorders and SCZ. This is accomplished through the review of clinical treatment trials targeting cognition in UD, BD, SCZ, and schizoaffective disorder (SAD) that obtained longitudinal structural MRI measures of the hippocampus.

2. Experimental procedures

2.1. Data sources

Studies were identified by searching PubMed and Embase from November 2017 to February 2018 in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (see Fig. 1 PRISMA flowchart) guidelines (see Supplementary file 1 for the complete search strings used). Eligible studies: assessed the effects of pro-cognitive treatments in mood disorders, SCZ or SAD on cognition, were written in English and used structural MRI measures of the hippocampus. Studies were excluded if they: were not original articles, did not use structural MRI, included subjects suffering from organic diseases or diseases other than mood disorders or SCZ/SAD, did not employ a treatment intervention; had no *cold* cognition measures (i.e. assessments of memory, working memory, attention etc.), did not have longitudinal cognition data, were preclinical studies or assessed the potential adverse treatment-effects on cognition.

2.2. Study selection

Two researchers (CBJ and CO) independently reviewed the combined results from the two databases according to the procedures outlined in Fig. 1. After completing the primary screening based on titles and abstracts, a secondary full-text screening was performed. Reasons for exclusion were independently recorded by CBJ and CO, and consensus reached in case of disagreement.

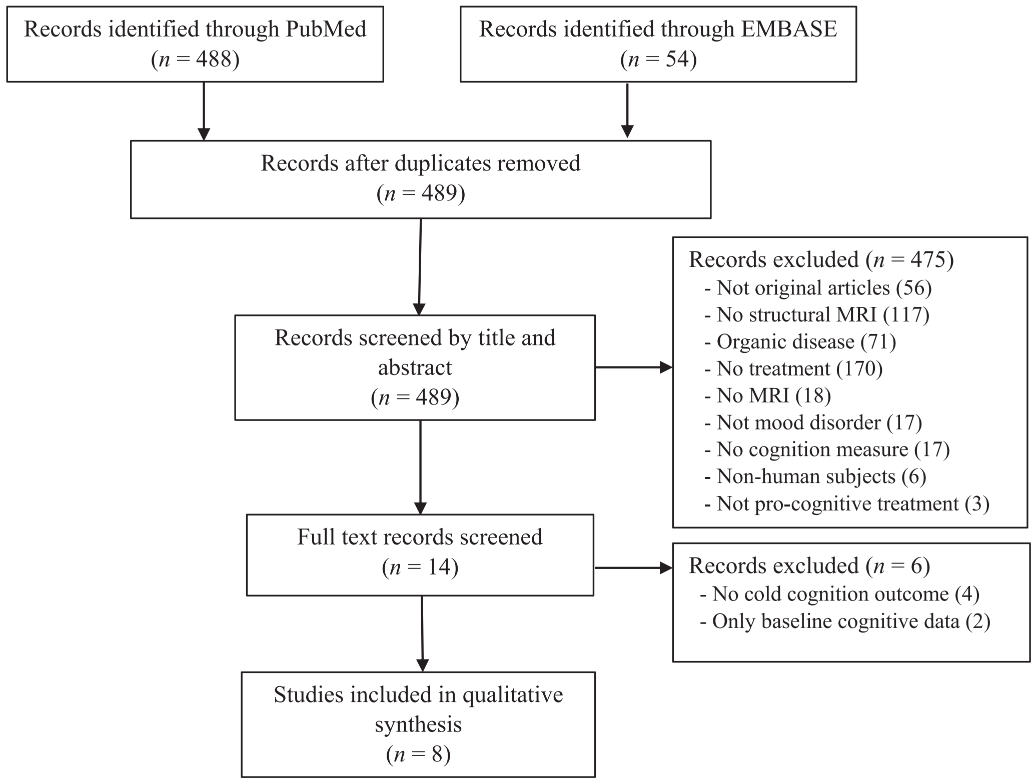

Fig. 1 Flow diagram of study selection according to PRISMA guidelines.

3. Results

3.1. Study characteristics

The search in PubMed yielded 488 hits, while the search in Embase provided 54 references (see Fig. 1 for the PRISMA flowchart). There were a total of 489 references after removing duplicates. Following title and abstract screening, 475 studies were excluded. After full-text screening, an additional six studies were excluded: four did not have any outcome measures of cold cognition, and two did not provide longitudinal cognitive data. In the end, eight studies met the inclusion criteria and were included in the review.

Table 1 and Supplementary Table 2 provide the characteristics of the included studies. Three of the studies included patients with SCZ or SAD (Eack et al., 2010; Pajonk et al., 2010; Wustenberg et al., 2011), three included patients with UD (Furtado et al., 2013; Krogh et al., 2014; Vythilingam et al., 2004), one included patients with BD (Yucel et al., 2007) and one study included a mixed sample of patients with UD and BD (Miskowiak et al., 2015).

Five of the studies were randomized controlled trials (RCTs) (Eack et al., 2010; Krogh et al., 2014; Miskowiak et al., 2015; Pajonk et al., 2010; Wustenberg et al., 2011). Two of the RCTs assessed the effect of EPO vs. saline across UD and BD (Miskowiak et al., 2015) and SCZ/SAD (Wustenberg et al., 2011), respectively. Two assessed the effects of exercise vs. table football amongst SCZ patients (Pajonk et al., 2010) or exercise vs. stretching exercise amongst UD patients (Krogh et al., 2014). Finally, one RCT assessed the effect of cognitive enhancement therapy (CET) vs. Enriched Supportive Therapy (EST) in patients with SCZ/SAD (Eack et al., 2010). Three studies were open-label. One was a sub-group analysis of an original RCT and assessed the effect of repeated transcranial magnetic stimulation (rTMS) in UD patients (Furtado et al., 2013). The other two open-label trials assessed the effect of lithium in BD patients (Yucel et al., 2007) or selective serotonin reuptake inhibitors (SSRIs) in UD patients (Vythilingam et al., 2004) (Table 1). Both latter studies included healthy control groups for comparison (Vythilingam et al., 2004; Yucel et al., 2007) (Supplementary Table 2).

The sample sizes varied with five studies including 10-40 participants (Furtado et al., 2013; Pajonk et al., 2010; Vythilingam et al., 2004; Wustenberg et al., 2011; Yucel et al., 2007); two studies including 40–70 participants (Eack et al., 2010; Miskowiak et al., 2015); and one study including 79 participants (Krogh et al., 2014) (Supplementary Table 2). In one study, cognition was the co-primary outcome along with mood (Furtado et al., 2013) or hippocampal structural changes (Vythilingam et al., 2004), respectively, while in the remaining six studies, hippocampal volume was the primary outcome and cognition the secondary outcome (Eack et al., 2010; Krogh et al., 2014; Miskowiak et al., 2015; Pajonk et al., 2010; Wustenberg et al., 2011; Yucel et al., 2007) (Table 1).

3.2. Pharmacological interventions

3.2.1. Antidepressants

In Vythilingham et al. (2004), $N = 38$ symptomatic patients with UD were included in an open-label trial to assess the effect of SSRIs administered over four to 10 months. Magnetic

Table 1 Main findings and study characteristics.

Treatment type	Treatment	Author	Patient group	Cognition primary or secondary outcome	Cognition measures	Treatment effect on cognition	Hippocampal structural changes	Correlation between changes in cognitive and hippocampal structural	Results
Biological	rTMS	Furtado et al. (2013)	UD	Co-primary with mood	WTAR, Brief Visuospatial Memory Test, RAVLT, TMT A and B, Digit Span (forwards and backwards) from the WAIS-III, COWAT, Stroop Test	Yes	Decline in left hippocampus across the entire cohort (specific to non-treatment responders)	Negative within the treatment group	rTMS improved verbal (recognition) and working memory and hippocampal loss was restricted to non-treatment responders. In treatment-responders, there was a significant association between improved verbal memory (delayed memory) and reduced left hippocampal volume.
	Aerobic exercise	Krogh et al. (2014)	UD	Secondary	Buschke's SRT, RCFT	No	None found	Positive across the entire sample	There was no significant effect of exercise vs. stretching on measures of cognition or hippocampal volume. There was a significant association between improved verbal memory and hippocampal volume across the entire sample.
		Pajonk et al. (2010)	SCZ	Secondary	RAVLT, Corsi block-tapping test	Yes	Augmentation: Hippocampus (overall)	Positive across the entire sample	The was a significant effect of aerobic exercise vs. table football on a composite score of short-term verbal memory and increased hippocampal volume. These changes were associated across the entire patient sample, but not within the exercise group. Across the entire aerobic group (SCZ and HCs) there was a significant increase in hippocampal volume.

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Table 1 (*continued*)

Treatment type	Treatment	Author	Patient group	Cognition primary or secondary outcome	Cognition measures	Treatment effect on cognition	Hippocampal structural changes	Correlation between changes in cognitive and hippocampal structural	Results
Behavioral	CET	Eack et al. (2010)	SCZ/ SAD	Secondary	Immediate and delayed recall from the revised WMS, List A, short-term and long-term recall from the CVLT, Digit Span, Vocabulary, Picture arrangement and Digit Symbol from the Revised WAIS, TMT B, WCST, Tower of London, Neurological Evaluation Scale	Yes	Protection from loss: Left hippocampus	Not significant	CET vs. EST improved cognition and protected against further hippocampal volume loss in SCZ and SAD. These effects were not significantly associated.
Pharmacological	Lithium	Yucel et al. (2007)	BD	Secondary	CVLT	Yes	Augmentation: Hippocampal head, body, tail	Positive	Lithium improved cognition and augmented hippocampal volume. These treatment-related were significantly associated.
	EPO SSRI	Miskowiak et al. (2015)	UD/ BD	Secondary	RAVLT total recall	Yes	Augmentation and protection from loss: Left hippocampus CA1-3	Positive across the entire sample and within the treatment group	Infusions with EPO improved verbal memory, increased left hippocampal volume and protected against further hippocampal volume loss. There was a significant association between cognitive improvement and hippocampal change across the entire sample.

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Table 1 (*continued*)

Treatment type	Treatment	Author	Patient group	Cognition primary or secondary outcome	Cognition measures	Treatment effect on cognition	Hippocampal structural changes	Correlation between changes in cognitive and hippocampal structural	Results
		Wustenberg et al. (2011)	SCZ	Secondary	RBANS Digit Span, Figure recall and Coding	Yes	Protection from loss: Left CA, subiculum, fascia dentate, entorhinal cortex	Positive	Infusions with EPO vs. placebo significantly protected from further loss, which was associated with improvements in a pre-selected cognitive sum score.
		Vythilingam et al. (2004)	UD	Co-primary with hip-pocampal structural changes	Vocabulary, Similarities, Picture Arrangement, and Block Design.from the Revised WAIS, Logical Memory and Visual Reproduction from the Revised WMS, Verbal and Visual SRT, CPT, TMT A and B	Yes	None	Not significant	There was a significant within-group improvement in immediate and delayed verbal memory and the verbal and visual SRT following SSRI treatment. There were no significant within-group changes in hippocampal volume, and no significant associations.

Abbreviations: rTMS: repetitive transcranial magnetic stimulation, UD: unipolar disorder, WTAR: Wechsler Test of Adult Reading; RAVLT: Rey's Auditory Verbal Learning Test, TMT: Trail Making Test, WAIS: Wechsler Adult Intelligence Scale, COWAT: Controlled Oral Word Association Test, SRT: Selective Reminding Test, RCFT: Rey's Complex Figure Test, SCZ: schizophrenia, HC: healthy control, CET: CET: cognitive enhancement therapy, SAD: schizoaffective disorder, WMS: Wechsler Memory Scale, CVLT: California Verbal Learning Test, WCST: Wisconsin Card Sorting Task, EST: enriched supportive therapy, BD: bipolar disorder, EPO: erythropoietin, RBANS: Repeatable Assessment for Neuropsychological Status, CA: cornu ammonis, SSRI: selective serotonin reuptake inhibitor, CPT: Continuous Performance Task.

resonance imaging (MRI) data was available for $N = 22$ (58% of the original sample) (sertraline: $N = 1$, fluoxetine: $N = 20$ and venlafaxine: $N = 1$) at follow-up. Within-group comparisons of cognition before and after treatment revealed improvements in immediate and delayed verbal memory and visual memory but no statistically significant changes in hippocampal structure, and only trend-level associations between cognitive and hippocampal volume change. There was no effect on total brain or medial lobe volume.

3.2.2. Erythropoietin (EPO)

In an RCT, patients with BD in full or partial remission or treatment-resistant UD were randomized to weekly EPO ($N = 42$) or saline ($N = 42$) infusions for eight weeks (Miskowiak et al., 2015). Magnetic resonance imaging (MRI) data was available for $N = 69$ patients (82% of the total sample; EPO: $N = 35$, saline: $N = 34$) at follow-up. The study found significant improvements in verbal learning in EPO vs. saline, which was associated with treatment-related augmentation and protection from further volume loss of the hippocampal volume in the left CA1-3 and subiculum. Increased sub-regional hippocampal volume increase was a significant predictor of improved verbal memory across the entire sample of EPO and saline treated patients (Miskowiak et al., 2015) as well as within the EPO-treated patients only (unpublished observation). This effect of EPO vs. saline infusions occurred in the absence of EPO-associated changes in cortical gray matter.

Another RCT assessed the effects of 12 weeks of weekly EPO infusions ($N = 16$) vs. placebo ($N = 16$) in patients with SCZ (Wustenberg et al., 2011), with MRI data available for $N = 32$ patients (100% of the entire sample) at follow-up. Based on findings from previous analyses (Ehrenreich et al., 2007), three Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) subscales (figure recall, digit span and coding) were selected to comprise a cognitive sum score spanning memory, working memory and psychomotor speed, to assess associations with hippocampal volume. Treatment with EPO vs. placebo was associated with protection from further volume loss in the left cornu ammonis, subiculum, fascia dentata in the hippocampus, and entorhinal cortex, which was associated with improved performance on the cognitive sum score (Wustenberg et al., 2011). EPO-associated volume increases were also reported for several other cortical and subcortical areas.

3.2.3. Lithium

The effect of lithium administration on cognition and hippocampal volume was assessed in an open-label study with $N = 12$ patients with BD in full or partial remission at a two-year and four-year follow-up (Yucel et al., 2007). Magnetic resonance imaging (MRI) data was available for $N = 12$ and 8 patients (100% and 80% of the entire sample) at the two-year and four-year follow-up, respectively. There was significant improvement at both follow-up assessments on immediate recall using the California Verbal Learning Test and augmentation of the bilateral hippocampal head, body, and tail volume. The study showed significant associations between volumetric hippocampal increase and improved verbal recall. In contrast, there was no effect of lithium on total cerebral volume.

3.3. Other biological interventions

3.3.1. Repeated transcranial magnetic stimulation (rTMS)

A total of $N = 29$ symptomatic UD patients, who had participated in an RCT and received either two weeks of five weekly rTMS sessions (bilaterial or left DLPFC) or sham treatment before shifting to rTMS for up to six weeks (Fitzgerald et al., 2006), were included in secondary analysis with an within-group design, to assess the effect of rMTS on cognition and hippocampal volume (Furtado et al., 2013). Magnetic resonance imaging data was available for $N = 23$ (79% of the rTMS sub-group sample) at follow-up. There was a significant improvement in one measure of verbal memory (recognition) and working memory in treatment-responders ($N = 15$) vs. non-responders ($N = 14$) (defined by a 50% reduction in depressive symptom severity). Left hippocampal volume was reduced over time across the rTMS treatment group, although post-hoc analyses showed that this effect was only significant in treatment non-responders. Non-specific improvement over time in delayed recall – which had been unaffected by rTMS – correlated with left hippocampal volume decrease amongst treatment-responders. However, it is difficult to interpret this association given the lack of an rTMS effect on this aspect of verbal memory and of hippocampal change within treatment responders. Volumetric increases in the rTMS group were also reported for the left amygdala.

3.4. Behavioral interventions

3.4.1. Aerobic exercise

The effect of 12 weeks of three 30-min exercise sessions ($N = 13$) vs. table football ($N = 11$) on cognition and hippocampal volume was assessed in an RCT including patients with SCZ (Pajonk et al., 2010). Magnetic resonance imaging data was available for $N = 8$ patients in the exercise and control groups, respectively (67% of the entire sample). There was significant improvement of immediate verbal learning and augmentation of the bilateral hippocampi in the exercise vs. table football group from baseline to end-of-treatment. These exercise-related structural changes in the hippocampi were associated with improved immediate learning across the entire patient group, which rendered non-significant within the exercise group alone possibly due to the small group size ($N = 13$). In contrast, there was no effect of aerobic exercise on total brain volume or gray matter.

Another RCT investigated the effects of aerobic exercise ($N = 41$) vs. stretching exercise ($N = 38$) for three months in symptomatic patients with UD. Magnetic resonance imaging (MRI) data were available for $N = 55$ patients (70% of the sample). This trial found no treatment-related improvements in cognition or changes in hippocampal volume (Krogh et al., 2014). However, across the entire sample there was a non-specific positive association between improved verbal memory and left hippocampal volume. Together, these findings suggest that lack of treatment efficacy is related to absence of hippocampal change and point to a *general* role of hippocampal volume change in verbal memory improvement. In contrast, no effect of aerobic exercise or non-specific changes over time were observed on total gray matter volume.

3.4.2. Cognitive enhancement therapy (CET)

In a RCT, the effect of CET ($N = 31$) vs. EST ($N = 27$) was assessed in patients with SCZ/SAD, with MRI data being available for $N = 39$ patients (67% of the sample) at the two-year follow-up (Eack et al., 2010). In the original trial, there was a significant effect on cognition for CET vs. EST (Eack et al., 2009), and in the follow-up study (Eack et al., 2010) protection from gray matter loss was observed in the left hippocampus in the CET vs. EST group. These hippocampal changes were not associated with cognitive performance, but there were significant associations between improved cognition and CET-related changes in overall gray matter and deaccelerated volume loss in left parahippocampal gyrus, respectively.

4. Discussion

The systematic review aimed to assess whether structural hippocampal change may be a common neurocircuitry biomarker for treatment-related cognitive improvements across neuropsychiatric disorders. Eight studies were included: five RCTs assessing the effect of EPO ($N = 35$) vs. saline ($N = 34$) in BD and UD (Miskowiak et al., 2015), of EPO ($N = 16$) vs. placebo ($N = 16$) in SCZ (Wustenberg et al., 2011), of aerobic ($N = 13$) vs. table football ($N = 11$) in SCZ (Pajonk et al., 2010), of aerobic ($N = 41$) vs. stretching exercise ($N = 38$) in UD (Krogh et al., 2014) and of CET ($N = 31$) vs. EST ($N = 27$) in SCZ/SAD (Eack et al., 2010). Three open-label studies with no control group assessed the effect of lithium in ($N = 12$) BD (Yucel et al., 2007), of SSRIs in ($N = 38$) UD (Vythilingam et al., 2004), and of rTMS in ($N = 29$) UD (Furtado et al., 2013). Positive associations between changes in the hippocampus and *treatment-specific* cognitive improvements were observed in three studies: the EPO trials in mood disorders and SCZ (Miskowiak et al., 2015; Wustenberg et al., 2011) and in the lithium trial in BD (Yucel et al., 2007). Further, *non-specific* associations between increases in hippocampal volume and in cognition were seen in the two aerobic trials in UD and SCZ (Krogh et al., 2014; Pajonk et al., 2010) as well as in the EPO trials in mood disorders (Miskowiak et al., 2015). In one negative trial showing no cognitive benefits of aerobic exercise in UD, patients also showed no hippocampal volume change (Krogh et al., 2014). In the remaining three studies of SSRIs or rTMS in UD or of CET in SCZ/SAD, hippocampal and cognitive changes were not associated (Eack et al., 2010; Furtado et al., 2013; Vythilingam et al., 2004).

Interestingly, the hippocampal volume increase observed in the EPO-trials in patients with mood disorders and patients with SCZ occurred only in the left hemisphere (Miskowiak et al., 2015; Wustenberg et al., 2011). Similarly, CET significantly counteracted volume loss in the *left* hippocampus at a two-year follow-up (Eack et al., 2010). Finally, the volume reduction in the left hippocampus was less pronounced in treatment-responders vs. non-responders following rTMS treatment of UD (Furtado et al., 2013). Wustenberg et al. (2011) proposed that the lateralization of the EPO treatment effect was due the most illness-related GM loss in the left hemisphere in SCZ. In mood disorders, the findings regarding lateralization of brain volume loss are less conclusive. Similar findings have been reported in UD (Bremner et al., 2000; MacQueen et al., 2003) and a systematic review of BD found that left hippocampus was smaller than the right hippocampus (Otten and Meeter, 2015). Nevertheless, healthy individuals also show smaller left than right hippocampal asymmetry (Yucel et al., 2002), suggesting that this may not be an illness-associated phenomenon. Indeed, no hippocampal volume reduction was observed in UD or SCZ compared with HC at baseline in two of the identified studies that had found positive correlations between increases in hippocampal volume and cognition (Pajonk et al., 2010; Yucel et al., 2007). In a recent clinical trial – that was not included in the review due to a lack of correlations between hippocampal and cognitive changes – SCZ patients were assigned to either endurance training or table football for six weeks, after which both groups were assigned add-on computerized cognitive training for a total treatment period of 3 months (Malchow et al., 2015). Neither of the groups showed increased hippocampal volume, despite non-specific within-group memory improvements in the endurance training group (Malchow et al., 2016, 2015). As opposed to the study by Pajonk et al. (2010), the SCZ patient in the endurance training group had smaller hippocampal volume compared to healthy controls. However, there were no difference in hippocampal volume between the patients in the table football group and the HC group (Malchow et al., 2016). Hence, the associations between changes in cognition and hippocampal volume does not seem to depend on pre-existing neuroplasticity deficits in the hippocampus.

The heterogeneity in the effect of exercise and endurance training with cognitive training on hippocampal volume and cognition in patients with SCZ (Malchow et al., 2016, 2015; Pajonk et al., 2010) could be due to differences in the polygenic risk scores (PRS). Specifically, PRS have been shown to be negatively associated with cognition (Nakahara et al., 2018), and with less or no hippocampal volume increase following exercise and cognitive training in SCZ (Papiol et al., 2017).

In terms of lithium, its positive effects on hippocampus and cognition could be due to its ability to counteract molecular hippocampal mechanisms induced by psychosocial stress (Brzozka et al., 2016). This has been shown in a pre-clinical study, where stress-induced cognitive impairment was counteracted by lithium treatment (Brzozka et al., 2016). For structural hippocampal change to be a valid neuro-circuitry biomarker model for pro-cognitive effects, it would have to meet five general biomarker model validation criteria (Macoveanu et al., 2018): It should (i) occur in response to pro-cognitive treatments, (ii) be observable in response to these treatments in both patients and HCs, (iii) be observable across treatment modalities, (iv) be absent if a treatment fails to improve cognition and (v) show directionality; i.e. the opposite change in response to treatments with adverse effects on cognition. The studies in this review indicate that criteria (i) and (iii) are met, as augmentation or deaccelerated loss of the hippocampus was associated with pro-cognitive effects following EPO-treatment, lithium treatment and aerobic exercise (Miskowiak et al., 2015; Pajonk et al., 2010; Wustenberg et al., 2011; Yucel et al., 2007). Notably, SSRI and rTMS treatment in UD patients was associated with improvement of cognition but no increase in hippocampal volume (Vythilingam et al., 2004). This does not necessarily contradict criterion (i) since cognitive improvements over time could be due to repeated testing (i.e., non-specific learning effects) given the within-group trial designs and improvements clinical state. The lack of an association between CET-related cognitive and hippocampal changes could also be due to the improvement in clinical state (Eack et al., 2010) – or alternatively, that the applied cognitive measure did not tap into hippocampus-dependent cognition. Criterion (ii) regarding similar effects in patients and HCs is also met, as aerobic exercise increased hippocampal volume not only in SCZ but also in HCs (Pajonk et al., 2010). However, the cognitive changes in the HC group were inconclusive, as some measures improved while others worsened and correlations between cognitive and hippocampal changes were not performed (Pajonk et al., 2010). In support of criterion (iv), the failure of aerobic exercise to improve cognition in UD patients (Krogh et al., 2014) was accompanied by an absence of hippocampal change. Criterion (v) was not elucidated by any of the identified studies, as we a priori excluded treatments with potential adverse effects on cognition. However, studies indicated that treatment with certain types of anti-psychotics, particularly in high doses, have cognitive side-effects (Husa et al., 2017) and neurotoxic effects on the hippocampus (Chakos et al., 2005; Chikama et al., 2017; Ebdrup et al., 2011; Thompson et al., 2009). However, the association between treatment-related cognitive side-effects and hippocampus are not uniform. In particular, electroconvulsive therapy (ECT) has short-term (<3 months) cognitive side-effects despite robust hippocampal volume augmentation (Nordanskog et al., 2014). This suggests that hippocampal volume increase does not always translate into improved cognitive skills and that this may depend on the nature of the particular treatment. To further examine the validity of hippocampal volume changes as a biomarker model, future cognition trials should include MRI-assessments pre- and post-treatment across both patient and healthy populations.

The findings of the review are limited by three of the studies being open-label, increasing the risk of any pro-cognitive effects being due to repeated testing. Further, the samples sizes were small in five of the studies and only a subset of the patients underwent MRI assessments, limiting the reliability and generalizability of the findings. Also, some studies included sub-optimal cognitive measures in terms of hippocampal target engagement, reducing the probability of detecting associated cognitive and hippocampal changes. Regarding the MRI analysis method, six of the included studies only performed ROI analysis of the total hippocampal volume. Although commonly used, hippocampal sub-regional changes may not be detected using this method. In this review, we specifically assessed whether *hippocampal* change is a common biomarker for cognitive improvement. Studies that reported negative treatment-effects, or did not specifically assess changes in the hippocampus, may therefore have been omitted. However, the included studies assessing other cortical and subcortical areas, consistently found morphological *hippocampal* change, suggesting that the hippocampus is in fact a more sensitive biomarker of pro-cognitive effect as compared to other brain regions. Finally, pooling trials with UD, BD and SCZ could complicate the interpretation of the findings. Nevertheless, this approach is aligned with the Research Domain Criteria (RDoC) approach to psychiatric illnesses (Kozak and Cuthbert, 2016) and seems critical for identification of a common neuro-circuitry biomarker for pro-cognitive effects across neuropsychiatric disorders.

Correlations between treatment-related hippocampal volume increase and cognitive improvements were fairly consistently observed across treatment modalities (EPO, lithium, aerobic exercise) and across several neuropsychiatric patient groups (in four of eight studies). This highlights structural hippocampus increase is a putative brain-based biomarker model for pro-cognitive effects. To further assess whether hippocampal volumetric change fulfills the general biomarker model criteria, future trials targeting cognition -or which may implicate cognitive side-effects- should include MRI assessments pre- and post-treatment in neuropsychiatric and healthy populations.

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Contributors

KWM and JM defined the aim and scope of the review. CJ and CVO performed the literature screening under supervision of KWM and JM. CJ, CVO and KWM wrote the first draft. All authors contributed to and approved the final manuscript.

Conflicts of interest

KWM has received consultancy fees from Lundbeck and Allergan within the last 3 years. CVO has received an honorarium from Lundbeck. JM and CJ report no conflicts of interest.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.01.105.

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