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The effect of N-acetylcysteine (NAC) on human cognition – a systematic review

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Abstract

Oxidative stress, neuroinflammation and neurogenesis are commonly implicated as cognitive modulators across a range of disorders. N-acetylcysteine (NAC) is a glutathione precursor with potent antioxidant, pro-neurogenesis and anti-inflammatory properties and a favourable safety profile. A systematic review of the literature specifically examining the effect of NAC administration on human cognition revealed twelve suitable articles for inclusion: four examining Alzheimer's disease; three examining healthy participants; two examining physical trauma; one examining bipolar disorder, one examining schizophrenia, and one examining ketamine-induced psychosis. Heterogeneity of studies, insufficiently powered studies, infrequency of cognition as a primary outcome, heterogeneous methodologies, formulations, co-administered treatments, administration regimes, and assessment confounded the drawing of firm conclusions. The available data suggested statistically significant cognitive improvements following NAC treatment, though the paucity of NAC-specific research makes it difficult to determine if this effect is meaningful. While NAC may have a positive cognitive effect in a variety of contexts; larger, targeted studies are warranted, specifically evaluating its role in other clinical disorders with cognitive sequelae resulting from oxidative stress and neuroinflammation.

Highlights:

- **Oxidative stress and inflammation are widely implicated as cognitive modulators, through a variety of vectors.**
- **N-acetylcysteine, a glutathione precursor, has demonstrated efficacy in reducing the severity of oxidative stress and neuroinflammation, with correlating cognitive improvement in pre-clinical models.**

- **Evidence for the efficacy of N-acetylcysteine as an adjunct monotherapy for human cognition is inconsistent but promising, though the weight of evidence is approximately equivalent.**

- **Combined interventions of N-acetylcysteine and other antioxidants have demonstrated efficacy for positively impacting human cognition in a range of contexts, but it is not possible to determine the degree to which N-acetylcysteine is contributing.**

- **There is considerable scope to evaluate the cognitive protective effects of NAC in clinical conditions associated with neuronal oxidative stress and inflammation.**

Introduction

Oxidative stress is a disturbance in the balance between the production of reactive oxygen species and antioxidant defences and may occur as a response to tissue damage, and may cause subsequent damage.. It has been implicated in cognitive impairment in a variety of conditions including intrinsic neuropsychiatric disease processes (Berk et al., 2013), impact-related trauma (Abdul-Muneer et al., 2014; Amen et al., 2011a; Hoffer et al., 2013), neurodegenerative disorders (Cahill-Smith and Li, 2014; Schrag et al., 2013), and post-operative cognitive dysfunction (Mason et al., 2010; Newman et al., 2007; Zywiel et al., 2014). Given the putative effect of oxidative stress on cognitive function, it is theoretically plausible that the application of an antioxidant agent may to some degree mitigate this dysfunction. Previous studies of the efficacy of antioxidant intervention for cognitive dysfunction in humans have reported mixed results, such as those for vitamin E (Farina et al., 2012), Acetyl-L-Carnitine (Hudson and Tabet, 2003), and folic acid (Malouf et al., 2003). N-Acetylcysteine (NAC) is a nutraceutical capable of replenishing brain glutathione and consequently protects against oxidative stress and is likely neuroprotective demonstrating pre-clinical efficacy in reducing markers of oxidative stress and the severity of cognitive dysfunction in animal models (Hsiao et al., 2012; Huang et al., 2010). Similar oxidative responses have been detected in humans (Moreira et al., 2007), though cognition has not been widely studied. To date, no review of the effect of the antioxidant N-Acetylcysteine on human cognition has been conducted, and will form the focus of this systematic review.

Oxidative stress as a mechanism of cognitive change

Oxidative stress has been implicated as a critical pathophysiologic factor in numerous conditions, including neurodegenerative diseases. Oxidative stress can lead to cellular dysfunction, increased rates of apoptosis, neuroinflammation, and alter the permeability of the blood brain barrier (BBB) to

neuropathic proteins, aggregate mechanisms which theoretically contribute to cognitive dysfunction (Enciu et al., 2013; Erickson et al., 2012).

Trauma has been regularly implicated as a precipitating factor to oxidative stress, inflammation, and subsequent cognitive dysfunction (Abdul-Muneer et al., 2014), and inflammation induced by trauma has been shown to share inflammatory sequelae in the BBB with long-term neurological disorders such as Alzheimer's disease (Erickson et al., 2012); epilepsy (Liu et al., 2012); stroke (Khatri et al., 2012); and multiple sclerosis (Lund et al., 2013); among other conditions.

Oxidative stress as a moderator of cognitive function has been examined as a likely sequel of an acute inflammatory immune response to traumatic tissue damage, including that sustained during surgery (Cai et al., 2011; Giannoudis et al., 2006); high impact contact sports (Amen et al., 2013; Amen et al., 2011a); and blast-induced mild traumatic brain injury (Hoffer et al., 2013), as well as being implicated in neurodegenerative and neuropsychiatric disorders (Cahill-Smith & Li, 2014; Guidl et al., 2006).This assertion is supported by strong indications within the pre-clinical literature that trauma can facilitate the production of reactive oxygen species associated with neuroinflammation and is associated with cognitive decline (Barrientos et al., 2012; Cibelli et al., 2010; Rosczyk et al., 2008; Vacas et al., 2013).

The hippocampus in particular appears to be highly vulnerable to the effects of neuroinflammation and pro-inflammatory cytokines (Vacas et al., 2013; & Montange et al., 2015) potentially leading to impairments of memory and learning (Chen et al., 2008; Montagne et al., 2015; Rachal Pugh et al., 2001). In humans, this vulnerability may be partially responsible for the exacerbated dementia conversion rate associated with amnestic mild cognitive impairment (MCI; Kline et al., 2012; Silbert et al., 2011). Therapeutic agents that moderate such vulnerabilities may theoretically have effects on the cognitive trajectory. The use of antioxidant agents, such as NAC, can be protective against the proliferation of cytokines and reactive oxygen species and increased rates of neuronal survival and decreased apoptosis have been observed in many models (Zhou and Ma, 2014). At present, while

there is a comparative lack of clinical data directly examining potential interventions for post-traumatic oxidative stress in humans, a growing body of research has examined potential mechanisms.

How NAC might work to mitigate oxidative stress

NAC has been examined in a wide range of chronic neuropsychiatric disorders, including bipolar disorder, schizophrenia, trichotillomania, depression and addiction among others (Berk et al.2013). NAC functions as a precursor to glutathione which is the principal antioxidant produced by the body. Glutathione assists in maintaining oxidative homeostasis by removing reactive oxygen species, reactive nitrogen species, and peroxides (Samuni et al., 2013; Berk et al., 2013).

NAC has been shown to reduce inflammatory cytokines and reduce markers of oxidative stress in a number of indications (Allameh et al., 2015; da Silva et al., 2015; Vidart et al., 2014; & Skov et al., 2014). Furthermore, NAC has also been shown to modulate immune system function and has been used for some time to prevent T-cell decline in HIV (Yang et al. 2013; & Treitinger et al. 2004). Further, there is clinical evidence to suggest NAC may be neuroprotective based on imaging data (Amen et al. 2011; Holmay et al. 2012; Amen et al. 2013; Levin et al. 2014). For example, Levin and colleagues observed that the administration of a combination of NAC and oral cysteamine bitartrate was able to significantly reduce leukocyte pathology in children with infantile neuronal ceroid lipofuscinosis. Similarly, Amen and colleagues detected significantly increased levels of regional cerebral blood flow to a host of brain organs after administration of a NAC-inclusive nutrient formulation. Curiously, improvements to some organs, in particular the hippocampus, only occurred in healthy participants (Amen et al, 2013) and not in participants with traumatic brain injury (Amen et al., 2011.). This is perhaps emblematic of NAC research as it pertains to human cognition, where NAC is rarely examined as a monotherapy but often as an adjunct to regular treatments, and even then as part of a nutrient formulation. Despite this, NAC has favourable effects in multiple models of mitochondrial dysfunction; in particular there is evidence to suggest that NAC can reduce

mitochondrial stress in Alzheimer's disease (Moreira et al., 2007). Recent pooled analyses of data in people with bipolar disorder and schizophrenia revealed significant improvement in working memory function compared to placebo controls, though this data was unpublished at the time of writing (Rapado-Castro et al., 2016*).*

Different indicative models of cognitive dysfunction are purported to have different mechanisms of deterioration, and the relevant mechanism through which NAC is theorized to work likewise differs. For example, cognitive dysfunction in Alzheimer's disease has been characterised by increased levels of amyloid and tau proteins in the brain (Cai et al., 2011, & Sinha et al., 2015), and NAC has demonstrated efficacy to mitigate this in animal models (Hsaio et al., 2012, & Sinha et al.,) though translational research into humans is scarce. In psychiatric disorders cognitive dysfunction is linked with NMDA dysregulation, and NAC is purported to act as an agonist for the glycine NMDA receptor (Singh et al., 2011). NAC is demonstrably broadly applicable from a theoretical perspective, though rarely clinically examined in isolation. However, mono-therapeutic NAC research is more common in animal models.

Animal models of cognitive dysfunction

There is considerable evidence that NAC is effective in mitigating cognitive dysfunction in a variety of animal models. In particular, NAC has shown striking pro-cognitive effects in multiple models in which oxidative or inflammatory damage is a feature of the pathological process. This includes models of metabolic dysfunction such as diabetes and other less common disorders of metabolism (Prakash, Karla, & Kumar, 2015; Rodrigues et al., 2013; Scaini et al., 2012; Kamboj, Chopra, & Sandhir, 2008), metal toxicity (Goncalves et al., 2010; Prakash & Kumar, 2009), stress (Moller et al, 2013), antioxidant depletion (Choy et al., 2010), and mitochondrial dysfunction (Sandhir et al., 2012; Otte et al., 2011). The common feature of these findings is the capacity for NAC to reverse or

ameliorate the induced cognitive dysfunction in a manner associated with reductions in oxidative damage, mitochondrial dysfunction or markers of inflammation.

Importantly, NAC has also shown efficacy in pre-clinical models of both age-related cognitive decline and models of Alzheimer's disease expressing elevated levels of the amyloidogenic proteins implicated, which can be ameliorated by NAC administration, and this improvement may be mediated by decreases in the toxic forms of these proteins (Hsiao, 2012; Parachikova et al., 2010) as well as by modulation of oxidative stress (Huang, et al., 2010). More gradual onset of cognitive deterioration changes is associated with accumulation of amyloidogenic proteins and oxidative damage in the brain. NAC appears to also be effective in preventing or attenuating age-related cognitive changes, and ameliorating the more subtle signs of age-related pathology in mice (Sinha et al., 2015; Thakurta et al., 2014).

Of note is the capacity for NAC to improve age-related changes in glutamate signalling, which is intrinsic to cognitive function. Supplementation with NAC prevented oxidative stress-driven changes in glutamate receptor activity associated with cognitive aging (Haxaire, 2012). This finding highlights an additional potentially therapeutic capacity for NAC to modulate the availability of glutamate in the brain, a process controlled by the levels of the NAC derivative cysteine. This is supported by studies in mice with deficits of specific glutamate transporters, who show early onset of age-related cognitive deficits. NAC significantly attenuated the learning and memory deficits in these mice (Cao, Li, & Zuo, 2012.)

Together these studies demonstrate the capacity for NAC to exert pro-cognitive effects in a variety of settings, and suggest that this versatile agent may be working through multiple interconnected pathways. This supports the hypothesis that NAC may be an effective agent in clinical settings of cognitive dysfunction.

This systematic review brings together the research exploring NAC as a potential adjunct therapy for cognitive change in a variety of indications.

Methods

Search Strategy

A PubMed database search and a Medline database search using the terms: n acetyl cysteine OR "NAC" OR antioxidant AND cognit* was conducted. Only studies examining human cognition were included. No time limit was imposed upon the search, up until the final search date of November 14th 2014. Additionally, the reference lists of applicable studies were manually examined for additional articles for inclusion. In total, 2175 articles were screened for inclusion, and a subset of 95 was selected for full text evaluation (See Appendix A). These articles were manually screened for relevance, first by title and then secondly by examining the abstract in cases where the title was not sufficient to exclude. If a paper appeared to meet inclusion criteria after reading the abstract it was flagged for full text examination. Upon communication with the authors of included studies, data from two additional articles were included and have since been published (Remington et al., 2015, Rapado-Castro et al., 2016). Rapado-Castro and colleagues performed pooled analyses of previously unpublished data (Berk et al., 2008a & 2008b). 12 articles were included in the qualitative analysis, with a total of 588 participants across studies.

Studies were included if human participants completed repeated-measure neurocognitive assessments and NAC was included as an intervention. We excluded studies that did not directly measure cognition both before and after intervention. Reviews or re-analyses of previously published data were not included. Assessments of general functioning; such as the Global Functioning Scale or subjective measures of cognition such as Child Autism Rating Scale; were not considered sufficient for inclusion.

Risk of Bias

The risk of bias was considered in line with the recommendations from the Cochrane Collaboration. The included studies were examined for potential biases, and the authors judgements are provided

in Appendix B. The majority of studies had moderate levels of bias, with the exception of Chan et al (2008) which had an entirely open-label design, and high degree of participant drop-out. Publication bias was investigated with funnel plot analysis.

Results

The characteristics of the included studies can be seen in Table 1. The sample size ranged from 12 to 106. The mean age of included participants across all studies ranged from 18 years to 85 years. The variability between studies, including dosage, design, participant demographics and pathologies, and intervention formulation demonstrated that the available evidence was not suitable for quantitative meta-analysis, and so a systematic review of the research was performed.

[INSERT TABLE 1 ABOUT HERE]

An examination of NAC as an adjunct treatment for cognition in Alzheimer's disease (AD)

Four studies examined the effect of NAC upon cognition in AD; three through the use of a nutrient combination including NAC in addition to treatment as usual (Chan et al., 2008; *n* = 14, Remington et al.,. 2008; *n* = 12, and Remington et al., 2015; *n* = 106), and one where NAC was administered in isolation with treatment as usual (Adair et al., 2001; *n* = 43). With the exception of Adair et al., the lack of exclusivity of NAC supplementation to treatment makes direct evaluation of its impact upon cognition difficult and therefore can at best be described as an approximation of any true effect due to NAC.

Adair and colleagues observed a statistically significant improvement on WMS performance within the NAC cohort at 3 months, and while this remained relatively stable, at 6 months the improvement was no longer significant. Further, the purported protective effect appears to have been confined to visual memory, with Adair and colleagues observing no change to verbal memory after intervention. This preservation of memory function appears consistent with research by Chan et al., (2008) and Remington et al., (2008) where no significant changes to memory function on the DRS were

observed. Given that memory impairment is the core presenting symptom in AD, NAC (and adjunct nutraceuticals in the cases of Chan et al. & Remington et al.) may have acted to delay the decline, though more rigorous examinations of memory are needed. Additionally, the NAC arm of the Adair study demonstrated significant improvement in the letter fluency task at 6 months in comparison to baseline, though no other comparisons were significant.

While heterogeneity was apparent across studies, a disease severity trend was observed in the studies examining AD. Part of the included research (Adair et al., 2001; Chan et al., 2008; Remington et al., 2008) tracks three different cohorts with AD at three different stages of the disease (probable but unconfirmed, early stage, and moderate-to-late stage). Both studies observing participants in the earlier stages of AD (Adair 2001 & Chan et al., 2008) observed a statistically significant improvement in initiation and executive function as measured by verbal fluency over the course of the trial, reaching significance at 6 months in the case of Adair et al (Letter Fluency), and 12 months in Chan et al (initiation/conceptualization subscale of the Mattis Dementia Rating Scale). Given that reduced verbal fluency in the early stages has been shown to be one of the few neuropsychological measures predictive of mortality in AD (Cosentino et al., 2006) findings of improvement on this test, in this population is particularly intriguing.

Comparative analysis amongst AD research literature was complicated by the heterogeneity of assessment types reported, particularly for the multi-ingredient formulation studies where NAC was not administered as an isolated, adjunct monotherapy. For instance, while Remington and colleagues (2008) reported the total performance of participants on the Mattis Dementia Rating Scale, the subscale scores were not provided. However, cross-study comparisons were possible through the examination of the clock drawing tasks. Both Chan and colleagues (2008) and Remington and colleagues suggested that clinically significant between-treatment group improvements were observed upon the clock drawing tasks at 3 months, though statistical significance was achieved in neither case. Replication of the studies with a larger sample achieved

both statistical and clinical significance (Remington et al., 2015). Additionally, sub-group analysis performed by Remington and colleagues (2015) corroborated previous findings that severity of dementia was significantly influenced by the intervention; cognitively healthy and early stage AD participants within the experimental groups demonstrated significant improvements over placebo groups. While cognition of participants with moderate and late stage dementia did not improve on intervention, decline was significantly delayed in comparison to control groups.

In sum, while there is some evidence to suggest that NAC supplementation in AD may be beneficial to preserving memory or improving language initiation and executive function, this is largely based upon a single study (Adair et al., 2001). As other substances were co-administered alongside NAC in this work (Chan et al., 2008, Remington et al., 2008, and Remington 2015), the contribution of NAC if any to the protective effect is impossible to determine and thus the evidence base can only be considered indicative. More trials are needed, particularly those that examine NAC supplementation in isolation with treatment as usual.

An examination of NAC as an adjunct treatment for cognition in psychiatric disorders and psychotic symptoms

The efficacy of NAC as an adjunct treatment for psychiatric disorders was examined by Dean et al. (2012; *n* = 47), and Rapado-Castro et al., (2016; *n* =58). A third study, Gunduz-Bruce et al., (2012; *n* = 16); proposed to approximate the psychotic and cognitive symptoms of schizophrenia in otherwise healthy participants through use of the drug ketamine. All three studies utilized a randomised, double-blind, placebo-controlled research design. Similarly, all three included studies included measures of mood and cognition, though the assessments used by Gunduz-Bruce and colleagues were largely computerised in comparison to the pen-and-paper tasks used by Dean et al., and Rapado-Castro et al. The administration of NAC did not appear to reduce the severity of psychotic symptoms for any sample, and the only significant cognitive outcome change was an improvement in working memory at 6 months in Rapado-Castro et al. The research samples differed significantly

between studies. The research by Dean et al., and Rapado-Castro et al., examined participants with diagnosed bipolar and schizophrenia disorders with a treatment intervention administration of 6 months; whereas Gunduz-Bruce and colleagues observed otherwise healthy participants receiving ketamine to approximate psychosis as an experimental condition, and administered a single treatment intervention dose. It is possible to interpret this as the potential for NAC supplementation being beneficial with sustained administration, but given the present lack of studies and the relatively small sample sizes used in the available evidence, the efficacy of NAC for improving cognition in psychotic disorders requires further exploration to establish.

An examination of NAC as an adjunct treatment for cognition following physical trauma

Two studies examined the efficacy of NAC as an adjunct treatment for cognitive dysfunction believed to result from physical trauma (Amen et al., 2011; *n* = 30, and Hoffer et al., 2013; *n* =81). Both studies differed substantially. Amen and colleagues (2011) examined retired professional athletes from the National Football League in the USA, all of whom had played professionally for at least 3 years and had suffered traumatic brain injury. Participants within this study received NAC only as part of a multi-ingredient formulation, whereas Hoffer et al. administered NAC as an adjunct to regular blast-trauma treatment. Statistically significant improvements to performance were observed upon measures of general cognitive function, proficiency, processing speed and accuracy, attention, reasoning, and memory. There was no significant overall change on either the spatial reasoning or reaction time tasks. The magnitude of effect was highly variable between participants with large proportions of participants showing both statistical and clinically significant improvement. For example, 14 of 30 participants demonstrated at least 50% improved performance on tasks measuring general cognitive function. Pre and post-intervention comparisons from brain imaging data suggested an increase in blood perfusion in the prefrontal cortex, anterior cingulate gyrus, parietal and occipital lobes, and the cerebellum of participants. However, the results are confounded by the presence of additional adjunct treatments and interventions that were not

controlled for within the analysis. In addition to being administered a nutrient combination, participants were also offered additional wellbeing and lifestyle education to assist with global function.

Hoffer and colleagues (2013) examined the effect of NAC in blast-induced traumatic brain injury in active-duty soldiers. The results were amongst some of the most promising observed throughout the literature, with statistically and clinically significant improvements associated with NAC administration, including reduction in symptom severity and duration. Cognitively, significant improvements upon the Trail-Making Tests A and B (TMT A & B) were recorded 7 days after the initial blast injuries. When treatment was administered within 24 hours after the injury, participants who received NAC were approximately twice as likely to report symptom resolution within 7 days compared to placebo; and over three times as likely to report complete symptom resolution when treatment was delivered within 24-48 hours. This suggests that the protective effects of NAC may significantly interact with current treatment strategies to address blast-induced traumatic brain injury, but effects were largely confined to administration within 24 hours of injury. However, in contrast with studies examining Alzheimer's disease (Adair et al., 2001; Chan et al., 2008; Remington et al., 2008), the participants assessed in Hoffer et al. did not show significant improvement in verbal fluency and executive function.

It is difficult to properly estimate the effect of NAC on cognition following physical trauma. The available evidence suggests that NAC positively affects cognition but this is based on a small number of studies that examined NAC in conjunction with co-administered interventions. In addition, the populations with head injuries sustained through years of professional sports and those sustained as a result of blast injuries are likely to be highly heterogeneous. The evidence can therefore be considered promising, but highly preliminary without replication.

NAC as a cognitive modulator in cognitively and psychiatrically healthy adults

Two studies (Amen et al., 2013; *n* = 30 & Chan et al., 2010; *n* = 115) examined the possibility that NAC in conjunction with a number of additional nutraceuticals may improve cognitive performance in cohorts without known cognitive impairment or psychiatric conditions. Neither Amen and colleagues nor Chan and colleagues examined the efficacy of NAC in isolation. Both studies revealed significant cognitive improvement within the intervention groups in comparison to controls. A third study, (Hauer et al., 2003) examined a cohort of cognitively healthy but physically frail elderly participants, aged over 65 years, with a combined intervention of resistance training and either NAC or placebo. All studies reported significant cognitive improvement within the intervention groups. Like the later research of Chan et al. (2010) and Amen et al. (2013) the cognitive changes observed by Hauer and colleagues were observed on the Trail Making and Digit Span tests (or analogous alternatives) examining executive function, working memory and short term memory. Further, Hauer and colleagues reported that the administration of NAC also appeared to modulate the production of TFN-alpha to a significantly greater degree compared with controls, though no such effect was detected for ING-1 or growth hormone. In combination with the other included findings, and given the contribution of executive function, working memory may be particularly receptive to NAC treatment in healthy adults.

Discussion

The results of the review revealed enormous variability across studies investigating the impact NAC has on cognition. Participant demographics, research design, sample size, treatment regimen, dosage strength and duration of invention all varied across studies. The examined studies suggest that the administration of NAC alone may be beneficial in some circumstances but the sum of the evidence must be described as equivocal. In combination with other substances, in conjunction with other treatments, there was some evidence that supplementation was beneficial compared with control groups on some measures of general cognition, executive function, processing speed, and

visuospatial reasoning, memory, verbal fluency, and spatial reasoning, but the proportion of this effect due to NAC is indeterminable.

Partialling out the effect of NAC supplementation from other confounding substances is difficult. Half of the included studies examined NAC as part of a vitamin or therapeutic combination, and of the remainder, only Gunduz-Bruce et al. (2011) examined the effect of NAC administration as a monotherapy. The studies where NAC demonstrated efficacy (either in combination with additional non-pharmaceutical treatments, alone, or as an adjunct with treatment as usual) were quite heterogeneous and varied in their treatment regimens and proposed avenue of oxidative stress. Evidence for the efficacy of NAC alone as a cognitive protector was equivocal. For example, NAC as an adjunctive treatment for bipolar disorder did not appear to attenuate associated cognitive deficits (Dean et al., 2012), whereas Rapado-Castro and colleagues (2016) demonstrated significantly improved working memory after an identical intervention regimen a pooled bipolar disorder and schizophrenia sample. By comparison, studies that examined efficacy of combined nutraceuticals were typically positive (see Amen et al., 2011, 2013; Chan et al., 2008, 2010; Hauer et al., 2003 etc.). The dose and administration regimens of NAC were also highly variable between studies.

Dean et al. used a significantly higher daily dose of NAC compared with both Amen et al. and Chan et al.; 1000mg twice per day in comparison to 400mg and 600mg twice daily, respectively, and substantially higher still compared with Hauer et al, (2003). Hauer and colleagues were able to detect significant cognitive improvement after administering relatively lower dose of 200mg per day for six weeks in adjunct physical resistance training in elderly participants with no psychiatric or cognitive diagnoses, though this was not significantly different from the control group at follow-up. In sum, there is presently a lack of evidence for the efficacy of NAC alone as a cognitive modulator, and any indications should be considered preliminary.

Dose response and the influence of administration length

The relationship between cognitive changes as a result of intervention, dose strength, and administration length within the included studies was not entirely clear. As seen in Table 1, both the study with the highest mean daily NAC intervention (Hoffer et al. 2013), and the studies with the longest dose administration (Berk et al., 2008a; Dean et al., 2012; Rapado-Castro et al., 2016) demonstrated significant cognitive changes for the experimental group. Conversely, the participants observed by Hauer et al. (2003) had both relatively short intervention times and the lowest intervention dose, but demonstrated significant cognitive improvements over controls. There was similar variability within the studies where no significant cognitive change was detected; two weeks of multi-ingredient intervention did not appear to effect cognitive change for the participants observed by Chan et al. (2010) but significant changes were detected when doses were continued for 3 months. By comparison, participants observed by Amen et al. (2011) with a mean administration length of 6 months and weaker dose reported significant cognitive improvement. Gunduz-Bruce et al. (2012) utilized a large dose on a single day, while Dean et al. used a comparable dose daily for over 6 months, but neither reported cognitive improvement. Taken as a whole, this suggests that there are additional confounds at play when determining successful NAC intervention, such as the presence or progression of disease.

Prolonged regimens appeared to show the highest degree of change for chronic conditions. Studies examining NAC as an intervention for chronic conditions such as Alzheimer's disease (Adair et al., 2001), bipolar disorder (Dean et al., 2012), and schizophrenia (Rapado-Castro et al., 2016). As part of a prolonged multi-ingredient antioxidant formulation, corroborative beneficial effects were further observed for Alzheimer's disease (Chan et al., 2008; Remington et al., 2015; Remington et al., 2008), and long-term physical trauma of high impact sport (Amen et al., 2011.) Evidence for NAC as an intervention for acute conditions associated with oxidative stress was equivocal; in an approximation model of psychosis Gunduz-Bruce et al. (2012) were unable to moderate the cognitive effects induced by ketamine in otherwise healthy participants, while Hoffer and colleagues

demonstrated considerable advantage for the inclusion of NAC as an adjunct treatment for brain injury (Hoffer et al., 2013).

A consideration of age and natural cognitive change

Chan and colleagues (2010) reported an interaction effect for age and combined antioxidant intervention efficacy. While there was a main effect for intervention response on cognitive performance, this effect diminished with increasing age, even in cognitively healthy participants. At face value, the results of this study complicate the understanding of other research – given that the participants were without detected cognitive impairments or psychiatric disorder, it is not clear by which mechanism the treatment regimen was able to promote cognitive improvement. Increasing age is an established risk factor for the onset of mild cognitive impairments and dementia (Armstrong, 2013), and so the ability to reliably distinguish between cognitive change through ageing rather than pathology is complicated. However it is possible that this is concordant with the results of Hoffer et al., (2013), suggesting the need to use the agent as soon as possible after the neuronal insult.

Implications and conclusions

There is ample evidence to suggest that increased levels of oxidative stress, inflammation, mitochondrial dysfunction and apoptosis are associated with clinically meaningful cognitive deterioration. Our review found that there is some evidence to suggest that the supplementation of NAC can be efficacious in reducing the severity of cognitive changes associated with a variety of disorders characterised by oxidative stress, though this is extremely preliminary and is subject to multiple caveats. While various individual positive results could be considered as evidence of potential clinical benefit of NAC administration, results more generally were inconsistent and subject to limitations of sample size, absence of control conditions, heterogeneity of assessment modalities and treatment regimens that prevent drawing firm conclusions to inform clinical practice. While there appears some promise for the possibility of NAC as a useful cognitive protector, there is a scarcity of strong evidence of an effect that could be attributed solely to NAC supplementation and

further research is warranted. Indeed, there was insufficient congruent data to conduct a meta-analysis. Additionally, while levels of oxidative stress were often cited as part of the rationale for investigating the benefits of antioxidant treatments, few studies included biomarkers of oxidative stress within the analyses. Further larger-scale clinical trials specifically designed to examine the ability of NAC to modulate cognitive outcomes in conditions associated with oxidative stress and neuroinflammation are warranted, and could have significant individual and public health benefits across a wide spectrum of disease.

Conflicts of Interest

Biomedica Australia is providing NAC and placebo capsules for a clinical trial being conducted by the authors investigating the ability of NAC to modulate cognitive trajectories in elderly patients undergoing major surgery.

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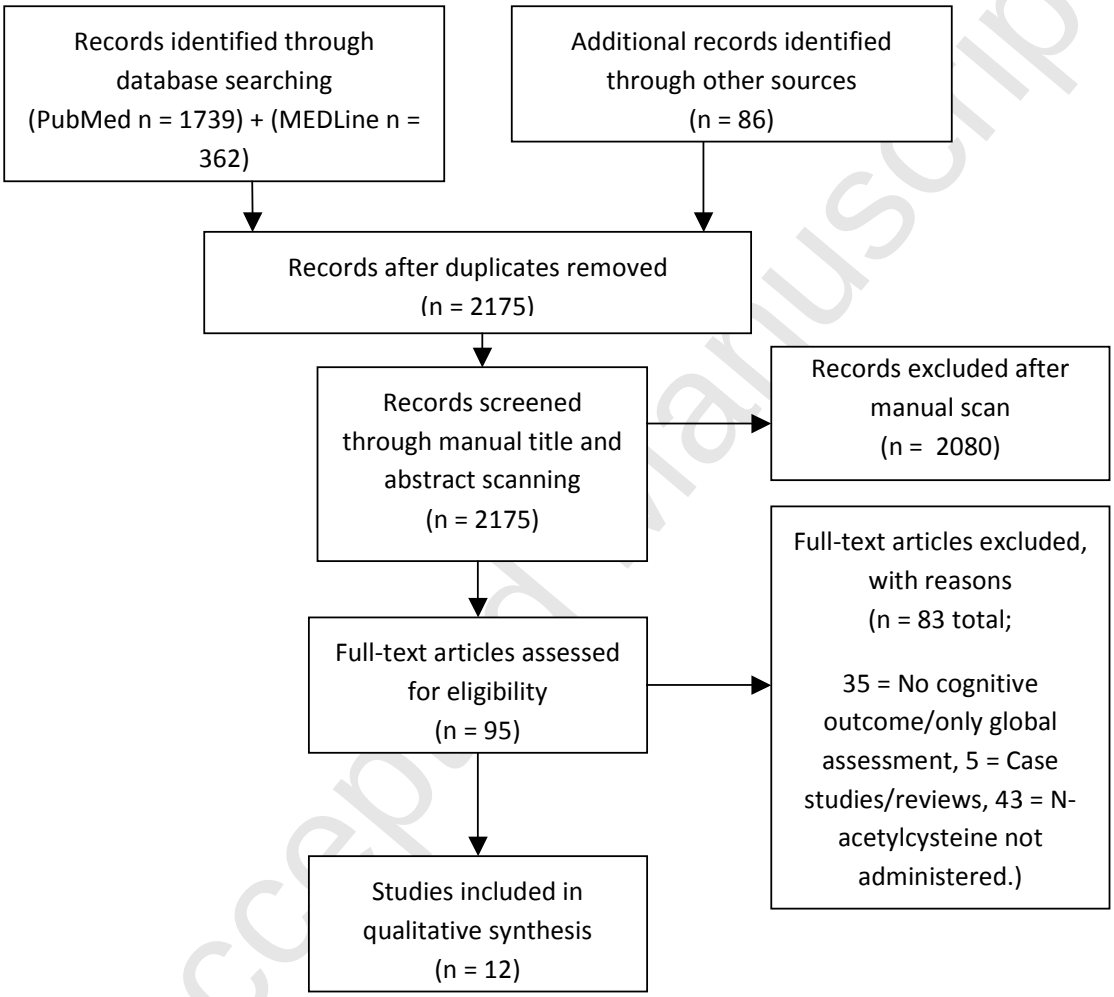
Appendix A



Search terms: PubMed: n acetyl cysteine OR "NAC" OR antioxidant AND cognit* Limited to humans.

Search details: PubMed.

("acetylcysteine"[MeSH Terms] OR "acetylcysteine"[All Fields] OR "n acetyl cysteine"[All Fields]) OR "NAC"[All Fields] OR ("antioxidants"[Pharmacological Action] OR "antioxidants"[MeSH Terms] OR "antioxidants"[All Fields] OR "antioxidant"[All Fields]) AND (cognit[All Fields] OR cognita[All Fields] OR cognitae[All Fields] OR cognitation[All Fields] OR cognite[All Fields] OR cognitech[All Fields] OR cognitex[All Fields] OR cogniti[All Fields] OR cognitia[All Fields] OR cognitial[All Fields] OR cognitian[All Fields] OR cognitice[All Fields] OR cognitician[All Fields] OR cognitie[All Fields] OR cognitief[All Fields] OR cognitieffunctioneren[All Fields] OR cognities[All Fields] OR cognitieve[All Fields] OR cognitif[All Fields] OR cognitife[All Fields] OR cognitifs[All Fields] OR cognitil[All Fields] OR cognitin[All Fields] OR cognitin's[All Fields] OR cognitins[All Fields] OR cognitio[All Fields] OR cognitio'[All Fields] OR cognitioin[All Fields] OR cognition[All Fields] OR cognition'[All Fields] OR cognition's[All Fields] OR cognition93[All Fields] OR cognitional[All Fields] OR cognitionand[All Fields] OR cognitionbehavior[All Fields] OR cognitiondisability[All Fields] OR cognitione[All Fields] OR cognitionincarnation[All Fields] OR cognitionis[All Fields] OR cognitionleiden[All Fields] OR cognitionm[All Fields] OR cognitionmaster[All Fields] OR cognitionnetherlands[All Fields] OR cognitionrelated[All Fields] OR cognitionresponse[All Fields] OR cognitions[All Fields] OR cognitions'[All Fields] OR cognitionstudy[All Fields] OR cognitionumr[All Fields] OR cognitiori[All Fields] OR cognitiove[All Fields] OR cognitique[All Fields] OR cognitition[All Fields] OR cognititve[All Fields] OR cognitiu[All Fields] OR cognitius[All Fields] OR cognitiv[All Fields] OR cognitiva[All Fields] OR cognitivas[All Fields] OR cognitive[All Fields] OR cognitive'[All Fields] OR cognitiveatlas[All Fields] OR cognitivebehavioral[All Fields] OR cognitivebehavioural[All Fields] OR cognitivebehaviourtherapy[All Fields] OR cognitiveconsilience[All Fields] OR cognitivedrugresearch[All Fields] OR cognitivedysfunction[All Fields] OR cognitiveflexibility[All Fields] OR cognitivefunctioning[All Fields] OR cognitivegroup[All Fields] OR cognitiveion[All Fields] OR cognitiveiy[All Fields] OR cognitiveliberty[All Fields] OR cognitively[All Fields] OR cognitively'[All Fields] OR cognitivement[All Fields] OR cognitiveness[All Fields] OR cognitiveneuroscience[All Fields]

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Search terms: EBSCO Host search of MEDLine Complete: Boolean/Phrase: n acetyl cysteine OR “NAC” AND cognit* AND antioxidant.

Limiters: Remove: Human Remove: Age Related: All Adult: 19+ years

Excluded articles after full-text review:

No cognitive outcome directly measured/only global functioning assessed:

(Abu Hashim et al., 2010; Alabdali et al., 2014; Alboni et al., 2013; Barkholt et al., 2008; Berk et al., 2008b; Berk et al., 2012; Carmeli et al., 2012; Cereser et al., 2001; Cervellati et al., 2014; Dresdale et al., 1982; Garcia et al., 2013; Grant et al., 2007; Karbasi et al., 2013; Kerksick et al., 2013; Khan et al., 2005; Lee et al., 2010; Lin et al., 2010; Lindblad et al., 2011; Magalhães et al., 2011; Magalhaes et al., 2012; Magalhães et al., 2013; Mantovani et al., 2003; Nasr, 2010; Oner and Muderris, 2011; Ozaydin

et al., 2013; Parr and Huitson, 1987; Rasi Hashemi et al., 2012; Rizk et al., 2005; Shahin et al., 2009; Shohrati et al., 2008; Sugino et al., 2004; Treitinger et al., 2004; Van Schooten et al., 2002; Wengreen et al., 2007)

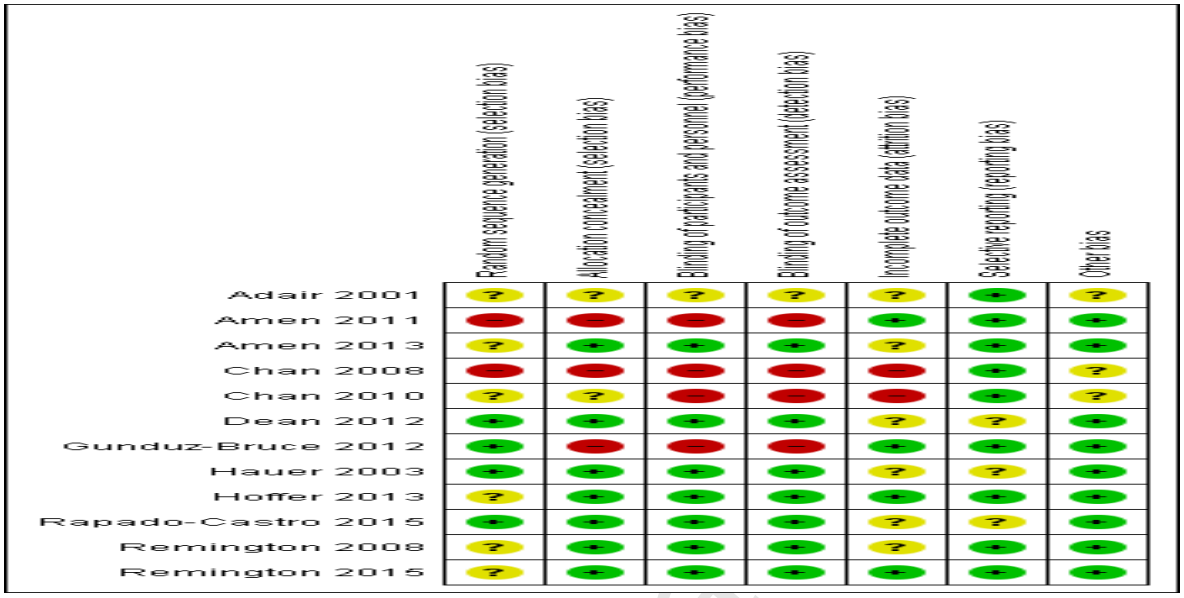
Case studies/Reviews:

(Berk et al., 2009; Grant et al., 2012; Manchanda et al., 2013; McCaddon and Davies, 2005; Singh and Singh, 2011)

N-Acetylcysteine not administered:

(Berr et al., 2000; Chui and Greenwood, 2008; Devore et al., 2010; Duffy et al., 2014; Duma, 2013; Faux et al., 2010; Galasko et al., 2012; Gassio et al., 2008; Giavarotti et al., 2013; Golub et al., 2011; Gonzalez-Reimers et al., 2014; Gray et al., 2008; Gray et al., 2003; Grodstein et al., 2003; Guidi et al., 2006; Iuliano et al., 2010; Jama et al., 1996; Kalmijn et al., 1997; Kesse-Guyot et al., 2011; Klugman et al., 2012; La Rue et al., 1997; Lott et al., 2011; Maxwell et al., 2005; McNeill et al., 2007; Mendelsohn et al., 1998; Padurariu et al., 2010; Paganini-Hill and Clark, 2007; Pecina et al., 2014; Reinecke et al., 2010; Savenkov et al., 2013; Smith and Fein, 2010; Sokolova and Shmyrev, 2011; Strydom et al., 2009; Sultana et al., 2008; Talarowska et al., 2012; Torres et al., 2011; Tsuruya, 2014; von Arnim et al., 2013; Whalley et al., 2014; Wu et al., 2014; Yaffe et al., 2004; Yasuno et al., 2012; Ye et al., 2013; Zhang et al., 2012

Appendix B



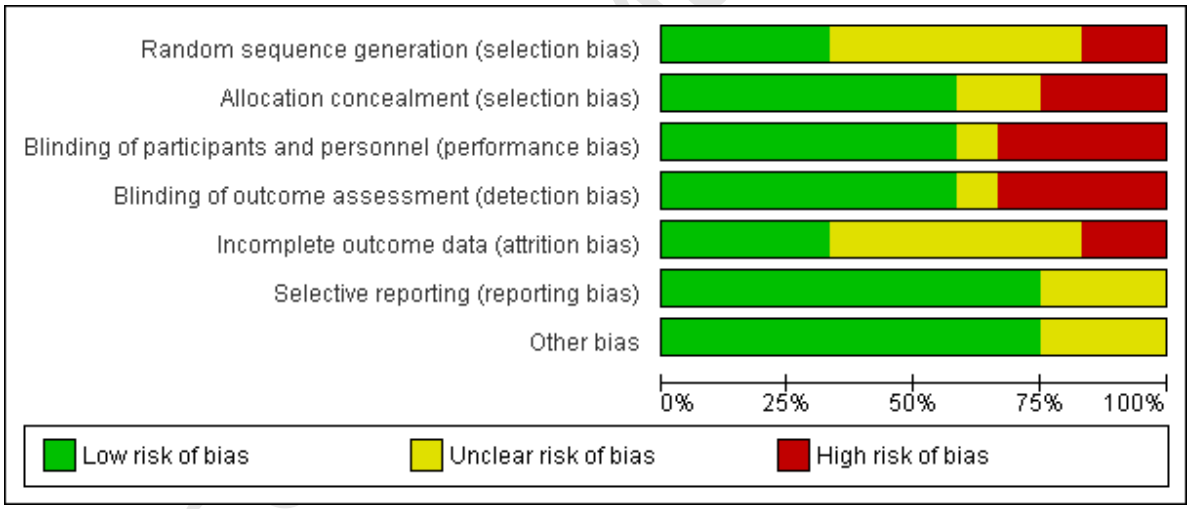


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Table 1. Clinical Trials of NAC with cognition as a primary or secondary endpoint

Study	Participants	Design	Cognitive Outcomes	Cognition as primary outcome	Intervention (NAC in bold)	Cognitive change results
Adair et al (2001).	43 participants who met criteria for having probable Alzheimer's disease. Age and gender demographics not supplied. Allocated to intervention (*n* =23) or placebo (*n* =20).	Double-blind, randomized control trial. Assessment of function at baseline, 3 months, and 6 months.	Mini Mental State Exam, Boston Naming Test, Gesture to Command, Weschler Memory Scale - Figure Reproduction (Immediate), Hopkins Verbal Learning Task – Immediate Recall Recognition, Letter fluency, Categorical Fluency, Judgement of Line Orientation.	*Primary:* MMSE, Activities of Daily Living. *Secondary:* Boston Naming Test, Gesture to Command, Figure Reproduction, Verbal Learning Task, Verbal Fluency, Judgement of Line orientation.	Placebo, or **NAC at 50mg/kg/day.** Intervention was spread over three doses, and was continued for 6 months.	No significant change on placebo condition over 6 months. Significant improvement for NAC group at 3 months WMS – Figure Reproduction compared to baseline; significant improvement for NAC group at 6 months Letter fluency compared to baseline. No change to MMSE or other cognitive measures.
Hauer et al. (2003).	36 community dwelling participants, cognitively healthy but physically frail and aged over 65 years. Allocated to intervention (*n* =20), or placebo (*n* =16). In the intervention group, the mean age was 77.3 years (SD = 8.8).	Double-blind, randomized control trial. Assessment of function at baseline, 3 weeks, 6 weeks, and 12-13 weeks.	Mini Mental State Exam, Modified Trail Making Test (Zahlen-Verbindungs Test), Digit symbol substitution.	*Primary:* Physical activity, strength, and motor function. *Secondary:* Biomarkers of oxidative stress, Modified Trail Making test, Digit symbol substitution.	Placebo, or **NAC 200mg per day for 6 weeks.** Concurrently, both treatment arms participated in resistance exercise 3 days a week for 6 weeks.	No significant cognitive change over the course of the trial for the placebo group, but significant cognitive improvement on the Trail Making Test and Digit symbol substitution test within the NAC group. However, there were no significant between-groups changes.
Chan et al. (2008).	14 Community-dwelling	Open-label, pilot	Dementia Rating	*Primary:* Clock Drawing	Placebo (treatment as	Improvement on DRS at 6

	early-stage Alzheimer's disease patients, 50 years or older. No specific age or gender information supplied.	trial. 12 months longitudinal study. Follow up at 3, 6, 9, 12 months.	Scale-2, Clock Drawing Test.	Test, Dementia Rating Scale, Activities of Daily Living, Neuropsychiatric Inventory.	usual), or Vitamin formulation (VF): Folic acid (400µg), Vitamins B12 (6ug) & E (30 IU), S-adenosylmethionine (SAM, 400mg), acetyl-carnitine (ALCAR, 500mg), and **NAC (600mg), taken twice daily.** Intervention continued daily for 12 months.	months, maintained at 12 months. Clinical improvement on Clock Drawing Test 1 between 6 & 12 months. No change on ADL scores. Improved symptoms on NPI over 12 months.
Remington et al. (2008).	12 community-dwelling moderate-to-late stage Alzheimer's disease patients, allocated to receive vitamin formulation (*n* = 6), or 6 treatment as usual (*n* = 6). No age or gender information supplied.	Randomized Placebo-controlled, subsequent open-label trial. Assessment of function at baseline, 3, 6, 9 months.	Dementia Rating Scale 2, Clox Drawing Test-I.	*Primary:* Dementia Rating Scale, Clock Drawing Test. *Secondary:* Activities of Daily Living, Neuropsychiatric Inventory.	Placebo (treatment as usual), or Vitamin Formulation (VF): Folic acid (400µg), Vitamins B12 (6ug) & E (30 IU), S-adenosylmethionine (SAM, 400mg), acetyl-carnitine (ALCAR, 500mg), and **NAC (600mg), taken twice daily.** Intervention continued daily for 9 months.	Participants in the VF group experienced significantly delayed rates of decline as measured on the Dementia Rating Scale and Clox Drawing Tests compared to the placebo group over 3 months. Caregiver reports indicated a significant improvement on Neuropsychiatric Inventory and Activities of Daily Living. Trial halted at 9 months when the participants were no longer able to continue the intervention.
Chan et al. (2010).	115 participants allocated to Intervention (n = 59) or placebo (*n* = 56). Age ranged from 18-86 years. No gender information was supplied.	Open label, cross-over, and placebo controlled trial. 2 weeks; 3, 6, 9, 12 month follow ups.	California Verbal Learning Test II, Trail Making Test. At week 2, the treatment group was also given the Digit Memory Test.	*Primary:* California Verbal Learning Test, Trail Making Test, Digit Memory Test.	Placebo, or Vitamin Formulation (VF): folic acid (400µg), Vitamins B12 (6µg) and E (30 IU), SAM (400mg), ALCAR (500mg), **NAC (600mg), taken twice daily.** Intervention continued for	At 3 and 12 months, Improvement in short-term recall in VF group, no change for delayed recall in either group. VF group also displayed significant improvement upon TMT, while the placebo group did not. Participants who were taken off

					6 months, was discontinued for 3 months, and initiated at 9 months for 3 months.	VF showed functioning consistent with non-treatment, but returned to improvement once VF was re-initiated.
Amen et al. (2011).	30 Retired National Football League (gridiron) players, who had presented with degrees of acquired brain injury and cognitive impairment. All participants were male, aged between 25-82 years (Mean = 57.27, SD = 12.37).	Open-label, repeated measures design. Follow up time ranged from 2 to 12 (*M* = 6) months after recruitment.	Microcog Assessment of Cognitive Function, a battery containing subtests measuring processing speed, processing accuracy, attention, reasoning, memory, spatial processing, reaction time, and general cognition function & proficiency.	*Primary:* Microcog Assessments (full battery). *Secondary:* SPECT scans of brain perfusion, subjective measures of mood, motivation, memory, attention, and sleep.	Pragmatic intervention of smoking and drug reduction, weight loss support if necessary. All participants received a daily formulation of fish oil (5.6g), unspecified multi-vitamins, and a combination of ginko, vinpocetine, actyl-l-carniltine, huperzine A, alpha-lipoic acid, and **400mg NAC.** Treatment continued for between 2 – 12 months.	After an average intervention length of 6 months, participants demonstrated significantly improved percentile scores on the following subtests: general cognitive functioning/proficiency, processing speed/accuracy, attention, reasoning, and memory, though these changes did not remain significant after conversion into Hedges *g*. No change on subtests of spatial processing or reaction time. No raw scores were reported. Significant increases in brain perfusion within the prefrontal cortex, anterior cingulate gyrus, parietal lobes, occipital lobes, and cerebellum where detected, but not in the temporal lobes and fusiform gyrus without alpha level adjustment (0.001 to 0.05).
Dean et al. (2012).	47 participants diagnosed with bipolar disorder, allocated to intervention (*n* =21) or placebo (*n* =26). The mean age of the	Randomized double-blind, control trial. Analysis of data from a larger study, including	Digit Span forward & backward, Trail Making Tests A & B, Word Learning, Verbal Fluency.	*Primary:* Montgomery-Asberg Depression Rating Scale, Young Mania Rating Scale. *Secondary:* Digit Span, Trail Making Tests, Word Learning, Verbal	Placebo, or **NAC (2000mg/day)** for 6 months.	No significant changes to cognitive measures over study period.

	intervention group is 44.6 (SD = 12.5), and 13 of the intervention group were women.	only participants who completed cognitive assessments (Berk et al, 2008).		Fluency.		
Gunduz-Bruce et al. (2012).	16 participants allocated to either NAC intervention (*n* = 8) or placebo (*n* = 8). The mean age was 27 years (SD = 5.6), 13 of the participants were male.	Randomized double blind, control trial. Participants were tested over 2 days.	Spatial Working Memory, Rapid Visual Processing.	*Primary:* Spatial Working Memory, Rapid Visual Processing, Positive and Negative Syndrome Scale, Visual Analogue Scale of mood states, Clinical Administered Dissociative States Scale. *Secondary:* Auditory Oddball Paradigm, Mismatch Negativity.	Placebo (inactive NAC), or active **NAC (2000mg and 1000mg divided doses).** Intervention consisted of a single dose. Cognitive dysfunction was simulated using ketamine.	NAC did not significantly mitigate the cognitive effects induced by ketamine. In addition, ketamine brought about significant cognitive symptom and behavioural changes that were not attenuated by NAC administration.
Amen et al. (2013).	30 healthy participants recruited from the community. Randomised to receive an intervention of brain-targeted nutrients, or a pseudo-placebo. 15 women were present in the sample, and 15 men. No age data was supplied beyond minimum of 18 years.	Randomised double blind control for initial 2 months, cross-over study for further 2 months.	WebNeuro battery, MicroCog battery.	*Primary:* Brain SPECT imaging, and Region of Interest analysis. *Secondary:* MicroCog Assessment battery, WebNeuro Assessment battery, Brief Symptom Inventory.	Pseudo-placebo containing nutrients but no NAC, or a formulation of brain-targeted nutrients, detailed in text but too large to include here. Contains **400mg NAC.** Intervention was administered once per day for 2 months, at which point the intervention and pseudo-placebo groups switched.	At the end of the study, the intervention group demonstrated significant cognitive improvements compared to baseline and placebo. Significant improvements were detected in executive function, reasoning, memory, and information processing efficiency and accuracy. In addition, significant increases in regional cerebral blood flow to 30 areas of the brain. During the withdrawal period of the cross-over, participants returned to baseline levels on cognitive and blood

						flow measures.
Hoffer et al. (2013).	81 participants allocated to either NAC intervention (*n* = 31) or placebo (*n* = 40). All participants were active duty military personnel with mild traumatic brain injury from explosions. 80 of the participants were male, with an age range of 18-43 (Median = 22) years.	Randomized double blind, placebo controlled trial. Assessment at baseline, 3 days, and 7 days after initiation.	Trail Making Tests, and Controlled Oral Word Association Tests.	*Primary:* Trail Making Tests, Controlled Oral Word Association Test. *Secondary:* Symptoms associated with blast-induced mTBI were recorded throughout the trial.	Placebo, or **NAC in staggered doses.** Participants were given **4g NAC** on the first day as a loading dose, then over the next 3 days **2x2g** morning and night per day. For the next 3 days, dosage was reduced to **2x1.5 g** daily before termination.	By day 7, participants in the NAC condition demonstrated significantly improved performance on both the TMT-A and TMT-B compared to the placebo group. The NAC group also had significantly fewer and less severe symptoms of mTBI compared to the placebo group. No group differences were found on the COWAT.
Remington et al. (2015).	106 participants with Alzheimer's disease randomized to receive either VF (*n* =62) or placebo (*n* =44). The mean age was 77.8 (SD = 8.4) years. No gender information supplied.	Randomized double-blind multi-site trial for 3 -6 months, open label trial for additional 6 months will all participants receiving VF.	Clox-1, Dementia Rating Scale.	*Primary:* Clox-1, Dementia Rating Scale. *Secondary:* Neuropsychiatric Inventory, Activities of Daily Living,	Placebo (treatment as usual), or Vitamin Formulation (VF): Folic acid (400µg), Vitamins B12 (6ug) & E (30 IU), S-adenosylmethionine (SAM, 400mg), acetyl-carnitine (ALCAR, 500mg), and **NAC (600mg), taken twice daily.**	By 3 months, the VF group had improved significantly on Clox and DRS performance, while the control group did not. However, neither arm demonstrated significant change to either Activities of Daily Living or the Neuropsychiatric Inventory.
Rapado-Castro et al., (2016)	58 participants with either bipolar disorder or schizophrenia. The intervention group had a mean age of 38.6 (SD = 12.2) years, and 34 of the sample were male.	Randomised doubled-blind, placebo controlled control trial. 24-week treatment period.	Digit Span forward & backward, Trail Making Tests A & B, Word Learning, Verbal Fluency.	*Primary:* Montgomery-Asberg Depression Rating Scale, Young Mania Rating Scale. *Secondary:* Digit Span, Trail Making Tests, Word Learning, Verbal Fluency.	Placebo, or **NAC (2000mg/day)** for 6 months.	At 24 weeks, participants within the NAC group demonstrated significantly better working memory compared with controls. No other significant changes observed.

Highlights:

- **Oxidative stress and inflammation are widely implicated as cognitive modulators, through a variety of vectors.**
- **N-acetylcysteine, a glutathione precursor, has demonstrated efficacy in reducing the severity of oxidative stress and neuroinflammation, with correlating cognitive improvement in pre-clinical models.**
- **Evidence for the efficacy of N-acetylcysteine as an adjunct monotherapy for human cognition is inconsistent but promising, though the weight of evidence is approximately equivalent.**
- **Combined interventions of N-acetylcysteine and other antioxidants have demonstrated efficacy for positively impacting human cognition in a range of contexts, but it is not possible to determine the degree to which N-acetylcysteine is contributing.**
- **There is considerable scope to evaluate the cognitive protective effects of NAC in clinical conditions associated with neuronal oxidative stress and inflammation.**