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ORIGINAL ARTICLE

Cognitive effects of adjunctive *N*-acetyl cysteine in psychosis

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Background. Cognitive deficits are predictors of functional outcome in patients with psychosis. While conventional antipsychotics are relatively effective on positive symptoms, their impact on negative and cognitive symptoms is limited. Recent studies have established a link between oxidative stress and neurocognitive deficits in psychosis. *N*-acetylcysteine (NAC), a glutathione precursor with glutamatergic properties, has shown efficacy on negative symptoms and functioning in patients with schizophrenia and bipolar disorder, respectively. However, there are few evidence-based approaches for managing cognitive impairment in psychosis. The present study aims to examine the cognitive effects of adjunctive NAC treatment in a pooled subgroup of participants with psychosis who completed neuropsychological assessment in two trials of both schizophrenia and bipolar disorder.

Method. A sample of 58 participants were randomized in a double fashion to receive 2 g/day of NAC ($n = 27$) or placebo ($n = 31$) for 24 weeks. Attention, working memory and executive function domains were assessed. Differences between cognitive performance at baseline and end point were examined using Wilcoxon's test. The Mann–Whitney test was used to examine the differences between the NAC and placebo groups at the end point.

Results. Participants treated with NAC had significantly higher working memory performance at week 24 compared with placebo ($U = 98.5$, $p = 0.027$).

Conclusions. NAC may have an impact on cognitive performance in psychosis, as a significant improvement in working memory was observed in the NAC-treated group compared with placebo; however, these preliminary data require replication. Glutamatergic compounds such as NAC may constitute a step towards the development of useful therapies for cognitive impairment in psychosis.

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Introduction

Psychotic disorders (both affective and non-affective disorders) are severe and disabling mental conditions characterized traditionally by positive symptoms (hallucinations and delusions) and negative symptoms (avolition or amotivation) alongside changes in mood (depression, mania) and alterations in information processing (cognitive deficits) (van Os & Kapur, 2009; Arango *et al.* 2014). Cognitive impairment has been shown to present from early in psychotic disorders (Zabala *et al.* 2010; Bora & Pantelis, 2015; Daglas *et al.* 2015) and to a lesser extent from the outset (Reichenberg *et al.* 2010) and in at-risk mental states (Fusar-Poli *et al.* 2012), thereby contributing to ongoing cognitive impairment over time (Reichenberg *et al.* 2010; Bombin *et al.* 2013). These changes in cognitive

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processing can be broadly partitioned into those that are trait related and those that are affected by mental state (Lopez-Jaramillo *et al.* 2010; Kozicky *et al.* 2014). Cognitive function serves as a proxy of the severity of psychosis and is associated with poor social, vocational and functional outcome (Martinez-Aran *et al.* 2002; Fett *et al.* 2011), and is also an important prognostic variable (Malhi *et al.* 2007; Fett *et al.* 2011) providing a meaningful target for interventions.

While conventional antipsychotics are relatively effective in alleviating psychosis, their impact on cognitive function is minimal largely because pharmacotherapy has mainly targeted dopamine dysfunction. Regulation of the putative 'hyperdopaminergic state' with antipsychotic drugs effectively counters the positive symptoms of psychosis, but their effects on negative and cognitive symptoms are modest (Kahn & Sommer, 2015). Thus, the development of novel treatments for cognitive dysfunction in psychotic disorders is of great importance. Along those lines, drug discovery for psychotic disorders has moved in recent decades beyond the 'dopamine hypothesis' towards approaches derived from pathophysiological investigations in this field (Davis *et al.* 2014; Debnath *et al.* 2015; Howes *et al.* 2015).

One such example is the role of glutamate transmission in the development and maintenance of cognitive and negative symptoms (Rajasekaran *et al.* 2015). Specifically, glutamate is thought to have a critical role in cognitive and negative symptoms through the activation of *N*-methyl-D-aspartate (NMDA) glutamatergic receptors. The NMDA receptor (NMDA-R), is involved in synaptic plasticity, auditory information processing and cognitive functions, such as inhibitory control, working memory (Morgan *et al.* 2004), learning and memory (Riedel *et al.* 2003), cognitive flexibility and information processing (Banks *et al.* 2014).

Altered glutamate levels have been linked to the cortical response during executive functioning tasks in people at high risk for developing psychosis (Fusar-Poli *et al.* 2011). This altered top-down procesing of sensory information has been proposed to mediate cognitive proceses such as altered attribution of salience or misattibution of meaningful emotion leading to cognitive bias (Kapur, 2003; Hoffman *et al.* 2007). In this regard, studies including key evoked sensory-related potentials such as mismatch negativity (MMN), a physiological indicator of the activity of NMDA receptors and a short-term memory paradigm in relation to sensory/auditory processing, describe a severe sensory auditory dysfunction both in schizophrenia (Gunduz-Bruce *et al.* 2012; Javitt *et al.* 2012) and in people at risk of developing psychosis (Shaikh *et al.* 2012).

In parallel, free radical scavenging in both psychotic bipolar disorder and schizophenia is unable to keep up with free radical production, leading to cumulative oxidative damage in critical brain regions, which eventuates in cognitive and behavioural symptoms (Ng *et al.* 2008). Glutathione (GSH) is one of the main cellular non-protein redox regulators and free radical scavenger in the brain. Dysregulation of the GSH system reduces activity of NMDA glutamatergic receptors (Kantrowitz & Javitt, 2010; Stone *et al.* 2010). An association between the observed GSH deficit during the first psychotic episode with global changes in cognition is noted (Martinez-Cengotitabengoa *et al.* 2014), particularly with high-order executive functions (Martinez-Cengotitabengoa *et al.* 2012), indicating that changes in GSH and cognitive function are closely linked and suggesting that oxidative damage may contribute to cognitive impairment. Furthermore, inflammatory mediators such as cytokines have also been associated with cognitive dysfunction in patients with a first episode of psychosis (Martinez-Cengotitabengoa *et al.* 2012; Bauer *et al.* 2014). In this regard, altered proinflamatory cytokines provoke glutamate hyperactivity leading to NMDA glutamate receptor activation, altered redox balance and oxidative stress accumulation (Hanson & Gottesman, 2005; Saetre *et al.* 2007) which can modify cognitive function (Wilson *et al.* 2002; Kahn & Sommer, 2015).

N-acetylcysteine (NAC) is emerging as a useful agent in the treatment of a wide range of psychiatric disorders (Deepmala *et al.* 2015). In addition to its glutamatergic modulation effects, NAC has been shown to potently make an impact on oxidative biology, both by increasing GSH levels and directly scavenging free radicals (Choy *et al.* 2010; Holmay *et al.* 2013). It also has been shown to decrease pro-inflammatory cytokines and enhance neurogenesis, mitochondrial function and regulate apoptosis (Berk *et al.* 2008*c*; Samuni *et al.* 2013). NAC attenuates the cognitive and behavioural effects of NMDA receptor antagonists in rodents (Gunduz-Bruce, 2009). By rescuing depleted levels of GSH in the brain, NAC restores cognitive deficits such as short-term spatial memory deficits in rats in a dose-dependent manner (Choy *et al.* 2010). In human studies, NAC improves core negative symptoms of schizophrenia (Berk *et al.* 2008*a*; Bulut *et al.* 2009), depressive symptoms in bipolar disorder (Berk *et al.* 2008*b*) and functioning in both (Berk *et al.* 2008*a*, *b*), as well as improving MMN in psychosis (Lavoie *et al.* 2008; Carmeli *et al.* 2012; Gunduz-Bruce *et al.* 2012).

To date, studies on global neurocognitive effects of NAC in humans have demonstrated inconsistent results which may reflect variance in study design (Deepmala *et al.* 2015). For example, the addition of NAC to standard treatment produced specific improvements in verbal abilities/executive control cognitive tasks in Alzheirmer's

disease in comparison with treatment-as-usual controls (Adair *et al.* 2001). More recently, adjunctive NAC administration provided significant gains in executive function in mild traumatic brain injury relative to controls (Hoffer *et al.* 2013). In contrast, NAC pretreatment did not reduce the effect of ketamine on cognitive performance in healthy subjects with ketamine-induced psychosis (Gunduz-Bruce *et al.* 2012) or in patients with bipolar disorder (Dean *et al.* 2012); however, the sample size in both studies was inadequate to detect small or moderate effect sizes. To our knowledge, no previous study has addressed this issue in individuals with psychosis (Deepmala *et al.* 2015).

The present study aims to assess the cognitive effects of adjunctive NAC treatment in participants with psychosis who underwent cognitive assessments in the context of two double-blind, randomized, placebo-controlled clinical trials in schizophrenia (Berk *et al.* 2008*a*) and bipolar disorder (Berk *et al.* 2008*b*). It was hypothesized that treatment with NAC would enhance cognitive functioning in participants with psychotic features. We anticipated a more specific improvement in superior cognitive functions (i.e. working memory, executive functioning and processing speed/attention) where there is a signal from preclinical and clinical studies and where other agents have shown promise (Miskowiak *et al.* 2014).

Method

Study participants and procedure

The overall pooled cohort consisted of individuals who participated in two multicentre, double-blind, randomized, placebo-controlled NAC trials in schizophrenia and bipolar disorder, respectively. A detailed description of the methodology, efficacy and outcome measures of the main studies has been provided elsewhere (Berk *et al.* 2008*a*, *b*, 2011). In brief, a total of 215 participants [i.e. 140 participants diagnosed with schizophrenia and 75 individuals with bipolar disorder; Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria] were recruited from private and public psychiatry out-patient facilities in Victoria, Australia and one public clinic in Lausanne, Switzerland. The trials were approved by each participating research and ethics committee. After providing written informed consent, all randomized participants received adjunctive 2000 mg of NAC (1000 mg twice daily) or matching placebo, in addition to usual treatment, in a double-blind fashion over 24 weeks. Adherence was monitored by pill counts of returned medication packs (Berk *et al.* 2008*a*, *b*).

Participants had to meet the following criteria for the respective studies: DSM-IV criteria for schizophrenia with a Positive and Negative Symptoms Scale score (PANSS) of $\geqslant$55 or at least two of the positive and/or negative items being >3, or have a Clinical Global Impression – Severity score $\geqslant$3 (Berk *et al.* 2008*a*); or criteria for bipolar disorder I or II with at least one documented episode of illness (depressive, manic or mixed) in the past 6 months (Berk *et al.* 2008*b*). We then further selected out those with psychotic bipolar symptoms based on the DSM-IV criteria for meeting psychotic features. General exclusions for both studies included: those with abnormal haematological findings, a systemic medical disorder or a history of anaphylaxis with NAC, those taking therapeutic amounts of NAC, selenium and/or vitamin C, pregnant or lactating. Individuals on other psychoactive medications were required to be on stable treatment of $\geqslant$1 month prior to commencing the study. The studies were registered on the Australian and New Zealand Clinical Trials Registry (schizophrenia trial ACTRN12605000363684; bipolar trial 1 no. 12605000362695) prior to enrollment.

Diagnosis was established at baseline using a structured clinical interview (Mini International Neuropsychiatric Interview for DSM-IV). The study design was broadly equivalent for both clinical trials. Clinical and functional outcome measures were assessed through a comprehensive set of rating scales that were included in the larger trials (Berk *et al.* 2008*a*). Assessments were performed by formally trained clinical practitioners or researchers who underwent inter-rater reliability assessments.

The present study examines cognitive outcome measures in participants with psychosis at end point (24 weeks). Cognitive impairments have been shown to be present across psychotic disorders (Reilly & Sweeney, 2014) with schizophrenia and bipolar disorder, with psychosis presenting more severe cognitive deficits (Hill *et al.* 2013). Therefore, the current analyses include only those subjects who fulfilled DSM-IV criteria for schizophrenia (n = 32) and bipolar disorder 'with psychotic features' (n = 26) that undertook the cognitive assessment. A comparison of the two diagnostic groups to determine potential differences that may have an impact on results was done before pooling the samples. Participants with schizophrenia and psychotic bipolar disorder did not differ in terms of duration of illness or cognitive performance at the time of the study entry (i.e. baseline). Of those, 31 participants (schizophrenia n = 17; bipolar disorder n = 14) received placebo and 27 participants (schizophrenia n = 15; bipolar disorder n = 12) were treated with NAC. There were no differences in baseline characteristics between those participants who completed and the ones who did not complete the cognitive testing (data not shown).

Clinical assessments

Clinical status at the time of baseline assessment was determined using the PANSS (Kay *et al.* 1987) (data available for schizophrenia participants only) and the Montgomery–Åsberg Depression Rating Scale (MADRS) (Williams & Kobak, 2008) together with the Young Mania Rating Scale (YMRS) (Young *et al.* 1978) (available for the bipolar disorder subsample only). Level of social, occupational and psychological functioning was measured using the Global Assessment of Functioning Scale (Hall, 1995) and the Social and Occupational Functioning Assessment Scale (Goldman *et al.* 1992) in both participant subgroups (schizophrenia and bipolar disorder).

Cognitive assessment

Cognitive measures were obtained at baseline and at the end of the 24-week treatment phase. Each individual underwent a brief neuropsychological battery assessing attention (digits forward from Wechsler Intelligence Scale for adults, WAIS-III), working memory (digits backwards from WAIS-III), and executive function (Trail Making Test, TMT derived scores – i.e. TMT B:A ratio, TMT B minus TMT A; and Controlled Oral Word Association Test) as cognitive functions previously described as being affected in both in schizophrenia and psychosis psychotic bipolar disorder (Heinrichs & Zakzanis, 1998; Bora *et al.* 2009; Mesholam-Gately *et al.* 2009). Raw scores were used in the statistical analyses because age-scaled scores have small variance.

Data analysis

An intention-to-treat analysis was conducted on all participants who had available cognitive data. Schizophrenia and psychotic bipolar disorder participants were pooled for the comparative analysis of treatment groups (NAC *v.* placebo). Normal distribution of quantitative variables was assessed by means of Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous data are presented as means and standard deviations. Frequencies and percentages were used to describe discrete variables. Independent Student's t tests or Pearson's χ^2 tests were used to compare demographic variables between participants in the NAC and placebo groups. For frequency data, χ^2 tests were employed.

To test for longitudinal changes in cognitive performance from baseline to the end of treatment (6-month time point) within each treatment group, Wilcoxon tests were used. Mann–Whitney tests were used to examine average treatment group differences (NAC *v.* placebo) at the end point. To rule out potential effects of age, gender or antipsychotic medication on cognitive performance, Spearman's rank-order correlation analyses were performed to examine associations between those possible confounders and cognitive outcome variables. To explore the association between diagnosis and cognitive change bivariate Spearman (rho) correlation analyses were used for the whole sample. Secondary exploratory Spearman correlations were also performed to assess the relationship between change (end point minus baseline) in symptoms and in cognition within each diagnostic subgroup evaluated. All variables were tested for collinearity assumptions. No autocorrelation or collinearity was observed in the *a priori* specified independent variables. Thus, corrections for multiple comparisons were not done because all comparison analyses were independent, they were specified '*a priori*' and collinearity assumptions were met (Gelman *et al.* 2009).

All statistical analyses were performed using IBM SPSS v21 (Statistical Package for the Social Sciences, IBM Corporation, USA). Statistical significance was set at $\alpha < 0.05$.

Ethical standards

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Sociodemographic and clinical characteristics

Participants in the NAC and placebo groups did not differ significantly in terms of age, gender, duration of the illness, antipsychotic treatment, severity of symptoms or functioning at the study entry (i.e. baseline visit, see Table 1 and online Supplementary Table S1). There were no significant between-group differences on any of the cognitive measures at baseline.

Cognitive function

A Wilcoxon signed-rank test showed that 24 weeks of treatment with NAC significantly improved working memory performance in adults with psychosis (digit span backwards: $Z = -2.13$, $p = 0.033$) (Table 2). When testing for overall between-group differences, Mann–Whitney tests revealed that participants treated with NAC had significantly higher working memory performance at the end of 24 weeks of treatment than the placebo group (digit span backwards: $U = 98.5$, $p = 0.027$), as shown in Table 2. No significant differences were found either within or between the NAC

Table 1. *Characteristics of participants at baseline*

Characteristic	NAC ($n = 27$)	Placebo ($n = 31$)	Test[a]
Age, years	38.6 (12.2)	41.0 (12.4)	$t = -0.75$, $p = 0.46$
Gender, *n* (%)			$\chi^2 = 0.95$, $p = 0.33$
Male	14 (52)	20 (65)	
Female	13 (48)	11 (36)	
Duration of illness, years	8.59 (7.4)	11.1 (10.0)	$t = -1.08$, $p = 0.29$
Cumulative antipsychotic dosage, mg[b]	540.5 (359.6)	470.5 (313.0)	$t = 0.65$, $p = 0.52$
PANSS[c]			
PANSS positive	13.6 (3.6)	14.3 (6.1)	$t = 0.35$, $p = 0.73$
PANSS negative	16.1 (3.7)	16.1 (4.6)	$t = -0.01$, $p = 0.99$
PANSS general	33.7 (7.4)	31.2 (6.7)	$t = -1.02$, $p = 0.32$
PANSS total	63.5 (11.3)	61.6 (15.0)	$t = -0.41$, $p = 0.69$
YMRS[d]	2.7 (2.7)	2.4 (1.8)	$t = 0.27$, $p = 0.79$
MADRS[d]	13.8 (11.6)	10.1 (6.8)	$t = 0.99$, $p = 0.33$
GAF	55.8 (13.7)	59.1 (14.6)	$t = -0.90$, $p = 0.65$
SOFAS	58.7 (11.9)	60.2 (14.0)	$t = -0.46$, $p = 0.37$

Data are given as mean (standard deviation) unless otherwise indicated.

NAC, *N*-acetylcysteine; PANSS, Positive and Negative Symptoms Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning; SOFAS, Social and Occupational Functioning Assessment Scale.

[a] Differences between the NAC and placebo groups based on two-sample *t* tests (equal variance) or Pearson's χ^2 test. Significance was set at ($p < 0.05$).

[b] Chlorpromazine equivalents were used to derive the antipsychotic dosage and to calculate the cumulative doses taken at baseline.

[c] Data available for the schizophrenia participants subgroup only: NAC $n = 15$; placebo $n = 17$.

[d] Data available for the bipolar disorder with psychotic features subgroup only: NAC $n = 12$; placebo $n = 14$.

and placebo groups following 24 weeks of treatment on measures of attention, or executive function.

These results were independent of age, gender or medication status. There were no significant associations between diagnosis and cognitive change. Among participants on NAC, improvements in cognitive flexibility (TMT ratio score) and executive control ability (TMT B minus TMT A) correlated with a decrease in depressive symptom severity: MADRS ($r_s = 0.83$ $p = 0.010$ and $r_s = 0.83$ $p = 0.010$, respectively). No other associations were found between change in cognition and change in symptom measures.

Discussion

Our results suggest that NAC makes an impact on cognitive function in psychosis. A significant improvement in working memory performance was observed in participants treated with NAC following 6 months (24 weeks) of adjunctive treatment (2000 mg/day), although other measures of attention, as well as executive function remained unchanged. In particular, working memory deficits constitute a core feature and one of the most important prognostic variables that is not adequately treated by currently available pharmacological therapies (Miskowiak *et al.* 2014). These results indicate the potential of glutamatergic compounds such as NAC in the development of novel therapies for cognitive dysfunction, specifically focusing on psychotic disorders such as schizophrenia and/or psychotic bipolar disorder.

Improvements in working memory have also been observed in studies in clinical samples such Alzheimer's disease (Chan *et al.* 2008) and traumatic brain injury (Amen *et al.* 2011) with strategies that use NAC within a nutraceutical formulation. These former positive results were replicated in healthy individuals (Chan *et al.* 2010; Amen *et al.* 2013), although the formulated brain enhancement supplement included a combination of nutrients like NAC and other compounds (i.e. folic acid, B_{12}, vitamin E, *S*-adenosylmethionine or acetyl-L-carnitine) and as such these reported cognitive effects cannot be attributable to NAC alone. As previously reviewed, comparable studies examining the use of adjunctive NAC in Alzheimer's disease (Adair *et al.* 2001) and brain traumatic injury (Hoffer *et al.* 2013) have likewise suggested the efficacy of NAC as a cognitive modulator, though working memory was not directly assessed.

The strongest evidence to date for the use of NAC for cognitive impairment in psychiatric disorders

Table 2. *Cognitive outcome measures for participants in the NAC and placebo groups at baseline and end point*

Outcome measures	Baseline	End point	p^a	NAC *v.* placebo: p^b
Attention				
Digit span forward				
NAC ($n = 27$)	9.78 (2.52)	9.47 (3.06)	0.716	
Placebo ($n = 31$)	9.68 (2.36)	10.10 (1.83)	0.519	0.568
Working memory				
Digit span backwards				
NAC ($n = 27$)	5.78 (2.31)	7.06 (1.90)	0.033*	
Placebo ($n = 31$)	5.74 (2.31)	5.55 (2.46)	0.464	0.027*
Executive function				
TMT ratio – TMT B:TMT A[c]				
NAC ($n = 27$)	1.53 (1.01)	1.45 (0.89)	0.937	
Placebo ($n = 27$)	1.32 (0.90)	1.62 (0.81)	0.211	0.438
TMT B minus TMT A[c]				
NAC ($n = 27$)	37.59 (21.74)	35.24 (24.37)	0.638	
Placebo ($n = 27$)	36.11 (39.50)	38.21 (26.81)	0.589	0.739
Verbal fluency – total				
NAC ($n = 26$)	34.50 (12.44)	33.24 (11.70)	1.000	
Placebo ($n = 30$)	35.87 (15.13)	36.85 (18.75)	0.139	0.855

Data are given as mean (standard deviation).

NAC, *N*-acetyl cysteine; TMT, Trail Making Test.

[a] Differences between cognitive performance at baseline and end point based on Wilcoxon's test.

[b] Differences between the NAC and placebo groups in cognitive performance at end point based on the Mann–Whitney test. There was no association of cognitive performance with age, gender or antipsychotic medication.

[c] Time to complete the TMT (version A or B) is considered in these formulae.

* $p < 0.05$.

comes from preclinical studies where NAC supplementation has shown to improve induced changes in spatial (Otte *et al.* 2011) and working memory and to concurrently decrease oxidative stress damage in rats (Jayalakshmi *et al.* 2007). Moreover, working memory deficits in rodents have been shown to be restored with treatment with NAC in a dose-dependent manner (Choy *et al.* 2010). Impairments in working memory have been proposed as a shared endophenotype of genetic vulnerability to schizophrenia and bipolar disorder (Kim *et al.* 2015) and described as a neurocognitive predictor of transition to psychosis in individuals at ultra-high risk (Bang *et al.* 2015). We postulate that improvements in working memory, related to glutamatergic function (Driesen *et al.* 2013), may be further mediated by the effects NAC has on free radical-mediated neurotoxicity, inflammation, apoptotic pathways, mitochondrial dysfunction or neurogenesis in neuropsychiatric disorders (Morris & Berk, 2015; Reus *et al.* 2015). NAC reverses oxidative damage through the synthesis of GSH and directly scavenging free radicals (Dean *et al.* 2011). NAC also decreases pro-inflammatory cytokines, reverses multiple models of mitochondrial toxicity, reduces apoptosis and enhances neurogenesis, factors also pertinent to the cognitive dysfunction observed in psychotic disorders (Berk *et al.* 2008*c*; Shungu, 2012; Dodd *et al.* 2013). In this regard, our results are consistent with those studies in psychosis that have demonstrated an association between oxidative stress (Martinez-Cengotitabengoa *et al.* 2014) and peripheral inflammatory markers and cognitive impairment (Martinez-Cengotitabengoa *et al.* 2012), as targets of NAC (Berk *et al.* 2013). However, more research on specific markers for neurotoxicity associated with cognitive impairment in psychosis would be needed to shed light on this issue.

These results need to be interpreted in the context of the methodological features of the study. The current findings are seated in the context of two larger clincial trials and the primary outcomes were based on symptom changes, not cognition. As such, cognitive functioning was not completed by all participants, which restricts our findings and requires replication. A specifically designed cognitive trial aimed to assess the effects of NAC on cognition should be implemented using a comprehensive neuropsychological battery, including different working memory domains (verbal, object and spatial), and a detailed exploration of superior learning, memory, and executive function abilities. The heterogeneity of the sample due to the differences

in clinical diagnoses is another confounder. Although the literature provides evidence of a similar cognitive profile across psychotic disorders (Martinez-Aran & Vieta, 2015), particularly related to working memory (Kim *et al.* 2015), the characteristics of the sample (stablished/chronic schizophrenia or bipolar disorder with psychotic features), together with the small sample size, prevented us from exploring the differences between early stages or diagnostic subgroups in detail. As we have previously suggested, NAC may possibly be more effective in the later stages (Rapado-Castro *et al.* 2015). Although it is well established that cognitive dysfunction is one of the characteristics of psychosis, the evolution and course of the cognitive deficits are still controversial. Most evidence suggests that cognitive deficits in psychosis appear stable (Gelman *et al.* 2009). However, a number of studies have also provided evidence indicating that some aspects of cognitive function might deteriorate over time as the disorder evolves (Lopez-Jaramillo *et al.* 2010; Kozicky *et al.* 2014; Rosa *et al.* 2014). Examining the effect of NAC on cognition at the time of a person's first psychotic episode or among individuals at ultra-high risk for psychosis would be informative of the potential benefits of NAC reversing plausible deleterious effects of biochemical processes on cognitive function triggered by redox imbalance. Finally, clinical status can have an effect on cognition (Lopez-Jaramillo *et al.* 2010; Kozicky *et al.* 2014). Even though this plausible interaction has been investigated, PANSS data were available for schizophrenia participants only whereas MADRS/YMRS scores were available for the bipolar disorder subsample only, which might not be fully representative of a broader overall pattern of symptom changes in this psychotic disorders group.

Notwithstanding the aforementioned limitations, the current study suggests an avenue for further exploration in a field that is critically lacking effective treatments. Cognitive impairment is a poorly treated and highly relevant dimension of psychosis that goes beyond traditional diagnostic boundaries (Millan *et al.* 2012). As outlined above, both schizophrenia and bipolar disorder are associated with a similar pattern of neurocognitive deficits that persist in remission and may even worsen over time (Krabbendam *et al.* 2005; Daban *et al.* 2006; Bora *et al.* 2009; Bora & Pantelis, 2015; Pantelis *et al.* 2015). Working memory has been associated with the presence of depressive symptoms (Potvin *et al.* 2008), negative symptoms and functional outcome in psychosis (Gonzalez-Ortega *et al.* 2013; Frydecka *et al.* 2014). Further, our results are consistent with the primary outcomes of the main clinical trials, where adjunctive NAC treatment improved not only measures of negative symptoms in schizophrenia (Berk *et al.* 2008*a*; Bulut *et al.* 2009) and depressive symptoms in bipolar disorder (Berk *et al.* 2008*b*) but also functioning in both (Berk *et al.* 2008*a*, *b*) and MMN in schizophrenia (Lavoie *et al.* 2008). The direction of the relationship between clinical and congnitive change remains to be clarified, however.

In order to further determine the mechanism of action of NAC on cognitive function in psychotic disorders, future studies should include a biological component to determine levels of GSH, changes in glutamate pathways (i.e. cysteine/glutamate exchanger), inflammatory cytokines and other peripheral markers. Moreover, employing direct measurements of the brain would be of relevance, for example linking peripheral markers to advanced functional imaging or magnetic resonance spectroscopy to disentangle the proposed mechanism of NAC. GSH measurements were collected only in a subgroup of participants (Lavoie *et al.* 2008) and were unable to be explored in the context of cognitive function. No other biological data were obtained, which limits the interpretation of the plausible biological mechanisms that may be operating with adjunctive administration of NAC. Identifying the specific mechanisms underlying cognitive effects of NAC administration could lead to a new therapeutic target, thus supplementing psycho/therapeutic approaches that have been used to date (Gray & Roth, 2007; Vreeker *et al.* 2015). The results derived from this study have the potential to improve the core cognitive impairment of schizophrenia and psychotic bipolar disorder with a novel, safe and relatively inexpensive therapeutic approach. Data on the long-term/maintenance effects of the intervention are also necessary. These results suggest that NAC may be a promising agent to treat cognitive dysfunction in psychotic disorders.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291716002932

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Declaration of Interest

None.

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