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ORIGINAL ARTICLE

The relationship between negative symptom subdomains and cognition

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Background. Negative symptoms and cognitive deficits in schizophrenia are partially overlapping. However, the nature of the relationship between negative symptoms and cognition remains equivocal. Recent reviews have demonstrated the presence of two negative symptom subdomains, diminished emotional expression (DEE) and avolition. In view of this, we sought to clarify the relationship between negative symptoms and cognitive domains.

Method. A total of 687 participants with schizophrenia were assessed on measures of psychopathology and cognition. Three cognitive factors, namely executive function, fluency/memory and speed/vigilance were computed from the cognitive tests. Confirmatory factor analysis was utilized to examine if a one-factor or two-factor negative model was applicable to our sample. Subsequently, the relationships between negative symptoms and cognition were examined using structural equation modeling.

Results. Results demonstrated that the two-factor model fitted the data well. While negative symptoms were mildly to moderately associated with cognition, we found that DEE had unique associations with cognition compared to social avolition, contributing to the validity of the constructs and suggesting the possibility of common underlying substrates in negative symptoms and cognition.

Conclusions. Our study highlighted the need to classify DEE and social avolition separately as both are necessary in refining the complex relationship between negative symptoms and cognition as well as potentially guiding treatment and management of schizophrenia.

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Introduction

While implicated in functional recovery, evident at first-episode psychosis and predicting conversion among people at ultra-high risk of psychosis, neither cognitive impairment nor negative symptoms have shown substantial improvement following antipsychotic treatment (Harvey *et al.* 2006; Perlick *et al.* 2008; Fusar-Poli *et al.* 2013). Current treatments in ameliorating these symptoms of schizophrenia have been limited (Levkovitz *et al.* 2010). In light of their collective impact on outcome, the focus has been on clarifying the relationship between negative and cognitive symptom domains (Foussias & Remington, 2010). While some have suggested negative symptoms and cognition are related but separable domains, the underlying associations remain unclear (Harvey *et al.* 2006).

Currently, negative symptoms remain an unmet therapeutic need for schizophrenia (Kirkpatrick *et al.* 2006). Negative symptoms have been shown to be distinct from other aspects of schizophrenia and are not merely secondary to psychotic symptoms, depression and anxiety (Keefe *et al.* 1992; Mueser *et al.* 1994; Peralta & Cuesta, 1995; Blanchard & Cohen, 2006; Strauss *et al.* 2013). Prior reports asserted that negative symptoms do not represent a unitary construct but rather show evidence for two distinct factors: 'diminished emotional expression' (DEE), consisting of alogia and blunted affect, and 'avolition', including apathy, amotivation, asociality and anhedonia (Keefe *et al.* 1992; Blanchard & Cohen, 2006; Kimhy *et al.* 2006; Nakaya & Ohmori, 2008; Horan *et al.* 2011; Kirkpatrick *et al.* 2011; Strauss *et al.* 2012; Liemburg *et al.* 2013; Fervaha *et al.* 2014*a*), which has shown to be useful in identifying distinct subgroups of patients

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(Strauss *et al.* 2013). There have been debates on whether to conceptualize negative symptoms as a whole or to delineate them into subdomains (Blanchard & Cohen, 2006; Strauss *et al.* 2012). Additionally, the diagnostic criteria in DSM-5 identifies these two negative symptom subdomains but still advocate considering negative symptoms as a whole (Messinger *et al.* 2011; Tandon *et al.* 2013).

As a whole, negative symptoms of schizophrenia have been consistently found to correlate with neuropsychological performance, with modest associations with executive function, verbal fluency, verbal memory and learning, attention/vigilance, working memory and processing speed (Addington, 2000; Nieuwenstein *et al.* 2001; Harvey *et al.* 2006; Dibben *et al.* 2009; Dominguez *et al.* 2009). Furthermore, DEE has been found to be associated with verbal fluency, memory, symbol coding and executive function (Cohen *et al.* 2013; Chang *et al.* 2014) while avolition was related to executive function, working memory, verbal fluency, visual information, verbal learning and memory and performance IQ (Roth *et al.* 2004; Faerden *et al.* 2009; Konstantakopoulos *et al.* 2011). While DEE and avolition appear to share overlapping cognitive domains, some studies found that DEE tended to be more strongly associated with cognition than social avolition (SA) (Liemburg *et al.* 2013; Hartmann-Riemer *et al.* 2015) while another study demonstrated no significant associations between negative symptom subdomains and cognition (Kring *et al.* 2013). Moreover, changes in negative symptoms do not predict changes in cognition, suggesting that negative symptoms do not directly cause cognitive impairment or vice versa (Bell & Mishara, 2006). Hence, the relationship between negative symptoms, particularly in subdomains, and cognition remain equivocal.

The Positive and Negative Syndrome Scale (PANSS) is among the most ubiquitous for psychopathology assessment in schizophrenia and includes negative symptoms as one of the domains measured (Kay *et al.* 1987). The negative symptom factor includes items from both the negative and general psychopathology subscales and can be separated into DEE and SA (Wallwork *et al.* 2012; Jiang *et al.* 2013), allowing for the examination of the validity of these two constructs.

The current study provides a unique opportunity to deconstruct negative symptoms, and further examine if the cognitive domains might be differentially associated with DEE and SA. In a previous study, our group reported on a model that included speed/vigilance, fluency/memory and executive function as the three main domains of cognitive impairment in schizophrenia (Lam *et al.* 2014). Contrary to other studies that examined individual cognitive tests, the use of these empirically derived cognitive domains in this study reduces the methodological variance between cognitive tests and allows us to obtain a clearer picture of the relationship between negative symptoms and cognitive domains. Hence, the aims of the present study were (i) to examine if a one-factor or two-factor negative symptom model fitted our data; and (ii) to identify the pattern of associations between negative symptoms and the three domains of cognition. We hypothesized that a two-factor negative symptom subdomain model would be valid in our sample and that DEE and SA would have mild to moderate associations with different domains of cognition, with DEE having consistently higher associations.

Method

Study participants

A total of 707 participants with schizophrenia were recruited from 2008 to 2011. Participants were recruited from outpatient clinics and inpatient wards from the Institute of Mental Health in Singapore, and from various community care centers across the country. All participants were ethnic Chinese, between the ages of 21 and 55 years, had at least 6 years of primary school education and could converse in English. A diagnosis of schizophrenia was ascertained using the Structured Clinical Interview for DSM-IV-TR Axis I Disorder, Patient Edition (First *et al.* 2015). Participants with history of mental retardation, substance abuse, neurological disease, head injury or color blindness were excluded from the study. The study was approved by the National Healthcare Group Domain Specific Review Board (DSRB). Written informed consent was obtained from all participants in the study.

Clinical measures

The severity of psychopathology was assessed using the PANSS which consists of 30 items across three dimensions: positive (seven items), negative (seven items), and general psychopathology (16 items). We utilized the negative factor items identified in Jiang *et al.*'s (2013) model as it had been previously validated in our local population. In Jiang *et al.*'s (2013) model, eight negative items were identified and these were separated into two factors based on past analyses (Liemburg *et al.* 2013; Fervaha *et al.* 2014*a*). The first factor corresponds to DEE and consists of blunted affect (N1), poor rapport (N3), lack of spontaneity and flow of conversation (N6), motor retardation (G7) and disturbance of volition (G13). The second factor corresponds to SA and consists of emotional withdrawal (N2), passive/apathetic social withdrawal (N4) and active social avoidance (G16).

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Neurocognitive measures

Cognitive performance was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe *et al.* 2004) consisting of Verbal Memory, Digit Sequencing, Token Motor, Semantic Fluency, Symbol Coding and Tower of London tasks; Benton Judgment of Line Orientation (JLO; Benton *et al.* 1983); Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning (Wechsler, 1999); Continuous Performance Test-Identical Pairs (CPT-IP; Cornblatt *et al.* 1988); and Wisconsin Card Sorting Test (Heaton *et al.* 1993). Using the age- and gender-adjusted scores from these tests, we previously published a cognitive model comprising three domains, namely executive function, fluency/memory and speed/vigilance (Lam *et al.* 2014). The executive function domain consisted of JLO and WASI Matrix Reasoning items. The fluency/memory domain consisted of BACS Semantic Fluency and Verbal Memory items. The speed/vigilance domain consisted of CPT-IP, BACS Token Motor and Symbol Coding items. Cognitive scores for these three domains were generated from the model using regression.

Statistical analyses

Using confirmatory factor analysis (CFA), we examined whether a one-factor or two-factor negative symptom model would fit our data. Following which, we examined the relationship between negative symptoms and cognition using structural equation modeling where we regressed cognition on negative symptoms (model 1). If the two-factor negative symptom model fitted better, both negative symptom factors will be considered in tandem to determine the unique contributions of each factor. Given that duration of illness and antipsychotic dosage might influence the relationship between negative symptoms and cognition (Dominguez *et al.* 2009; Bagney *et al.* 2013), we then examined model 1 while controlling for these variables (model 2).

Similar to our previous PANSS CFA (Jiang *et al.* 2013), all PANSS items were treated as ordinal data. A good model fit was determined if the model demonstrated a Comparative Fit Index (CFI) >0.950, Tucker–Lewis Index (TLI) >0.960, Root Mean Square of Approximation (RMSEA) <0.080 and/or Weighted Root Mean Square Residual (WRMR) <0.900 (Schreiber *et al.* 2006). Data was analyzed using the lavaan package (Rosseel, 2012) using R software v. 3.0.3 (R Core Team, 2014).

Ethical standards

The authors assert that 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

Demographics

Of the 707 participants, 20 (2.8%) had missing scores on one or more of the nine selected PANSS items and were excluded from this study. The demographics of the remaining 687 participants are presented in Table 1.

Negative symptom subdomains model

First, we examined whether the one-factor or two-factor model would fit our data. The two-factor model [CFI = 0.978, TLI = 0.967, RMSEA = 0.077, 90% confidence interval (CI) 0.062–0.093, and WRMR = 0.928] fitted the data better than the one-factor model (CFI = 0.915, TLI = 0.880, RMSEA = 0.147, 90% CI 0.133–0.162, and WRMR = 1.782). All indicators had significant loadings more than 0.40 (all $p < 0.001$, Figs 1 and 2). Additionally, in the two-factor model, DEE and SA were moderately correlated.

Relationship between negative symptoms and cognition

Subsequently, the relationships between the negative symptom subdomains and the cognitive domains were examined using two models. In all models, the cognitive domains were highly correlated with each other (Tables 2 and 3). In model 1 (Table 2), we examined the relationship between DEE and SA on the three cognitive domains through the regression of the three cognitive domains on DEE and SA. The model demonstrated good fit (CFI = 0.964, TLI = 0.946, RMSEA = 0.071, 90% CI 0.060–0.082, and WRMR = 1.057). DEE had significant associations with cognition but not SA. The variance accounted for executive function, fluency/memory and speed/vigilance by negative symptoms was 7.5%, 16.3% and 20.1%, respectively.

In model 2 (Table 3), we investigated the relationship between negative symptoms subdomains on cognition with duration of illness, daily dosage of antipsychotic medication in chlorpromazine equivalents, age of onset of illness and PANSS positive score as covariates. The models demonstrated good fit (CFI = 0.961, TLI = 0.944, RMSEA = 0.057, 90% CI 0.049–0.065, and WRMR = 1.237). A similar pattern was observed where DEE had significant associations with cognition but not SA. The variance accounted for executive function, fluency/memory and speed/vigilance was 11.7%, 19.3% and 23.8%, respectively.

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Table 1. *Demographics of the study sample*

	n	(%)
Males	363	52.8
Medications (%)		
Anticholinergics	361	42.5
Antidepressants	213	31.0
Mood stabilizers	131	19.1
Benzodiazepines	150	21.8
	Mean	S.D.
Age (years)	39.29	9.65
Total years of education	11.83	3.07
Duration of illness (years)	15.69	9.96
Age of onset (years)	23.68	7.18
Daily dosage of antipsychotic medication in chlorpromazine equivalents (mg)	572.15	780.56
PANSS Total score	50.25	14.49
PANSS Positive score	12.33	5.27
PANSS Negative score	12.91	5.61
PANSS General psychopathology score	25.02	7.27
Executive function score[a]	−0.36	0.51
Fluency/memory score[a]	−0.52	0.55
Speed/vigilance score[a]	−0.49	0.45

PANSS, Positive and Negative Syndrome Scale.
[a] Z scores are reported.

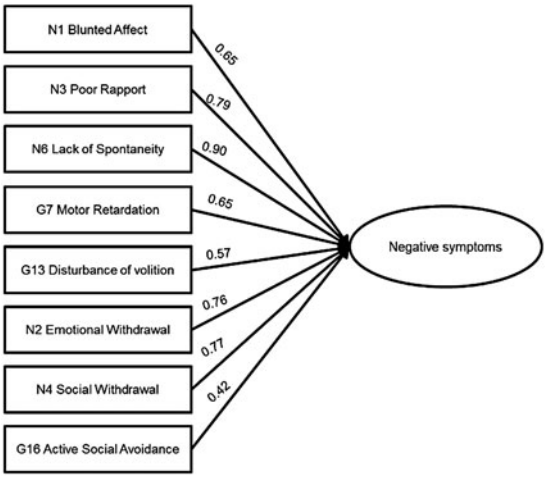

Fig. 1. This model demonstrates the results from the confirmatory factor analysis of the one-factor negative symptom model. The standardized regression coefficients between the variables are shown above each path. All paths are significant ($p < 0.001$).

Discussion

This study attempted to clarify the associations between negative symptoms and cognitive domains. First, our study validated the two widely accepted subdomains of negative symptoms, namely DEE and SA (Keefe *et al.* 1992; Blanchard & Cohen, 2006; Kimhy

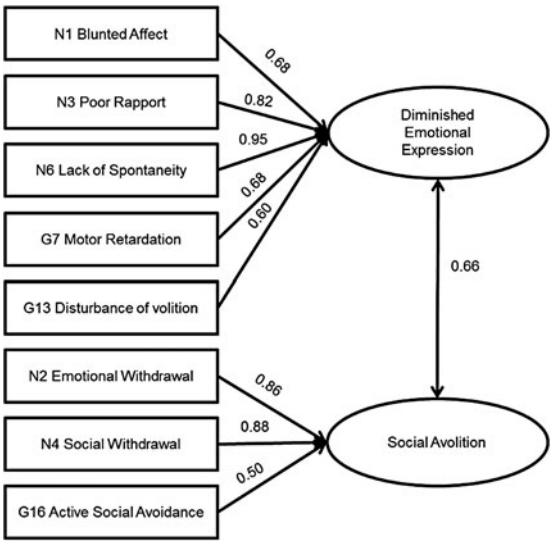

Fig. 2. This model demonstrates the results from the confirmatory factor analysis of diminished emotional expression and social avolition. The standardized regression coefficients between the variables are shown above each path. All paths are significant ($p < 0.001$).

et al. 2006; Nakaya & Ohmori, 2008; Horan *et al.* 2011; Kirkpatrick *et al.* 2011; Strauss *et al.* 2012; Liemburg *et al.* 2013; Fervaha *et al.* 2014*a*). Previous studies that examined negative symptoms and cognition found small to moderate associations with executive function, verbal fluency, verbal memory, attention, vigilance, visual memory (Addington, 2000; Nieuwenstein *et al.* 2001; Roth *et al.* 2004; Harvey *et al.* 2006; Keefe *et al.* 2006; Dibben *et al.* 2009; Dominguez *et al.* 2009; Faerden *et al.* 2009; Konstantakopoulos *et al.* 2011; Chang *et al.* 2014; Fervaha *et al.* 2014*b*; Millan *et al.* 2014; Hartmann-Riemer *et al.* 2015). Our study replicated and extended these findings by demonstrating that negative symptoms were consistently related to cognitive domains with stronger associations for speed/vigilance and fluency/memory compared to executive function. Additionally, by separating negative symptoms into DEE and SA, we found that these negative symptom subdomains had differential associations on cognition where DEE also showed unique associations with cognition. Although the impact of duration of illness, antipsychotic medication, age of onset of illness and level of positive symptoms were examined, they did not affect the relationship between negative symptoms and cognition, as was found in recent meta-analyses (Nieuwenstein *et al.* 2001; Dibben *et al.* 2009; Dominguez *et al.* 2009).

Our study demonstrated that the two-factor negative symptoms model fitted the data well and DEE and SA were moderately correlated with one another. While some have argued that the use of a one-factor model

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Table 2. *The relationship between diminished emotional expression and avolition on cognition*

Paths	Unstandardized estimate	Unstandardized standard error	Standardized estimate	*Z*	*p*
DEE → N1 Blunted affect	1.000		0.665		
DEE → N3 Poor rapport	1.203	0.063	0.800	19.220	<0.001
DEE → N6 Lack of spontaneity	1.419	0.067	0.944	21.045	<0.001
DEE → G7 Motor retardation	1.090	0.067	0.725	16.375	<0.001
DEE → G13 Disturbance of volition	0.918	0.067	0.611	13.796	<0.001
SA → N2 Emotional withdrawal	1.000		0.871		
SA → N4 Social withdrawal	1.002	0.053	0.873	18.893	<0.001
SA → G16 Active social avoidance	0.550	0.053	0.479	9.967	<0.001
DEE → speed/vigilance	−0.332	0.047	−0.490	−7.037	<0.001
DEE → fluency/memory	−0.334	0.055	−0.403	−6.053	<0.001
DEE → executive function	−0.217	0.050	−0.281	−4.329	<0.001
SA → speed/vigilance	0.035	0.037	0.068	−0.952	0.341
SA → fluency/memory	−0.001	0.044	−0.001	−0.017	0.987
SA → executive function	0.007	0.041	0.011	0.159	0.874
DEE ↔ SA	0.381	0.029	0.658	12.993	<0.001
Executive function ↔ fluency/memory	0.215	0.013	0.865	16.188	<0.001
Executive function ↔ speed/vigilance	0.158	0.010	0.798	15.503	<0.001
Fluency/memory ↔ speed/vigilance	0.185	0.011	0.909	16.194	<0.001

DEE, Diminished emotional expression; SA, social avolition.

is more parsimonious and have advocated for it (Blanchard & Cohen, 2006; Strauss *et al.* 2012), our study demonstrated the utility of separating negative symptoms into its corresponding subdomains as DEE had differential associations to cognition compared to SA, contributing to the validity of these constructs. Similar to prior reports (Liemburg *et al.* 2013; Strauss *et al.* 2013; Rocca *et al.* 2014), we further emphasize the importance of differentiating the DEE and SA constructs.

To further refine the relationship between negative and cognitive variables, we also examined the unique associations between the negative symptom subdomains and three domains of cognition. Hartmann-Riemer *et al.* (2015) found an association between DEE and verbal learning and memory, mental planning and composite cognitive score and failed to find any association between avolition and cognition. Likewise, we replicated the differential effects of DEE with cognition but had a different pattern; while DEE was significantly associated with all three domains, it had the highest association with speed/vigilance.

Harvey *et al.* (2006) proposed that negative symptoms and cognition are separate yet dependent domains with shared concepts, etiologies, outcomes and measurements. Given that impairments in digit symbol coding are prominent in early psychosis and one of the most impaired cognitive domains in schizophrenia (Dickinson *et al.* 2007), the high correlation between DEE and speed/vigilance in our sample could be reflective of underlying substrates that are common in the early phase of the disorder but longitudinal data in early episode schizophrenia is needed to confirm this. Possible common substrates include the overlaps in neural bases, level of cognitive resource and functional status. DEE is associated with impairments in ventromedial and dorsolateral prefrontal cortex (PFC), anterior cingulate gyrus, temporal cortex, amygdala, dorsal striatum and hippocampus (Gruber *et al.* 2014; Millan *et al.* 2014). Though further work is necessary to confirm candidate structures associated with DEE, apparent overlapping structures including PFC, hippocampus and left superior temporal gyrus are also associated with processing speed (Sanfilipo *et al.* 2002). In contrast, avolition has been linked to abnormalities in the interaction between PFC and the ventral and dorsal striatum, mainly in the nucleus accumbens and caudate, which are more associated with reward and anticipatory mechanisms (Gruber *et al.* 2014; Millan *et al.* 2014). Hence, differing underlying neural substrates could be responsible for the differential associations between negative symptom domains and speed/vigilance and more research will be needed.

Cognitive resource limitation theory also posited that the lower level of cognition in schizophrenia decreases the amount of cognitive resources available for expression of emotions, leading to higher levels of diminished expression (Cohen *et al.* 2012). Studies have also found that functional status had stronger associations with avolition compared to DEE

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Table 3. *The relationship between cognition, DEE and avolition, controlling for duration of illness, daily dosage of antipsychotic medications in chlorpromazine equivalents, age of onset of illness and PANSS total score*

Paths	Unstandardized estimate	Unstandardized standard error	Standardized estimate	*Z*	*p*
DEE → N1 Blunted affect	1.000		0.668		
DEE → N3 Poor rapport	1.222	0.063	0.816	19.516	<0.001
DEE → N6 Lack of spontaneity	1.414	0.069	0.944	20.606	<0.001
DEE → G7 Motor retardation	1.067	0.067	0.712	15.863	<0.001
DEE → G13 Disturbance of volition	0.885	0.068	0.591	13.084	<0.001
SA → N2 Emotional withdrawal	1.000		0.864		
SA → N4 Social withdrawal	1.011	0.050	0.874	20.170	<0.001
SA → G16 Active social avoidance	0.551	0.057	0.476	9.661	<0.001
DEE → speed/vigilance	−0.304	0.047	−0.451	−6.529	<0.001
DEE → fluency/memory	−0.301	0.055	−0.365	−5.426	<0.001
DEE → executive function	−0.194	0.050	−0.252	−3.868	<0.001
SA → speed/vigilance	0.034	0.037	0.065	0.919	0.358
SA → fluency/memory	−0.002	0.045	−0.003	−0.040	0.968
SA → executive function	0.011	0.042	0.019	0.273	0.785
CPZ → speed/vigilance	<−0.001	<0.001	−0.173	−4.949	<0.001
CPZ → fluency/memory	<−0.001	<0.001	−0.164	−4.116	<0.001
CPZ → executive function	<−0.001	<0.001	−0.170	−3.953	<0.001
Illness duration → speed/vigilance	−0.006	0.002	−0.128	−2.947	0.003
Illness duration → fluency/memory	−0.006	0.002	−0.102	−2.313	0.021
Illness duration → executive function	−0.004	0.002	−0.084	−1.887	0.059
Age of onset → speed/vigilance	0.003	0.002	0.055	1.467	0.142
Age of onset → fluency/memory	0.005	0.003	0.062	1.578	0.115
Age of onset → executive function	0.005	0.003	0.070	1.712	0.087
PANSS positive score → speed/vigilance	−0.002	0.003	−0.026	−0.694	0.488
PANSS positive score → fluency/memory	−0.002	0.004	−0.023	−0.590	0.555
PANSS positive score → executive function	−0.004	0.004	−0.042	−1.057	0.291
DEE ↔ SA	0.388	0.029	0.672	13.356	<0.001
Executive function ↔ fluency/memory	0.205	0.013	0.859	16.075	<0.001
Executive function ↔ speed/vigilance	0.149	0.010	0.787	15.471	<0.001
Fluency/memory ↔ speed/vigilance	0.176	0.011	0.906	16.225	<0.001

DEE, Diminished emotional expression; PANSS, Positive and Negative Syndrome Scale; SA, social avolition; CPZ, daily dosage of antipsychotic medications in chlorpromazine equivalents in mg.

(Foussias & Remington, 2010; Fervaha *et al.* 2014*a*; Foussias *et al.* 2014; Rocca *et al.* 2014). Hence, level of cognitive resources and functional status might be important extraneous variables to consider in the relationship between negative symptoms and cognition. Another possible explanation could be that DEE is more psychometrically stable as it consists of two more PANSS items and its indicators had higher loadings compared to SA, resulting in stronger associations with cognition. Therefore, the results seem to support the idea that both negative symptom subdomains and cognition are separate but related domains.

Clinically, the differential relationships of the negative symptom subdomains and cognition are promising and could inform prognosis and treatment planning and development. Our results offer a preliminary view that negative symptom subdomains and cognition are important features that could be capitalized upon to further elucidate biological substrates that underlie the illness and further research is needed to uncover these substrates. A further application is to utilize negative symptom domains to reduce heterogeneity and understand the variation within schizophrenia via subtyping approaches (Blanchard & Cohen, 2006; Strauss *et al.* 2013). However, future studies would be needed to further refine these subtyping strategies.

Our study furthers the literature as we included a large sample and used cognitive domains that were derived through methodological reduction and the pooling of cognitive tests. Nonetheless, our study had several methodological limitations. First, the

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study utilized PANSS which does not assess other negative symptoms like anhedonia or non-SA, limiting the generalizability of our findings which future research could possibly address. The subdomains have also been criticized where DEE tended to include items that are observed while SA tended to include items that are questioned (Blanchard & Cohen, 2006; Harvey *et al.* 2006). Furthermore, PANSS G13 Disturbance of Volition might seem appropriate to be included in the SA factor but was included in the DEE factor instead. This item is rated based on observations of how the participant is able to initiate, sustain and control one's behavior in terms of actions and speech during the interview. Hence, it could be more reflective of alogia and blunted affect and was retained in the DEE factor. Therefore, the method of assessment reflects the nature of the items and limitations in the scope of the PANSS negative items. Additionally, potential confounders like general intelligence, social cognition and functional outcomes were also not measured in our study and might be of interest (Gold *et al.* 1999; Dibben *et al.* 2009). Last, this being a cross-sectional study, causality cannot be determined. Hence, we were unable to conclude on the independence of negative and cognitive domains as others have (Harvey *et al.* 2006; Foussias & Remington, 2010; Chang *et al.* 2014).

In conclusion, our study highlights the importance of considering both diminished emotional expression and SA separately in examining the relationship between negative symptoms and cognition, as valuable information related to the individual subdomains might be masked when considered as a whole. Our findings provide a platform for future research looking at refining the complex relationship between negative symptoms and different aspects of cognition, especially in elucidating possible common substrates, and have potential clinical implications for the treatment and management of negative symptoms and cognition in schizophrenia.

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Declaration of Interest

Richard Keefe has received investigator-initiated research funding support from the Department of Veterans Affairs, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Hygiene Inc., and the Singapore National Medical Research Council. He has received honoraria, served as a consultant, or advisory board member for Abbott, Abbvie, Akebia, Amgen, Astellas, Asubio, AviNeuro/ChemRar, Biogen Idec, BiolineRx, Biomarin, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, EnVivo, FORUM, GW Pharmaceuticals, Helicon, Lundbeck, Merck, Minerva Neurosciences Inc., Mitsubishi, Novartis, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, Targacept. He receives royalties from the BACS testing battery, the MATRICS Battery (BACS Symbol Coding) and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT), and is a shareholder in NeuroCog Trials and Sengenix Inc. Jimmy Lee has received an honorarium and served as a consultant for Roche in the past 3 years. All other authors declare that there are no conflicts of interest in relation to the subject of this study.

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