The Relationship between Negative Symptoms and MATRICS Neurocognitive Domains : A Meta-Analysis and Systematic Review

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Abstract

Background: Negative symptoms (NS) are a core symptom domain in schizophrenia spectrum disorders and are associated with poorer social and vocational functioning, and with increased likelihood and durations of hospital admission. NS are not well understood, limiting available interventions. However, numerous studies have reported associations between neurocognitive domains and NS severity. Thus, one promising area in understanding NS is in relation to neurocognition. Currently, the specificity of the relationship between NS and neurocognition is unknown, meaning that there is no consensus regarding which neurocognitive domain is most strongly associated with NS. There is a need to systematically examine the relationship between NS and various neurocognitive domains within study samples.

Methods: A systematic search of Ovid PsycINFO, Ovid MEDLINE and Web of Science was performed for articles published since 2004 (year of MATRICS Consensus publication). Inclusion criteria were: 1) individuals with schizophrenia spectrum disorders, first episode psychosis or clinical high risk 2) assessed all six MATRICS neurocognitive domains (processing speed, attention, working memory, verbal learning & memory, visual learning & memory, reasoning & problem solving), 3) reported correlations between all six MATRICS neurocognitive domains and global NS. A three-level random effects hierarchical meta-analysis was performed to assess the relationship between NS (global, expressive, and experiential dimensions) and the six MATRICS neurocognitive domains.

Results: 21 studies were included in the review (n= 3,619). All MATRICS neurocognitive domains had small significant correlations with global NS (r= -0.16 to -0.20,

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p<.0001). This relationship was significantly moderated by diagnosis and the moderating effect of sex/ gender trended on significance. Analysis of a subset of the studies revealed that MATRICS neurocognitive domains also had small significant correlations with the two NS dimensions, expressive and experiential. Correlations were stronger with the expressive NS dimension.

Conclusions: This review is novel in assessing the relationship between multiple neurocognitive domains and NS within the same sample, by synthesizing close to two decades of research. Our results suggest that there is a non-specific relationship between neurocognition and NS, and that expressive NS may have a stronger relationship with neurocognitive functioning- based on the MATRICS classification of neurocognition and the neurocognitive assessments used in the included studies. This has implications on our understanding of NS and neurocognition, as well as their treatments. As we gain better understanding of the directionality of the NS-cognition relationship, it could suggest that NS, particularly in the expressive domain, could be improved by targeting cognition globally or that neurocognitive treatments could be more effective if NS are addressed first. Further implications of these results are discussed.

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Background

Negative symptoms (NS) represent a core symptom domain in schizophrenia and related psychotic disorders. NS refer to marked reductions in goal-directed behavior and expression. They are consistently associated with poorer functioning, increased likelihood and duration of hospital admission, and increased likelihood of re-admission following discharge (Patel et al., 2015; Rabinowitz et al., 2012). NS have a stronger relation with functioning than positive symptoms in schizophrenia (Rabinowitz et al., 2012) and are related to vocational outcomes, such as ability to gain employment (Evans et al., 2004). NS include two dimensions which impact behaviours (i.e., experiential dimension) and expressivity (i.e. expressive dimension). The experiential dimension includes avolition (lack of motivation), anhedonia (lack of pleasure) and asociality (lack of motivation to engage in social activities), and the expressive dimension includes blunted affect (diminished facial, vocal and gesture expression) and alogia (poverty of speech) (Kirkpatrick & Fischer, 2006; Messinger et al., 2011).

NS have been linked to various biological factors (e.g. gamma-aminobutyric acid transporter gene, glutamatergic genes, white matter reductions in frontal lobes, structural abnormalities in temporal lobes), psychological processes (e.g. self-stigma) and cognitive factors (neurocognition, social cognition, metacognition) (Chan et al., 2019; Faith et al., 2020; Lyne et al., 2018; McLeod et al., 2014; Pelletier-Baldelli & Holt, 2020). Despite the past few decades of research, factors relating to NS are still not well understood (Correll & Schooler, 2020; Harvey et al., 2006). Current evidence-based interventions (e.g. cognitive-behavioural, metacognitive therapy, cognitive remediation therapies), only have small to moderate effectiveness on NS

(Aleman et al., 2017; Penney et al., 2022; Sitko et al., 2020; Vita et al., 2021). However, one promising approach in understanding NS may be in elucidating its relationship with neurocognition, as both represent trait-like entities and numerous studies examining associations between cognitive measures and NS have revealed significant associations (de Gracia Dominguez et al., 2009; Hovington & Lepage, 2012; Lepage et al., 2021; Pillny et al., 2022).

Among neurocognitive domains, those identified from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus are of particular interest as they have been identified as those most impaired in schizophrenia but amenable to treatment. The six MATRICS neurocognitive domains include processing speed, attention, working memory, verbal learning and memory, visual learning and memory, and reasoning and problem solving. All MATRICS neurocognitive domains have been previously associated with NS.

MATRICS Neurocognitive Domains and Negative Symptoms

Verbal and non-verbal memory domains have been robustly associated with NS. Memory has been associated with several steps of motivated behaviour including internally representing and maintaining goals, representing the values of outcomes and plans (e.g. by recalling past rewarding stimuli (Bodapati et al., 2019)) and translating emotion to behaviour (Gold et al., 2008; Heerey & Gold, 2007). Recall of past rewarding stimuli has been specifically linked to visual memory (Bodapati et al., 2019). Deficits in speech production (alogia), have also been hypothesized to be due to problems maintaining enough information in working memory (Becker et al., 2012). In addition, associations between verbal memory and global NS have been found in adolescents with early onset psychosis (Mørch-Johnsen et al., 2022) and first episode psychosis

patients with primary (Hovington et al., 2013) and persistent NS (Lepage et al., 2021). The association between anhedonia and visual memory has been demonstrated both in schizophrenia (Bodapati et al., 2019; Szendi et al., 2006) and first episode psychosis (Faerden et al., 2009). Finally, memory has generally been suggested to play a role in emotion processing, and it's deficits have been linked to blunted affect (Gur et al., 2002; Mothersill et al., 2016).

Reasoning and problem solving, also known as executive functioning, encompasses higher-level neurocognitive processes involving decision making and additional complex strategic planning. This domain has been associated with NS, particularly avolition which is also known as apathy. The link between avolition and neurocognition has been demonstrated in schizophrenia (Konstantakopoulos et al., 2011; Roth et al., 2004) and first episode psychosis (Faerden et al., 2009). The link between executive functioning and avolition has also been observed in other neurodegenerative disorders, including MCI dementia (Drijgers et al., 2011) and Parkinson's disease (Meyer et al., 2015). This relationship has been hypothesized to be due to the overlapping brain areas (prefrontal areas and frontal-subcortical circuitry) implicated in avolition and executive functioning (Faerden et al., 2009). Attention has also been associated with NS, specifically anhedonia, as those with schizophrenia have been observed to have attentional biases towards threatening or negative stimuli and reduced attention toward positive stimuli (Navalón et al., 2021; Strauss et al., 2008). Finally, processing speed has also been linked to NS in schizophrenia (McDowd et al., 2011) and severe mental illnesses with psychotic features (Luther et al., 2020). However, this association was not found in another study (Mørch-Johnsen et al., 2022).

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Studies have also found those with greater NS severity demonstrated impaired brain activity during cognitively demanding tasks. Liemburg and colleagues (2015) observed impaired functioning in parietal and thalamic regions during an executive functioning task in schizophrenia samples with greater avolition severity. Ehrlich and colleagues (2012) also found that higher NS were associated with reduced dorsal striatal activation when their participants with schizophrenia completed a working memory task. Similar biological mechanisms (e.g. dopamine dysregulation, prefrontal cortical thickness, hippocampal volume) are also hypothesized to underlie both cognitive deficits and NS (Alkan et al., 2021; Duan et al., 2021; Tronchin et al., 2020). For instance, dopamine is implicated in modulating the functional parameters of working memory and in processes of effortful cognitive action (Westbrook & Braver, 2016).

Present study

In sum, there is a consistent association between neurocognitive functioning (in multiple neurocognitive domains) and NS. However, there is limited knowledge on which neurocognitive domain is most strongly associated with NS, which would be important in understanding shared mechanisms between NS and neurocognition and with implications on the treatment development. Considering that multiple neurocognitive domains are significantly impaired in schizophrenia spectrum disorders and that each of these domains have been significantly associated NS, there is a need to systematically examine the association between MATRICS neurocognitive domains and NS within samples. Previous reviews have explored the relationship between specific neurocognitive domains, like episodic memory, and found significant moderate negative associations with NS (Pillny et al., 2022). Studies examining multiple cognitive

domains simultaneously have found significant correlations with certain neurocognitive domains, but not others (Hovington et al., 2013; Lepage et al., 2021). However, the generalizability of these studies is limited due to relatively small sample sizes.

A review conducted in 2009 assessed the relationship between nine neurocognitive domains, which included all MATRICS domains, and their association with NS (de Gracia Dominguez et al., 2009). Authors observed small significant associations between most neurocognitive domains and NS. They identified verbal fluency as the neurocognitive domain most strongly correlated with NS, relative to the other neurocognitive domains ($\hat{\mu}_p$= -0.291). However, recent studies have suggested that assessments of verbal fluency and alogia tap into the same conceptual construct (Fervaha et al., 2016; Marder & Galderisi, 2017). Five of the six MATRICS neurocognitive domains that were assessed in that same review had significant relationships with NS. These MATRICS neurocognitive domains included reasoning and problem solving ($\hat{\mu}_p$= -0.14), speed of processing ($\hat{\mu}_p$= -0.167), attention/ vigilance ($\hat{\mu}_p$= -0.134), verbal learning and memory ($\hat{\mu}_p$= -0.214), and visual learning and memory ($\hat{\mu}_p$= -0.126). The relationship between NS and verbal working memory was not significant in the review. However, a limitation of the review conducted by de Gracia Dominguez and colleagues (2009) is that results cannot be used to interpret which neurocognitive domain is most strongly associated with NS. This is because the number of studies for each cognitive domains varied (e.g. 10 studies assessing verbal working memory-NS relationship compared to 23 studies assessing speed of processing-NS relationship), which could bias the results of the study.

Thus, to address such limitations, we sought to examine and compare the relationship between MATRICS neurocognitive domains (processing speed, attention, working memory,

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verbal learning and memory, visual learning and memory, reasoning and problem solving) and NS (global, expressive dimension, experiential dimension) from studies that assessed all MATRICS neurocognitive domains. This is the first review, to our knowledge, that has assessed the correlation of all six MATRICS neurocognitive domains within the same sample, allowing us to robustly compare the relationship between each neurocognitive domain and NS. Understanding which cognitive domain is most strongly associated with NS would allow us to better appreciate the relationship between neurocognition and NS, and lead to potential therapeutic applications. Limiting the review to examination of studies which assess all MATRICS neurocognitive domains will allow us to examine, for the first time, the selectivity and specificity of the association between NS and neurocognition (as assessed by the MATRICS). In addition, we seek to build on work from previous studies and reviews by considering the role of potential moderating factors (demographic, illness severity, study related factors) in the relationship. We are also extending current work on neurocognition and NS by conducting analyses on the relationship between the MATRICS neurocognitive domains and NS two-factor dimensions (expressive, experiential).

Methods

Data Sources and Literature Search

This review was registered on PROSPERO (CRD42022328828) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed (Page et al., 2021). Ovid PsycINFO, Ovid MEDLINE and Web of Science were searched for articles from Jan 1, 2004 (year of MATRICS Consensus release) through March 27, 2023. The

initial search was done from Jan 1, 2004 to May 11, 2022. Additional search in Web of Science was done for articles published after May 11, 2022.

Inclusion and Exclusion Criteria

Studies were included if they were written in English; included participants with schizophrenia spectrum disorders or first episode psychosis according to the DSM-III to V or to the ICD 9 or 10 ; assessed all six neurocognitive domains of interest using a single battery comprised of valid neuropsychological tests; assessed NS globally (all five symptoms); and reported a correlation between all six neurocognitive domains and global NS. See Supplementary Note for more information regarding diagnoses included in the schizophrenia spectrum. For studies involving samples of people with first episode psychosis or clinical high-risk for developing a schizophrenia spectrum disorder, only studies including data specific to the group of participants who transitioned to schizophrenia spectrum disorders were included. For studies including clinical high-risk samples, only data following an individual's transition were extracted. Authors were contacted for additional information if the relationship between MATRICS neurocognitive domains and NS was reported, but all relevant correlations were not publicly available. Studies were excluded if they were book chapters, meta-analyses, reviews, conference abstracts, conference proceedings (published records of conference), dissertations and commentaries.

Data Extraction

Four evaluators (CA, JR, HC, LL) conducted an initial screening of the studies based on the title and abstract using the CADIMA software version 2.2.3 (https://www.cadima.info/index.php) and

a second screening of the full-text in Covidence (https://www.covidence.org/). In the event of discrepancies, the evaluators met to discuss study inclusion. Relevant information from the included studies were then extracted by CA in an Excel template, in which 50% of the extracted papers were verified for accuracy by an external evaluator (DP, JR).

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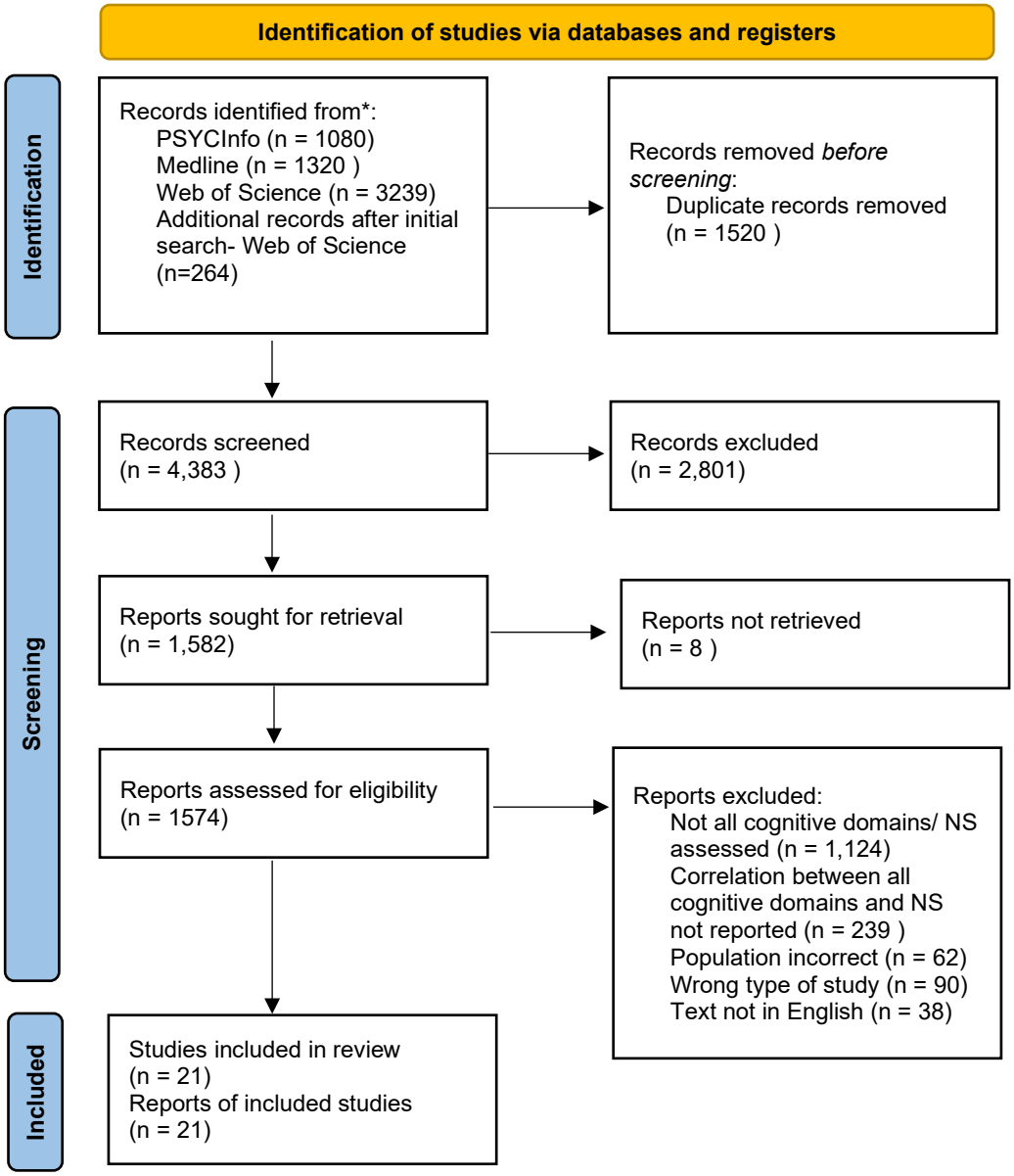
Figure 1



PRISMA Flowchart (Search between May 23, 2022 to March 27, 2023)

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Extraction of primary effect sizes

Each correlation between NS and cognitive tasks was extracted and categorized based on its corresponding cognitive domain. Certain studies assessed the MATRICS neurocognitive domains using validated neuropsychological tests that assessed all relevant domains, rather than the MATRICS Consensus Cognitive Battery. For those studies, the cognitive tasks were categorized according to the domains specified by the MATRICS Consensus and a previous meta-analysis (Khalil et al., 2022; Nuechterlein et al., 2008). When tasks were not classified in the MATRICS Consensus nor in the previous meta-analysis, tasks were classified by consensus by two experts in neuropsychology (KL, GS).

Extraction of moderator variables

Moderator variables were also extracted and coded. Variables related to the study included, type of cognitive battery used (1= MATRICS Consensus Cognitive Battery, 2= Mixed battery which included various validated neuropsychological tests or other batteries), NS scale generation (1= first generation, 2= second generation), and study quality as assessed by the MMAT (see below). Demographic variables were also extracted including age, sex/gender (ratio of males to females), ethnicity/race (coded based on the majority of the sample reported in the papers 1= Caucasian, 2= Chinese, 3= African-American). Variables related to illness included the duration of illness (in years), age at onset of illness, medication dosage (chlorpromazine equivalent in mg) and positive symptom severity. Other moderating variables (NS assessment style, cognitive assessment administration format, intelligence quotient, depression, functioning, positive symptoms, negative symptoms, cognitive domain scores) were extracted but not

included in the final analyses, mainly due to lack of studies reporting the variable (see Supplementary Table 3 for detailed methodology and notes on certain variables).

Study Quality assessment

DP and CA also assessed the quality of the studies using the Mixed Methods Appraisal Tool, 2018 Version, which critically appraises quantitative, qualitative and mixed-methods studies included in systematic mixed-studies reviews (Hong et al., 2018). The MMAT outlines a set of criteria and screening questions to provide an overall quality score which assesses methodological quality of various studies, including quantitative descriptive studies (scored out of five). See Supplementary Table 2 for methodological quality criteria and results.

Statistical Analyses

All statistical analyses were carried out using the 'rma.mv' function of the Metafor package in R Studio software version 4.0.3. The α level for significance was set at $P < .05$. Numerous studies reported multiple effect sizes for the same neurocognitive domain. Traditional meta-analyses include only one effect size for each outcome variable per study. However, the selection of a single effect size to represent each outcome variable could introduce bias and result in loss of important information. Thus, a multi-level meta-analysis was used, which considers and aggregates all reported effect sizes, while considering the dependency of those effect sizes from the same study given that it is sampled from the same population.

All extracted correlation effect sizes were converted to Pearson correlation. Next, these correlations were calculated in terms of Fisher's z, three-level meta-analyses using random

effects models to examine the association between NS (global, experiential dimension, expressive dimension) and each MATRICS neurocognitive domain. The levels within the hierarchal model included reported effect sizes (level 1; within study), studies (level 2; between study) and the aggregated effect size represented the third level. Moderator analyses were also conducted using the same three-level random effects model.

Results

Twenty-one eligible studies were included in our review (N= 3,619 participants), comprised of 23 distinct participant groups. See Table 2 for information on study participants, Table 3 for information on study characteristics and Supplementary Table 4 for neurocognitive tests used to assess each domain.

Table 2

Characteristic	Mean (SD)
Age	35.99 (7.12)
Age of illness onset	24.38 (2.24)
Years of Education	12.08 (1.5)
Duration of illness	12.44 (7.45)
Positive Symptoms - Positive and Negative Symptom Scale [a]	16.64 (6.21)
% of Sample taking medication	91.44 (22.55)
Medication dose equivalent (mg)	334.53 (199.05)
Number of Psychiatric Hospitalizations	2.63 (1.51)
Frequency	
Sex (M/F)[b]	Male (2339)
	Female (1233)
Patient Status	Outpatient (11)
	Inpatient (4)
	Inpatient and outpatient (3)
	Not reported (3)

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Diagnosis	Schizophrenia only (11) Schizophrenia and other schizophrenia spectrum disorders/ psychosis (10)
Cognitive Battery	MATRICS Consensus Cognitive Battery (11) Mix of neuropsychological tests (9) Cogstate (1)
Negative Symptom scale generation [c]	First (17) Second (4)
Negative Symptom Scale	Positive and Negative Symptom Scale - Negative (14) Scale for the Assessment of Negative Symptoms- with attention (1) Scale for the Assessment of Negative Symptoms- without attention (1) Brief Negative Symptom Scale (3) Brief Psychiatric Rating Scale- Negative (1) Clinical Assessment Interview for Negative Symptoms (1)

Characteristics of populations in the 21 studies included in the review

[a]Note that Scale for the Assessment of Positive Symptoms (SAPS) scores were converted to Positive and Negative Syndrome Scale- Positive (PANSS positive) to aggregate the average positive symptom score (van Erp et al., 2014)
[b] Not all studies reported the sex/ gender ratio for the full sample included in the correlation analyses. Sex and gender were aggregated, see Supplementary Table 3 for rationale.
[c] First generation negative symptom scales include Scale for the Assessment of Negative Symptoms or the Positive and Negative Syndrome Scale, second generation scales include Brief Negative Symptom Scale (BNSS) and the Clinical Assessment Interview for Negative Symptoms (CAINS)

Table 3

Study (Year)	N	Country	Negative Symptom Assessment	Cognitive Assessment	Population	MMAT Score

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Bagney (2015)	80	Spain	PANSS Negative	MCCB	Schizophrenia	4
Bell (2005)	267	USA	SANS	Mixed	Schizophrenia, schizoaffective disorder	5
Bozikas (2004)	58	Greece	PANSS Negative	Mixed	Schizophrenia	4
Chen (2014)	49	China	PANSS Negative	CogState	Schizophrenia	5
Chen (2014)	108	China	PANSS Negative	CogState	Schizophrenia	5
Comparelli (2012)	52	Italy	PANSS Negative	Mixed - domains classified in paper	Schizophrenia, Schizophreniform, Schizoaffective	5
Comparelli (2012)	27	Italy	PANSS Negative	Mixed - domains classified in paper	Schizophrenia, Schizophreniform, Schizoaffective	5
Cuesta (2021)	98	Spain	CAINS	Mixed battery	Schizophrenia (35), Schizoaffective (23, schizophreniform (5), bipolar with psychotic symptoms (26), other psychoses (9)	2
DalSanto (2020)	132	Spain	PANSS Negative	MCCB	Schizophrenia	5
Fonseca (2017)	99	Brazil	PANSS Negative	MCCB	Schizophrenia (100)	4
Galderisi (2014)	921	Italy	BNSS	MCCB raw score	Schizophrenia	4
Khalil (2020)	109	Egypt	PANSS Negative	Mixed	Schizophrenia	3
Lepage (2021)	425	Canada	SANS	Mixed	Schizophrenia/ Schizophreniform (257),	4

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					Schizoaffective disorder (119), Delusional disorder/Psychosis (49)	
Lin (2013)	302	Taiwan	SANS	Mixed - domains classified in paper	Schizophrenia	4
Lindgren (2020)	54	Finland	BPRS	Mixed battery	Schizophrenia (32), Affective psychosis (12), other psychotic disorder (10)	5
Liu (2019)	72	China	PANSS Negative	MCCB	Schizophrenia (100)	3
Minor (2014)	68	USA	PANSS Negative	MCCB	Schizophrenia (46), Schizoaffective disorder (22)	5
Paul (2023)	245	United States	BNSS	MCCB	Schizophrenia/ Schizoaffective disorder	3
Sevy (2020)	118	USA	PANSS Negative	MCCB	Schizophrenia (106), schizoaffective (26)	4
Strauss (2012)	100	USA	BNSS	MCCB	Schizophrenia (88), schizoaffective (12)	4
Tan (2018)	54	Australia	PANSS Negative	MCCB t-score	Schizophrenia, Schizoaffective disorder	5
Thomas (2018)	103	Australia	PANSS Negative	Mixed	Schizophrenia, schizoaffective disorder	5
Yang (2019)	65	China	PANSS Negative	MCCB	Schizophrenia	4

Characteristics of studies and populations (23) included in review

Note. MCCB= MATRICS Cognitive Consensus Battery, Mixed = various validated neuropsychological assessments used to form a single battery (Supplementary Table 4)

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All six MATRICS neurocognitive domains showed small significant negative associations with NS. See Table 4 and Figure 2.

Table 4

Neurocognitive domain	*k*	*n*	*r [95% CI]*	*p*	$I^2_{Level\ 3}$	$I^2_{Level\ 2}$
Processing speed	49	3536	-0.20 [-0.24, -0.16]	<.0001	0.38	0.14
Attention	36	3491	-0.17 [-0.22, -0.11]	<.0001	0.54	0
Working memory	43	3534	-0.20 [-0.26, -0.15]	<.0001	0.64	0
Verbal Memory and Learning	51	3533	-0.20 [-0.25, -0.14]	<.0001	0.61	0
Visual Memory and Learning	38	3400	-0.16 [-0.23, -0.09]	<0.0001	0.74	0
Reasoning and problem solving	52	3528	-0.16 [-0.20, -0.11]	<.0001	0.41	0

Pooled correlation of three-level meta-analytic model of correlation between MATRICS neurocognitive domains and negative symptoms from 21 studies

Note. k=number of effect sizes. Studies reported one or more effect size per cognitive domain-NS relationship. Hence this resulted in differences in the number of effect sizes between different MATRICS neurocognitive domains.

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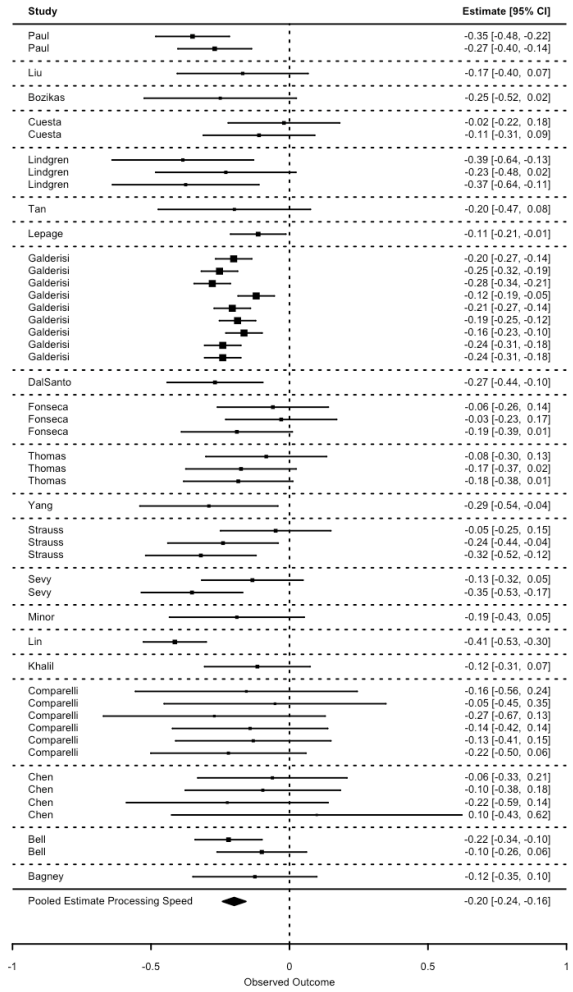
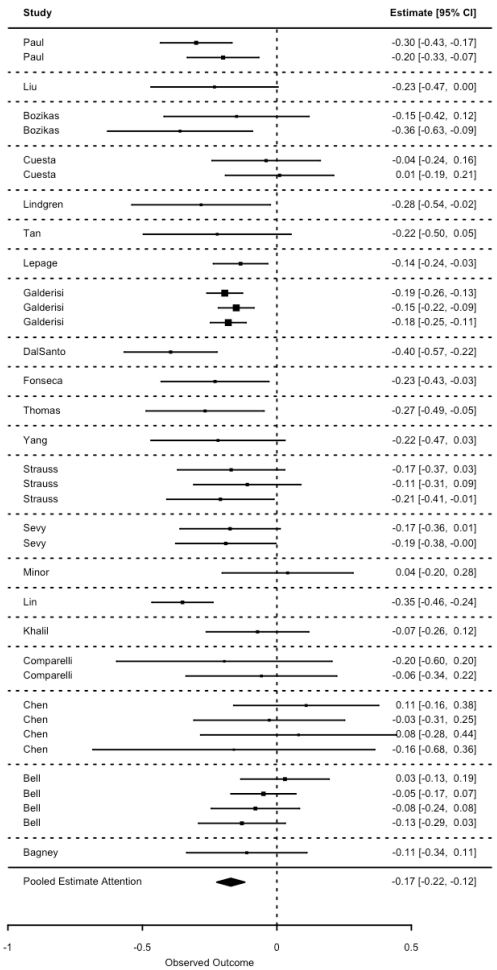
Figure 2

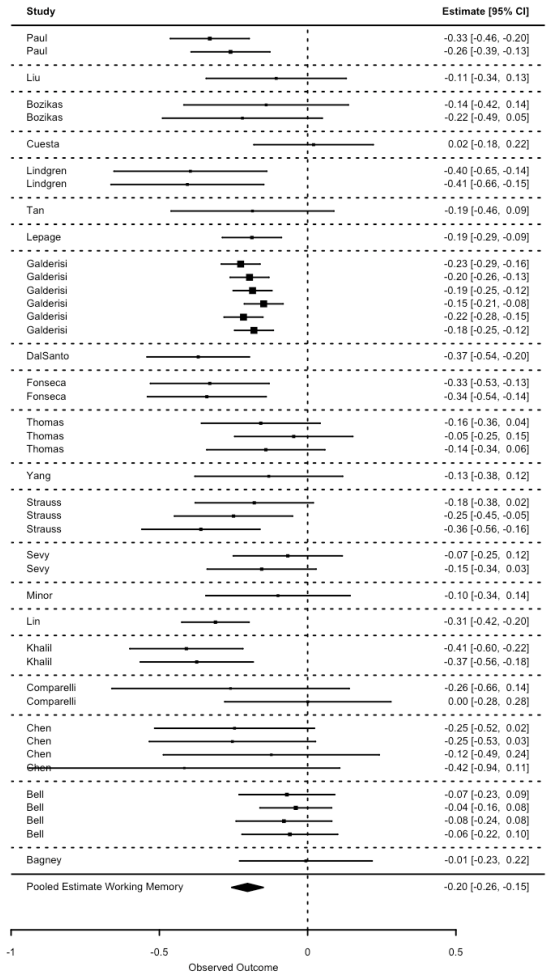
Processing Speed



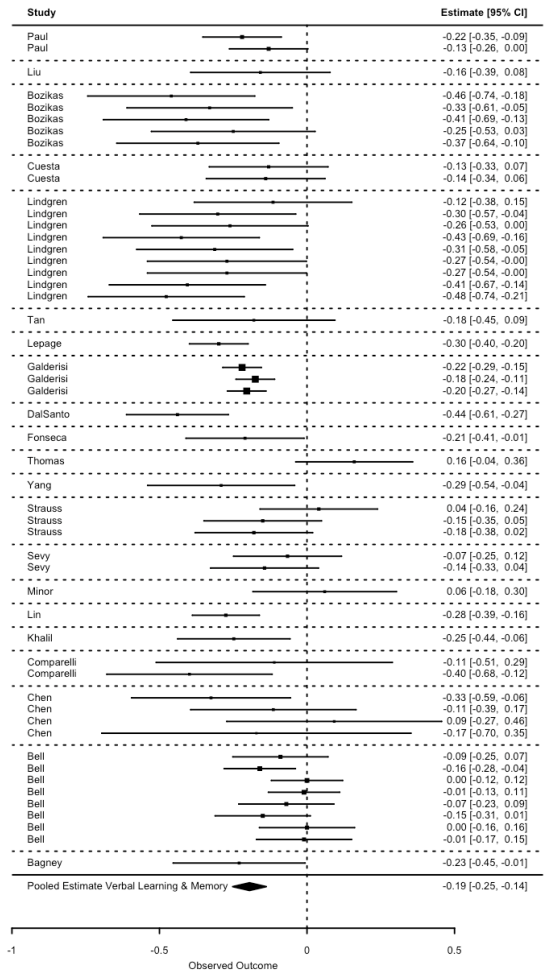
Attention



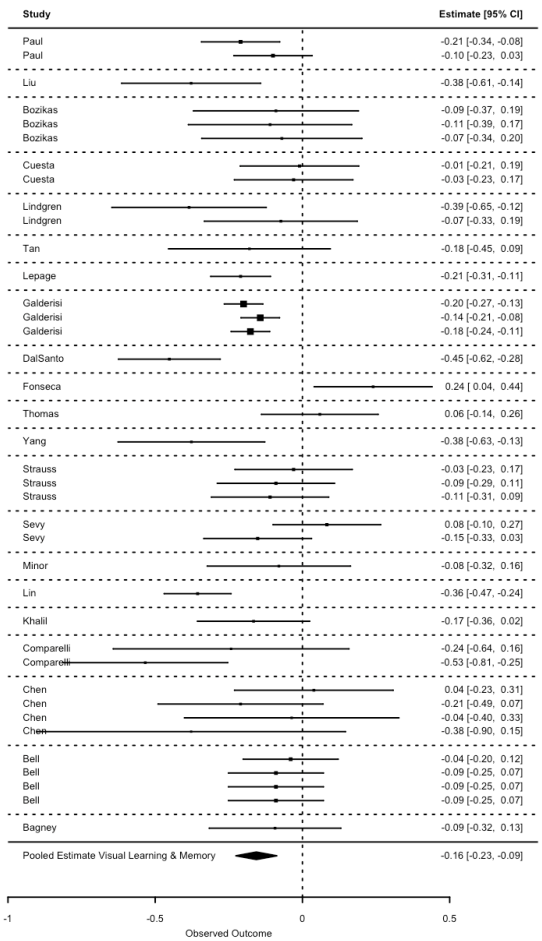
Working Memory



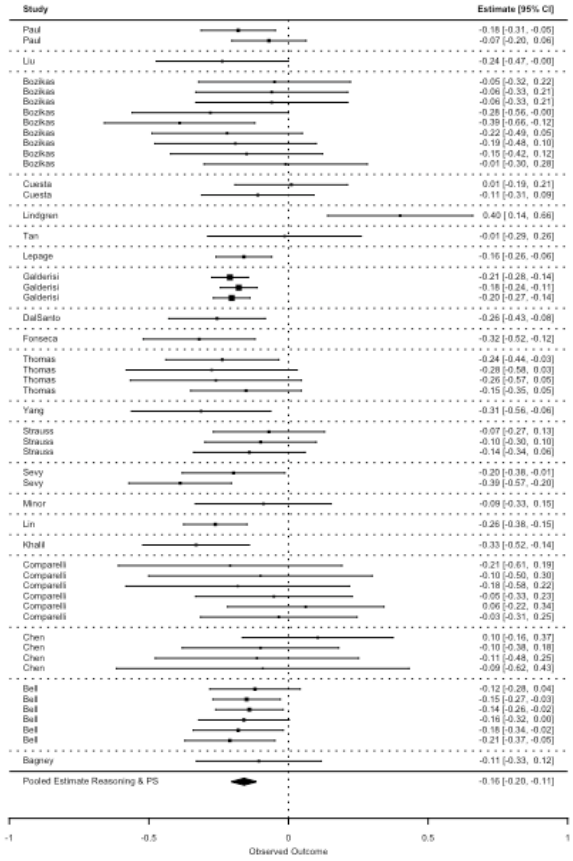
Verbal Learning & Memory



Visual Learning & Memory



Reasoning & Problem Solving



Forest plots from six meta-analyses between MATRICS neurocognitive domains and global NS

MATRICS neurocognitive domains correlation with NS dimensions (expressive and experiential)

Four of the 21 studies reported correlations between the MATRICS neurocognitive domain and the two NS dimensions. The correlation between expressive NS and reasoning and problem solving was close to significance (p = 0.06*)* and non-significant between experiential NS and visual memory and learning (*p* = 0.22*)*. All other correlations were negative and statistically significant. Across all cognitive domains, expressive NS had a stronger negative correlation compared to the negative correlations observed for experiential NS. The difference in correlation effect size between expressive and experiential dimensions was greatest for visual learning and memory ($r_{\Delta \text{ Expressive - Experiential}} = 0.11$) and working memory ($r_{\Delta \text{ Expressive - Experiential}} = 0.09$). See Table 6.

Moderator analyses

As all MATRICS neurocognitive domain correlations with NS were within the same small effect size range; correlations from all MATRICS domains were aggregated into a single model for the moderator analyses. Patient diagnosis ($F(1, 233)$ = 7.80, $p < .01$) was a significant moderator between MATRICS neurocognition and NS, where studies including schizophrenia-only populations had a stronger correlation compared to studies which included both schizophrenia and other non-affective psychoses (e.g. schizoaffective disorder). Sex/ gender (ratio males to female) approached significance (β = 0.01*,* $F(1, 267)$ = 4.03, p = 0.05). A greater male to female ratio predicted a stronger relationship between neurocognition and NS. Non-significant moderators (See Supplementary Table 5) included patient status, generation of the negative symptom scale, cognitive battery, age, age of illness onset, years of education, medication dosage, duration of illness, and positive symptom severity.

Table 6

Neurocognitive domain	*n*	NS Dimensions	
		$r_{Expressive}$	$r_{Experiential}$
Processing speed	1342	-0.25**	-0.17***
Attention	1313	-0.20*	-0.15*
Working memory	1342	-0.23**	-0.14*
Verbal Memory and Learning	1343	-0.21**	-0.16*
Visual Memory and Learning	1339	-0.18**	-0.07
Reasoning and problem solving	1338	-0.19	-0.15*

Pooled correlation of three-level meta-analytic model of correlation between MATRICS neurocognitive domains and negative symptom dimension (expressive: alogia, blunted affect; experiential: avolition, anhedonia, asociality) from four studies

Note. *= p <0.05, ** p <0.001, *** p <0.0001
Note. Studies included in this analysis are Sevy et al., 2020, Galderisi et al., 2014, Cuesta et al., 2021, Paul et al., 2023.

Study quality and publication bias

All studies were moderate to high quality (MMAT score of 3-4 out of 5). The risk of non-response bias (MMAT quantitative descriptive study assessment question 4.4) could not be assessed in most studies. Publication bias was assessed by visually inspecting funnel plots and by conducting the Egger's regression tests. All Egger's regression tests were non- significant (p > 0.05), indicating no publication bias. Visual inspection of funnel plots also suggested low/ no publication bias. See Supplementary Table 6 and Supplementary Figure 1.

Discussion

The relationships between all MATRICS neurocognitive domains and NS were all statistically significant and in the small effect size range (r = -0.20 to r = -0.16, p's <0.0001), when pooling studies using batteries which assess all six neurocognitive domains. Significant relationships were observed between both expressive and experiential NS and most neurocognitive domains (r = -0.25 to r= -0.15). Expressive NS exhibited numerically stronger correlations with all neurocognitive domains compared to experiential NS. Furthermore, diagnosis emerged as a significant moderating variable, while sex/gender showed a trend towards significance.

Our methodology enables us to demonstrate that there is a consistent and modest level of association between all MATRICS neurocognitive domains and NS. By exclusively reviewing articles that assess all neurocognitive domains within the same population, we provide evidence for a nonspecific association between global NS and MATRICS neurocognitive domains. These observed effect size aligns with the effect size ranges from other meta-analyses. This includes a meta-analysis by Pillny and colleagues (2022) between NS and the specific neurocognitive domain, episodic memory (r= -0.23), and that of de Gracia Dominguez (2009) between NS and nine neurocognitive domains (r= -0.07 to -0.291). It is important to note that neurocognitive processes that have been associated with NS, such as reward processing, were not examined in this study (Foussias & Remington, 2010; Goldsmith & Rapaport, 2020).

The observed correlations of similar magnitude between all neurocognitive domains and NS are consistent with the concept that a general neurocognitive deficit, commonly referred to as the g-factor, is associated with global NS, rather than specific neurocognitive domains (Carroll, 2003, pp. 5-21; Dickinson & Gold, 2008). However, it is important to acknowledge the potential

limitations in considering neurocognitive domain performance independently of generalized cognitive performance. Insufficient data which hindered our ability to moderate the analysis by a more comprehensive cognitive measure, such as intelligence quotient (IQ), may have affected our considerations of neurocognitive domain performance in isolation from the influence of the g-factor. The available psychometric instruments have also been suggested to have limitations in assessing cognitive performance independently of the g-factor (Dickinson & Gold, 2008).

In our subsequent analysis of the two dimensions of NS indicate that neurocognitive domains exhibit varying degrees of association with each of the NS dimensions when considered separately. Notably, expressive NS demonstrated a stronger relationship with MATRICS neurocognitive domains compared to experiential NS. Specifically, our findings indicate that neurocognitive domains such as visual learning and memory, as well as working memory, play a significant role in influencing expressive NS, whereas their influence on experiential NS appears to be less pronounced.

In line with current research trends there is an increasing recognition of the significance of exploring NS within the framework of two or five factors (Blanchard & Cohen, 2006; Kirkpatrick et al., 2006; Strauss et al., 2018). Our findings align with prior studies that highlight distinct correlational relationships between NS structures and neurocognition when utilizing a dimensional approach to investigate NS (Paul et al., 2023). Thus, emphasizing the importance of investigating the association between neurocognition and NS while considering NS dimensionally.

Diagnosis was a significant moderating variable, which could suggest the existence of a diagnosis-specific mechanism in the NS-neurocognition relationship (Hovington & Lepage, 2012). For instance, visual memory has been found to predict anhedonia (physical) in

schizophrenia, but not in bipolar disorder (Bodapati et al., 2019). On the other hand, the lower correlation effect might be attributed to a statistical phenomenon known as restriction of range, which results in a weaker correlation than the true correlation due to the limited variance in scores (Bland & Altman, 2011). Thus, if there were differences between the severity of cognitive impairments or NS between diagnoses, this would cause a restricted range in scores, impacting the correlation strength. We theorize that there could be a restriction in range because lower NS severity has been observed in non-affective psychotic disorders such as schizophreniform and schizoaffective disorder, when compared to schizophrenia (Bobes et al., 2009). Due to the lack of available data, we were not able to control for the restricted range in scores, but a post-hoc analysis of a subset of our data did not reveal significant differences in NS range between the two diagnostic groups (see Supplementary Table 7).

Sex/ gender was a moderator at trend-level significance. Studies with a higher proportion of males to females had larger NS-neurocognition correlations. This could suggest that the NS-neurocognition relationship differs between sex/gender, which aligns with gender differences observed in the NS-cognition relationship in a study by Wójciak and colleagues (2021). In their study they found that the NS-cognition relationship differed across cognitive domains between males and females (Wójciak et al., 2021). These differences could be due to underlying sex-specific neuroanatomical function differences (Mendrek & Mancini-Marïe, 2016; Salminen et al., 2022). Alternatively, this moderator could be due to a restricted range of scores. We speculate that there may be a restricted range in scores as males with schizophrenia have been found to have poorer neurocognitive functioning in certain domains (e.g. verbal learning and memory) compared to females (Bozikas et al., 2010; Buck et al., 2020). This could lead to females having a narrower range of scores in their neurocognitive abilities compared to males, as

males tend to have greater neurocognitive impairment. The possible narrower range of scores could result in a statistical phenomenon that weakens the observed correlation between NS and MATRICS neurocognitive domains, even if the true correlation strength is the same. Overall, the presence of only one significant moderating variable among the clinical, study and illness related variables (eleven moderating variables examined) demonstrates the robust nature of the relationship between NS and neurocognition.

The non-significance of most of our moderating variables could suggest specific relationships could exist at individual levels. For instance, individual-level differences in NS and/or neuropsychological profiles exist and may play a role in determining the strength and direction of the relationship between neurocognition and NS (Kremen et al., 2004; Paul et al., 2022). However, it is important to note that our moderator analyses require validation in a larger sample and important moderators (e.g. intelligence quotient, persistent NS) were not explored.

In sum, our results demonstrate a non-specific, but robust relationship between MATRICS neurocognitive domains and global NS, with some unique correlations when NS were investigated dimensionally. Notably, the associations exhibited greater strength with expressive NS compared to experiential NS.

Future studies examining the relationship between neurocognitive functioning and NS should adopt designs that can offer deeper insights into the directionality of these relationships, such as longitudinal studies. Additionally, investigating neurocognition globally (g-factor) and NS based on the five-dimension model can provide a more comprehensive understanding of their associations. Furthermore, exploring diagnosis-specific relationships can have implications for how we study and treat NS symptoms that exist across different diagnostic categories, such as anhedonia.

The relationship between NS and neurocognition has treatment implications for those with schizophrenia spectrum disorders, although the directionality of the relationship must first be clarified. While there is strong evidence for a cross-sectional relationship between NS and neurocognition, as demonstrated in the current study, there is less consensus on the directionality of this relationship. Some studies suggest that neurocognitive deficits precede and contribute to NS. When investigating the onset of these symptoms, cognitive deficits are well documented to emerge during the premorbid stage, prior to NS which has an onset in the prodromal stage (revised in (Correll & Schooler, 2020). Longitudinal studies have demonstrated the impact of neurocognitive deficits on NS, with deficits in working memory being associated with greater risk of severe apathy after one-year (Raffard et al., 2016). Another study using structural neuroimaging revealed that in first episode psychosis, impaired working memory predicted the loss of prefrontal thickness over four years, and that increasing NS severity over four years was significantly related to prefrontal cortical thinning (Tronchin et al., 2020). Mediation studies in schizophrenia spectrum disorders (Buck et al., 2020) and schizophrenia (Lipkovich et al., 2009) demonstrated that baseline verbal memory levels and changes in processing speed, respectively, influenced functioning indirectly through the mediating role of NS. Experimental studies have similarly revealed the impact of neurocognition on NS. For instance, Cohen et al. (2014) demonstrated that depleting neurocognitive resources by requiring participants to complete a working memory and attention task (one-back task) impaired aspects of speech in individuals with schizophrenia, but not healthy controls. This impaired speech was similar to the NS of alogia (Cohen et al., 2014). Bègue et al. (2022) conducted an fMRI study in individuals within the psychosis continuum, which encompasses those with psychotic symptoms ranging from subclinical to clinical level of severity. They observed that during high cognitive load, more

severe apathy was associated with reduced activity in cognition-reward regions (Bègue et al., 2022). They proposed that decreased activity in cognition-reward regions, resulting from impaired flexible cognitive resource allocation, is associated with apathy in the psychosis continuum.

Some research also suggests an opposite direction of influence, where reductions in NS were associated with greater improvements in executive functions and verbal working memory in first episode psychosis (Bora & Murray, 2014). Additionally, baseline NS were found to be related to occupational functioning up to twenty years later, mediated by processing speed and general knowledge, without evidence of NS mediating the relationship between neurocognition and occupational functioning at any follow-up timepoints (Luther et al., 2020).

Thus, the relationship between neurocognition and NS exist on multiple levels, from brain to behaviour. This relationship has important treatment implications for improving NS by targeting general neurocognition, and/or by improving general neurocognition by targeting NS. Specifically, we identified stronger associations between expressive NS and specific neurocognitive domains, highlighting potential targets for treating expressive NS. This aligns with previous research showing that treatments targeting neurocognition, such as cognitive remediation, are more effective in treating expressive NS compared to other evidence-based treatments, such as cognitive-behavioral therapy which seem more effective in treating experiential NS (Riehle et al., 2020). Future investigations of neurocognitive treatments could assess methods of tailoring it for NS. Previous research on cognitive remediation therapy has highlighted the effectiveness of adding additional components, such as bridging activities that simulate real-world scenarios and incorporate goal setting, to enhance outcomes beyond the established neurocognitive gains from such interventions, including improved functioning and

occupational outcomes (Bowie et al., 2016). Alternatively, if NS has an influence on neurocognition, targeting NS, especially expressive NS, before implementing neurocognitive interventions may enhance their effectiveness (Luther et al., 2020; Saperstein & Medalia, 2016).

Strengths and Limitations

This meta-analysis presents several strengths, including synthesizing nearly two decades of research and being the first to systematically review and meta-analyze the relationship between multiple neurocognitive domains and NS concurrently. By including articles that assessed all six MATRICS neurocognitive domains within the same sample, this study allowed for a robust comparison of correlation strength between domains. The multi-level approach ensured that all relevant datapoints were included, reducing possible bias. Additionally, this review included a comprehensive examination of moderators, including those not previously evaluated in meta-analyses investigating the relationship between neurocognitive domains and NS.

This study also has several limitations. First, the effect sizes reported in this review can only be concluded to represent the relationship between neurocognition and NS when cognition is measured using the assessments represented in the included studies (see Supplementary Table 4). Second, results of the meta-analysis only reflect the relationship as a cross-sectional level, thus further studies are needed to elucidate the directionality of this relationship. We also did not assess other cognitive domains (e.g. social cognition and metacognition) which have been associated with NS. Variability between neuropsychological tests that claim to measure the same neurocognitive domain could cause discrepancies between results. Nonetheless, we attempted to address this concern by adhering to MATRICS guidelines when classifying neurocognitive

domains and revealing the non-significant impact of neurocognitive assessment type on the relationship through our moderator analysis. Additionally, the strict inclusion criteria resulted in the exclusion of numerous papers, which could have biased the study towards larger research groups capable of administering comprehensive neuropsychological batteries. Finally, in our moderator analyses we were unable to correct for the potential restriction in range, due to limited data available (Bland & Altman, 2011; Hunter & Schmidt, 2004), and several important moderators (e.g. persistent NS, deficit syndrome) were not assessed due to lack of reported information (Buchanan, 2007).

Conclusion

In conclusion, our review paper highlights the non-specific and robust relationship between MATRICS neurocognitive domains and NS in psychosis, with potential implications for the development of treatments for schizophrenia spectrum disorders. Additionally, we identified distinct associations between specific neurocognitive domains and NS dimensions, particularly a greater numerical association between neurocognition and the expressive NS dimension, compared to the experiential dimension. This suggests that interventions targeting neurocognition could possibly have greater impacts on expressive compared to experiential NS. The robust relationship, as demonstrated by the limited number of significant moderating factors, suggests that the relationship remains across various patient populations and is robust against methodological limitations.

Funding Sources

This work was supported by the Canadian Institutes of Health Research (CIHR, 183720)

Acknowledgements

We thank all authors who provided supplementary data and information. We would like to thank K. Lavigne and G. Sauvé for reviewing the MATRICS classifications and guidance on methodology. We would also like to thank É. Thibaudeau for contributions in the initial project conceptualization.

References

Aleman, A., Lincoln, T. M., Bruggeman, R., Melle, I., Arends, J., Arango, C., & Knegtering, H. (2017). Treatment of negative symptoms: Where do we stand, and where do we go? *Schizophrenia Research*, *186*, 55–62. https://doi.org/10.1016/j.schres.2016.05.015

Alkan, E., Davies, G., & Evans, S. L. (2021). Cognitive impairment in schizophrenia: Relationships with cortical thickness in fronto-temporal regions, and dissociability from symptom severity. *Npj Schizophrenia*, *7*(1), Article 1. https://doi.org/10.1038/s41537-021-00149-0

Becker, T. M., Cicero, D. C., Cowan, N., & Kerns, J. G. (2012). Cognitive control components and speech symptoms in people with schizophrenia. *Psychiatry Research*, *196*(1), 20–26. https://doi.org/10.1016/j.psychres.2011.10.003

Bègue, I., Brakowski, J., Seifritz, E., Dagher, A., Tobler, P. N., Kirschner, M., & Kaiser, S. (2022). Cerebellar and cortico-striatal-midbrain contributions to reward-cognition processes and apathy within the psychosis continuum. *Schizophrenia Research*, *246*, 85–94. https://doi.org/10.1016/j.schres.2022.06.010

Blanchard, J. J., & Cohen, A. S. (2006). The Structure of Negative Symptoms Within Schizophrenia: Implications for Assessment. *Schizophrenia Bulletin*, *32*(2), 238–245. https://doi.org/10.1093/schbul/sbj013

Bland, J. M., & Altman, D. G. (2011). Correlation in restricted ranges of data. *BMJ*, *342*, d556. https://doi.org/10.1136/bmj.d556

Bobes, J., Arango, C., Garcia-Garcia, M., & Rejas, J. (2009). Prevalence of Negative Symptoms in Outpatients With Schizophrenia Spectrum Disorders Treated With Antipsychotics in Routine Clinical Practice: Findings From the CLAMORS Study. *The Journal of Clinical Psychiatry*, *70*(3), 15446. https://doi.org/10.4088/JCP.08m04250yel

Bodapati, A. S., Jenkins, L. M., Sharma, R. P., & Rosen, C. (2019). Visual memory uniquely predicts anhedonia in schizophrenia but not bipolar disorder. *Journal of Neuropsychology*, *13*(1), 136–146. https://doi.org/10.1111/jnp.12124

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin*, *40*(4), 744–755. https://doi.org/10.1093/schbul/sbt085

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: Meta-analytic study. *The British Journal of Psychiatry*, *195*(6), 475–482. https://doi.org/10.1192/bjp.bp.108.055731

Bozikas, V. P., Kosmidis, M. H., Peltekis, A., Giannakou, M., Nimatoudis, I., Karavatos, A., Fokas, K., & Garyfallos, G. (2010). Sex Differences in Neuropsychological Functioning Among Schizophrenia Patients. *Australian & New Zealand Journal of Psychiatry*, *44*(4), 333–341. https://doi.org/10.3109/00048670903489833

Buck, G., Lavigne, K. M., Makowski, C., Joober, R., Malla, A., & Lepage, M. (2020). Sex Differences in Verbal Memory Predict Functioning Through Negative Symptoms in Early Psychosis. *Schizophrenia Bulletin*, *46*(6), 1587–1595. https://doi.org/10.1093/schbul/sbaa054

Carroll, J. B. (2003). Chapter 1 - The Higher-stratum Structure of Cognitive Abilities: Current Evidence Supports g and About Ten Broad Factors. In H. Nyborg (Ed.), *The Scientific Study of General Intelligence* (pp. 5–21). Pergamon. https://doi.org/10.1016/B978-008043793-4/50036-2

Chan, S. K. W., Kao, S. Y. S., Leung, S. L., Hui, C. L. M., Lee, E. H. M., Chang, W. C., & Chen, E. Y. H. (2019). Relationship between neurocognitive function and clinical symptoms with self-stigma in patients with schizophrenia-spectrum disorders. *Journal of Mental Health*, *28*(6), 583–588. https://doi.org/10.1080/09638237.2017.1340599

Cohen, A. S., McGovern, J. E., Dinzeo, T. J., & Covington, M. A. (2014). Speech Deficits in Serious mental Illness: A Cognitive Resource Issue? *Schizophrenia Research*, *160*(0), 173–179. https://doi.org/10.1016/j.schres.2014.10.032

Correll, C. U., & Schooler, N. R. (2020). Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatric Disease and Treatment*, *16*, 519–534. https://doi.org/10.2147/NDT.S225643

de Gracia Dominguez, M., Viechtbauer, W., Simons, C. J. P., van Os, J., & Krabbendam, L. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological Bulletin*, *135*, 157–171. https://doi.org/10.1037/a0014415

Dickinson, D., & Gold, J. M. (2008). Less Unique Variance Than Meets the Eye: Overlap Among Traditional Neuropsychological Dimensions in Schizophrenia. *Schizophrenia Bulletin*, *34*(3), 423–434. https://doi.org/10.1093/schbul/sbm092

Drijgers, R. L., Verhey, F. R. J., Leentjens, A. F. G., Köhler, S., & Aalten, P. (2011). Neuropsychological correlates of apathy in mild cognitive impairment and Alzheimer's disease: The role of executive functioning. *International Psychogeriatrics*, *23*(8), 1327–1333. https://doi.org/10.1017/S1041610211001037

Duan, X., He, C., Ou, J., Wang, R., Xiao, J., Li, L., Wu, R., Zhang, Y., Zhao, J., & Chen, H. (2021). Reduced Hippocampal Volume and Its Relationship With Verbal Memory and Negative Symptoms in Treatment-Naive First-Episode Adolescent-Onset Schizophrenia. *Schizophrenia Bulletin*, *47*(1), 64–74. https://doi.org/10.1093/schbul/sbaa092

Evans, J. D., Bond, G. R., Meyer, P. S., Kim, H. W., Lysaker, P. H., Gibson, P. J., & Tunis, S. (2004). Cognitive and clinical predictors of success in vocational rehabilitation in schizophrenia. *Schizophrenia Research*, *70*(2), 331–342. https://doi.org/10.1016/j.schres.2004.01.011

Faerden, A., Vaskinn, A., Finset, A., Agartz, I., Ann Barrett, E., Friis, S., Simonsen, C., Andreassen, O. A., & Melle, I. (2009). Apathy is associated with executive functioning in first episode psychosis. *BMC Psychiatry*, *9*, 1. https://doi.org/10.1186/1471-244X-9-1

Faith, L. A., Lecomte, T., Corbière, M., Francoeur, A., Hache-Labelle, C., & Lysaker, P. H. (2020). Metacognition Is Uniquely Related to Concurrent and Prospective Assessments of Negative Symptoms Independent of Verbal Memory in Serious Mental Illness. *The Journal of Nervous and Mental Disease*, *208*(11), 837–842. https://doi.org/10.1097/NMD.0000000000001219

Fervaha, G., Takeuchi, H., Foussias, G., Agid, O., & Remington, G. (2016). Using poverty of speech as a case study to explore the overlap between negative symptoms and cognitive dysfunction. *Schizophrenia Research*, *176*(2), 411–416. https://doi.org/10.1016/j.schres.2016.05.019

Foussias, G., & Remington, G. (2010). Negative Symptoms in Schizophrenia: Avolition and Occam's Razor. *Schizophrenia Bulletin*, *36*(2), 359–369. https://doi.org/10.1093/schbul/sbn094

Gold, J. M., Waltz, J. A., Prentice, K. J., Morris, S. E., & Heerey, E. A. (2008). Reward processing in schizophrenia: A deficit in the representation of value. *Schizophrenia Bulletin*, *34*(5), 835–847. https://doi.org/10.1093/schbul/sbn068

Goldsmith, D. R., & Rapaport, M. H. (2020). Inflammation and Negative Symptoms of Schizophrenia: Implications for Reward Processing and Motivational Deficits. *Frontiers in Psychiatry*, *11*. https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00046

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., Kohler, C., Alsop, D., Maldjian, J., Ragland, J. D., & Gur, R. C. (2002). An fMRI Study of Facial Emotion Processing in Patients With Schizophrenia. *American Journal of Psychiatry*, *159*(12), 1992–1999. https://doi.org/10.1176/appi.ajp.159.12.1992

Harvey, P. D., Koren, D., Reichenberg, A., & Bowie, C. R. (2006). Negative symptoms and cognitive deficits: What is the nature of their relationship? *Schizophrenia Bulletin*, *32*(2), 250–258. https://doi.org/10.1093/schbul/sbj011

Heerey, E. A., & Gold, J. M. (2007). Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. *Journal of Abnormal Psychology*, *116*(2), 268–278. https://doi.org/10.1037/0021-843X.116.2.268

Hong, Q. N., Gonzalez-Reyes, A., & Pluye, P. (2018). Improving the usefulness of a tool for appraising the quality of qualitative, quantitative and mixed methods studies, the Mixed Methods Appraisal Tool (MMAT). *Journal of Evaluation in Clinical Practice*, *24*(3), 459–467. https://doi.org/10.1111/jep.12884

Hovington, C. L., Bodnar, M., Joober, R., Malla, A. K., & Lepage, M. (2013). Impairment in verbal memory observed in first episode psychosis patients with persistent negative symptoms. *Schizophrenia Research*, *147*(2–3), 223–229. https://doi.org/10.1016/j.schres.2013.04.006

Hovington, C. L., & Lepage, M. (2012). Neurocognition and neuroimaging of persistent negative symptoms of schizophrenia. *Expert Review of Neurotherapeutics*, *12*(1), 53–69. https://doi.org/10.1586/ern.11.173

Hunter, J. E., & Schmidt, F. L. (2004). *Methods of Meta-Analysis: Correcting Error and Bias in Research Findings*.

Khalil, M., Hollander, P., Raucher-Chéné, D., Lepage, M., & Lavigne, K. M. (2022). Structural brain correlates of cognitive function in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *132*, 37–49. https://doi.org/10.1016/j.neubiorev.2021.11.034

Kirkpatrick, B., Fenton, W. S., Carpenter, W. T., & Marder, S. R. (2006). The NIMH-MATRICS Consensus Statement on Negative Symptoms. *Schizophrenia Bulletin*, *32*(2), 214–219. https://doi.org/10.1093/schbul/sbj053

Kirkpatrick, B., & Fischer, B. (2006). Subdomains Within the Negative Symptoms of Schizophrenia: Commentary. *Schizophrenia Bulletin*, *32*(2), 246–249. https://doi.org/10.1093/schbul/sbj054

Konstantakopoulos, G., Ploumpidis, D., Oulis, P., Patrikelis, P., Soumani, A., Papadimitriou, G. N., & Politis, A. M. (2011). Apathy, cognitive deficits and functional impairment in schizophrenia. *Schizophrenia Research*, *133*(1), 193–198. https://doi.org/10.1016/j.schres.2011.07.003

Kremen, W. S., Seidman, L. J., Faraone, S. V., Toomey, R., & Tsuang, M. T. (2004). Heterogeneity of schizophrenia: A study of individual neuropsychological profiles. *Schizophrenia Research*, *71*(2), 307–321. https://doi.org/10.1016/j.schres.2004.02.022

Lepage, M., Bodnar, M., Raucher-Chéné, D., Lavigne, K. M., Makowski, C., Joober, R., & Malla, A. K. (2021). Neurocognitive functions in persistent negative symptoms following a first episode of psychosis. *European Neuropsychopharmacology*, *47*, 86–97. https://doi.org/10.1016/j.euroneuro.2021.02.008

Lipkovich, I. A., Deberdt, W., Csernansky, J. G., Sabbe, B., Keefe, R. S., & Kollack-Walker, S. (2009). Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: A path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. *BMC Psychiatry*, *9*(1), 44. https://doi.org/10.1186/1471-244X-9-44

Luther, L., Suor, J. H., Rosen, C., Jobe, T. H., Faull, R. N., & Harrow, M. (2020). Clarifying the direction of impact of negative symptoms and neurocognition on prospective work functioning in psychosis: A 20-year longitudinal study. *Schizophrenia Research*, *220*, 232–239. https://doi.org/10.1016/j.schres.2020.03.012

Lyne, J., O'Donoghue, B., Roche, E., Renwick, L., Cannon, M., & Clarke, M. (2018). Negative symptoms of psychosis: A life course approach and implications for prevention and

treatment. *Early Intervention in Psychiatry*, *12*(4), 561–571. https://doi.org/10.1111/eip.12501

Marder, S. R., & Galderisi, S. (2017). The current conceptualization of negative symptoms in schizophrenia. *World Psychiatry*, *16*(1), 14–24. https://doi.org/10.1002/wps.20385

McDowd, J., Tang, T.-C., Tsai, P.-C., Wang, S.-Y., & Su, C.-Y. (2011). The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. *Psychiatry Research*, *187*(3), 329–334. https://doi.org/10.1016/j.psychres.2011.01.017

McLeod, H. J., Gumley, A. I., Macbeth, A., Schwannauer, M., & Lysaker, P. H. (2014). Metacognitive functioning predicts positive and negative symptoms over 12 months in first episode psychosis. *Journal of Psychiatric Research*, *54*, 109–115. https://doi.org/10.1016/j.jpsychires.2014.03.018

Mendrek, A., & Mancini-Marïe, A. (2016). Sex/gender differences in the brain and cognition in schizophrenia. *Neuroscience & Biobehavioral Reviews*, *67*, 57–78. https://doi.org/10.1016/j.neubiorev.2015.10.013

Messinger, J. W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A. D., & Malaspina, D. (2011). Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical Psychology Review*, *31*(1), 161–168. https://doi.org/10.1016/j.cpr.2010.09.002

Meyer, A., Zimmermann, R., Gschwandtner, U., Hatz, F., Bousleiman, H., Schwarz, N., & Fuhr, P. (2015). Apathy in Parkinson's disease is related to executive function, gender and age but not to depression. *Frontiers in Aging Neuroscience*, *6*, 350. https://doi.org/10.3389/fnagi.2014.00350

Mørch-Johnsen, L., Smelror, R. E., Andreou, D., Barth, C., Johannessen, C., Wedervang-Resell, K., Wortinger, L. A., Díaz, R., Victoria, G., Ueland, T., Andreassen, O. A., Myhre, A. M., Rund, B. R., Ulloa, R. E., & Agartz, I. (2022). Negative Symptom Domains Are Associated With Verbal Learning in Adolescents With Early Onset Psychosis. *Frontiers in Psychiatry*, *12*, 825681. https://doi.org/10.3389/fpsyt.2021.825681

Mothersill, O., Knee-Zaska, C., & Donohoe, G. (2016). Emotion and Theory of Mind in Schizophrenia—Investigating the Role of the Cerebellum. *The Cerebellum*, *15*(3), 357–368. https://doi.org/10.1007/s12311-015-0696-2

Navalón, P., Serrano, E., Almansa, B., Perea, M., Benavent, P., Domínguez, A., Sierra, P., Cañada, Y., & García-Blanco, A. (2021). Attentional biases to emotional scenes in schizophrenia: An eye-tracking study. *Biological Psychology*, *160*, 108045. https://doi.org/10.1016/j.biopsycho.2021.108045

Nuechterlein, K., Green, M., Kern, R., Baade, L., Barch, D., Cohen, J., Essock, S., Fenton, W., Frese, F., Gold, J., Goldberg, T., Heaton, R., Keefe, R., Kraemer, H., Mesholam-Gately, R., Seidman, L., Stover, E., Weinberger, D., Young, A., & Marder, S. (2008). The MATRICS Consensus Cognitive Battery, Part 1: Test selection, reliability, and validity. *The American Journal of Psychiatry*, *165*, 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, n71. https://doi.org/10.1136/bmj.n71

Patel, R., Jayatilleke, N., Broadbent, M., Chang, C.-K., Foskett, N., Gorrell, G., Hayes, R. D., Jackson, R., Johnston, C., Shetty, H., Roberts, A., McGuire, P., & Stewart, R. (2015). Negative symptoms in schizophrenia: A study in a large clinical sample of patients using a novel automated method. *BMJ Open*, *5*(9), e007619. https://doi.org/10.1136/bmjopen-2015-007619

Paul, N. B., Strauss, G. P., Gates-Woodyatt, J. J., Barchard, K. A., & Allen, D. N. (2023). Two and five-factor models of negative symptoms in schizophrenia are differentially associated with trait affect, defeatist performance beliefs, and psychosocial functioning. *European Archives of Psychiatry and Clinical Neuroscience*. https://doi.org/10.1007/s00406-022-01507-4

Paul, N. B., Strauss, G. P., Woodyatt, J. J., Paul, M. G., Keene, J. R., & Allen, D. N. (2022). Cluster analysis of negative symptoms identifies distinct negative symptom subgroups. *Schizophrenia Research*, *246*, 207–215. https://doi.org/10.1016/j.schres.2022.06.021

Pelletier-Baldelli, A., & Holt, D. J. (2020). Are Negative Symptoms Merely the "Real World" Consequences of Deficits in Social Cognition? *Schizophrenia Bulletin*, *46*(2), 236–241. https://doi.org/10.1093/schbul/sbz095

Penney, D., Sauvé, G., Mendelson, D., Thibaudeau, É., Moritz, S., & Lepage, M. (2022). Immediate and Sustained Outcomes and Moderators Associated With Metacognitive Training for Psychosis: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *79*(5), 417–429. https://doi.org/10.1001/jamapsychiatry.2022.0277

Pillny, M., Krkovic, K., Buck, L., & Lincoln, T. M. (2022). From Memories of Past Experiences to Present Motivation? A Meta-analysis on the Association Between Episodic Memory

and Negative Symptoms in People With Psychosis. *Schizophrenia Bulletin*, *48*(2), 307–324. https://doi.org/10.1093/schbul/sbab120

Rabinowitz, J., Levine, S. Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C. G., & Kapur, S. (2012). Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data. *Schizophrenia Research*, *137*(1), 147–150. https://doi.org/10.1016/j.schres.2012.01.015

Raffard, S., Gutierrez, L.-A., Yazbek, H., Larue, A., Boulenger, J.-P., Lançon, C., Benoit, M., Faget, C., Norton, J., & Capdevielle, D. (2016). Working Memory Deficit as a Risk Factor for Severe Apathy in Schizophrenia: A 1-Year Longitudinal Study. *Schizophrenia Bulletin*, *42*(3), 642–651. https://doi.org/10.1093/schbul/sbw002

Riehle, M., Böhl, M. C., Pillny, M., & Lincoln, T. M. (2020). Efficacy of Psychological Treatments for Patients With Schizophrenia and Relevant Negative Symptoms: A Meta-Analysis. *Clinical Psychology in Europe*, *2*(3), Article 3. https://doi.org/10.32872/cpe.v2i3.2899

Roth, R. M., Flashman, L. A., Saykin, A. J., McAllister, T. W., & Vidaver, R. (2004). Apathy in schizophrenia: Reduced frontal lobe volume and neuropsychological deficits. *The American Journal of Psychiatry*, *161*(1), 157–159. https://doi.org/10.1176/appi.ajp.161.1.157

Salminen, L. E., Tubi, M. A., Bright, J., Thomopoulos, S. I., Wieand, A., & Thompson, P. M. (2022). Sex is a defining feature of neuroimaging phenotypes in major brain disorders. *Human Brain Mapping*, *43*(1), 500–542. https://doi.org/10.1002/hbm.25438

Saperstein, A. M., & Medalia, A. (2016). The Role of Motivation in Cognitive Remediation for People with Schizophrenia. In E. H. Simpson & P. D. Balsam (Eds.), *Behavioral*

Neuroscience of Motivation (pp. 533–546). Springer International Publishing. https://doi.org/10.1007/7854_2015_373

Sitko, K., Bewick, B. M., Owens, D., & Masterson, C. (2020). Meta-analysis and Meta-regression of Cognitive Behavioral Therapy for Psychosis (CBTp) Across Time: The Effectiveness of CBTp has Improved for Delusions. *Schizophrenia Bulletin Open*, *1*(1), sgaa023. https://doi.org/10.1093/schizbullopen/sgaa023

Strauss, G. P., Allen, D. N., Duke, L. A., Ross, S. A., & Schwartz, J. (2008). Automatic affective processing impairments in patients with deficit syndrome schizophrenia. *Schizophrenia Research*, *102*(1–3), 76–87. https://doi.org/10.1016/j.schres.2008.01.014

Strauss, G. P., Nuñez, A., Ahmed, A. O., Barchard, K. A., Granholm, E., Kirkpatrick, B., Gold, J. M., & Allen, D. N. (2018). The Latent Structure of Negative Symptoms in Schizophrenia. *JAMA Psychiatry*, *75*(12), 1271. https://doi.org/10.1001/jamapsychiatry.2018.2475

Szendi, I., Kiss, M., Racsmány, M., Boda, K., Cimmer, C., Vörös, E., Kovács, Z. A., Szekeres, G., Galsi, G., Pléh, C., Csernay, L., & Janka, Z. (2006). Correlations between clinical symptoms, working memory functions and structural brain abnormalities in men with schizophrenia. *Psychiatry Research*, *147*(1), 47–55. https://doi.org/10.1016/j.pscychresns.2005.05.014

Tronchin, G., Akudjedu, T. N., Kenney, J. P., McInerney, S., Scanlon, C., McFarland, J., McCarthy, P., Cannon, D. M., Hallahan, B., & McDonald, C. (2020). Cognitive and Clinical Predictors of Prefrontal Cortical Thickness Change Following First-Episode of Psychosis. *Psychiatry Research: Neuroimaging*, *302*, 111100. https://doi.org/10.1016/j.pscychresns.2020.111100

van Erp, T. G. M., Preda, A., Nguyen, D., Faziola, L., Turner, J., Bustillo, J., Belger, A., Lim, K. O., McEwen, S., Voyvodic, J., Mathalon, D. H., Ford, J., & Potkin, S. G. (2014). Converting Positive and Negative Symptom Scores Between PANSS and SAPS/SANS. *Schizophrenia Research*, *152*(1), 289–294. https://doi.org/10.1016/j.schres.2013.11.013

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., & Wykes, T. (2021). Effectiveness, Core Elements, and Moderators of Response of Cognitive Remediation for Schizophrenia: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Psychiatry*, *78*(8), 848–858. https://doi.org/10.1001/jamapsychiatry.2021.0620

Westbrook, A., & Braver, T. S. (2016). Dopamine Does Double Duty in Motivating Cognitive Effort. *Neuron*, *89*(4), 695–710. https://doi.org/10.1016/j.neuron.2015.12.029

Wójciak, P., Domowicz, K., Zabłocka, M., Michalak, M., & Rybakowski, J. K. (2021). Association of Negative Symptoms of Schizophrenia Assessed by the BNSS and SNS Scales With Neuropsychological Performance: A Gender Effect. *Frontiers in Psychiatry*, *12*. https://www.frontiersin.org/articles/10.3389/fpsyt.2021.797386