Characterising demographic, clinical and functional features of cognitive subgroups in schizophrenia spectrum disorders: A systematic review

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Abstract

Considerable cognitive heterogeneity is present within the schizophrenia spectrum disorder (SSD) population. Several subgroups characterised by more homogenous cognitive profiles have been identified. It is not yet clear however, whether these subgroups represent different points along a continuum of cognitive symptom severity, or whether they reflect unique profiles of the disorder. One way to determine this is by comparing subgroups on their non-cognitive characteristics. The aim of the present review was to systematically summarise our current understanding of the non-cognitive features of the cognitive subgroups of schizophrenia spectrum disorder (SSD). Thirty-five relevant studies were identified from January 1980 to March 2020. Cognitive subgroups were consistently compared on age, sex, education, age of illness onset, illness duration, positive, negative and disorganised symptoms, depression and psychosocial functioning. It was revealed that subgroups were consistently distinguished by education, negative symptom severity and degree of functional impairment; with subgroups characterised by worse cognitive functioning performing/rated worse on these characteristics. The lack of consistent subgroup differences for the majority of the non-cognitive characteristics provides partial support for the notion that cognitive subgrouping in SSD is not simply reflecting a rehash of previously identified clinical subtypes. However, as subgroups were consistently distinguished by three characteristics known to be associated with cognition, our understanding of the extent to which the cognitive subgrouping approach is representing separate subtypes versus subdivisions along a continuum of symptom severity is still not definitive.

Keywords: psychosis, schizoaffective disorder, cognitive heterogeneity, cluster analysis, cognitive trajectory

1. Introduction

Cognitive dysfunction is highly prevalent amongst the schizophrenia spectrum disorders (SSD). Widespread and pervasive cognitive impairments have been documented at both the global and domain-specific level and are commonly said to be universally experienced by all with the disorder (Carruthers *et al.*, 2015, Fioravanti *et al.*, 2005, Henry and Crawford, 2005, Keefe *et al.*, 2005, Tandon *et al.*, 2009). As such, cognition is typically investigated in SSD using a 'whole group'/ 'group-average' approach. However, considerable cognitive heterogeneity exists within the population. Researchers have been increasingly employing various statistical techniques in an attempt to characterise the variability in cognitive function present in SSD. In response, two lines of empirical inquiry have emerged, one which focusses on the heterogeneity in current cognitive ability and one which investigates differences in the trajectory of cognitive symptoms.

Studies examining the variability in current cognitive function have shown that by scrutinising the cognitive performances of SSD participants more closely, several subgroups characterised by more homogenous cognitive profiles can be identified. A review of the pertinent literature inferred that, despite differences in the methods used to subgroup participants (e.g., predetermined performance criteria, exploratory data-driven clustering) or the number of subgroups which were investigated in individual studies (ranging from two-to-five), SSD participants were best represented as having one of three cognitive profiles (Carruthers *et al.*, 2019b). This included a globally impaired subgroup characterised by widespread and severe deficits that are typically greater than 1.5 standard deviations below healthy control comparisons; an intermediate subgroup characterised by either a generally moderate degree of cognitive impairment or a study-specific combination of cognitive strengths and weaknesses approximately 0.5 to 1.5 standard deviations below healthy controls; and a relatively intact subgroup whose cognitive performance falls within 0.5

standard deviations of healthy control comparisons. Likewise, when investigating differences between premorbid and current cognitive functions, three putative cognitive symptom trajectories have been reliability characterised (Carruthers et al., 2019b); labelled as putative due to the consistent use of proxy measures to estimate patient premorbid function in lieu of longitudinal data. This included a compromised trajectory, characterised by widespread cognitive deficits which are present before and after the onset of psychosis; a deteriorated trajectory defined by a relatively intact level of functioning prior to the onset of psychosis, followed by a decline in cognitive function to a moderate-to-severe level of current impairment; and a preserved trajectory, characterised by a near-normal level of cognitive functioning that perseveres post psychosis onset (see Weickert et al., 2000). The presence of the relatively intact and preserved subgroups contradicts typical conceptualisations of cognition in SSD being impaired in *all* patients.

Cognitive subgroups of SSD have been identified using predetermined performance criteria (e.g. Heinrichs *et al.*, 2017), as well as more exploratory data-driven techniques (see Green *et al.*, 2019b). They have been derived using domain-specific measures (e.g. Carruthers *et al.*, 2019a), as well as comprehensive assessment batteries (e.g. Van Rheenen *et al.*, 2017). What has emerged from this methodologically-diverse body of literature is a reasonably comprehensive understanding of the *cognitive* characteristics of these subgroups (see Carruthers *et al.*, 2019b). However, it is still not clear whether they represent different points on a continuum of cognitive symptom severity, or whether they reflect unique variations of the disorder.

Several studies have reported distinct neuroanatomical differences across cognitive subgroups (e.g. Van Rheenen *et al.*, 2018, Vaskinn *et al.*, 2015), indicating that these subgroups may have some discreet neurobiological validity (Karantonis *et al.*, 2020a, Karantonis *et al.*, 2020b). Most investigations of cognitive subgroups in SSD also assess non-

cognitive features like demographic characteristics or clinical symptomology, to provide a form of external validation for the subgroups being characterised (e.g., Carruthers et al., 2019a, Van Rheenen et al., 2017, Wells et al. 2015). Such non-cognitive characterisation may provide valuable insight into the validity of these subgroups as representing unique variations of the disorder as opposed to simply representing different points on a continuum of cognitive symptom severity. A detailed synthesis of the current empirical evidence pertaining to the demographic, clinical and psychosocial functioning characteristics of the cognitive subgroups of SSD is therefore warranted and represents the aim of this systematic review.

2. Method

2.1. Search protocol

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009), where appropriate. This is a review of data previously collected, but not reported on. The protocol for the original review (Carruthers *et al.*, 2019b) was registered at the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42018108473). The databases PubMed, Scopus and Web of Science were used to locate relevant literature, with the original searches limited to full-length empirical articles published between the 1st of January 1980 and 1st of March 2019. A secondary search was conducted using the same search protocol from the 1st of March 2019 up to the 1st of March 2020 to capture any recently published studies. The search syntax employed was optimized for each database, with search terms based upon three concepts: schizophrenia, cognition, and cognitive subgroups (see Appendix 1 for full search syntax). Reference lists of published reviews related to the topic and personal reference libraries of authors were checked for additional relevant works.

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2.2. Study selection, data extraction and synthesis.

Originally, titles, abstracts and keywords of each record were scanned by a single reviewer (SPC) at stage one and were included if they met the following criteria: the article was 1) written in English; 2) investigated cognitive subgroups; and 3) included participants with schizophrenia or schizoaffective disorder or first episode psychosis participants. At stage two, two reviewers (SPC, SLR) independently screened full-text articles. A record was eligible if: 1) subgroups were based on non-social cognition; 2) cognitive performance was compared between subgroups; and 3) subgroups presented were comprised of SSD participants only. Studies that included demographic or clinical variables into the subgrouping methodology were excluded. Studies employing single summary metrics of cognitive function that were comprised in-part by a measure of social cognition or a comprehensive neuropsychological test battery that included a social cognitive domain were eligible. The full-text articles of cross-diagnostic investigations (e.g. schizophrenia-bipolar disorder; Karantonis *et al.*, 2020c, Lewandowski *et al.*, 2018) were screened for the reporting of any SSD-only results. Multiple studies sharing the same participant pool were still eligible if the subgrouping methodology employed or variables compared differed.

For the current review, all studies that met the above stage two eligibility criteria were screened again by one reviewer (SPC). To be eligible for inclusion in the current review, studies had to have 1) statistically compared subgroups on ratings of clinical symptomology and 2) investigated participants diagnosed with schizophrenia or schizoaffective disorder only. Eligible studies were reviewed based upon the following subgroup characteristics: age, sex, education, age of onset, illness duration, positive symptoms, negative symptoms, disorganised symptoms, depression and functional outcomes.

This review adopted a broad perspective to the eligible body of literature to synthesise results. Because of the considerable methodological variability across the included studies, comparison of results between studies using different methods and between studies with differing subgroup numbers was deemed impractical by the authors. In support of this decision, it has been previously concluded that despite the methodological variability both between and within the two broad statistical techniques used to subgroup participants (e.g., predetermined performance criteria and data-driven), and irrespective of the number of subgroups examined in individual studies (ranging from two-to-five), a consistent pattern best represented by three cognitive subgroups emerged (Carruthers et al., 2019b). As such, differences in study methodology will be disregarded for the purpose of this review. Summaries of study methodology and results presented in tables will however be separated based on a) the number of subgroups investigated and b) the broad type of subgrouping methodology employed (i.e., predetermined performance criteria, predetermined data-driven, and exploratory data-driven). Furthermore, subgroups will be referred to as relatively intact, intermediate impairment and severely impaired when possible, with study specific labelling utilised when required.

3. Results

3.1. Search Summary

The search yielded a total of 2616 records, from which 35 met the inclusion criteria. Included studies were divided into two broad categories based on the cognitive focus of subgrouping; current cognitive function and putative cognitive symptom trajectory. By examining the current cognitive performance of participants, 27 studies classified participants into either two (13 studies), three (9 studies) or four or more (5 studies) subgroups. The remaining eight studies classified participants into two (1 study), three (4 studies) or four (1

study) subgroups that represented putative cognitive symptom trajectories. Although some study specific differences were present, for these eight studies metrics of current cognitive ability were typically compared against estimates of premorbid function to determine if participants followed either a preserved - characterised by relatively intact premorbid and current cognitive function; deteriorated - characterised by relatively intact premorbid and moderately-to-severely impaired current cognitive function; or compromised - characterised by severe impairments to both premorbid estimates and current cognitive function – cognitive trajectory (see Weickert *et al.*, 2000).

Overall, 21 studies classified participants into cognitive subgroups based upon predetermined performance criteria, four studies classified participants into a predetermined number of subgroups using data-driven techniques, with the remaining 10 studied utilising exploratory data-driven classification techniques. Brief summaries of the methods and cognitive domains utilised by each study to subgroup their samples are presented in Table 1 and Table 2 and will be largely omitted from the current synthesis due to the non-cognitive/non-methodological focus. For a more detailed description of the methodologies employed in each study see Carruthers *et al.* (2019b).

Results specific to our review aims are summarised in Table 3 and Table 4. The key findings are organised in the below sections by age, sex, education, age of onset, illness duration, positive, negative and disorganised symptoms as well as depression and psychosocial functioning. Within this, we first present the findings of studies in which cognitive subgroups were derived based on current cognitive functioning, following by the findings of studies in which cognitive subgroups were derived based on putative symptom trajectory.

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3.1.1. Age

3.1.1.1. Subgroups based on current cognitive function.

Eleven studies classified participants into subgroups using age-adjusted data (see Table A in Appendix). Of these 11 studies, two reported significant age differences between patient subgroups. Bowie *et al.* (2006) investigated three memory-based subgroups and found that the impaired subgroup was younger than both the intermediate and relatively intact subgroups, which did not differ. In comparing four emergent subgroups based on attention and executive function, Liu *et al.* (2011) found that a relatively intact subgroup and an executive function-deficit subgroup were younger than an attention-deficit subgroup but not the attention and executive function deficit subgroup.

Of the remaining 12 studies that did not use age-adjusted data to subgroup participants, two reported significant age differences between patient subgroups. Investigating two subgroups based on executive function, Butler *et al.* (1992) reported that the relatively intact patients were found to be significantly younger than the impaired patients; with the subgroup defining difference in perseveration maintained after covarying for age. Employing a similar tripartite memory-based classification to that used by Bowie *et al.* (2006), Turetsky *et al.* (2002) reported that the impaired subgroup was younger than the intermediate subgroup, with neither subgroup differing in age from the relatively intact subgroup.

3.1.1.2. Subgroups based on putative symptom trajectory

One of the eight studies comparing age reported a significant difference between subgroups. Wells *et al.* (2015) reported that the preserved subgroup was older than both the deteriorated and compromised subgroups, which did not differ.

3.1.2. Sex

3.1.2.1. Subgroups based on current cognitive function.

Eight studies classified participants into subgroups using sex/gender-adjusted data (see Table B in Appendix) Of these eight studies, one reported a significant difference in the distribution of female and male participants between patient subgroups. Based on participant performance on a multidimensional neuropsychological battery, Van Rheenen *et al.* (2017) reported that the relatively intact subgroup had a more even distribution of male and female participants, with a disproportionally higher number of males in the remaining intermediate and impaired subgroups.

Of the 12 studies that did not use sex/gender-adjusted data to subgroup participants, two reported a significant difference in the distribution of female and male participants between patient subgroups. Turetsky *et al.* (2002) reported a higher proportion of males in the memory impaired subgroup, compared to a higher proportion of females in the intermediate and relatively intact subgroups. In contrast, Carruthers *et al.* (2019a) reported a higher proportion of females in the impaired subgroup, compared to a higher proportion of males in the intermediate and relatively intact subgroups whilst comparing three emergent subgroups based on executive function.

3.1.2.2. Subgroups based on putative symptom trajectory

One of the eight putative symptom trajectory studies comparing sex reported a significant difference in the distribution of male and female participants between patient subgroups. Wells *et al.* (2015) reported a higher proportion of males in the compromised subgroup compared to the preserved subgroup; both of which reportedly did not differ from the deteriorated subgroup. Sex was not adjusted for during the cognitive subgrouping procedure of this study.

3.1.3. Education

3.1.3.1. Subgroups based on current cognitive function.

Two studies classified participants into subgroups using education-adjusted data (see Table C in Appendix), with both detecting significant differences in education between patient subgroups. Bowie *et al.* (2006) reported that memory impaired patients had completed less years of formal education compared to the relatively intact patients. The intermediate subgroup did not significantly differ in years of education from both the relatively intact or impaired subgroups. In contrast, Liu *et al.* (2011) detected two pairwise differences. The impaired subgroup in their study was reported to have completed less years of education compared to the intermediate-executive deficit subgroup, with the intermediate-attention deficit subgroup found to have completed less years of education compared to the relatively intact subgroup.

Of the 14 studies that did not use education-adjusted data to subgroup participants, eight reported a significant difference in education between patient subgroups. Overall, relatively intact subgroups were consistently found to have higher educational attainment than the impaired subgroups. In a series of studies conducted by the same lab comparing two cognitive subgroups, impaired patients had a reduced high school completion rate compared to relatively intact patients; this finding was detected when the subgroups were based on verbal ability (Heinrichs *et al.*, 2008), general cognitive ability (Heinrichs *et al.*, 2015) and verbal-declarative memory (Heinrichs *et al.*, 2017). Similarly, Kremen *et al.* (2000) and Rüsch *et al.* (2007) each reported on two study-specific subgroups based on multiple neurocognitive domains and executive function, respectively, and both found that the impaired patients had completed fewer years of formal education compared to the relatively intact patients. Bowie *et al.* (2006) found that the memory impaired subgroup had completed

fewer years of formal education compared to the relatively intact memory subgroup, but not the intermediate subgroup; with the relatively intact and intermediate subgroups found not to differ.

Seaton *et al.* (1999) compared four emergent subgroups based on participant intelligence quotient (IQ), using the Weschler Adult Intelligence Scale-Revised (WAIS-R). These authors reported that patients with impaired IQ, had successfully completed fewer years of education than those with high IQ and those with a specific motor deficit, but not compared to those with a low-average IQ. In comparing four emergent cognitive subgroups based on participant performance on a comprehensive neurocognitive test battery, Geisler et al. (2015) reported that a subgroup characterised by diminished intellectual function completed fewer years of education compared to the remaining subgroups defined by diminished fluency, diminished verbal learning and motor control, and diminished face memory and processing speed. Dawes *et al.* (2011) reported on five emergent subgroups uniquely based on profiles of relative cognitive strengths and weaknesses, and found that a subgroup characterised by relative strengths in verbal comprehension and visual learning/memory, with a relative weakness in abstraction successfully had completed more years of education than the four remaining subgroups characterised by differing combinations of cognitive strengths and weaknesses spanning multiple neurocognitive domains.

3.1.3.2. Subgroups based on putative symptom trajectory

Six of the eight studies which compared education between subgroups detected a significant difference. The preserved subgroup was consistently found to have the highest educational attainment. Two studies reported that preserved patients completed more years education compared to the deteriorated and compromised patients (Kremen *et al.*, 2008, Wells *et al.*, 2015) and another three studies detected significantly more years of education

amongst the preserved patients compared to the compromised patients only (Czepielewski *et al.*, 2017, MacCabe *et al.*, 2012, Potter and Nestor, 2010). Wells *et al.* (2015) also reported that the deteriorated subgroup completed more years education compared to the compromised subgroup. Comparing a slightly different combination of putative symptom trajectories, Weinberg *et al.* (2016) reported that the preserved subgroup completed more years of education than two subgroups reflecting severely and moderately deteriorated symptom trajectories, which did not differ.

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3.1.4. Age of onset

3.1.4.1. Subgroups based on current cognitive function

Three of the 18 studies comparing the age of onset of patient subgroups detected significant differences. Comparing two cognitive subgroups, Kremen *et al.* (2000) reported that the impaired patients had a younger age of onset compared to the relatively intact patients. Likewise, when comparing three memory-based subgroups, Turetsky *et al.* (2002) found that the impaired subgroup had an earlier age of onset compared to the relatively intact subgroup but not the intermedaite subgroup, which did not differ. Using a unique combination of data-driven methodologies, Hill *et al.* (2002) compared four emergent cognitive subgroups based on profiles of relative weaknesses and strengths. It was reported that a subgroup characterised by prominent memory dysfunction but more intact executive skills had an earlier age of onset compared to a subgroup characterised by relatively intact cognitive function. No other age of onset between-subgroup differences were detected.

3.1.4.2. Subgroups based on putative symptom trajectory

Two of the seven studies comparing the age of onset of patient subgroups detected significant differences. Compromised patients were reported by Kremen *et al.* (2008) as having a younger age of onset compared to both deteriorated and preserved patients. In contrast, Wells *et al.* (2015) reported that the deteriorated subgroup had a younger age of onset compared to the preserved subgroup, with no other differences detected.

3.1.5. Illness duration

3.1.5.1. Subgroups based on current cognitive function

Six of the 18 studies comparing illness duration of patient subgroups detected significant differences. Butler *et al.* (1992), Kremen *et al.* (2000) and Ortiz-Gil *et al.* (2011) all compared illness duration across two cognitive subgroups and reported that the relatively intact patients were characterised by a shorter illness duration compared to impaired patients. In comparing three memory-based subgroups, Turetsky *et al.* (2002) reported that the relatively intact subgroup was characterised by a shorter illness duration compared to the intermediate subgroup, but not the impaired subgroup. After both characterising four subgroups, the low-average IQ subgroup investigated by Seaton *et al.* (1999) had a shorter illness duration compared to a motor deficit subgroup, whilst Geisler *et al.* (2015) reported that a subgroup characterised by diminished IQ had a reduced illness duration compared to a verbal learning/motor control deficit subgroup.

3.1.5.2. Subgroups based on putative symptom trajectory

No significant differences were detected in any of the five studies that examined illness duration between subgroups.

3.1.6. Positive symptoms

3.1.6.1. Subgroups based on current cognitive function

Five of the 25 studies comparing positive symptom ratings between patient subgroups reported significant differences. Using the Brief Psychotic Rating Scale (BPRS), McDermid Vaz and Heinrichs (2006) employed two different subgrouping methodologies to examine two and three memory-based subgroups. Whilst comparing the two memory-based subgroups, it was reported that the impaired subgroup exhibited a more severe global positive symptom score compared to the relatively intact subgroup. Furthermore, whilst using a similar tripartite memory-based subgrouping methodology to that of Turetsky *et al.* (2002), it was found that the intermediate subgroup had a larger global positive symptom score compared to the impaired subgroup, but not the relatively intact subgroup. The relatively intact and impaired subgroups did not reportedly differ. Similarly, Turetsky *et al.* (2002) reported that patients with intermediate and relatively intact memory received a greater delusion symptom score, as rated using the Scale for the Assessment of Positive Symptoms (SAPS), compared to memory impaired patients. Furthermore, the memory impaired and intermediate subgroups were also found to have a greater SAPS formal through disorder symptom rating compared to the relatively intact subgroup.

In comparing four study-specific cognitive subgroups on the SAPS, Hill *et al.* (2002) reported that a subgroup characterised by relatively intact cognitive functioning had greater delusion symptom ratings compared to a moderately impaired subgroup. Geisler *et al.* (2015) also compared four study-specific emergent subgroups on the SAPS and reported that a subgroup characterised by diminished processing speed and face memory, and diminished IQ had a greater SAPS total symptom score compared to a subgroup with diminished fluency skills.

3.1.6.2. Subgroups based on putative symptom trajectory

One of the eight studies comparing positive symptom ratings across subgroups detected a significant difference. According to Wells *et al.* (2015), patients following a compromised symptom trajectory were found to have reported more hallucinations than patients following a preserved symptom trajectory, as measured using the Diagnostic Interview for Psychosis (DIP). Conversely, patients with preserved cognition reported a greater lifetime incidence of delusions compared to the compromised patients.

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3.1.7. Negative symptoms

3.1.7.1. Subgroups based on current cognitive function

Ten of the 25 studies comparing negative symptom ratings between patient subgroups reported significant differences. More severe negative symptom ratings were consistently detected amongst subgroups with worse cognitive impairment. Whilst comparing DIP global negative symptom scores between two cognitive subgroups based on participant performance on a neuropsychological battery, Green *et al.* (2013) reported that cognitively impaired patients were rated as having more severe global negative symptoms compared to relatively intact patients. Guimond *et al.* (2016) compared two verbal memory-based subgroups and reported that patients characterised by impaired verbal memory received worse total negative symptom ratings on the Assessment of Negative Symptoms (SANS) compared to patients with relatively intact verbal memory. McDermid Vaz and Heinrichs (2006) compared BPRS global negative symptom scores between both two and three memory-based subgroups. For the two subgroups, memory impaired patients exhibited worse global negative symptom ratings compared to relatively intact patients, whilst for the three subgroups, the intermediate

subgroup was found to exhibit more severe negative symptoms compared to the relatively intact subgroup; no other differences were detected.

Comparing three memory-based subgroups on both specific and global negative symptom scores from the SANS, Turetsky *et al.* (2002) reported that the impaired and intermediate patients were rated as having more severe alogia, attention and global negative symptoms compared to the relatively intact patients. The intermediate subgroup was also found to have more severe affective flattening, anhedonia-asociality and avolition-apathy symptom ratings compared to the relatively intact subgroup and more severe affective flattening compared to the impaired subgroup. Likewise, patients with intermediate or impaired memory were reported by Bowie *et al.* (2004) to have more severe overall negative symptoms as rated by the Positive and Negative Syndrome Scale (PANSS) compared to the relatively intact patients. The impaired subgroup received a more severe PANSS negative symptom rating compared to the intermediate memory subgroup. Employing a unique tripartite subgrouping methodology based on verbal learning potential, Vaskinn *et al.* (2008) reported that patients characterised as being non-learners had more severe PANSS total negative symptom ratings compared to patients labelled as high achievers and learners.

Using a neuropsychological battery to characterise three cognitive subgroups, Ammari *et al.* (2010) reported that cognitively impaired patients had a more severe PANSS total negative symptom rating in comparison to relatively intact patients. The intermediately impaired subgroup did not reportedly differ in negative symptom ratings from either the relatively intact or impaired subgroups. Carruthers *et al.* (2019a) reported that patients with impaired executive function had a more severe negative symptom rating compared to patients with intermediate and relatively intact executive function, which did not differ. Whilst comparing four cognitive subgroups, Liu *et al.* (2011) reported that the impaired subgroup had more severe SANS total symptom ratings compared to the relatively intact and

intermediate-executive deficit subgroups. The intermediate-attention deficit subgroup was also found to have a more severe total negative symptom rating compare to the three remaining subgroups.

3.1.7.2. Subgroups based on putative symptom trajectory

Six of the eight studies comparing negative symptom ratings between patient subgroups reported significant differences. The preserved subgroup consistently rated as having less severe negative symptoms. Four studies administered the SANS to investigate negative symptoms across subgroups, with consistent results. Czepielewski *et al.* (2017) reported that patients following a compromised cognitive trajectory were rated higher on the SANS total symptom score compared to preserved patients. Likewise, Potter and Nestor (2010) found that the compromised subgroup had more severe SANS negative symptom ratings compared to the preserved subgroup, as well as the deteriorated subgroup. Patients following a deteriorated symptom trajectory were also found to have a higher SANS negative symptom rating than preserved patients.

MacCabe *et al.* (2012) found that patients with a high IQ following a putatively deteriorated trajectory and those classified as having typical IQ had a more severe SANS total negative symptom rating compared to patients with a high IQ classified as following a putatively preserved trajectory. The typical IQ subgroup was also reported to have more severe negative symptoms in comparison to the deteriorated subgroup. Wells *et al.* (2015) indicated that compromised patients received worse affective flattening, anhedonia-asociality and avolition-apathy SANS symptom ratings in comparison to preserved patients, but not the deteriorated patients, which also did not differ. Using the PANSS, Weinberg *et al.* (2016) reported that the severely deteriorated subgroup had larger PANSS total negative symptom ratings in comparison to the preserved and moderately deteriorated subgroups, which did not

differ. Similarly, Yasuda *et al.* (2020) found that deteriorated patients were rated higher on the total PANSS negative symptom score compared to preserved patients.

3.1.8. Disorganised symptoms

3.1.8.1. Subgroups based on current cognitive function

One of five studies comparing disorganised symptom severity across subgroups detected a significant difference. Calculated using the bizarre behaviour and positive formal thought disorder symptom scores from the SANS, Liu *et al.* (2011) reported that the relatively intact subgroup had a higher disorganised symptom score in comparison to the impaired subgroup. Furthermore, the intermediate-attention deficit and the impaired subgroups had worse disorganised symptom scores compared to the intermediate-executive function deficit subgroup.

3.1.8.2. Subgroups based on putative symptom trajectory

Kremen *et al.* (2008) was the only study to compare disorganised symptoms between subgroups and did not detect any between subgroup differences.

3.1.9. Depression

Four studies investigating current cognitive function and two studies investigating putative symptom trajectories compared depressive symptoms across subgroups, with no significant differences detected in any study.

3.1.10. Psychosocial functioning

3.1.10.1. Subgroups based on current cognitive function

Six of the ten studies comparing psychosocial functioning between patient subgroups detected significant differences. Cognitively impaired subgroups were rated as having more severe functional impairments. Kremen *et al.* (2000) and Green *et al.* (2013) both compared functional differences between two cognitive subgroups using the General Assessment Scale and the Global Assessment of Functioning (GAF) respectively and found that impaired patients were more functionally disadvantaged compared to the relatively intact patients. Greater levels of unemployment were also found by Green *et al.* (2013) amongst the impairment subgroup. Whilst Heinrichs *et al.* (2008), Muharib *et al.* (2014) and Ammari *et al.* (2010) all found that cognitively impaired patients were rated worse on both the Multidimensional Scale of Independent Functioning and the University of California San Diego Performance Skills Assessment (UPSA) compared to relatively intact patients. Bowie *et al.* (2004) reported that amongst three memory-based subgroups, the impaired patients scored lower on the physical self-maintenance subscale of the Alzheimer's Disease Assessment Scale, as well as the impulse, self-care, social and total subscales of the Social Adaptive Functioning Evaluation (SAFE) in comparison to patients with intermediate and relatively intact memory. The intermediate subgroup was also found to be more impaired on the social and total SAFE subscales compared to the relatively intact subgroup.

3.1.10.2. Subgroups based on putative symptom trajectory

Two of the three studies comparing functional outcomes between patient subgroups detected significant differences. Ammari *et al.* (2014) reported that premorbidly impaired and deteriorated patients were rated as more impaired on the UPSA compared to preserved patients. Whilst Wells *et al.* (2015) found that the compromised subgroup was rated worse on the GAF than both the deteriorated and preserved subgroups. Compromised patients were

also reported as being less likely to be employed within 12 months of participating compared to both the deteriorated and preserved patients.

4. Discussion

The aim of this systematic review was to summarise the current evidence concerning the demographic, clinical and psychosocial characteristics of the cognitive subgroups of SSD. Across all studies reviewed, there was little evidence to suggest that subgroups differed in age or sex, positive, disorganised or depressive symptom severity, age of onset or illness duration. Conversely, the synthesis revealed that subgroups were consistently distinguished by education, negative symptom severity and degree of functional impairment. Overall, SSD patients classified as having more severe cognitive impairments were found to have completed fewer years of formal education, exhibit more severe negative symptoms and have more severe functional impairments compared to patients with relatively intact or preserved cognitive function.

More years of formal education was found to be a consistent feature unique to the better performing cognitive subgroups. That is, SSD patients with relatively intact cognition appeared to have engaged in formal schooling for a longer period than those with cognitive impairments. For trajectory-based cognitive subgrouping studies, this effect is not surprising. This is because subgroups in these studies are categorised according to the disparity between their current and premorbid cognition, where measures of the latter assess crystallised intelligence and are highly correlated with educational attainment (DeQuardo *et al.*, 1995, Marriott and Care, 2004). That the educational attainment effect was also evident in studies of subgroups derived from measures of current cognitive functioning suggest clear parallels in the two subgrouping approaches. It is also consistent with evidence of normal levels of

crystallised intelligence in cognitively intact SSD patients, but lower levels in patients who are cognitively impaired (Karantonis *et al.*, 2020c, Van Rheenen *et al.*, 2017).

Unfortunately, the available evidence does not allow for clear inferences on the developmental directionality of this effect. That is, we are not able to tell whether innate cognitive ability influenced the capacity of this subgroup to persist with formal education, or whether persistent engagement in formal education in this subgroup protected against illness-related cognitive impairment. Whilst years of formal education do not necessarily equate to scholastic ability, attaining a higher level of education has been associated with better neuropsychological test performance (Le Carret *et al.*, 2003, Van Der Elst *et al.*, 2006). This may be related to educational attainment fostering crystallised intelligence, which in turn builds cognitive reserve (Stern, 2002). In SSD, cognitive reserve as indexed by higher premorbid IQ, has been shown to facilitate the maintenance of adaptive cognitive function in spite of the adverse effects of age/illness (Van Rheenen *et al.*, 2019). In light of this, further studies examining covariation in educational and cognitive trajectories across cognitive subgroups of SSD are warranted.

Members of patient subgroups characterised by better cognitive performance were also consistently rated as having less severe negative symptoms compared to their more cognitively impaired counterparts. Lower ratings for global and specific negative symptoms were prevalent in both the relatively intact (current cognitive function) and preserved (putative symptom trajectory) cognitive subgroups; this observation suggests that the association between cognition and negative symptomology persists regardless of the subgrouping methodology and further highlights the parallels amid the two approaches. Much empirical research, meta-analytical reviews, and expert commentaries have examined the link between negative symptoms and cognition in SSD (e.g. de Gracia Dominguez *et al.*, 2009, Foussias & Remington, 2010, Hovington and Lepage, 2014, Yolland *et al.*, 2020), with

the prevailing consensus being that more severe negative symptoms are associated with worse cognitive impairment. The findings of this review appear to add further support towards this assertion. Although several studies did not detect any significant difference in negative symptoms across subgroups (e.g. Butler *et al.*, 1992, Muharib *et al.*, 2014) or between relatively intact and intermediate patient subgroups (Ammari *et al.*, 2010, Carruthers *et al.*, 2019b), worse negative symptomology was typically more characteristic of subgroups defined by worse cognitive functioning.

Much like most of the literature surrounding negative symptoms and cognition in SSD, the results of the present review do not permit any commentary as to whether negative symptoms impair cognition, if cognitive impairments facilitate more pronounced negative symptomology or if negative symptoms and cognitive impairment are two co-occurring yet distinct manifestations of SSD. Notwithstanding this limitation, the identification of a subgroup of SSD patients characterised by severe cognitive dysfunction and more pronounced negative symptoms is noteworthy. Negative symptoms *and* cognitive impairments are considered to be resistant to conventional pharmacological treatments (Bobes *et al.*, 2010, Choi *et al.*, 2013, Fusar-Poli *et al.*, 2015). Both are uniquely linked to more severe daily disability amongst individuals with SSD (Strassnig *et al.*, 2018), with negative symptoms also found to partially mediate some of the longitudinal relationships between cognition and functional outcomes (Bowie *et al.*, 2008, Ventura *et al.*, 2009). Taken together, it is reasonable to suggest that the subgroup of SSD patients who are characterised by severe cognitive impairments and also suffer from pronounced negative symptoms are likely to experience worse daily disability due to the disorder.

Finally, patients characterised by more severe cognitive impairments were consistently rated worse on assessments of global and domain specific psychosocial functioning compared to patients with relatively intact or preserved cognitive function. The

link between cognitive dysfunction and functional impairments has been well documented in the broader SSD literature, with the prevailing consensus being that worse cognitive function predicts more severe functional impairment (Fett *et al.*, 2011, Green *et al.*, 2019a, Halverson *et al.*, 2019). Unsurprisingly, the cognitive subgrouping literature reviewed here supported the contention that the functional capacity of patients with SSD is linked to their cognitive ability. Whilst not novel, these findings further highlight the importance of considering the cognitive capacity of patients before engaging them in psychosocial skills training that targets functional outcomes.

Overall, this review provided a summation of the state of the current evidence concerning the clinical, demographic and functional characteristics of the cognitive subgroups of SSD. The lack of consistent differences between subgroups for the majority of the non-cognitive characteristics reviewed above provides partial support for the notion that cognitive subgrouping in SSD is not simply reflecting a rehash of previously identified subtypes of SSD. This is tempered however, by evidence that three characteristics well known to be associated with cognition in SSD *were* consistently different between the cognitive subgroups. That is, with some exceptions, patients characterised by relatively intact levels of cognitive function were consistently found to have attained a higher level of education, whilst being rated as having less severe negative symptoms and a better functional capacity compared to patients characterised by more severe levels of cognitive impairment. Although there were some instances of mixed results pertaining to the intermediate subgroup, it was apparent that being allocated to a subgroup with more severe cognitive impairments corresponded to worse evaluations on these three characteristics. Thus, despite evidence that the majority of the non-cognitive characteristics reviewed here did not differ amongst subgroups, the fact that the three features most commonly linked to cognition in non-subgroup studies of SSD differed between subgroups – and did so whilst adhering to a

sequence from better to worse – blurs understandings about the extent to which the cognitive subgrouping approach is representing separate subtypes versus subdivisions along a linear continuum of cognitive symptom severity. It is likely that this cognitive subgrouping approach may represent too narrow of a strategy to investigate the meaningful symptom heterogeneity present within SSD; and in its current form may simply be identifying subdivisions along a linear cognitive continuum. Broader batteries which combine paper-and-pencil cognitive assessments with other biomarkers such as saccade and auditory evoked responses, such as that used in a latent profile analysis by Clementz et al., (2016), may provide more detailed and useful insights into the marked symptom heterogeneity present within SSD.

Irrespective of this, the considerable body of literature on the cognitive and non-cognitive features of SSD cognitive subgroups highlight one area of research that may benefit from this approach; cognitive remediation. Indeed, patients with SSD who can be identified as having relatively intact levels of current cognitive function and low negative symptom severity are likely to respond better to cognitive based treatments targeting functional outcomes compared to patients in subgroups characterised by more severe cognitive impairments and worse negative symptoms (Reser *et al.*, 2019). Future cognitive subgrouping research should thus move beyond simply characterising the cognitive and clinical features of these subgroups to directing attention toward understanding the potential therapeutic benefits that may arise from separately targeting specific subgroups with different interventions. At the very least, future interventions that target cognition or functional outcomes need to be cognisant of the meaningful cognitive heterogeneity that exists within the SSD population, and the potential effects the interplay of subgroup membership and associated clinical characteristics may have on outcomes. Furthermore, the findings of the current systematic review also encourage future cognitive subgrouping research to consider

the educational level and negative symptoms of SSD patients prior to subgrouping. This is to ensure that any emergent cognitive subgroups accurately reflect cognitive capacities rather than being confounded by education and/or negative symptoms.

5. Declarations

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Table 1. Methodological summary of studies investigating subgroups based on current cognitive function

Study	SD Sample	Subgrouping: Domain	Subgrouping: Measure	Cognitive subgroups [predetermined performance criteria[#]]: *n* (% of *N*)	Non-cognitive measures compared between subgroups
Two subgroups: Predetermined performance criteria					
Butler et al. (1992)	8 Sz	Executive function	WCST	WCST Non-Impaired: [≤ 30 Perseverative Responses]: 20 (46) WCST Impaired: [> 30 Perseverative Responses]: 24 (54)	BPRS, SANS, SAPS
Guimond et al. (2016)	0 Sz	Verbal learning	HVLT	Low-to-Mild Verbal Memory Impairment [HVLT z-score > -1.4]: 23 (46) Moderate-to-Severe Verbal Memory Impairment [HVLT z-score ≤ -1.4]: 27 (54)	SANS, SAPS
Heinrichs et al. (2008)[a]	51 SSD	Vocabulary	WAIS-III	Verbally Superior [Vocabulary ≥ 14]: 25 (17) Comparison Patients [Vocabulary < 14]: 126 (83)	MINF, PANSS, UPSA
Heinrichs et al. (2015)[a]	6 SSD	Multiple	MCCB	Cognitively Normal Range [overall composite score, 40-60]: 18 (18) Cognitively Below Normal Range [overall composite score, 20-39]: 19 (20)	PANSS
Heinrichs et al. (2017)[a]	59 SSD	Verbal learning	HVLT	Normal Range [-1 ≤ composite CVLT z-score ≤ 1]: 23 (17) Below Normal Range [-1 > composite CVLT z-score < 1]: 129 (83)	MINF, PANSS
Kremen et al. (2000)[b]	6 Sz	Multiple	Study specific battery	Neuropsychologically Within Normal Limits [< 2 domain z-scores ≥ 2 *s.d.* below HC]: 17 (23) Neuropsychologically Abnormal [≥ 2 domain z-scores ≥ 2 s.d. below HC or 1 domain z-score ≥ 3 s.d. below HC or "neuropsychologically meaningful" within-person domain discrepancies]: 58 (77)	GAS, SANS, SAPS
Kremen et al. (2001)[b]	6 Sz	IQ	WAIS-R	Average IQ [IQ, 95-110]: 20 (27) Low Average IQ [IQ, 81-94]: 16 (44)	SANS, SAPS
McDermid Vaz & Heinrichs (2006)[a]	02 Sz	Verbal learning	HVLT	Memory Impaired [total immediate recall < 2 *s.d.* from HC norms] 43 (78) Memory Unimpaired [total immediate recall ≥ 2 *s.d.* from HC norms]: 12 (22)	BPRS, SIP
Muharib et al. (2014)[a]	00 SSD	Multiple	MCCB	Normal Range Cognition [overall composite score ≥ 40]: 14 (14) Cognitively Impaired [overall composite score < 39]: 21 (21)	MINF, PANSS, UPSA
Ortiz-Gil et al. (2011)	9 Sz	Multiple	BADS, RBMT	Cognitively Preserved [RMBT ≥ 8; BADS ≥ 12]: 23 (47) Cognitively Impaired [RMBT < 7; BADS < 8]: 26 (53)	CGI, PANSS
Palmer et al. (1997)	71 Sz	Multiple	Study specific battery	Neuropsychologically Normal [≤ 1 domain rating ≥ 5; Global Index < 5[$]]: 44 (28) Neuropsychologically Impaired [≥ 2 domain ratings ≥ 5; Global Index ≥ 5[$]]: 124 (72)	BPRS, HAM-D, SANS, SAPS
Rüsch et al. (2007)	3 Sz	Executive function	WCST	High WCST Performers [≥ 5 categories achieved]: 30 (57) Poor WCST Performers [≤ 2 categories achieved]: 21 (37)	PANSS
Two subgroups: Exploratory data-driven					

Cobia et al. (2011)	9 Sz	ultiple	Study specific battery	Neuropsychologically Near Normal: 45 (57) Neuropsychologically Impaired: 32 (43)	SANS, SAPS
Green et al. (2013)	17 SSD	ultiple	Study specific battery	Cognitively Spared: 323 (52) Cognitive Deficit: 294 (48)	DIP, GAF, NES
Three subgroups: Predetermined performance criteria					
Amami et al. (2010)[a]	54 SSD	ultiple	CVLT, WAIS-III	Cognitively Normal [Total immediate recall, 43-60; Vocabulary, Matrix Reasoning, 8-13]: 24 (16) Verbal Memory Impaired [Total immediate recall < 43; Vocabulary, Matrix Reasoning, 8-13]: 26 (17) Generalized Impairment [Total immediate recall < 43; Vocabulary, Matrix Reasoning < 8]: 23 (15)	MSIF, PANSS, UPSA
Bowie et al. (2004)	89 Sz	emory	CERAD Word List Task	Cortical [Delayed recall, Learning, Recognition z-score ≥ -1]: 34 (4) Subcortical [Delayed recall, Learning z-score < -1; Recognition z-score ≥ -1]: 156 (26) Unimpaired [Delayed recall, Learning, Recognition z-score < -1]: 238 (40)	ADAS, PANSS, SAFE
Vaskinn et al. (2008)[c]	10 SSD	earning potential	VLT	High Achievers [Immediate recall Trial 1 z-score ≥ 0]: 24 (21) Learners [Immediate recall Trial 1 z-score < 0; Learning slope z-score ≥ 0]: 61 (56) Non-learners [Immediate recall Trial 1, Learning slope z-score < 0]: 25 (23)	GAF, PANSS
Vaskinn et al. (2014)[c]	39 Sz	Q	WASI-II	Superior IQ [IQ ≥ 120]: 20 (10) Normal IQ [IQ, 100-115]: 111 (57) Low IQ [IQ, 80-95]: 65 (33)	GAF, IDS-C, PANSS
Three subgroups: Predetermined data-driven					
McDermid Vaz & Heinrichs (2006)[a]	02 Sz	erbal learning	CVLT	Cortical: 15 (27) Subcortical: 28 (51) Unimpaired: 12 (22)	BPRS, SIP
Tursetsky et al. (2002)	16 Sz	erbal learning	CVLT	Unimpaired: 59 (51) Subcortical: 36 (31) Cortical: 21 (18)	BPRS, SANS, SAPS
Three subgroups: Exploratory data-driven					
Carruthers et al. (2019)	10 SSD	xecutive function	WCST	Relatively Intact: 72 (34) Moderate Impairment: 114 (54) Severe Impairment: 24 (12)	BPRS
Van Rheenen et al. (2017)	67 Sz	ultiple	MCCB	Relatively Intact: 75 (13) Mild-Moderate: 262 (47) Relatively Severe: 227 (40)	BPRS
Four or more subgroups: Predetermined data-driven					
Geisler et al. (2015)	29 Sz	ultiple	Study specific battery	Diminished Fluency: 38 (30) Diminished Verbal Learning/Motor Control: 26 (20) Diminished Face Memory/Processing Speed: 21 (16) Diminished IQ: 44 (34)	CDSS, SANS, SAPS, SAS
Four or more subgroups: Exploratory data-driven					
Dawes et al. (2011)	14 SSD	ultiple	Study specific battery	K1: 19 (13) K2: 38 (26) K3: 40 (28) K4: 17 (12) K5: 30 (21)	HAM-D, PANSS

Hill et al. (2002)	51 Sz	ultiple	S tudy specific battery	Cluster 1: 15 (10) Cluster 2: 76 (50) Cluster 3: 41 (27) Cluster 4: 19 (13)	BP RS, SANS, SAPS
Liu et al. (2011)	49 Sz	ttention, Executive functioning	C PT, WCST	Non-deficit: 106 (19) Executive Function Deficit: 109 (20) Attention Deficit: 146 (27) Attention & Executive Function Deficit: 188 (34)	SA NS, SAPS
Seaton et al. (1999)	02 Sz	Q	W AIS-R	High: n.s. Motor Deficit: n.s. Low: n.s. Impaired: n.s.	BH PR, BPRS, SANS

Note: [a,b,c] denote studies with likely sample overlap; [#]Where applicable; [$] Each domain was co-rated by two neuropsychologists from 1 (above average) to 9 (severe impairment), as well as a global index.

ADAS, Alzheimer's Disease Assessment Scale; BADS, Behavioural Assessment of the Dysexecutive Syndrome; BHPR, Bunney-Hamburg Psychosis Rating; BRPS, Brief Psychotic Rating Scale; CEARD, the Consortium to establish a registry for Alzheimer's disease; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; DIP, Diagnostic Interview for Psychosis; GAF, Global Assessment of Functioning; GAS, Global Assessment Scale; HAM-D Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptomatology-Clinician rated; IQ, intelligence quotient; ISLT, International Shopping List Task; MCCB; MATRICS Consensus Cognitive Battery; MSIF, Multidimensional Scale of Independent Functioning; NES, Neurological Evaluation Scale; n.s., not stated; PANSS, Positive and Negative Syndrome Scale; RBMT, Rivermead Behavioural Memory Test; SAFE, Social Adaptive Functioning Evaluation; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; *s.d.*, standard deviation SIP, Sickness Impact Profile; SSD, schizophrenia spectrum disorder; Sz, schizophrenia; UPSA, University of California San Diego Performance Skills Assessment; WAIS, Weschler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test

Table 2. Methodological summary of studies investigating subgroups based on putative symptom trajectory

Study	Sample	Measure		Cognitive subgroups [predetermined performance criteria[#]]: *n* (% of *N*)	Non-cognitive measures compared between subgroups
		Estimated premorbid IQ	current IQ		
Predetermined performance criteria					
Amamari et al. (2014)	101 SSD	WRAT-3: Reading	AIS-III	Preserved Patients [epIQ, cIQ ≥ 90; epIQ-cIQ$_{diff}$ < 10]: 32 (32) Deteriorated Patients [epIQ-cIQ$_{diff}$ ≥ 10]: 26 (26) Premorbidly Impaired Patients [epIQ, cIQ < 90; epIQ-cIQ$_{diff}$ < 10]: 13 (14)	MSIF, PANSS, UPSA
Czepielewski et al. (2017)	74 Sz	WAIS-III: Vocabulary	MS-III	pIQ+/COG+ [pIQ, COG ≥ 10th percentile of HC distribution]: 25 (27) pIQ+/COG- [pIQ ≥ 10th percentile of HC distribution > COG]: 31 (34) pIQ-/COG- [pIQ, COG < 10th percentile of HC distribution]: 36 (39)	SAPS, SANS
Kremen et al. (2008)	60 Sz	WRAT-3: Reading	AIS-R	Preserved [epIQ ≥ 90; epIQ-cIQ$_{diff}$ < 10]: 22 (28) Deteriorated [epIQ-cIQ$_{diff}$ ≥10]: 40 (50) Compromised [epIQ, cIQ < 90; epIQ-cIQ$_{diff}$ ≤ 10: 18 (22)	SANS, SAPS
McCabe et al. (2012)	80 SSD	NART	AIS-III	High IQ-intact [epIQ > 115; epIQ-cIQ$_{diff}$ < 10]: 10 (20) High IQ-decline [epIQ > 115; epIQ-cIQ$_{diff}$ > 10]: 24 (48) Typical IQ [epIQ < 110]: 16 (32)	SANS, SAPS
Yasuda et al. (2020)	71 Sz	JART	AIS-III	Preserved IQ [epIQ ≥ 90; epIQ-cIQ$_{diff}$ < 10]: 54 (32) Deteriorated IQ [epIQ-cIQ$_{diff}$≥10]: 111 (65)	GAF, PANSS
Predetermined data-driven					
Potter & Nestor (2010)	33 SSD	WRAT-3: Reading	AIS-III	Preserved: 21 (29) Deteriorated: 21 (29) Compromised: 31 (42)	PANSS
Exploratory data-driven					
Weinberg et al. (2016)	66 SSD	WTAR	AIS-III	Putatively Preserved: 25 (26) Moderately Deteriorated: 33 (34) Severely Deteriorated: 27 (28) Compromised: 11 (12)	DASS, PANSS, SF-36, SQLS
Wells et al. (2015)	34 Sz	WTAR	BANS	Preserved: 157 (29) Deteriorated: 239 (45) Compromised: 138 (26)	GAF, SANS, SAPS

Note: [#]Where applicable; DASS, Depression Anxiety and Stress Scale; cIQ, current IQ; COG, current cognition; epIQ, estimated premorbid IQ; epIQ-cIQ$_{diff}$, difference between epIQ and cIQ; GAF, Global Assessment of Functioning; IQ, intelligence quotient; MSIF, Multidimensional Scale of Independent Functioning; NART, National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; pIQ+/COG+, intact premorbid IQ, current cognitive functioning; pIQ+/COG-, intact premorbid IQ, impaired current cognitive functioning; pIQ-/COG-, impaired premorbid IQ, current cognitive functioning; JART, Japanese version of the National Adult Reading Test; RBANS; Repeatable Battery for the Assessment of Neuropsychological Status; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey Version 2; SQLS, Schizophrenia Quality of Life Scale; SSD, schizophrenia spectrum disorder; Sz, schizophrenia; UPSA, University of California San Diego Performance Skills Assessment; WAIS, Weschler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WMS; Weschler Memory Scale; WRAT-3, Wide Range Achievement Test 3; WTAR, Wechsler Test of Adult Reading

Table 3. Result summary of studies investigating subgroups based on current cognitive function

Study	Multiple comparison correction reported	Age	Sex / Gender	Education	Age of onset	Illness duration	Positive symptoms	Negative symptoms	Disorganised symptoms	Depression	Functional outcome
Two subgroups: Predetermined performance criteria											
Butler et al. (1992)	x						✓	✓	✓	-	-
Guimond et al. (2016)	x						✓	✓	✓	-	-
Heinrichs et al. (2008)[a]	x	#					✓	✓	✓	-	✓
Heinrichs et al. (2015)[a]	√						✓	✓	✓	-	-
Heinrichs et al. (2017)[a]	√	#	&				✓	✓	✓	-	x
Kremen et al. (2000)[b]	√	#	&				✓	✓	✓	-	✓
Kremen et al. (2001)[b]	x	#					✓	✓	✓	-	-
McDermid Vaz & Heinrichs (2006)[a]	x	#	&				-	✓	✓	-	-
Muharib et al. (2014)[a]	√						✓	✓	✓	-	✓
Ortiz-Gil et al. (2011)	x	#	&				-	-	-	-	-
Palmer et al. (1997)	√	#	&				✓	✓	✓	✓	-
Rüsch et al. (2007)	√						✓	✓	✓	-	-
Two subgroups: Exploratory data-driven											
Cobia et al. (2011)	√						✓	✓	✓	-	-
Green et al. (2013)	√						✓	✓	✓	-	✓
Three subgroups: Predetermined performance criteria											
Ammari et al. (2010)[a]	x	#					✓	✓	✓	-	✓
Bowie et al. (2004)	√	#	&	$			✓	✓	✓	-	✓
Vaskinn et al. (2008)[c]	√	#	&				✓	✓	✓	-	x
Vaskinn et al. (2014)[c]	x						✓	✓	✓	✓	x
Three subgroups: Predetermined data-driven											
McDermid Vaz & Heinrichs (2006)[a]	x	#	&				-	✓	✓	-	-
Turetsky et al. (2002)	x						-	-	-	-	-
Three subgroups: Exploratory data-driven											
Carruthers et al. (2019)	√						✓	✓	✓	✓	-
Van Rheenen et al. (2017)	√	#	&				-	-	-	-	-
Four or more subgroups: Predetermined data-driven											
Geisler et al. (2015)	x						✓	✓	✓	✓	-

Four or more subgroups: Exploratory data-driven											
Dawes et al. (2011)	√	#	&								x
Hill et al. (2002)	√						/ x				
Liu et al. (2011)	√	#	&	$							
Seaton et al. (1999)	x										
Number Significant / Total Tested		/ 23	/ 20	0 / 16	/ 18	/ 18	/ 25	0 / 25	/ 5	/ 4	/ 10
% Significant		7%	5%	3%	7%	3%	0%	0%	0%	%	0%
Number Significant / Total Tested following removal of studies which did not report correcting for multiple comparisons		/ 15	/ 14	/ 11	/ 11	/ 11	/ 13	/ 15	/ 3	/ 2	/ 6
% Significant		3%	%	4%	8%	%	%	7%	3%	%	0%

Note: [a,b,c] denote studies with likely sample overlap; [#] studies that adjusted for age prior to subgrouping; [&] studies that adjusted for sex prior to subgrouping; [$] studies that controlled for education; √, significant subgroup differences reported; x, no significant subgroup differences reported; -, variable not compared

Table 4. Result summary of studies investigating subgroups based on putative symptom trajectory

Study	Multiple comparison correction reported	Age	Sex / Gender	Education	Age of onset	Illness duration	Positive symptoms	Negative symptoms	Disorganised symptoms	Depression	Functional outcome
Predetermined performance criteria											
Ammari et al. (2014)	√	#						x			√
Czepielewski et al. (2017)	√							x			
Kremen et al. (2008)	x	#						x			
MacCabe et al. (2012)	√	#						x			
Yasuda et al. (2020)	√	#						x			
Predetermined data-driven											
Potter & Nestor (2010	√	#						x			
Exploratory data-driven											
Weinberg et al. (2016)	√	#						x			x
Wells et al. (2015)	√	#						√			√
Number Significant / Total Tested		/ 8	/ 8	/ 8	/ 7	/ 5	/ 8	1 / 8	/ 1	/ 2	2 / 3
% Significant		3%	5%	5%	9%	%	3%	1 5%	%	%	6 7%
Number Significant / Total Tested following removal of studies which did not report correcting for multiple comparisons		/ 7	/ 7	/ 7	/ 6		/ 7	1 / 7	/ 0	/ 2	2 / 3
% Significant		4%	9%	1%	7%		4%	1 6%	%	%	6 7%

Note: # studies that controlled for age prior to subgrouping; √, significant subgroup differences reported; x, no significant subgroup differences reported; -, variable not compared

Appendix

Scopus Search Syntax

(TITLE-ABS-KEY (*schizo** OR *psychosis*) AND TITLE-ABS-KEY (*cognit** AND *cluster*) OR TITLE-ABS-KEY (*cognit** AND *heterogeneity*) OR TITLE-ABS-KEY (*cognit** AND *"neuropsychologically normal"*) OR TITLE-ABS-KEY (*cognit** AND *subgroup*)) AND DOCTYPE (*ar*) AND PUBYEAR > *1979*

PubMed Search Syntax

((schizophrenia spectrum and other psychotic disorders[MeSH Terms])) AND (cognition[Title/Abstract] OR cognitive[Title/Abstract] OR neuropsychology[Title/Abstract] OR neuropsychologically[Title/Abstract] OR intelligence[Title/Abstract] OR intellect[Title/Abstract] OR memory[Title/Abstract] OR learning[Title/Abstract] OR attention[Title/Abstract] OR vigilance[Title/Abstract] OR speed of processing[Title/Abstract] OR executive[Title/Abstract] OR flexibility[Title/Abstract] OR reasoning[Title/Abstract] OR problem solving[Title/Abstract]) AND (cluster[Title/Abstract] OR subgroup[Title/Abstract] OR subtyp[Title/Abstract] OR heterogeneity[Title/Abstract])) AND ("1980/01/01"[Date - Publication] : "3000"[Date - Publication]))

Web of Science Search Syntax

((TS=(schizo* OR psychosis) AND (TS=(cognit* AND cluster) OR TS=(cognit* AND subgroup) OR TS=(cognit* AND subtype) OR TS=(cognit* AND heterogeneity) or TS=(cognit* AND "neuropsychologically normal"))) OR (TI=(schizo* OR psychosis) AND (TI=(cognit* AND cluster) OR TI=(cognit* AND subgroup) OR TI=(cognit* AND subtype) OR TI=(cognit* AND heterogeneity) or TI=(cognit* AND "neuropsychologically normal")))) AND LANGUAGE:(English) AND DOCUMENT TYPES: (Article)

Table A. Summary of method reportedly used to age-adjust performance on subgrouping variables prior to subgrouping.	
Study	Method
Current cognitive function	
Two subgroups: Predetermined performance criteria	
Heinrichs et al. (2008)	Age-scaled WAIS-III Vocabulary scores.
Heinrichs et al. (2017)	Raw CVLT data were converted to standardised scores using the CVLT manual's age- and sex-stratified norms.
Kremen et al. (2000)	Regression equations based on HCs were used to predict neuropsychological test scores, given an individual's age, sex and parental education. Age-, sex- and parental education-adjusted standardised residuals were used to subgroup participants.
Ortiz-Gil et al. (2014)	Cognitive subgroups matched on age and gender
Palmer et al. (1997)	Raw data were converted to age-, education- and gender-corrected *T*-scores.
Three subgroups: Predetermined performance criteria	
Ammari et al. (2010)	Age-scaled WAIS-III Vocabulary and Matrix Reasoning scores.
Bowie et al. (2004)	Standardised based on age-, education-, gender- and ethnicity-adjusted HC norms.
Vaskinn et al. (2008)	Raw CVLT data were converted to age- and gender-corrected z-scores based on normative data.
Three subgroups: Exploratory data-driven	
Van Rheenen et al. (2017)	Raw data were converted to age- and gender-corrected *T*-scores.
Four or more subgroups: Exploratory data-driven	
Dawes et al. (2011)	Raw BVMT and HVLT data were adjusted for age, other tests were adjusted for age, education and in some cases gender and ethnicity.
Liu et al. (2011)	CPT and WCT performance were adjusted for age, education and sex based on HC sample.
Putative symptom trajectory	
Predetermined performance criteria	
Ammari et al. (2014)	Age-adjusted IQ and premorbid IQ
Kremen et al. (2008)	Age-adjusted IQ and premorbid IQ
MacCabe et al. (2012)	Age-adjusted IQ and premorbid IQ
Yasuda et al. (2020)	Age-adjusted IQ and premorbid IQ
Predetermined data-driven	
Potter and Nestor (2010)	Age-adjusted IQ and premorbid IQ
Exploratory data-driven	
Weinberg et al. (2016)	Age-adjusted IQ and premorbid IQ

Wells et al. (2015)	Composite IQ score based on age-adjusted RBANS and age-adjusted premorbid IQ.

Note: BVMT, Brief Visual Memory Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; HVLT, Hopkins Verbal Learning Test; HC, healthy control; RBANS, The Repeatable Battery for the Assessment of Neuropsychological Status; WCST, Wisconsin Card Sorting Test; WAIS-III, Weschler Adult Intelligence Scale

Table B. Summary of method reportedly used to adjust for sex prior to subgrouping.	
Study	Method
Current cognitive function	
Two subgroups: Predertmined performance criteria	
Heinrichs et al. (2017)	Raw CVLT data were converted to standardised scores using the CVLT manual's age- and sex-stratified norms.
Kremen et al. (2000)	Regression equations based on HCs were used to predict neuropsychological test scores, given an individual's age, sex and parental education. Age-, sex- and parental education-adjusted standardised residuals were used to subgroup participants.
Ortiz-Gil et al. (2014)	Cognitive subgroups matched on age and gender
Palmer et al. (1997)	Raw data were converted to age-, education- and gender-corrected *T*-scores.
Three subgroups: Predertmined performance criteria	
Vaskinn et al. (2008)	Raw CVLT data were converted to age- and gender-corrected z-scores based on normative data.
Three subgroups: Exploratory data-driven	
Van Rheenen et al. (2017)	Raw data were converted to age- and gender-corrected *T*-scores.
Four or more subgroups: Exploratory data-driven	
Dawes et al. (2011)	Raw BVMT and HVLT data were adjusted for age, other tests were adjusted for age, education and in some cases gender and ethnicity.
Liu et al. (2011)	CPT and WCT performance were adjusted for age, education and sex based on HC sample.
Note: BVMT, Brief Visual Memory Test; CPT, Continuous Performance Test; CVLT-II, California Verbal Learning Test; HVLT, Hopkins Verbal Learning Test; HC, healthy control; MCCB; MATRICS Consensus Cognitive Battery; WCST, Wisconsin Card Sorting Test	

Table C. Summary of method reportedly used to adjust for education prior to subgrouping.	
Study	Method
Current cognitive function	
Three subgroups: Predetermined performance criteria	
Bowie et al. (2004)	Standardised based on age-, education-, gender- and ethnicity-adjusted HC norms.
Four or more subgroups: Exploratory data-driven	
Liu et al. (2011)	CPT and WCT performance were adjusted for age, education and sex based on HC sample.
Note: CPT, Continuous Performance Task; HC, healthy control; WCST, Wisconsin Card Sorting Test	