COGNITIVE IMPAIRMENT IN PSYCHOSIS

LANDSCAPE REPORT

CONTENTS

1. EXECUTIVE SUMMARY

INTERVENTION/ METHODOLOGY	VOLUME OF RESEARCH (in early psychosis)	EFFICACY (from systematic reviews or meta-analysis)	BARRIERS	RECOMMENDATIONS
PHARMACEUTICAL	Medium ■■◪□	Small effects ●○○○	• Non-adherence • Trial recruitment • Study design	• Well-powered antipsychotic dose reduction trials • Shared decision-making research • Alternative research designs
NUTRIENTS	Low ■□□□	Small effects ●○○○	• Inconsistencies in the application/ assessment of nutrients • Cognition not assessed as a primary outcome • Usually given adjunctively, so difficult to determine unique effects	• Account for interaction with pharmaceuticals • Acceptability research
COGNITIVE REMEDIATION AND COMPENSATION	Medium ■■◪□	Small effect (inconsistent) ●○○○	• Engagement/attrition • Resources/costs • Non-personalised interventions	• Co-designed compensatory interventions for early psychosis • Combine with psychosocial interventions (e.g., supported education/employment) • Investigate mechanisms of treatment effects • Develop briefer and simplified programs for non-experts
SOCIAL COGNITION INTERVENTIONS	Low ■□□□	Medium-large effect (inconsistent) ●●◪○	• Engagement/attrition • Inconsistencies in assessment scales • Resources/costs	• Designed for early psychosis • Enhanced engagement (blended digital, and shorter interventions) • Investigate key ingredients • Bridging and adjunct therapies
SLEEP INTERVENTIONS	None □□□□	Unknown ○○○○ ?	• Cognition not assessed as a primary outcome	• Trial sleep interventions in early psychosis • Investigate relationship between cognition and sleep in early psychosis • Pre-clinical sleep model research to guide new treatments
EXERCISE, MIND-BODY, MINDFULNESS	Low ■□□□	Small effect (inconsistent) ●○○○	• Engagement • Lack of consideration of psychosocial factors (e.g., motivation, withdrawal, paranoia)	• Exploration of use globally, including barriers and facilitators • Modify mindfulness-based therapies for cognitive impairment • Adjunct therapies • Supervised programs

(Table continues)

INTERVENTION/ METHODOLOGY	VOLUME OF RESEARCH (in early psychosis)	EFFICACY (from systematic reviews or meta-analysis)	BARRIERS	RECOMMENDATIONS
DIGITAL INTERVENTIONS, VIRTUAL REALITY	Low ■□□□	Inconclusive ○○○○ ?	• Limited interventions/ investigations • Engagement • Integration with existing service contexts	• Blended and adapted interventions • VR for social cognition and general cognition • Industry partnerships • Telehealth
BRAIN STIMULATION	Low ■□□□	Inconclusive ○○○○ ?	• Engagement - with frequent clinic attendance • Trial designs • Limited theoretical models of stimulation parameters	• Large multi-site trials of multi-session interventions • Home-administered protocols • Cost effective individualised treatments • Investigator brochure
PEER WORK	Low ■□□□	Inconclusive ○○○○ ?	• Limited investigations • Focus on general mental health • Implementation issues	• Exploratory research • Upskill workforce in cognition • Targeted peer support - family, vocational, decision making • Strengths-based approach
LIVED EXPERIENCE	Low ■□□□	Inconclusive ○○○○ ?	• Limited investigations	• True co-design research • Consistent frameworks • Shared decision making
IMPLEMENTATION SCIENCE	Low ■□□□	Inconclusive ○○○○ ?	• Limited adoption • Limited tailored strategies	• Hybrid effectiveness-implementation designs • Cost-effectiveness research
SUMMARY	Volume of investigations is variable (but low in most areas)	Inconsistent effects across domains (but generally small or inconclusive)	• Limited investigations/ evidence • Non-adherence/attrition rates • Engagement • Lack of involvement of key stakeholders • Lack of implementation research	• Investigate whether age or stage of illness moderates outcomes • Implementation research and metrics • Lived experience involvement to determine priorities, needs, barriers, facilitators and co-design interventions

TABLE LEGEND

CRITERIA FOR VOLUME OF RESEARCH

None	no investigations for UHR or FEP
Low	few clinical trials, no reviews
Medium	1-3 systematic reviews and/or meta-analysis, or at least two systematic reviews and/ or meta-analysis and recent trials if the systematic reviews were conducted a few years prior
High	>3 systematic reviews and/or meta-analysis and recent trials if systematic reviews were conducted a few years prior

CRITERIA FOR LEVEL OF EFFICACY

Small	small effect sizes for domains or global functions
Medium	medium effect sizes for domains or global functions
Large	large effect sizes for domains or global functions
Inconclusive	significant and non-significant findings across different trials
Inconsistent	effects within domains are not consistent across different trials or reviews

2. BACKGROUND

Psychotic disorders affect approximately 1% of the population and usually emerge prior to the age of 25 (1, 2). They are the most severe and disabling of all mental disorders, and the social and economic costs of psychotic disorders are disproportionately high relative to their prevalence (3, 4). Early intervention for psychosis is cost-effective and clinically most effective in reducing the burden associated with the illness (5-7). Cognitive impairment is a core feature of psychotic disorders (8), therefore best practice should involve tailored treatment that addresses cognitive impairment when applicable (3, 9).

Research has consistently shown that large and widespread cognitive impairments (mean performance that is 0.7-1.5 standard deviations below healthy peers in *all* domains of cognitive functioning) are experienced by people with first-episode psychosis (FEP) (10, 11) (Figure 1). These impairments are evident before the commencement of antipsychotic medication (12). Cognitive impairments emerge early, often well before the onset of full-threshold psychotic disorder, as shown in population cohort studies (13, 14) and studies of people at ultra-high or clinical high risk for psychosis (UHR/CHR) (15). Small to moderate cognitive impairments are observed in UHR/CHR cohorts (15-17) (Figure 1), with larger impairments observed in the subgroup that later transition to first-episode psychosis (15). Cognitive impairments at the time of the first psychotic episode tend to be as severe as the impairments observed in more persisting illness (Figure 1) and persist during periods of symptomatic remission (17, 18), with recent longitudinal evidence suggesting there may be further deterioration in some cognitive domains many years after the first-episode (19, 20). The importance of identifying and treating cognitive impairment is also emphasised by its inclusion in some clinical practice guidelines around the world (3, 21) and through its inclusion in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a domain of psychotic disorders that must be considered in clinical practice (22).

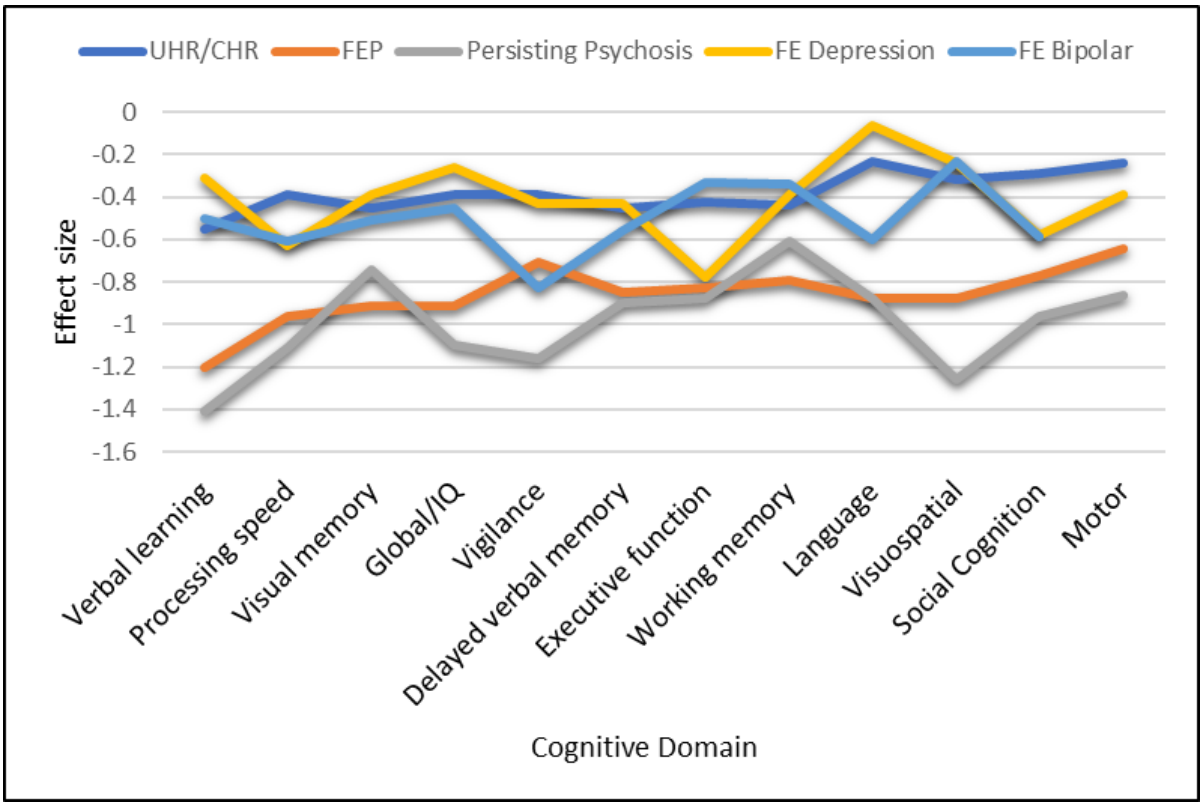

Figure 1. Severity of cognitive impairment relative to healthy populations in UHR/CHR, FEP, persisting psychosis, first-episode depression* and first-episode bipolar* disorder (data extracted from meta-analyses (11, 15, 23-30)). *data on language, visuospatial, social cognition and motor, not only first-episode depression/bipolar. *Note:* Social cognition refers to 'theory of mind' measures.

These group-level findings, however, mask significant variability in cognitive ability among people with psychotic disorders. An extensive body of cross-sectional research has parsed the cognitive heterogeneity observed in psychosis using data-driven cluster analytic approaches. Recent reviews suggest the presence of between 2-5 latent cognitive subgroups across the psychotic disorder spectrum (31, 32). These latent subgroups differ on the *degree* rather than *type* of cognitive impairment observed. Specifically, no impairment, mild-moderate impairment, and severe impairment is often observed across subgroups. A similar pattern of cognitive clusters is found in UHR/CHR cohorts (33). Thus, individual variability in cognitive ability should be carefully considered when designing and interpreting trials of interventions for cognition in psychosis (34).

> *"I couldn't concentrate at work, kept making mistakes…and just overall wasn't learning as fast as the others were…that is why I got fired from the job."*
>
> *"[Cognitive problems] made me feel like I was an idiot."*
>
> *"I am often very foggy and concentrating is almost impossible. It's so frustrating because I used to have an amazing memory and now I really struggle."*

While psychotic and other psychiatric symptoms generally respond to medication and psychotherapy, cognitive impairments often interfere with full functional recovery, including the ability to achieve vocational success and independent living (35). These personal costs are paralleled by enormous caregiver burden and societal and economic costs, which include direct health service use, unemployment, productivity loss, and premature death (36). Qualitative research with FEP patients has shown that cognitive impairments are distressing and negatively impact self-confidence, vocational functioning and activities of daily living (37). This is consistent with quantitative studies, where cognitive impairment is strongly associated with poor long-term functional outcomes, such as gaining and maintaining employment, (35, 38, 39). This is a significant problem because functioning in areas such as employment is rated by young patients as a more important treatment goal than alleviation of psychiatric symptoms (40, 41). Given the impact of, and relationship between, cognitive impairment and functional disability in psychotic disorders, the US Food and Drug Administration (FDA) determined that, for approval of a cognitive-enhancing drug for schizophrenia, concurrent change on a co-primary measure of functional outcome is required (42). The recognition of the need for the transfer of cognitive gains to functional improvement in daily life is also strongly endorsed through expert consensus on cognitive remediation for schizophrenia (43, 44). Thus, cognitive enhancement *and* improvements in functioning should both be considered when designing and evaluating interventions for cognitive impairment in psychosis.

The *specificity* of the cognitive impairments observed in psychotic disorders (that is, whether they are also observed in other mental disorders) remains an area of ongoing debate. There are now a number of commentaries and reviews suggesting that cognitive impairment is a transdiagnostic feature of psychopathology (45-49). Indeed, before cognitive impairment was included as one of the dimensional domains for clinical consideration in psychotic disorders in the DSM-5, there was significant debate as to whether cognitive impairment should be included as part of the diagnostic criteria of schizophrenia (50, 51). The decision was made *not* to include cognitive impairment as a specific diagnostic criterion for schizophrenia because it was recognised that cognitive impairment is not specific to schizophrenia and is thus not useful for differential diagnosis (52). Similarly, population cohort studies show that below-average cognitive function in childhood and adolescence is associated with a 2-3 times greater risk for *any* mental disorder later in life (53, 54). Higher levels of *general* psychopathology in adulthood are associated with poorer cognitive functioning at age three (48). Meta-analytical evidence shows significant impairments in multiple cognitive domains early in the course of several mental illnesses, including psychotic disorders (11), bipolar disorder (26, 55), and major depression (25, 56, 57). The differences observed between psychotic disorders and other disorders tends to be in the *number of people affected* by cognitive impairment (58) and the *severity* of cognitive impairment, with more people with psychosis experiencing cognitive impairment and impairments tending to be larger than other conditions (26, 59) (Figure 1). Current work is exploring whether there are some cognitive processes outside traditional cognitive batteries (for example, predictive processing, multisensory integration) that may be more specifically affected in psychotic disorders (60, 61), but this is preliminary and not addressed in this report. In sum, cognition is a critical determinant in recovery from mental illness, with greatest impacts observed in psychosis; there is a great need to investigate tailored treatments for cognitive impairment before chronic progression has occurred, to improve functional outcomes.

3. CURRENT RESEARCH AND DESIGN LANDSCAPE

3.1 SCOPE AND METHODOLOGY

POPULATION

Given the early emergence of cognitive impairment in psychotic disorders, the focus of this landscape report was on *early intervention* for cognitive impairment in psychosis. Thus, the populations of interest included:

i. Help-seeking at **ultra-high or clinical high risk for psychosis (UHR/CHR)**. Search terms included "psychosis risk" OR "prodrom*" OR "ultra-high risk" OR "clinical high risk" OR "genetic high risk" OR "at risk mental state" OR "at-risk mental state" OR "basic symptoms".
ii. **Recent-onset or first-episode psychosis (FEP)**: defined as full-threshold psychotic disorder within the previous five years. Search terms included "first episode psychos*" OR "recent onset psychos*" OR "first onset psychos*" OR "early psychos*" OR "early onset psychos*" OR "first episode schizophren*" OR "recent onset schizophren*" OR "first onset schizophren*" OR "early schizophren*" OR "early onset schizophren*".

The full spectrum of psychotic disorders was considered, including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-induced psychotic disorder, psychotic disorder not otherwise specified, and depression/bipolar disorder with psychotic features. All age groups were considered.

If there was limited investigation of a particular intervention in UHR/CHR or FEP populations, we broadened the scope to consider interventions that could have great impact on these populations in the future. For example, we considered why and how results emerging from more persisting psychosis populations (for example, chronic/established schizophrenia) or other mental health populations (for example, attention-deficit/hyperactivity disorder: ADHD) could be translated to a younger/high-risk/more recent-onset psychosis population and the particular advantages and challenges that could emerge from doing so.

INTERVENTIONS

Cognitive enhancement or remediation interventions can be broadly categorised into three modes of delivery: biochemical, behavioural, and physical (62). **Biochemical cognitive interventions** include pharmaceutical, nutritional or natural agents that alter biochemistry and enhance function. **Behavioural cognitive interventions** comprise strategies or actions that an individual must use or perform to experience cognitive enhancement. They can include ensuring optimal duration and quality of sleep, exercise, cognitive training, and use of compensatory strategies. **Physical interventions**, such as non-invasive brain stimulation, may also augment cognitive function by directly modulating neural activity. Examples include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). This categorisation was used to guide the scope of interventions included in the report.

OUTCOMES

As cognitive impairment is more strongly associated with functional outcomes than are psychotic symptoms (39, 63), we focused on both **cognitive enhancement** and **functional outcomes** of interventions for cognition in psychosis. For a review or study to be considered, either cognition alone, or both cognition and functioning outcomes were required. As all fundamental cognitive and social cognitive domains are found to be impaired in psychotic disorders, both global and domain-specific cognitive outcomes were considered. Global functioning or specific domains, such as activities of daily living, social functioning, and vocational functioning were considered.

SOURCES OF INFORMATION

A scoping literature review (covering a publication timeframe from 1990-current) and a small number of interviews with mental health professionals in psychosis care from low- and middle-income resource settings were the sources of information for this report.

The **Scoping Review** was based on searching the following sources of information:

i. Orygen's 'Evidence Finder' database (EFD): https://www.orygen.org.au/Training/Evidence-Finder. The EFD is populated from EMBASE, MEDLINE, PsycINFO and Cochrane Library databases. Priority was given to summarising the key or most recent systematic reviews/meta-analyses relating to the particular intervention. Individual studies were only included if no systematic reviews had been published. The EFD includes all randomised and non-randomised controlled trials, and systematic reviews (including meta-analyses) of interventions targeting mental health disorders, including psychosis.
ii. Preprint repositories: https://psyarxiv.com/ (psychology), https://www.medrxiv.org/ (medicine) and https://www.biorxiv.org/ (science).
iii. Clinical trial registries: https://clinicaltrials.gov/, https://www.anzctr.org.au/, https://bepartofresearch.nihr.ac.uk/ and https://www.isrctn.com/. The journal *TRIALS* was searched for recently published protocols (past three years only).
iv. Grey literature, focusing on low- and middle-income resource settings, was searched including CADTH, EThOS, HMIC, OpenGrey, and The Grey Literature Report databases.

A small number of **interviews with mental health professionals in low- and middle-income resource settings** were conducted because it was anticipated that these settings would be poorly represented in the scientific literature reviewed above. The director of Orygen Global facilitated introductions to potential interviewees. Six people who were familiar with the psychosis treatment systems in Zambia, Nigeria, Kenya, Brazil and India volunteered to contribute and were interviewed via Zoom or provided written responses via email (between 26 August and 18 September 2021). The interviews/information gathered was facilitated through the use of a semi-structured interview schedule (provided separately from this report). The information gathered from these interviews is summarised in section 3.13.

STRENGTH AND QUALITY OF ASSESSMENT

The strength and quality of systematic reviews and meta-analyses was assessed using "A Measurement Tool to Assess Systematic Reviews" Version 2 (AMSTAR-2) (64), which is an updated version of the original AMSTAR and is designed to better capture review quality and confidence in findings. Strength of evidence was judged based on whether the intervention had been subject to systematic review (that is, several RCTs), the aggregate effect size, publication bias, and heterogeneity in existing data.

3.2 PHARMACEUTICALS

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Antipsychotics

Antipsychotic medications (APs) have long been the first-line intervention for the treatment of psychotic disorders. They are often key to stabilising the individual's positive psychotic symptoms. A common characteristic of many APs is that they act as dopamine D2 receptor antagonists, as excess activity in the mesolimbic pathway is associated with positive psychotic symptoms, and reduced activity in the mesocortical pathway with negative symptoms (65). APs are broadly divided into **typical** (or "first-generation") and **atypical** (or "second-generation"), with atypical APs only transiently occupying D2 receptors (66) and having been introduced as a solution to the extrapyramidal side effects which are commonly seen following treatment with typical APs (65, 66). While APs are generally an effective treatment for psychotic symptoms, it is possible that higher occupancy of D2 receptors through higher AP dosage may exacerbate the cognitive impairments that often accompany psychotic disorders (67).

Small molecules for cognitive enhancement

Antipsychotic medications primarily target the dopamine pathway. However, cognitive dysfunction in psychotic disorders is complex, involving many different neurotransmission systems (68). Small molecule drugs are a class of medications with low molecular weight, capable of modulating biochemical processes. They can easily cross the cell membrane to act within cells, and are generally taken orally as inactive prodrugs, which become active *in vivo* (69). Small molecule drugs developed to enhance cognition in psychotic disorders have been designed to act on a number of neurotransmission systems, including glutamatergic, cholinergic, serotonergic, dopaminergic, GABAergic, and noradrenergic systems. A summary of pro-cognitive agents that have been trialled in psychotic disorders, and the neurotransmission systems they act on, can be found in Table 1. Most of the research into cognitive-enhancing medication has been conducted in adult populations with established psychotic disorders, mainly schizophrenia, with the exception of modafinil and minocycline, which are discussed separately below.

Table 1. Pro-cognitive agents

Neurotransmission system	Agent	Neurotransmission system	Agent
Glutamatergic	Ampakine CX 516	**Cholinergic**	Donepezil
	D-Cycloserine		Galantamine
	Amantadine		Nicotine
	Glycine		DMXB-A
	Pregnenolone		Tropisetron
	Minocycline		Varenicline
	D-serine		TC-5619
	Benzoate		RG3487
	Org 25935		Encenicline
	Sarcosine		ABT-126
Serotonergic	Mianserin	**Dopaminergic**	D-amphetamine
	Citalopram	**GABAergic**	MK-0777
	Latrepirdine	**Noradrenergic**	Atomoxetine
	Fluvoxamine		Norepinephrine
	AVN-211		

While the exact mechanism of **modafinil** in cognitive enhancement is unknown, modafinil acts on several neurotransmission systems, including dopaminergic, glutamatergic, serotonergic, noradrenergic and GABAergic systems (70). As a psychostimulant, modafinil promotes wakefulness. However, it is structurally different to amphetamine, and exhibits different effects in the central nervous system. Although first marketed for the treatment of narcolepsy, other uses of modafinil have been explored, including potential pro-cognitive effects (70).

Minocycline is a tetracycline medication, traditionally used for its broad-spectrum antibiotic properties to treat infection (71). Due to its high lipid solubility and small molecular size, minocycline readily crosses the blood-brain barrier, where it exerts anti-inflammatory effects and has neuroprotective properties (71). Pre-clinical models of neurodegenerative disease have also highlighted the anti-apoptotic actions of minocycline (72). These non-antibiotic properties may allow minocycline to prevent, or even reverse, neuropathic brain changes that contribute to cognitive impairment in people with psychotic disorders.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

Antipsychotics

The most recent systematic review addressing the relationship between APs and cognition was conducted by Karson and colleagues (73). This systematic review included 19 studies, seven of which reported on cognitive outcomes in FEP. Taken together, the studies included in this review demonstrated that both typical and atypical APs provided small but durable benefits for cognitive functioning (both randomised and non-randomised trials) over follow-up periods from six months to two years. A slightly older meta-analysis by Désaméricq and colleagues (74) compared the impact of multiple APs in nine studies (six of which were also identified in the Karson review). This meta-analysis identified that olanzapine and quetiapine were associated with significantly greater improvement in composite cognitive scores than amisulpride and haloperidol. When considering separate cognitive domains, the authors also identified several significant differences in the effect of the various APs. Ziprasidone was associated with a significantly greater improvement in memory than amisulpride or haloperidol, and olanzapine was also associated with a greater improvement in memory than haloperidol. Quetiapine was associated with the largest improvements in tasks of attention and processing speed, but both ziprasidone and olanzapine also provided more improvement than amisulpride, risperidone, and haloperidol. Finally, quetiapine and olanzapine were associated with significantly greater improvement in executive functioning than amisulpride. All other comparisons between the five APs were non-significant. In summary, this meta-analysis did find significant differences in the profile of cognitive change following treatment with different APs (74). However, all of these changes had a small effect size (0.06-0.34). Neither of these reviews investigated the impact that other factors (such as age or gender) might have on the effect of APs on cognition, and therefore further examination of the possible contribution of these factors is required. Given that these reviews are several years old, more recent trials were also searched. Hou and colleagues (75) recently published a randomised controlled trial comparing the impact of three atypical antipsychotics. FEP Participants in this trial were randomised to receive olanzapine, aripiprazole, or risperidone, and cognition was assessed using an adapted version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery at six- and 12-month follow-ups. All groups showed slight improvement over the follow-up period with no significant differences between the three medications.

In summary, the literature identified here suggests **the use of APs for treatment of FEP may confer significant but small benefits for cognition**. However, even following antipsychotic-related improvement, the cognitive functioning of individuals with FEP was still significantly impaired relative to healthy controls (73). Findings comparing different APs on cognitive change are largely inconclusive. A major issue with the literature in this area is the lack of study designs that include a placebo group. As such, it is difficult to identify whether improvements were a direct result of AP treatment, or due to other factors such as practice effects, cognitive development, or general recovery. A study that aimed to overcome this issue was the STAGES trial (76), which recruited AP-naïve individuals in Melbourne, Australia. Participants were randomised to receive APs or placebo for six months, both in conjunction with intensive psychosocial treatment, at baseline and followed-up over a six-month period. Findings indicated no significant difference between the two groups on social and occupational functioning at follow-up (77), and cognitive findings will follow shortly.

There is very little research on the effect of antipsychotic medication on cognition in individuals at UHR and the studies that have been conducted are inconclusive. No reviews or RCTs on the impact of APs on cognition in UHR were identified. One naturalistic study of individuals at CHR assessed cognition at baseline and after receiving six months of treatment in a CHR clinic (78). Individuals at CHR who were treated with second-generation APs showed significant decline in verbal learning and sustained attention during the treatment period with a small effect size. Yet, at six-month follow-up, all groups (healthy controls, CHR who were pharmaceutical naïve, on antidepressants, or second-generation APs) improved with small to large effect sizes. A recent meta-analysis by Mei et al., (79) showed no significant benefit of antipsychotic medication in preventing transition to psychosis or reduction of attenuated psychotic symptoms. While risperidone in combination with CBT appeared to confer some benefit over the short term (six months), these benefits were not sustained in longer-term follow-up (79). Given that there is no clear benefit of AP medication for preventing transition, balanced with the potential side effects of such medications, there is even less literature examining secondary outcomes such as cognition.

Ongoing trials of antipsychotics

Adherence to medication is a major clinical issue in psychotic disorders, affecting half of patients with schizophrenia (80), and is a common confounding factor in the evaluation of antipsychotic treatment efficacy. Given this, a trial is underway in first-episode schizophrenia exploring the symptomatic and cognitive benefit of treating patients with long-acting paliperidone palmitate compared with oral risperidone (https://clinicaltrials.gov/ct2/show/NCT01451736). A recent study comparing these domains in FEP found greater symptom improvement in those who received long-acting formulations, as well as a trend towards dose reduction; however, this study did not measure cognitive function (81).

The effect of the atypical antipsychotic blonanserin on cognition is currently being investigated in a study of patients with first-episode schizophrenia (https://clinicaltrials.gov/ct2/show/NCT03784222). However, this study is not a randomised controlled trial, so any cognitive improvement noted would require further research to determine if the effect of blonanserin is greater than placebo.

Antipsychotic dose reduction

Once APs have been initiated, current clinical guidelines suggest that medication should be maintained over at least the first year of treatment (82, 83). Such medications, however, can be associated with a number of negative side effects such as weight gain, changes to blood pressure and blood sugar, drowsiness and lack of motivation. Prolonged or high-dose exposure may impact the dopaminergic systems of the brain and impair cognition (67). Recent research has attempted to balance the successful treatment of psychotic symptoms against these potentially negative side effects by trialling antipsychotic dose reduction. One dose-reduction trial in FEP found a beneficial impact of dose reduction on cognitive outcomes; participants who were assigned to a guided dose-reduction strategy demonstrated significantly greater improvement in processing speed at three-month follow-up compared to those assigned to medication maintenance (84). While there are limited trials in this area, dose reduction may be beneficial for cognitive performance. There are several dose-reduction trials underway, including the REDUCE (85), HAMLETT (86) and TAILOR (87) studies in Australia, the Netherlands and Denmark, respectively, which will all report on cognitive outcomes.

Small molecules for cognitive enhancement

Modafinil

A study of modafinil in 17-35-year-olds experiencing FEP found that verbal working memory, spatial working memory errors, and strategy use improved following a single dose of the medication. However, no effect was observed in impulsivity measures, sustained attention, attentional set-shifting, learning or fluency (88). In the same population, modafinil was noted to improve recognition of sad faces, but had no effect on any other domain of emotion processing (89).

Minocycline

One RCT of minocycline measured cognition in people experiencing a first episode of schizophrenia, schizophreniform, or schizoaffective psychosis. Participants were within five years of symptom onset, and received either placebo or minocycline for a period of 12 months. This study found that there was no effect of minocycline on IQ, or on brain function while completing the N-back test during magnetic resonance imaging (MRI) (72). The researchers concluded that minocycline does not improve cognition or functioning, although a comprehensive cognitive functioning battery was not implemented in the trial.

EVIDENCE FROM OTHER POPULATIONS

Antipsychotic dose reduction

The most recent meta-analysis investigating the impact of dose reduction on cognition was conducted by Tani and colleagues (2020) (90). This review focused on the outcomes of dose-reduction trials for individuals with schizophrenia or schizoaffective disorder, with two studies reporting cognitive outcomes following dose reduction. The findings demonstrated that dose reduction was associated with an increased risk of psychotic relapse, but also with significant improvement in cognitive performance (90). However, these studies only reported a composite cognitive score, and were not restricted to FEP. This review also investigated the factors associated with successful dose reduction. They identified the following factors to be significantly associated with risk of relapse following dose reduction: earlier publication date, study duration of ≥1 year, stable illness, age ≤40 years, outpatient setting, illness or treatment duration ≤10 years, use of typical or long-acting injectable APs, mild or lower symptom severity, reduction rate ≥50%, post-reduction chlorpromazine-equivalent dose ≤200 mg/day, and reduction duration ≤2 months (90). As such, considering these associations in the context of the current report, it is possible that a more gradual dose reduction which still remains above the minimum effective dose, earlier in the course of illness, may be more likely to strike the balance between reduced risk of psychotic relapse and improvement in cognitive performance.

Small molecules for cognitive enhancement

A recent meta-analysis has indicated that there may be a small positive effect of cognitive enhancers acting on the glutamatergic system in terms of overall cognition and working memory in schizophrenia (91). Sub analyses also showed that, while cholinergic agents as a group had no effect on cognition, cholinesterase inhibitors did have a small positive effect on working memory. Drugs targeting serotonergic, dopaminergic, GABAergic and noradrenergic neurotransmission had no effect on cognition, and there was no significant effect of cognitive-enhancing drugs in schizophrenia overall (91). Other reviews and meta-analyses have reported similar findings (92-94), concluding that current evidence does not indicate existing cognitive-enhancing drugs as a promising avenue for reducing cognitive impairment in schizophrenia.

Modafinil

While studies in FEP suggest that modafinil may improve some cognitive domains, these findings are in contrast to a Cochrane Review of modafinil for schizophrenia and related disorders. This comprehensive systematic review and meta-analysis reported no effect on cognition (95), suggesting that modafinil may be differentially effective in younger populations, or those experiencing FEP.

However, the review points out the low quality of studies in this area to date, and with so few studies of cognition in FEP/younger people, it is hard to draw clear conclusions based on the available literature. Modafinil may be of interest for cognitive improvement in psychotic disorders, but future trials must be adequately powered, include comprehensive measurement of cognition, and report outcomes using state of the art guidelines (for example, CONSORT).

Minocycline

A meta-analysis of minocycline versus placebo in adults with schizophrenia or schizoaffective disorder found no significant group difference in global cognition. However, executive functioning scores were significantly higher in the minocycline group following treatment, but with a small effect size (96). A second meta-analysis reported no effect of minocycline on cognitive functioning in adults with schizophrenia (97).

Ongoing trials and development of small molecules for cognitive enhancement

Small molecule glycine transporter-1 (GlyT1) inhibitor BI 425809 is in development to improve cognitive impairment in schizophrenia. Believed to enhance glutamatergic neurotransmission, and neural plasticity, this small molecule represents a promising treatment avenue. A phase II trial of BI 425809 in adults with schizophrenia showed improvements in MATRICS MCCB scores compared with placebo, particularly at higher doses (10mg and 25mg) (98). Another phase II trial is currently underway, combining computerised cognitive training (CCT) with BI 425809 (99), and three multi-centre phase III trials of BI 425809 in adults with schizophrenia have recently opened recruitment (https://clinicaltrials.gov/ct2/show/NCT04860830, https://clinicaltrials.gov/ct2/show/NCT04846881, https://clinicaltrials.gov/ct2/show/NCT03745820).

Also acting on the glutamatergic neurotransmission system is BIIB 104, currently in phase II trials in schizophrenia patients with cognitive impairment (https://clinicaltrials.gov/ct2/show/NCT03745820).

A Phase III trial of raloxifene, a selective oestrogen receptor modulator, is currently underway in young to middle-aged men and women with schizophrenia https://clinicaltrials.gov/ct2/show/NCT03043820. Raloxifene has been repeatedly trialled for the treatment of cognitive deficits in schizophrenia, with a previous systematic review and meta-analysis finding it had no significant effects on cognition (100). However, it is important to note that the majority of participants in previous studies were post-menopausal women, and these findings may not necessarily apply to younger populations, males, or people in the early stages of a psychotic disorder.

Phase I trials of the effects of levetiracetam, siltuximab, tocilizumab, and nimodipine on cognition in participants with schizophrenia are ongoing. A summary of current trials can be found in Table 2.

Table 2. Ongoing trials of small molecules for cognitive enhancement

Agent	Population	Phase	Classification	Recruiting sites (country)	Clinical trial registration
BI 425809	Schizophrenia	II and III	Cognitive enhancer	USA, China, Czechia, Denmark, Germany, Korea, Mexico	https://clinicaltrials.gov/ct2/show/NCT04860830 https://clinicaltrials.gov/ct2/show/NCT04846881 https://clinicaltrials.gov/ct2/show/NCT03745820
BIIB 104	Schizophrenia	II	Cognitive enhancer	USA, Germany, Japan, Spain, UK	https://clinicaltrials.gov/ct2/show/NCT03745820
Raloxifene	Schizophrenia	III	Selective oestrogen receptor modulator	Netherlands	https://clinicaltrials.gov/ct2/show/NCT03043820
Levetiracetam	Schizophrenia	I and II	Anti-convulsant	USA	https://clinicaltrials.gov/ct2/show/NCT02647437 https://clinicaltrials.gov/ct2/show/NCT03034356
Siltuximab	Schizophrenia, Schizoaffective disorder	I and II	Monoclonal antibody	USA	https://clinicaltrials.gov/ct2/show/NCT02796859
Tocilizumab	Schizophrenia, Schizoaffective disorder	I	Immuno-suppressant	USA	https://clinicaltrials.gov/ct2/show/NCT02874573
Nimodipine	Schizophrenia, Schizoaffective disorder	I	Calcium channel blocker	USA	https://clinicaltrials.gov/ct2/show/NCT03671525

STRENGTH/QUALITY OF THE EVIDENCE

Antipsychotics

The quality of the evidence identified here was mixed; a summary of the included reviews is presented in Supplementary Table 1. Of the two reviews identified which considered the impact of APs on cognition, one (74) received AMSTAR ratings suggesting *moderate* confidence in the evidence, while the other (73) received a *critically low* evaluation. The systematic review which considered the effect of AP dose-reduction (90) received a *high* confidence rating. However, it must be noted that this review only identified two studies reporting cognitive outcomes. In summary, future evidence would benefit from improvements such as protocol pre-registration, a more comprehensive assessment of risk of bias and associated impact on the findings, and the role of funders in the conduct and interpretation of individual studies.

Small molecules for cognitive enhancement

The quality of the systematic reviews and meta-analyses was *moderate to high* (Supplementary Table 2). However, the quality of individual studies in each was identified as being generally low, due to methodological issues, in particular sample size and insufficient reporting. It is important to note that none of the reviews focused on UHR/CHR, FEP or young populations.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

Medication nonadherence

Medication nonadherence is common in psychotic disorders, affecting up to 50% of patients with schizophrenia, and represents a significant challenge in successful treatment. One solution is to move towards treatment with long-acting injectable (LAI), rather than oral antipsychotic medication. Despite LAI antipsychotics' effectiveness in preventing relapse, they are underutilised worldwide, particularly in those early in the course of illness. A systematic review identified barriers to the use of LAI, and noted that in both clinicians and patients, feelings of coercion, and inadequate education/knowledge prevented utilisation (101). Adequate education and discussion time between patient and clinician regarding treatment options may help overcome these barriers, and allow for stable medication doses to be achieved more easily. In addition, a second systematic review found that self-efficacy, which can be mediated by a good doctor-patient relationship, consistently promoted antipsychotic medication adherence (102).

Lack of shared decision-making

Shared decision-making (SDM) in healthcare has become increasingly important in recent times (103). This approach is particularly relevant for people receiving antipsychotic medication due to the undesirable side effects that often occur. Despite similar efficacy and varying side effect profiles, patients – especially younger patients – are not routinely offered a say in which medications they are prescribed. SDM may not always be appropriate for those with acute psychotic symptoms, with a recent systematic review identifying serious mental illness, as well as patient education and confidence, as barriers to SDM in those receiving antipsychotic medication (103). However, once medication has stabilised, the patient and clinician should work collaboratively to find a balance between managing psychotic symptoms, and the potential for reduced side effects and improved cognition.

Recruitment to dose-reduction trials

While dose reduction represents a promising opportunity to reduce AP side effects and improve cognition following stabilisation of psychotic symptoms, recruitment into such trials is notoriously difficult. The investigators of the above mentioned dose-reduction trials have recently published an editorial on this matter (104) and identified a number of barriers to recruitment. One primary difficulty of recruiting individuals into RCTs in this field is that potential participants often feel strongly about their AP treatment (in both directions: either feeling fearful of potential relapse, or strongly disliking the side effects of their medications) and therefore do not want to be randomised.

Study design

Methodological issues within studies of cognitive-enhancing drugs, such as small sample size, as well as the relatively small number of studies concerning mechanisms other than those targeting the glutamatergic and cholinergic systems may mean that the potential effects of some agents could not be detected. In addition, very little research has included young people, or people with first-episode psychotic disorders, or people with high-risk mental states. Instead, research has tended to focus on adults with a diagnosis of schizophrenia, and benefits of APs may be maximal at earlier stages of illness. In addition, studies investigating cognitive decline in psychotic disorders tend to recruit individuals without screening for deficits in cognition, with a recent review finding that just over 10% of studies included assessment of cognition as part of their eligibility criteria (34). The same review found that none of the included research stratified participants based on cognitive ability. Thus, potential medication effects may be masked by patient heterogeneity (including patients with no cognitive impairment), resulting in false negative findings and halting further research.

3.3 NUTRIENTS AND COMPLEMENTARY MEDICINES

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Nutrient and complementary medicine is a rapidly growing area of research. What were once labelled pejoratively as alternative treatments are quickly finding a home in modern medical journals (105) and clinical settings. People with psychosis are at increased risk of experiencing nutritional deficiencies (106). Nutrients are critical for health, including neurodevelopment and optimal neuronal function and thus are important to consider in relation to cognitive functioning in psychosis. This section will cover promising nutrient interventions including naturally occurring food and nutrient extracts, amino acids, hormones and herbal supplements for treating cognitive impairment in psychosis.

Lipids

Inflammation plays a role in psychotic disorders and inflammatory processes have been posited as a contributor to the cognitive impairments observed in psychosis (107). Due to their anti-inflammatory properties (108), the essential **omega-3 poly-unsaturated fatty acids (n-3 PUFAs)** eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been highly researched in the treatment of psychotic disorders. Similarly, the omega-3 precursor, **alpha-lipoic acid (ALA)** may also confer antioxidant benefits (109) and has emerged as a potential complementary treatment for schizophrenia, including in addressing the side effects of antipsychotic medication (109).

Vitamins

Several hypotheses regarding cognitive impairment in psychosis have derived from vitamin deficiencies. Specifically, **vitamin B** (including B6, B12, and folic acid) regulates homocysteine levels, which are known to be elevated in schizophrenia. Vitamin B deficiency is associated with neurodevelopmental and cognitive problems and may play a role in addressing elevated homocysteine and psychosis. **Vitamin C** has antioxidant properties and deficiency has thus been linked to depressive symptoms and impaired cognition (110). Finally, **vitamin D** has a role in calcium homeostasis and acts as a neuroprotective agent involved in neurotransmitter expression and neurodevelopment. Deficiency in vitamin D has been implicated as a key risk factor for the development of and symptom expression in schizophrenia, including cognitive deficits in this population (111, 112).

Amino Acids

Amino acids consist of synthesised supplements with a particular focus on N-Methyl-D-aspartic acid (NMDA) derivatives. NMDA receptors are critical for cognitive functioning, particularly learning and memory. Several amino acids play a crucial role as potential biomarkers for cognitive deficits in psychotic disorders (113, 114). As supplements, they may reduce the level of cognitive impairment experienced by those with psychosis. Two key amino acids that have been investigated for their potential cognitive benefits include **taurine** (115) and **n-acetylcysteine (NAC),** a precursor nutraceutical for glutathione (GSH) in the brain (116). Decreased levels of GSH have been associated with increased oxidative stress in people with schizophrenia (117).

Hormones

Hormonal therapies involve the supplementation of naturally occurring hormones that may fluctuate in certain populations and genders; a link between hormones and cognitive functioning has been well-established in general population samples (118). Recent studies have identified **Oxytocin (OT)** as having significant beneficial effects on symptoms of schizophrenia, including cognition (119). The steroid **Dehydroepiandrosterone (DHEA)** has been reported to have neuroprotective benefits including protection against apoptosis (cell death) (120). A precursor to progesterone, **Pregnenolone** has demonstrated enhancements in learning and memory in clinical and preclinical research (121). The hormone **Erythropoietin (EPO)** has demonstrated synaptogenic and neurotrophic activity (122) that may be beneficial in treating symptoms of schizophrenia. **Davunetide** is a peptide that has demonstrated possible benefits for mild cognitive impairment (MCI) and Alzheimer's dementia (AD) (123) and thus may also be beneficial for psychosis-related cognitive impairments.

Compounds

Compounds are organic small molecules that have low molecular weight, but may have significant impact in regulation of biological processes. Two compounds were identified that may have cognitive benefits in psychotic populations. **Sulforaphane (SFN)** has demonstrated antioxidant and anti-inflammatory benefits (124). Further, previous work with **Dimebon (DB)** has focused on its ability to improve cognitive functioning in various populations (125).

Cannabidiol

A component of the cannabis plant, **cannabidiol (CBD) oil** has anti-inflammatory properties with reported positive benefits on positive and negative symptoms of schizophrenia (126). Emerging studies are exploring whether CBD may also confer benefits to cognition.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

Lipids

While n-3 PUFAs have been investigated as a treatment in UHR/CHR (127-129), no reviews have focused on n-3 PUFAs in ameliorating cognitive deficits in early psychosis. One study highlighted its positive effects on functioning and symptoms within a UHR population (130); however, cognitive outcomes were not reported. The cognitive outcomes of a large multi-site international trial of n-3 PUFAs (131, 132), will be reported in the near future. No identified studies have investigated ALA in UHR/FEP.

Vitamins

A recent RCT showed that 12-week vitamin B supplementation (B12, B6 and folic acid) in FEP prevented the cognitive decline (particularly in attention/vigilance) seen in those on placebo (133). No other studies have examined vitamin supplementation in UHR/CHR or FEP.

Amino Acids

One systematic review reported that taurine demonstrated improvements in total symptoms, psychotic symptoms, and functioning in FEP; however, there were no effects on negative symptoms or cognitive outcomes (134). The included data was based on just one RCT in FEP (135). A recent review in chronic schizophrenia and FEP (117) reported benefits of NAC in executive functioning (136), processing speed (136, 137) and working memory (136, 138), yet only benefits in working memory remained following statistical (meta-) analysis. Further research is currently underway in FEP (139) that may provide greater insight into the use of NAC at an earlier stage of illness.

Hormones

A systematic review reported that OT was not beneficial in improving social cognition in early-onset psychosis populations (140). Two reviews assessed the effect of pregnenolone on cognitive outcomes in schizophrenia and schizoaffective disorder (120, 141), with both highlighting positive effects on attention in recent-onset and chronic schizophrenia (142-144). One review also outlined positive findings for executive function (143), verbal memory (142), visual attention (143), and working memory (143, 144).

Compounds

No studies have examined the effects of compounds on cognition in UHR/FEP. Research into SFN is currently underway, with two published protocols outlining their intended use in CHR and FEP samples (145, 146).

Cannabidiol

There is no evidence for CBD effects on cognition in UHR (147) or FEP. However, cognitive outcomes are being measured in two trials in early psychosis currently underway in Denmark (https://clinicaltrials.gov/ct2/show/NCT04105231) and the USA (https://clinicaltrials.gov/ct2/show/NCT04411225).

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

Lipids

In a meta-analysis of anti-inflammatory supplementation in adults with persistent psychotic disorders, pooled data indicated n-3 PUFA consumption (versus placebo) was associated with improved working memory, of small effect (108). Further, a recent study reported that low levels of blood n-3 PUFAs was associated with cognitive impairment in schizophrenia (128). Despite this, investigations have been heavily focused on improving symptoms, with limited investigations for the use or benefits of n-3 PUFAs in cognitive functioning. One open-label ALA study reported benefits in attention and memory in adults with schizophrenia (148). However, as this was a single-arm pilot trial, outcomes should be interpreted with caution.

Vitamins

A systematic review and meta-analysis of 18 RCTs of supplementation with various vitamins in schizophrenia found that no studies reported on cognition outcomes, but recommended this in future research (149). A recent RCT (150) reported improved global cognition following vitamin D supplementation in treatment-resistant schizophrenia (d=0.17).

Amino Acids

In a systematic review and meta-analysis of NAC supplementation in schizophrenia, small improvements in processing speed (SMD=0.27) and moderate improvements in working memory (SMD=0.56) were reported (117). The current evidence for supplemented Glycine for improving cognitive outcomes in schizophrenia populations has been negative (151, 152). A recent meta-

analysis by Marchi et al., (153) reported that, overall, Sarcosine did not have any significant impact on cognitive outcomes as an add-on treatment for people with schizophrenia. D-cycloserine has also reported few benefits to cognitive outcomes in treatment resistant schizophrenia population (154). According to one systematic review and meta-analysis, neither d-serine nor glycine were effective in reducing cognitive deficits in schizophrenia (155). However, since this review, research into d-serine has increased. D-serine, a potent NMDA co-agonist, has shown to improve depressive and general cognitive symptoms in schizophrenia (154). A meta-analysis by Tsai and Lin (152) on NMDA agonists (again in chronic schizophrenia) reported that the pooled data for d-serine was significant for moderately improving cognitive outcomes (ES=0.42), and demonstrates greater bioavailability than its comparator, glycine.

Hormones

Evidence from meta-analysis shows that OT does not significantly improve social cognitive outcomes in schizophrenia (156), although this is based on only three small studies. A systematic review of hormonal interventions (120) highlighted specific benefits of DHEA in sustained attention and visual and movement skills in inpatients and outpatients with schizophrenia (144). A systematic review by Fond et al. (157) reported benefits of EPO in improving executive functions, attention, delayed memory, and language in chronic schizophrenia patients (158). One recent meta-analysis (159) noted improvements in the domains of verbal learning and memory in patients with chronic schizophrenia following davunetide supplementation. However, these results derive from a single study (160).

Compounds

Improved cognitive outcomes were reported in a small group of patients with schizophrenia following SFN supplementation (161). Work into the effects of DB has not shown any significant benefits for people with schizophrenia (162).

Cannabidiol

The evidence for CBD in improving cognition in chronic schizophrenia (163-165) and acute psychosis (166) is weak. Furthermore, a combination of Delta-9-tetrahydrocannabinol (THC) and CBD oil worsened cognitive outcomes in adults with psychosis (167).

STRENGTH/QUALITY OF THE EVIDENCE

Research into the potential benefits of nutrients and other supplements for cognitive function in early psychosis is very limited and a field worthy of further exploration. The characteristics of each review are summarised in Supplementary Table 3. Based on the AMSTAR-2, only two systematic reviews were rated as *high* quality (108, 126). One review was rated as *low* as publication bias was not assessed (117). Several reviews were rated as being of *critically low* quality due to lack of meta-analysis (109, 120, 168). Despite a comprehensive review, Tsai and Lin (169) did not meet the criteria for a well-constructed meta-analysis. One of the more comprehensive meta-analyses by Cho, Lee (141) missed two critical criteria (no published protocol and risk of bias accountability) resulting in a *critically low* grading. Similarly, Firth, Stubbs (149) did not include two critical domains including missing a published protocol and a lack of justified exclusions from the review. Across all reviews, trials have been conducted predominantly in Australia (35%), USA (29%), Israel (18%), Iran (8%), Spain (6%) and Tehran (4%).

CHALLENGES TO PROGRESS OR IMPLEMENTATION

Disparities in preparation, cultivation, and presentation between nutrients, difficulties in assessing biological nutrient levels and intake levels, lack of consideration of gender/age effects, and inconsistent interactions with pharmacological treatment are likely contributors to heterogeneous outcomes. Thus, the lack of consistency in nutritional treatments is a prominent barrier. Finally, cognition is often measured as a secondary outcome in nutrient studies in psychosis and therefore, studies have not been powered to properly assess their potential pro-cognitive effects. Ciappolino, Mazzocchi (170) specifically highlighted the lack of cognitive outcomes in RCTs investigating n-3 PUFA supplementation in populations with psychosis.

3.4 COGNITIVE REMEDIATION AND COMPENSATION

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Cognitive remediation and cognitive compensation are two behavioral interventions developed to address the impact of cognitive impairment on functioning in psychosis. They are the two most widely researched interventions for cognitive impairment in psychosis and are recommended within some clinical practice guidelines for the treatment and management of schizophrenia (3, 21). While there is some overlap between the two treatments, they are separate forms of behavioral intervention with different modes of action.

Cognitive remediation represents a group of training-based interventions that target areas of cognitive impairment, with the goal of translating cognitive gains into greater functioning (for example, independent living skills, occupational performance). The aim is to directly improve cognitive functioning, or the self-management of these skills, to ultimately enhance functional outcomes. Core consensus-recommended features of cognitive remediation include: (1) facilitation by trained therapists, (2) repetitive practice of cognitive skills, (3) methods for developing problem-solving strategies, and (4) procedures to transfer cognitive change into everyday functioning, with an emphasis on integrating therapy into psychosocial rehabilitation (43, 171). Treatment characteristics vary

between approaches, although in general, therapy tends to be computer-assisted and delivered over multiple sessions per week (M=2.6; SD=1.3; approx.1-hour in length) for up to three months (M=15.2 weeks, SD=14.3) (171). Many computerised programs have been developed and commercialised, but there is yet to be strong empirical evidence favoring one program over another (for example, HAPPYneuron Pro, BrainHQ, Cognitive Interactive Remediation of Cognitive and Thinking Skills [CIRCuiTS], Neuropsychological Approach to Cognitive Remediation [NEAR], COGPACK, etc.).

Cognitive compensation methods aim to circumvent (or 'work around') the impact of cognitive impairment on functioning through the use of techniques, skills or strategies. Functioning is therefore the primary intervention target, with gains in cognition commonly viewed as a co-primary or secondary outcome. Techniques used in compensatory interventions may include: (1) internal self-management strategies (such as mental imagery or association), (2) external or environmental strategies (for example, calendar or Webster-pak for remembering appointments or medications, respectively), or (3) errorless learning. These techniques may be self-initiated or facilitated by a third-party, depending on the cognitive strengths of the individual and the goals of the intervention. Similar to cognitive remediation, treatment duration varies significantly between intervention protocols (median: 24 weeks, range: 1-96 weeks) (172). Cognitive Adaptation Training (CAT) and Compensatory Cognitive Training (CCT) are two of the most commonly researched manualised 'compensation-only' treatments in adults with psychosis (173, 174). Interventions that combine elements of cognitive remediation and compensation are viewed as hybrid treatment models (for example, Thinking Skills for Work) (175, 176).

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

Cognitive remediation

Revell and colleagues (2015) have conducted the only meta-analysis of cognitive remediation in early psychosis (k=11; 615 participants; M_{age}=21.8 years, 63% male) (177). The main findings from this review were that cognitive remediation therapy had a non-significant effect on global cognition (d=0.13, p=0.14). Sensitivity analyses revealed a small significant effect in the verbal learning and memory domain (d=0.23, p<0.05), which suggested that this domain may be more sensitive to change in people earlier in their course of illness. The review also showed that cognitive remediation had a small impact on global functioning (d=0.18, p<.05), yet only with adjunctive psychiatric rehabilitation (d=0.39 vs 0.03, p<.05). The importance of integrative cognitive remediation therapies to address functional impairment has also been demonstrated in clinical populations with persistent psychosis (171). Since the meta-analysis by Revell (177), few trials have been conducted in people with early/first-episode psychosis. For example, only eleven of the 130 studies in the systematic recent review by Vita, Barlati (171) (described below) were in people under 25 years of age with a diagnosis of FEP, with only four of these reports published since 2015. This highlights the lack of cognitive remediation trials (or potential lack of publication of null findings) in early psychosis populations. Of note, the trials in FEP that have been conducted in the past 5 years have produced varied findings. Some have shown evidence of cognitive improvement following cognitive remediation in people with FEP (178, 179) (discussed in a narrative synthesis by Miley, Hadidi (180)), whereas others have not shown a unique treatment effect of cognitive remediation on cognitive function relative to control groups (181) or have shown similar cognitive gains to compensatory interventions (182). Furthermore, the impact of treatment on functioning in FEP remains mixed (178, 179, 183-185).

Glenthoj, Hjorthoj (186) have produced the most up to date systematic review in 2017 of pilot studies and controlled trials of computer-assisted cognitive remediation in UHR (k=6, 327 participants; M_{age}=21.72 years). There is no meta-analysis of this literature. Despite the small number of studies, Glenthoj, Hjorthoj (186) showed emerging support for a positive cognitive treatment effect in people at UHR for psychosis (for example, gains in measures of attention, processing speed, memory). This included data from two out of the three RCTs that were reviewed. Nevertheless, the impact of functioning was equivocal, with only two of the four studies that measured functional outcomes showing any change after treatment. Follow-up assessments were also not routinely conducted in most studies, which meant that the durability of cognitive improvement was unclear. Trials published since the review by Glenthoj, Hjorthoj (186) have continued to reveal inconsistent cognitive and functional treatment effects in individuals at UHR (187, 188).

Cognitive compensation

Even fewer studies have examined the impact of cognitive compensatory interventions in UHR/CHR and FEP when compared to cognitive remediation, with no systematic reviews of this literature. Data from adults with psychotic disorders may offer some insight into the usefulness of this intervention in less chronic groups (172). When scrutinising the studies included in a recent meta-analysis (172), two trials recruited young people with FEP (M_{age}=24.9) and aimed to evaluate the impact of NEUROCOM (combined compensation and remediation intervention) and Compensatory Cognitive Training (CCT). Of note, these studies did not show any change in functional capacity after 3-4 months of treatment relative to control groups, despite evidence of cognitive improvement (189, 190). It is important to note, however, that these findings contrast with a small pilot study of CAT in FEP by Allott, Killackey (191), which showed preliminary support for improved vocational functioning and quality of life, as well as a recent trial showing that both CAT and cognitive remediation in FEP may enhance self- and informant-rated community functioning and goal-attainment (182). More cognitive compensation trials are underway in FEP according to trial protocols available at the time of this report (192).

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

Considerably more research has been conducted in schizophrenia and severe mental illness cohorts. Systematic reviews and meta-analyses in adults with persistent psychosis have shown that cognitive remediation can produce small-to-moderate improvements in global cognition and functioning that are sustained over time (*d*=0.29 and *d*=0.22, respectively) (171). The benefit of cognitive remediation in adults with psychosis was documented in a seminal review by Wykes, Huddy (44) who synthesised data from 40 RCTs published between 1973-2009 (2,104 participants, M_{age}=35.8 years, 67% male). Vita, Barlati (171) have provided the most recent updated review that included 130 RCTs published up to February 2020 (8,851 participants, M_{age}=36.7 years, 68% male), providing further empirical support and highlighting the substantial growth of research in adults with psychosis over the last 10 years. Complementing the strong cognitive remediation support base, Allott, van-der-EL (172) examined the evidence for cognitive compensatory treatment in schizophrenia in a meta-analysis of 25 RCTs (1654 participants, M_{age}=38.9 years, 64% male). This report showed that compensatory treatment could produce moderate gains in global functioning (for example, competitive employment, medication adherence; *g*=0.46), with longer interventions associated with larger functional gains.

STRENGTH/QUALITY OF THE EVIDENCE

The strength of evidence of the main systematic reviews and meta-analyses reviewed in the evidence summary was evaluated using the AMSTAR-2 evaluation tool. The characteristics of each review are summarised in Supplementary Table 4. In total, 147 cognitive remediation and 26 cognitive compensation trials were included in the four systematic reviews and meta-analyses evaluated in this report. Geographically, most cognitive remediation trials were based in Europe (45%), North America (33%) or Asia (18%), with a small proportion in Australia or South America (4%). In contrast, most compensatory trials were based in North America (81%). No trials have been based in Africa.

Overall, the strength of evidence from three of the four reviews is *critically low* based on the presence of two critical flaw(s) on the AMSTAR-2 (177, 193, 194). The strength of evidence from the one remaining review was *low* due to one critical flaw (172). Specifically, all four reports provided a PRISMA flow chart of the included/excluded studies at each stage of the review; however, none provided a complete list of the excluded studies, which constituted a critical flaw (that is, AMSTAR-2 item 7). In addition, two reviews did not appear to publish a review protocol *a priori* (that is, AMSTAR-2 item 2) (177, 194), while one review did not adequately describe their search strategy (that is, AMSTAR-2 item 4) (186). Evidence of critical flaws in every review is disappointing given that these issues were raised in a past methodological appraisal of systematic reviews of cognitive remediation in schizophrenia (195).

CHALLENGES TO PROGRESS OR IMPLEMENTATION

Together, there is largely inconsistent evidence from the studies examining the impact of cognitive remediation and compensation on cognitive and functional outcomes in UHR and FEP. While there appears to be a need for more efficacy trials, the equivocal findings to date also raise the question of whether these forms of intervention are the best way to be addressing cognition and its impact on functioning in early psychosis populations. For example, some people with FEP have indicated that cognitive remediation exercises are 'boring' or can induce anxiety, even if generally perceived to be helpful (196). These views could impact treatment sustainability for many people. Novel approaches to treatment, such as those focused on cognitive strengths, may need to be considered (197). In addition to the relatively limited number of efficacy trials, it is also apparent that no study in UHR or FEP has carefully considered implementation science at the outset. This remains a significant gap on a global scale (198). Concerns about acceptability of cognitive remediation is well documented in clinical trials, with attrition rates ranging from 10-52% according to one recent review of UHR studies (199). Compensatory training has been found to be acceptable by youth mental health clinicians (200), but there is no data regarding the cognitive treatment preferences of UHR and FEP individuals, or the factors that may promote successful implementation.

Studies to date have focused on demonstrating efficacy (that is, internal validity) and identifying predictors of treatment response or adherence in adults with schizophrenia (171, 201, 202). This research is critical in early psychosis populations. Nevertheless, the existing literature has not sufficiently prioritised research on the implementation of interventions in real-world contexts (198, 203). This is despite recognition of its importance by leading cognitive remediation and compensation experts (182, 204, 205). Without consideration of factors that impact implementation at the outset of future efficacy trials in UHR/FEP populations, it is likely that knowledge translation will be met with similar roadblocks to those now seen in the adult literature. Implementation science provides frameworks and methods for evaluating and supporting the translation of evidence-based treatment into routine care, offering promise for growing the evidence on how to support uptake of cognitive remediation and compensation in real-world settings (see section 3.12 *Implementation Science*).

Several impediments to the translation of cognitive enhancing interventions into mental health practice have been discussed previously (198, 205). These include: (1) costing and capacity/infrastructure issues influenced by a lack of funding, adequately trained workforce, and equipment, (2) potential priority issues where cognition is not seen as a valued treatment target, (3) inadequate personalisation of interventions, and (4) minimal evidence about the context of implementation. These views expand upon barriers described by some adult and youth mental health clinicians in staff surveys, which in summary, have reflected a lack of resources,

training/supervision opportunities, and organisational or leadership support, as well as general logistical issues (that is, IT, transport, and so on) (196, 206). The absence of evidence regarding the context for implementation may be the most critical issue hindering the clinical use of cognitive treatments. While the survey data on potential barriers in adults is a helpful starting point for FEP and UHR populations, we do not currently have an in-depth understanding of the obstacles or facilitators of treatment uptake from the perspective of core stakeholders including consumers, clinicians, service managers or the contextual factors that support integration of cognition-focused treatments. These perspectives may differ between stakeholder groups and settings. For example, one recent feasibility study showed that cognitive remediation in a coordinated specialty care service may be acceptable to some FEP individuals and can be associated with perceived cognitive and functional improvements (196). In contrast, however, clinician perspectives from the same health service indicated that compensatory skills training was more appealing than computer-based exercises (200). Pleasingly, one implementation-focused trial is currently being conducted across multiple early intervention services in the United Kingdom. The goals of this study include: (1) personal recovery outcomes as well as typical measures of cognition and functioning, (2) cost-effectiveness of treatment and best modes of treatment, and (3) satisfaction of service-users and staff involved in implementation (207).

There is also a need for a global cultural shift toward prioritising the assessment and treatment of cognition in youth mental health settings (200, 206, 208). Medalia, Saperstein (205) described their process for promoting cognitive health and offering cognitive remediation treatment across a group of adult public health services in New York, with a focus on staff education and opportunities for training. Similar investment needs to occur in early psychosis settings, where the impact of cognitive deficits and the need for timely intervention are critical (for example, potential for disrupted academic or occupational achievement). Orygen recently developed a suite of freely available training resources aimed at increasing clinician awareness and understanding of cognitive deficits, screening and treatment options in in early psychosis (www.orygen.org.au/training/resources/cognition). Sustainable workforce development should be a priority area for future implementation-effectiveness trials given the high staff turnover rates in mental health services.

It is also important to consider financial barriers to implementation. Few studies have conducted comprehensive economic evaluations in early intervention settings. One small cost-utility analysis recently provided data to support meta-cognitive remediation therapy as a cost-effective addition to coordinated specialty care, with capacity to enhance quality-adjusted life years in the first 6 months of care (209). While promising, additional data from economic evaluations where cognitive or functional outcomes can be monetised (for example, number of admissions, employment tenure) are desperately needed in early intervention settings.

3.5 SOCIAL COGNITION INTERVENTIONS

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Social cognitive training programs within the psychosis research field are quite heterogeneous but can generally be categorised into three forms: comprehensive, targeted, and combined.

Comprehensive social cognitive programs are the most abundant and target at least two of the four key social cognitive domains that are impaired in psychosis (that is, emotion recognition, theory of mind [ToM], social perception and attributional style/bias). These interventions typically involve drill-and-practice exercises, psychoeducation and strategy games. Media often employed to assist in training include verbal vignettes, cartoon series, video clips, movies and animated short films (210). Some comprehensive programs additionally include mimicry and role-playing, and most are delivered in a group setting to allow for modeling and experiential learning. Notably, the structure and intensity of training programs vary considerably, with the duration ranging between 2 and 28 weeks (on average 18 weeks), and sessions conducted fortnightly to three times a week. The most frequently studied comprehensive social cognitive interventions are Social Cognition and Interaction Training (SCIT; 11 trials) (211) and Social Cognition Skills Training (SCST; 3 trials) (212).

Targeted social cognitive programs typically only address one social cognitive domain, most commonly facial emotion recognition, though some alternatively target ToM (213-215), or prosodic emotion recognition (216). Targeted interventions tend to rely more heavily on computer-based programs, photos and motion pictures, and are usually of shorter duration (on average 7 weeks) compared to comprehensive interventions. The targeted social cognitive intervention that has been most frequently tested is Training of Affect Recognition (4 trials) (217).

Combined interventions generally refer to purpose built programs that have social cognitive training embedded with neurocognitive training, but they can also refer to a trial that implements separate social cognitive and neurocognitive interventions simulatenously or sequentially. Combined programs are less common than comprehensive and targeted programs. The most well-known combined program is Cognitive Enhancement Therapy (CET; 2 trials) (218), which is a year-long intervention. On occasion, combined interventions may refer to social cognitive training combined with broad based psychological therapy and/or social skills training, for example Integrated Psychological Therapy (219). It is important to note that while there are over 20 different social cognitive

interventions that exist presently in the psychosis field, most have been tested in only one or two clinical trials, despite many being first developed over 10 years ago.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

To date, one relevant systematic review has been conducted in first episode psychosis (FEP), which examined various interventions targeting social cognitive deficits (220). This review comprised only 5 studies; one used cognitive remediation without a social cognitive training component, two used pharmacological treatments (modafinil), one used a computerised combined social cognitive training program, and one used comprehensive social cognitive training plus oxytocin. Authors reported on individual study findings, where two of the three trials that used cognitive training found emotion recognition to improve significantly post-intervention. There was no change in other social cognitive abilities, and authors did not report on treatment effects for neurocognition or functioning.

Five RCTs have been conducted in early psychosis since the systematic review; three in FEP and two in UHR. In the FEP trials, all used SCIT as their social cognitive intervention. Vidarsdottir and colleagues found SCIT (combined with two other neurocognitive interventions) had significant small to medium effects (η^2= 0.10 - 0.19) in reducing hostile attributions and improving ToM (and several neurocognitive abilities) compared to a wait-list control plus treatment as usual (TAU) (221). The intervention was well attended (~78%; though it was delivered over 12-weeks rather than the traditional 24) and participants more often rated SCIT as the most useful component. However, the sample was small, the analyses lacked correction for multiple comparisons, and the use of a wait-list control may have exaggerated the efficacy of this suite of psychosocial interventions, given waitlists are suggested to have a nocebo effect (222). Li and colleagues found performance on measures of global social cognition (managing emotions), processing speed and attention/vigilance, improved significantly for the early-onset schizophrenia participants that received SCIT plus paliperidone, relative to participants that received paliperidone only (223). These were medium to large effects (*d*= 0.67 to 0.86), but there were no differences for other measures including functioning. Remarkably, there were no drop-outs; all 206 participants completed the program, suggesting the intervention was well tolerated by youth (mean age 16 years). The most recently published trial in FEP presented preliminary evidence from a very small sample of participants (N=11), which found SCIT to have a significant large positive effect on overall functioning and a trend level effect on reducing attributional bias towards blame (*d*= 1.44 and 1.20, respectively) (224). However, given Rocha et al.'s extremely small sample size, findings should be viewed with caution. Overall, these three RCTs were conducted in Iceland, China and Portugal, respectively, suggesting that SCIT is adaptable and acceptable to culturally diverse early psychosis populations, and within both inpatient and outpatient settings. Lastly, the OPUS YOUNG RCT is currently underway (due to be completed late 2025) and is expected to shed further light on the efficacy of SCIT when integrated with comprehensive specialised care for adolescents (aged 12-17) with FEP (225).

Few RCTs have been conducted in UHR populations. Friedman-Yakoobian and colleagues tested a novel combined social cognitive intervention, Cognition for Learning and for Understanding Everyday Social Situations (CLUES) modeled after CET, in a feasibility trial in the USA (226). CLUES had significant medium to large effects on social functioning post-treatment (*d*= 0.72), and at 3-months follow up (*d*= 1.04), when compared to Enriched Acceptance and Commitment Therapy (active control). In addition, CLUES had significant large effects on ToM performance at treatment end (*d*= 1.00), and global social cognition (managing emotions) at 3-months follow up (*d*= 0.99). However, this study is limited by the small sample size (N=38) and relatively high attrition rates (10 dropouts). The largest cognitive training RCT conducted in UHR to date (N=146; age range 18-40) in Denmark combined SCIT with a well-established neurocognitive program and compared this to TAU (227). Speed of performance on only one measure of emotion recognition improved at treatment end, while visual memory and executive functioning improved at 12-months follow up. Surprisingly, this 20-week intervention had no effect on global neurocognition, global functioning or a large number of individual cognitive measures. This trial had a 30% attrition rate, with participants attending on average around half of the scheduled sessions.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

A large number of clinical trials have examined the effectiveness of social cognitive training interventions in individuals with established schizophrenia spectrum disorders, and multiple systematic reviews have been published. Most recently, Yeo et al. conducted a meta-analysis examining broad, comprehensive, and targeted training programs in both inpatient and outpatient settings (210). Forty-two RCTs with a total of 1,868 participants were included. Overall, moderate effects of social cognitive training interventions were found for emotion recognition (*g*= 0.55; *p*< .001), ToM (*g*= 0.36; *p*< .01), and social perception (*g*= 0.46; *p*< .05); however, no significant effects were found for attributional style or social functioning (210). Importantly, the authors reported that differences in baseline symptoms, gender distribution, antipsychotic medication dose, IQ, sample age, education, age at onset (mean age 13yrs), or duration of illness did not interact with treatment benefits. This suggests that the effects of social cognitive training are robust across different clinical and demographic profiles and should theoretically be effective in early stages of illness.

In another similarly comprehensive meta-analysis, Nijman and colleagues compared targeted versus broad-based social cognitive training interventions, with and without combined treatment with neurocognitive training, on a range of social cognitive and functional outcomes (223). From 46 studies, 1,979 participants, medium to large improvements were observed across individual social cognitive domains and treatment type, with broad-based interventions improving emotion processing (*d*= 0.46), social perception (*d*= 1.35) and

ToM (*d*= 0.42), while targeted interventions improved emotion processing (*d*= 0.68) and social perception only (*d*= 1.36). However, in contrast to the review by Yeo et al. (210), additional improvements in social functioning were also observed for broad-based social cognitive training (*d*= 0.82). There was no effect on attributional style and overall, the inclusion of neurocognitive training did not enhance the effects of social cognitive training on any outcomes of interest. A third meta-analysis specifically investigated effects of social cognitive training on ToM, and reported a medium effect for improving overall ToM outcomes (*g*= 0.53; *p*< .001), and large (*g*= 0.60; *p*< .001) and medium (*g*= 0.42; *p*< .001) effect sizes for improving subdomains of cognitive and affective ToM, respectively (228).

These findings, together with findings from earlier reviews (229), consistently demonstrate improvements in emotion recognition, ToM and social perception outcomes for people with established psychotic illness. There is limited evidence for social cognitive training to improve attributional style; while earlier studies reported small effects (229), more recent comprehensive meta-analyses suggest no effect (210, 223). Finally, some reviewers have reported significant improvements in social functioning (223), while others have found no change (210). This adds to the already mixed findings, in both established illness and the limited findings in UHR and FEP, that bring into question whether social cognitive treatments translate to meaningful improvements in community and social functioning (230). Inconsistencies however, may be the result of methodological differences in the measures used to assess functioning, the structure of the programs themselves, engagement in the programs and high rates of attrition in some studies.

STRENGTH/QUALITY OF THE EVIDENCE

Of the published systematic reviews and meta-analyses of social cognitive interventions for psychosis (Supplementary Table 5), only one has specifically focused on early stages of illness (220), and the overall confidence in this review was rated *critically low*. No previous review has exclusively examined social cognitive training interventions in early psychosis. Due to the paucity of clinical trials specific to FEP and UHR populations, there is insufficient data to be able to draw any reliable conclusions at this point in time. However, as outlined above and in accordance with AMSTAR-2 standards, moderate to high quality meta-analyses and systematic syntheses of the literature for social cognitive training in later stage illness are beginning to emerge (210, 223, 228). Given the moderate to large effects of social cognitive training observed in persisting psychosis populations, high-quality trials that address current limitations (discussed below) are encouraged in early psychosis samples.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

Engagement has long been a prominent issue in the treatment of young people with mental health difficulties, including the treatment of social cognitive impairments. For example, both Glenthøj et al. and Friedman-Yakoobian et al. had poor engagement with their interventions, which were 5-6 months in duration (227). Related to this, it is not yet clear whether social cognitive interventions designed for people with established psychotic illness will transfer directly to a *youth population* that has unique developmental and cultural needs; generalisability to early intervention remains a challenge.

A significant barrier to trialling and evaluating social cognitive training interventions in psychosis (across all stages) has been a lack of well-validated measures for assessing outcomes related to social cognition (231). Many tasks used in clinical trials do not have appropriate psychometric properties, and the recent completion of a multi-phase study that evaluated the most widely used measures for assessing social cognition, the Social Cognition Psychometric Evaluation (SCOPE) study (232), highlights this issue. Recommendations have been made regarding the appropriateness of some tools to use in clinical trials, though currently only tasks assessing ToM and emotion processing have been identified as marginally suitable.

Access to funding is an additional challenge in the implementation of social cognition training, given these tend to be resource heavy, requiring one to two clinical facilitators running face-to-face group or individual sessions. While some larger scale studies have begun to examine the cost-effectiveness of cognitive remediation programs in early intervention (233), such studies are yet to be conducted for programs specifically targeting social cognition.

Few psychosis studies have specifically assessed the feasibility of implementing social cognitive training into clinical practice. Two studies evaluated the feasibility and acceptability of SCIT in community mental health services in the USA and Australia, and found SCIT to be well-tolerated and, overall, successfully implemented (234, 235). This is supported by the fact that SCIT has been translated into seven languages and implemented in 10 countries (236). However, SCIT has only been shown to be successfully implemented in adult settings, and implementation trials are lacking for other social cognitive training interventions, especially in early intervention psychosis services.

3.6 SLEEP INTERVENTIONS

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Sleep disturbance is reported in up to 80% of individuals with psychosis (237), including those at UHR/CHR (238-242) and with early psychosis (243, 244). Epidemiological studies suggest that sleep disturbance predicts the development (245) and persistence (246)

of psychotic experiences. Enduring cognitive impairment co-occurs with sleep disturbance across the clinical spectrum, from those at UHR/CHR (239) through to persisting psychosis (247, 248). These observations have led to hypotheses that sleep disturbance may be aetiologically related both to the development of psychosis (245) and cognitive impairment in this population (249).

Several modes of action have been proposed to explain the associations between sleep disturbance and cognitive impairment in psychosis. Most developed is the observation that patients with schizophrenia have abnormalities in aspects of sleep architecture that support memory consolidation, such as thalamocortical sleep spindles, slow wave oscillations and hippocampal sharp waves (249, 250). These observations have led to trials investigating modulation of these sleep features using hypnotic drugs, as detailed below. In addition, a number of genetic (for example, stable tubule only polypeptide [STOP] null mice), prenatal (for example, MAM-17 neurodevelopmental model) and neurotransmitter (for example, kynurenine pathway) models identified in pre-clinical studies suggest a possible link between cognitive and sleep impairments in psychosis (249). Finally, sleep deprivation models of schizophrenia have shown that experimentally-controlled sleep deprivation leads to brain changes that mimic both psychotic symptoms (245) and cognitive impairments commonly observed in psychosis, including in attention, working memory, executive function and memory (251).

Several sleep interventions have been considered in psychosis (252-254). These include psychological interventions (mainly cognitive behavioural therapy for insomnia: CBT-i), pharmacological interventions (for example, hypnotics, melatonin, and benzodiazepines), and others (for example, light exposure therapy and continuous positive airway pressure [CPAP]). Despite the substantial evidence linking sleep disturbance and cognitive impairment in psychosis (248, 249, 255, 256), relatively few published sleep intervention trials (and no published reviews) have addressed cognitive outcomes.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

No evidence.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

Cognitive-behavioural therapy for sleep problems

Several small RCTs conducted in the United Kingdom have investigated CBT-i for individuals with psychosis. CBT-i interventions typically include multiple components, including sleep hygiene education, stimulus control, sleep restriction, relaxation, regulating daily routines and cognitive strategies to address unhelpful sleep beliefs (257), with some including light/dark exposure for circadian entrainment (258). Result have suggested such interventions are effective in improving sleep (258-260) and nightmares (260) in individuals with psychosis and those at UHR (261). While a large RCT found that reductions in paranoia and hallucinations in a non-clinical sample were mediated by sleep improvement following an online sleep intervention (262), the evidence regarding whether CBT-i interventions improve psychotic symptoms, functioning and wellbeing is mixed in psychosis trials (258-261). Importantly, none of the CBT-i trials identified included cognitive functioning as an outcome. While there is no evidence of differential effects of sleep interventions in relation to cognitive outcomes, one study found that, amongst adults with psychosis and insomnia, strong or partial response to CBT-i was associated with being younger, female, and having higher levels of negative mood and quality of life pre-treatment. Non-responders were more likely to be male, with more severe psychotic illness and higher impulsivity pre-treatment (263).

Hypnotics (z drugs) and sleep oscillations

Sleep spindles are oscillations that occur during non-rapid eye movement Stage 2 sleep that play an important role in memory consolidation (264). Sleep spindle deficits have been reliably observed in individuals with psychosis, including in early psychosis (265) and also in first-degree relatives (266). Hypnotics such as zolpidem and eszopiclone that are used to treat insomnia have been found to increase sleep spindles and have been explored as possible treatments for improving impaired memory consolidation in individuals with schizophrenia. To date, three trials of eszopiclone conducted in North America have reported improvements in sleep (267) and increased spindle density (268), but results are mixed in relation to improvements in memory and other cognitive domains; one study found improvements in working memory (267) whereas others have reported no change in cognitive performance (268, 269). Manoach and colleagues (250) have suggested that interventions may need to enhance and co-ordinate networks of sleep oscillations, including hippocampal sharp-wave ripples and cortical slow oscillations in addition to sleep spindles, to improve cognition in psychosis.

Melatonin

Melatonin is a hormone produced in the pineal gland. It has multiple functions relevant to sleep and cognition in psychosis, including modulating circadian rhythms, and affecting cortical functioning via its influence on cortisol, as well as dopamine and norepinephrine in the frontal cortex (270-272). Low melatonin levels observed in individuals with schizophrenia have been linked to sleep disturbance in this group (270, 271). Accordingly, melatonin treatment was found to be effective in improving sleep quality in patients with chronic schizophrenia in a small Israeli RCT that did not consider cognitive performance (273). In addition, two small, uncontrolled trials conducted in Europe found that agomelatine, a synthetic analogue of melatonin primarily used as an atypical anti-depressant, was

associated with small improvements in overall cognitive function, reasoning/problem solving (272) and executive function (274), in individuals with schizophrenia.

Other sleep therapies

Benzodiazepines are commonly used for the treatment of sleep disturbance, anxiety and agitation in schizophrenia (275). However, the long-term use of these drugs has been associated with a range of cognitive impairments, including attention and working memory, and they are not recommended for long-term sleep treatment in this population (276).

A recent systematic review and meta-analysis (277) found that light/dark exposure therapy, used to entrain circadian rhythms, improved sleep outcomes in a number of neuro-psychiatric illnesses. However, this review did not identify any specific studies of psychosis, and nor were cognitive outcomes considered.

Finally, a recent review of CPAP to treat obstructive sleep apnoea in women with schizophrenia (278) found that it was effective in improving sleep and preliminary evidence that it may improve attention, vigilance, and memory, but further work is needed to determine whether CPAP confers benefits in cognitive function.

Studies currently in progress

Three research groups are currently recruiting into clinical trials examining the effects of sleep interventions on cognitive functioning in psychosis. Jones and colleagues (279) in the United Kingdom, are conducting a parallel group, open label trial investigating the effectiveness of online CBT-i relative to treatment as usual (TAU) on social functioning and cognition in early psychosis. The cognitive outcomes include sustained attention, visual episodic memory, working memory, and emotional recognition. The trial aims to recruit a total of 44 participants by November 2022, yet results may be underpowered.

Paunio and colleagues (280) in Finland are conducting an RCT examining the effects of individual and group CBT-i on sleep, quality of life, sustained attention and functional ability in people with schizophrenia or schizoaffective disorder, relative to TAU. The trial has a recruitment target of 122 participants by September 2024.

A single-blind, randomised, cross-over trial by Manoach and colleagues (281) in the USA is investigating the effects of auditory stimulation (playing quiet sounds during sleep) on sleep quality and memory in schizophrenia. The trial is aiming to recruit 70 participants by July 2023.

Finally, although not addressing cognitive functioning, in the United Kingdom, Waite and colleagues (282) are investigating the feasibility and acceptability of CBT-i in young people at UHR for psychosis. The trial aims to recruit 40 participants by December 2022, although larger samples will be needed when testing efficacy. A feasibility trial conducted with a smaller sample of 12 UHR participants identified potential clinical related benefits of CBT-i (261).

STRENGTH/QUALITY OF THE EVIDENCE

Not applicable.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

A small number of studies have considered the implementation of sleep interventions for psychosis, both from a clinician and patient perspective, with limited consideration of cognitive outcomes.

Barrett and colleagues (283) reported on a survey of clinicians working with patients with psychosis. Clinicians reported that sleep problems were highly prevalent in this population, with associated negative consequences including 92% believing that poor sleep impacted cognitive functioning. Despite the near ubiquity of sleep disturbance identified in this population, structured assessment and the use of recommended treatments for sleep problems were reportedly rare. Clinicians identified several barriers to implementation, including their own lack of knowledge regarding sleep assessments and treatments, a belief that sleep treatments were too demanding for both clinicians and patients, a lack of focus on sleep in mental health services, and concerns that sleep disturbance in this population was caused by medication side-effects and therefore was not amenable to behavioural treatment approaches.

More positively, Waite and colleagues (284) surveyed 10 patients with psychosis who had recently completed a course of CBT-i. Patients unanimously reported satisfaction with the treatment and attributed a number of positive changes to it, including improvements in sleep, capacity to cope with psychotic experiences, general wellbeing, mood, hope, sense of self and social functioning. Also, in support of implementation, the same research group (257) identified 12 key factors that specifically impact sleep in patients with schizophrenia (for example, sleep as an escape from distressing experiences like voices, and neuroleptic medication side effects) and recommend adaptations to typical CBT-i approaches to ensure these 12 factors can be properly addressed. Cognitive factors were not directly considered.

The current evidence base regarding the benefits of sleep interventions on cognitive function in individuals with psychosis is promising, but in its infancy. The interventions that appear to hold the most promise include CBT-i (despite no published studies reporting cognitive outcomes), treatments targeting sleep oscillations (such as hypnotics), and melatonin/agomelatine. No published studies have examined the effectiveness of these interventions in UHR/CHR and early psychosis populations, although one clinical trial (213) is currently in progress.

3.7 EXERCISE, MIND-BODY AND MINDFULNESS

DESCRIPTION OF INTERVENTION(S) AND MODE OF ACTION

Lifestyle interventions show promise for treating many of the negative symptoms seen in serious mental illness (285), as well as cognitive impairment. Here we examine the effect of **exercise-based interventions (EBIs)** and **mindfulness-based interventions (MBIs).**

Exercise-based interventions

EBIs involve the use of structured and repetitive physical activity with the objective of improving or maintaining physical fitness and ability, for example, sport, aerobic exercise, and strength or resistance-based exercise. *Mind-body*, *Yoga or Tai Chi Interventions* could be considered separately given that they are proposed to benefit cognition in ways that may be distinct from the physical activity itself. However, given the limited evidence available for sub-domain investigation within this section, these interventions were included under EBIs. As exercise leads to a host of changes within the body, there is no single mechanism that adequately explains the effects of EBIs on the brain and subsequent cognitive functioning (286). Exercise may lead to cognitive enhancement via cellular and molecular signalling pathways (for example, increased brain-derived neurotrophic factor; BDNF), changes to brain structure and function (for example, increased hippocampal volume), and subsequent altered mental states or higher order behaviours (for example, improved mood and sleep) (286). However, as the biological processes differ across disease states, the mechanisms will vary between individuals and populations. In schizophrenia, mechanisms of action are unclear, with increases in brain volume and BDNF holding most promise (287).

Mindfulness-based interventions

MBIs are a heterogeneous group of processes and practices that relate to present-focused attention, awareness, acceptance, and non-judgement (288). While exact mechanisms for improved cognition following MBIs are unclear, Larson, Steffen (289) suggest mindfulness practice may enhance one's awareness of attentional focus, subsequently allocating cognitive resources in a more goal-directed manner.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

A recent systematic review explored the effectiveness of group-based exercise interventions for first-episode and early psychosis (290). The authors identified only five studies, of which two reported data from the same single-arm intervention study, and only two of the remaining four were RCTs. In total, three examined cognitive outcomes. While in Sweden, Hallgren, Skott (291) found no statistically significant effect of exercise on any cognitive outcomes, the remaining two studies were supportive. In Hong Kong, Lin, Chan (292) reported statistically significant improvements in verbal acquisition, working memory, and attention in a yoga group, and verbal retention and working memory in an aerobic exercise group. There was a positive correlation between the number of sessions attended and change in working memory, and the cognitive effects observed at three months were maintained 18 months later for both intervention groups. In the USA, Nuechterlein, Ventura (293) found a large effect size for improvement in overall cognitive function using the MATRICS Consensus Cognitive Battery, for combined cognitive training and exercise compared to cognitive training alone. Of the three studies which reported outcomes for global functioning, all found evidence of significant improvements.

Individual programs have also been conducted; however, these are preliminary. For example, in the United Kingdom, Firth, Carney (294) conducted a feasibility trial of personalised exercise for individuals with FEP. Thirty-one participants were included in the intervention, with seven in the control arm. Of the twenty participants who completed cognitive assessments, verbal short-term memory showed the greatest change (d=0.88, p<0.001). Moderate improvements in social cognition (d=0.67, p=0.009), processing speed (d=0.40, p=0.086 and d=0.65, p=0.009), executive functioning (d=0.48, p=0.043) and inhibitory control (d=0.53, p=0.044) were not significant after Bonferroni adjustment. With regard to global functioning, there was significant improvement in the SOFAS (d=0.72, p<0.001). Follow-up at six months showed that these cognitive benefits had largely reverted back to baseline, with only 55% continuing to exercise after six months.

There are many recent systematic reviews and meta-analyses which have explored the impact of MBIs in psychosis (295-298), although none report cognitive outcomes. Two published trials were found that reported cognitive outcomes for MBIs in the early psychosis population. A single-site RCT found that responses to the Stroop Colour Word Test (assessing inhibitory control) was significantly improved in the treatment group as compared to control (299). Second, a single-blind, multicentre RCT found no evidence

of improved attention/vigilance, speed of processing, or general cognitive functioning as compared to treatment as usual (300). A range of studies are underway to explore MBIs for cognition in psychosis. A MBI targeting social cognition in FEP is currently underway in Spain (https://clinicaltrials.gov/ct2/show/NCT03309475; estimated completion date: December 2024), with a feasibility trial already complete (301). An eight-week Mindfulness Based Stress Reduction program for Schizophrenia in France (https://clinicaltrials.gov/ct2/show/NCT03318640; June 2022) will also assess changes in attention.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

Expanding beyond early psychosis, Firth, Stubbs (302) conducted a meta-analysis on the effects of aerobic exercise on cognitive functioning in people with chronic schizophrenia. This included ten eligible trials (seven RCTs), including 592 participants with a mean age of 37.3 years. Exercise improved global cognition (g=0.33, p=.001), in addition to working memory (g=0.39, p=.024, n=282), social cognition (g=0.71, p=.002, n=81), and attention/vigilance (g=0.66, p=.005, n=104). Effects on processing speed, verbal memory, visual memory and reasoning and problem solving were not significant. Of note, an analysis of three studies which combined cognitive remediation with exercise (293, 303, 304) found no significant additive effect (g=0.21, p=.45, n=76), although conclusions should be cautious given the small sample size. Additionally, this meta-analysis found no significant differences based on sample characteristics such as age, gender, or duration of illness.

Given the lack of evidence regarding MBIs for cognition in psychosis, other populations were explored. Two recent meta-analyses demonstrated mixed efficacy (305, 306). Whitfield, Barnhofer (306) included both clinical (39%; none with psychosis) and healthy (61%) adults across 56 unique samples (n=2,931) and found a significant improvement in cognition favouring MBIs (K=45, g=0.15, p=0.004). There were also significant improvements in executive function (combined; K=29, g=0.15, p=0.022) and working memory (K=13, g=0.23, p=0.002). Other broad categories of attention, declarative memory, cognitive aging, construction, and visual perception did not improve significantly. Excluding older adults, Im, Stavas (305) included both clinical (20%; none with psychosis) and healthy (80%) adults across twenty-five samples (n=1,439), but observed only a small effect for executive function (standardised mean difference: SMD=0.29). No significant effects on attention (SMD=0.07), working memory (SMD=0.16), or long-term memory (SMD=0.12) were observed.

STRENGTH/QUALITY OF EVIDENCE

The systematic review of Shannon, McGuire (290) and meta-analysis of Firth, Stubbs (302) were assessed using the AMSTAR-2 tool, both scoring *critically low*. This was primarily due to lacking pre-registered protocols (item 2), the exclusion of non-English language studies (item 4), and insufficient recording of excluded studies (item 7) (307). Details of these reviews are included in Supplementary Table 6. No meta-analyses were available examining the effects on cognition in individuals experiencing early psychosis.

A strength of the reviewed literature is the relative diversity with which studies are completed, when accounting for the small selection of studies to date. Of those exploring EBIs - including Firth, Carney (294) and those within reviews from Shannon, McGuire (290) and Firth, Stubbs (302) - three studies were conducted in the United States, two in Germany, two in China, and one in each of the Netherlands, England, Sweden, Portugal, Hong Kong, Brazil, and India. The two studies described exploring MBIs in psychosis were completed in Spain (299) and Chile (300).

CHALLENGES TO PROGRESS OR IMPLEMENTATION

Studies have reported individuals with high risk for psychosis as engaging in less physical exercise, and perceiving more barriers to participation. Barriers include psychological factors (for example, reduced motivation, depression, anxiety), beliefs about self (low confidence and self-perceptions about fitness and ability), with subsequent social withdrawal (308, 309). Further, positive symptoms associated with psychosis such as paranoia and suspiciousness may prevent individuals engaging with public spaces such as sport settings or gyms (309). Therefore, studies will often need to obtain their own fitness equipment and exercise space given participation in more public environments is problematic. Motivation in particular has been highlighted as a possible cause of high attrition and poor adherence within EBIs in this population (310).

Given so little has been done to explore the effects of MBIs on cognition in psychosis, barriers to implementation remain unclear. However, a key concern are the cognitive deficits seen in psychosis which may interfere with the ability to engage with MBIs. Adaptations of MBIs are required to accommodate for deficits within this population, primarily in attention and memory. This includes implementing shorter exercises, reduced periods of silence, consistent verbal instructions, and more thorough psychoeducation (295).

3.8 DIGITAL, INCLUDING VIRTUAL REALITY

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Digital interventions involve the use of technologies such as computer programs, the internet, smartphone apps or virtual reality (VR) to deliver mental health treatment, see Table 3 (311). The widespread availability of digital technology and unique capabilities for providing accessible support in daily life make them well suited for supporting treatments to enhance cognition. Providing continuous access to treatment in daily life ensures support is available on demand within the everyday contexts where it is needed. Delivering interventions such as cognitive remediation via technology can address limitations in the availability of evidence-based treatment for early psychosis (312). Real world learning can occur through delivering interventions in daily life using smartphone apps, or within simulated virtual environments in the case of VR (313). Further, the use of technologies to support treatment may hold natural appeal for young people (314), for whom traditional treatments tend to lack engagement (315).

Table 3. Types of digital interventions

Digital technology	Potential use for treatment of cognitive impairment in early psychosis
Smartphone apps	Notification reminders for everyday tasks to compensate for memory, planning and organisation difficulties
Computer programs	Standardised, automated delivery of cognitive remediation training via a laptop or tablet (can be done remotely or in clinic)
Online and internet-based technologies	Online, self-guided programs providing psychoeducation and training materials on enhancing cognitive skills
Virtual and augmented reality	Learning and practice of cognitive skills in real world scenarios within a virtual environment

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

Despite the potential of digital interventions for enhancing cognition in early psychosis, few studies have been conducted. No systematic reviews nor meta-analyses in early psychosis were identified through our search methodology, nor were there any in persisting psychosis populations. However, broader reviews of treatments targeting cognitive impairment in these populations have included groups of interventions delivered via technology (177, 193), and individual trials have been conducted which enable some early insight into the potential of these interventions.

Cognitive remediation is one of the most widely investigated treatments for cognitive impairment in psychosis, and is typically delivered via a computer (316). These interventions traditionally involve automated ‘drill and practice’ type exercises targeting training of specific cognitive domains with increasing levels of difficulty, such as the speed of recognising certain cues or memorising stimuli for recall. Some versions involve applying these cognitive skills to everyday scenarios through simulated real-world environments (for example, (317)). A meta-analysis by Revell et al. (2015) identified 11 RCTs of cognitive remediation in early psychosis, of which five involved computerised delivery (177). For global cognition outcomes, moderator analysis revealed a smaller effect size for computerised (d=0.09) compared to paper and pen (d=0.16) techniques, however both were small and the difference was not significant. Effect sizes for functional outcomes were also small and did not differ significantly between intervention types (computer d=0.15, paper and pencil d=0.20). Similar effects have been found in persisting psychosis populations, although these tend to be larger for some outcomes (global cognition and working memory, but not for functioning) when human support is provided (316). These findings indicate that cognitive remediation can be delivered effectively via a computer, however the involvement of human support improves outcomes.

Very few studies have explored technologies beyond computer-based cognitive training, however some early work has been conducted on smartphone and VR-based interventions. A small RCT in China found that a memory and attention training app called ‘SMART’ (318), employing the ‘LAMP’ platform (311), was effective in improving attention, but not memory, abilities in a UHR sample. This effect was related to greater time spent using the app. Most VR intervention studies have focused on social cognition or functional recovery. Two systematic reviews identified six RCTs and five non-randomised trials of VR interventions for social cognition or cognitive rehabilitation in psychosis (319, 320), only one was in an early psychosis population in the United Kingdom (321). These interventions involved real-world virtual environments to facilitate training in social skills (for example, virtual conversations with avatars; Park et al., 2011; Rus-Calafell et al., 2014), cognitive training (for example, decision making; Chan et al., 2010), functional rehabilitation (for example, performing everyday tasks; Amado et al., 2016), and vocational recovery (for example, job interview training; Smith et al., 2015) (322-326). All found some evidence of improvements in cognitive functioning (particularly memory, attention, and planning), social cognition (particularly emotion recognition and thinking biases) and vocational outcomes (job offers).

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

Beyond psychosis, research has explored the use of digital interventions for disorders in which cognitive impairment is the primary presenting feature, such as neurocognitive disorders and dementia (327). Jahn et al identified nine RCTs of immersive VR for cognitive training across neurocognitive and psychiatric disorders, including three within persisting psychosis samples. The interventions involved performing tasks in real-world environments, such as making judgements about emotions and meaning when conversing with others. Whilst mostly pilot studies, the strongest effects were observed for attention and executive functioning across a range of conditions, suggesting these interventions offer promising transdiagnostic potential. In clinical populations of young people outside psychosis, digital technologies have been used for a variety of clinical purposes, though cognitive targets remain understudied. Nonetheless, findings in this literature point towards digital interventions being a feasible and acceptable vehicle for mental health treatment in young people, with larger effects observed for those that involve some human support or when 'blended' with standard treatments (314, 328).

Together, these findings indicate that some forms of digital interventions for cognitive enhancement can be effective, with well-established evidence for human-supported computer-based cognitive remediation. There is too little evidence to confirm whether this is also the case for other technologies, although VR and smartphone interventions are promising (particularly VR for improving social cognition and functional outcomes). Notably, one VR intervention to support social skills in an early psychosis service in the United Kingdom was identified within clinical trials registries (https://clinicaltrials.gov/ct2/show/NCT04310475). This study involves 10 VR therapy sessions with goal setting and homework tasks in 10 participants; assessing feasibility, acceptability, and psychometrics.

STRENGTH/QUALITY OF THE EVIDENCE

Not applicable.

COMMERCIALLY AVAILABLE DIGITAL INTERVENTIONS FOR COGNITION

There is a well-recognised gap between industry and research in the field of digital mental health (311). For example, a review conducted in 2019 found that only 3% of commercially available mental health apps had any evidence base (329). This is also the case for digital interventions for cognition.

Searches using the term 'cognition' were conducted of major app stores (Google Play, Apple App Store, Steam VR, Oculus) to identify any commercially available smartphone apps, online programs and VR platforms that offered promises of cognitive enhancement. Ten VR platforms, and several hundred smartphone apps or online programs, were identified. None of the resultant hits specifically referred to enhancing cognition in psychotic conditions. However, several claimed that the platforms were suitable for clinical populations. Most of the VR applications identified involved arcade style games in which users complete tasks which rely on cognitive skills such as decision making, attention and reaction time (for example, CogVR; ENHANCE). Others referred to skills that may be linked to cognitive engagement such as playing musical instruments or engaging in physical exercise (for example, Jam Studio VR). A significant number of applications were identified in Apple and Android app stores. Similar to the VR applications, the majority of these appeared to involve completing gamified tasks employing cognitive skills such as memory, reaction time and pattern recognition (for example, CogniFit). Similar results were found for online programs, which often enabled access via a computer or smartphone (for example, BrainHQ).

Some of the applications identified specifically claimed to enhance cognition. However, no links to clear scientific evidence were provided. Commercially developed cognitive training technologies should be approached with particular caution due to concern regarding the validity of their scientific claims (330). Whilst many of the tasks that users engage in within the applications appeared similar to those employed within validated cognitive treatments, it was not possible to screen all of these apps for quality and evidence base. In the absence of published scientific evidence, it is not possible to validate any claims for clinical efficacy.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

Poor long-term engagement with digital interventions is a well-recognised barrier to implementation. Motivation difficulties, as well as over-exposure to digital products in youth populations, may make this issue particularly challenging for young people with early psychosis (331). Research suggests that the best solutions for overcoming these issues include: 1) involving human support, such as peer support or coaching (332) to enhance engagement, or 'blending' digital interventions with standard care (for example, (333)); and 2) working more closely with end users, using participatory design methods, and industry partners, to design more engaging, compelling and purpose-built digital interventions (334).

Another major barrier to implementation concerns the complexities of integrating digital interventions within existing service contexts. Staff and service user attitudes, organisational readiness, and degree technology 'fit' within existing service systems, are all factors known to influence the success of implementation within routine care (335). Solutions to these problems highlighted in the literature include: 1) designing digital interventions for implementation contexts; 2) designing alongside service providers and users; 3) conducting trials within the implementation context to ensure findings are readily transferable and generalisable; 4) drawing on

knowledge from the fields of implementation science; 5) ensuring technologies are flexible and adaptable to the changing implementation context over time; and 6) staff training and support to shift attitudes and build knowledge on the use of technology to support service delivery.

3.9 BRAIN STIMULATION

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Non-invasive brain stimulation methods, such as **transcranial magnetic stimulation (TMS)** and **transcranial electrical stimulation (tES)**, have seen increasing research interest as an alternative treatment option for people with neuropsychiatric conditions. TMS currently has US FDA approval as a clinical treatment for major depression and obsessive-compulsive disorder. tES is currently still in development, although the most commonly used method (transcranial direct current stimulation: tDCS) has approval for treatment of depression in some jurisdictions (for example, Europe and Australia). TMS involves the application of strong magnetic pulses to modulate brain activity via the principle of electromagnetic induction. The magnetic pulses induce small transient electrical currents within the cortex underlying the magnetic coil, which in turn produce short-term neuroplastic changes during and after stimulation (336), direct priming or entrainment of neural activity (337), and short-term metabolic changes (338). Repeated treatments cause changes in brain volume and more lasting metabolic changes (339, 340). tES instead involves the passing of small (that is, usually 1-2mA) electrical currents through the brain via electrodes placed on the head. The modes of action depend on the form of tES. tDCS involves administering a direct unidirectional current that produces depolarisation and hyperpolarisation of cortical neurons (341) which in turn cause neuroplastic (342) and functional neuromodulatory changes (343) that outlast the period of stimulation. Transcranial alternating current stimulation (tACS) instead involves the application of an alternating oscillatory current for the purpose of modulating endogenous oscillatory neural activity. Emerging research suggests that these effects on neural activity outlast the period of stimulation (344) and modulate functional networks (345).

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

Research into the effectiveness of brain stimulation treatments for improving cognitive functioning in the early psychosis population has been preliminary, with no systematic reviews or meta-analyses. One pilot randomised double blinded sham-controlled trial (RCT) in the US investigated the efficacy of 10 daily treatments of high frequency repetitive (rTMS) in 20 people with early phase psychosis (346). Bilateral rTMS was administered to the left and right dorsolateral prefrontal cortex (DLPFC). Cognitive functioning was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) at pre-treatment, post-treatment and 2 weeks follow-up. Results showed evidence for improvement at follow-up on the BACS Composite Score with active rTMS, though not with sham rTMS. Limitations included a lack of adjustment for multiple comparisons and assessment of participant blinding. A large multicentre double-blind sham-controlled trial involving 300 participants in China at clinical high risk for psychosis is currently in progress (https://clinicaltrials.gov/ct2/show/NCT04853485). Participants are randomised based on their symptom profile (prominent negative or positive) and level of cognitive functioning to a rTMS intervention targeting the particular brain regions/biotype associated with the symptom profile. Those with cognitive dysfunction will receive active or sham rTMS targeted by an individual MRI scan and functional connectivity with the left hippocampus. Cognitive functioning will be assessed within half an hour after rTMS using the MATRICS Consensus Cognitive Battery and global functioning will also be assessed. While this study will provide important new knowledge about short-term acute cognitive effects from a single rTMS treatment, it remains unclear from the trial record whether efficacy will also be evaluated following repeated treatments. One sham-controlled tDCS study in the US has investigated the cognitive effects of a single treatment applied over the cerebellum in young people with nonclinical psychosis (non-help seeking individuals experiencing psychosis symptoms) (347). The NCP group showed a significantly greater rate of procedural learning on a motor task after active tDCS compared to sham tDCS. Participant blinding was not assessed. A controlled clinical trial of 10 treatments of active or sham tDCS in 70 participants with early-stage psychosis (https://clinicaltrials.gov/ct2/show/NCT03071484) is currently in progress in Brazil (348). Importantly, this trial includes follow-ups at 1- and 3-months' post treatment *and* assessment of functioning status. The estimated study completion date is August 2021. To the best of our knowledge tACS has not yet been trialled in this population.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

A systematic review and meta-analysis investigated the efficacy of high frequency repetitive TMS (rTMS) for improving cognition in people with schizophrenia (349). The review included 9 sham-controlled trials. Significant effects favouring active rTMS were found for working memory (ES = 0.34) and global cognition (ES = 0.15). The AMSTAR-2 rating of this review was *critically low*, with the potential impact of risk of bias and heterogeneity not satisfactorily considered in the analysis, reporting and interpretation of results. Another systematic review instead examined the effects of low frequency rTMS across healthy and clinical populations (350). The review included 5 studies conducted in patients with psychotic illness with mixed study designs. Across cognitive domains, the majority of studies found no significant effect. No meta-analysis was conducted and the AMSTAR-2 rating of this review was *moderate*. A recent systematic review and meta-analysis examined the efficacy of non-invasive brain stimulation for improving working memory in schizophrenia or schizoaffective disorder (351). This review included 9 sham-controlled trials which used rTMS. Small, though non-significant, effects favoured active rTMS for both working memory accuracy (ES = 0.11) and reaction time (ES =

0.23). The AMSTAR-2 rating of this review was *moderate*. For tDCS, a systematic review which included 32 studies with mixed study designs (29 randomised and sham-controlled), found that the majority of studies reported significant effects on memory, cognitive control and attention (352). Fifteen out of 17 studies which administered a single session of tDCS reported a significant effect on at least one cognitive function, while mixed results were found for the 15 studies which conducted multisession interventions. No meta-analysis was conducted and the AMSTAR-2 rating was *moderate*. Another systematic review and meta-analysis in schizophrenia, schizoaffective disorder or psychosis included 14 parallel group randomised sham controlled trials (353). The meta-analysis on generalised cognitive functioning outcomes included 7 studies and found a small sized though non-significant effect (ES = 0.22) favouring active tDCS. The AMSTAR rating was *moderate*. A recent systematic review and meta-analysis which included 12 sham-controlled studies of tDCS conducted in children and adults with attention deficit/hyperactivity disorder (ADHD) found small-sized though non-significant effects favouring active tDCS for improving attention [ES = 0.18], inhibition [ES = 0.21] and processing speed (ES = 0.14) (354). The AMSTAR rating was *moderate*. There is evidence from one meta-analysis suggesting that females may derive greater cognitive benefit from tDCS (355). No meta-analysis has been conducted to examine the efficacy of tACS for improving cognition in schizophrenia. A recent systematic review described 7 studies with mixed designs (including 2 double blind RCTs) (356). Neither of the two small RCTs (n= 10:(357) and n=22: (358)) reported significant effects of tACS on cognition. The AMSTAR-2 rating was *critically low* as a comprehensive search strategy was not used and risk of bias was neither assessed nor discussed.

STRENGTH/QUALITY OF THE EVIDENCE

There have been no systematic reviews or meta-analysis for these treatments in UHR/CHR or FEP. Only two small sham-controlled studies (1 with rTMS and 1 with tDCS) have so far been conducted examining the cognitive effects of non-invasive brain stimulation in early phase psychosis and young people with non-clinical psychosis, respectively. Both studies reported small-sized significant effects with active treatment. A systematic review and meta-analysis of tDCS in children and adults with ADHD of moderate quality provided evidence of small-sized, though non-significant, effects on cognition (354). Heterogeneity was significant for 2 out of 3 of the cognitive outcomes. Evidence of cognitive effects in people with schizophrenia with rTMS and tDCS has been mixed with overall small-sized effects, primarily from single session studies. There is currently minimal evidence available assessing the efficacy of tACS for improving cognition. See Supplementary Table 7 for a summary of the evidence.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

rTMS treatment involves attending a clinic or hospital, usually daily, over several weeks. This could be an impediment for recruitment and/or issue for attrition for younger populations due to transport issues and/or other competing commitments (for example, school). This similarly applies to lab-administered tDCS/tACS. Relative to tDCS, tACS involves a wider range of treatment parameters (that is, with different possible frequencies and waveforms and whether current is applied with a direct current offset or not). Basic studies are required to elucidate which tACS parameters are optimal for improving cognition. With tACS, the alternating current can produce phosphenes (359) which could pose an impediment for effective blinding in sham-controlled trials.

For rTMS, efforts for improving efficacy for improving cognition increasingly involve the use of individualised targeting based on either structural and/or functional MRI brain scans (neuro-navigation), which are associated with additional costs, expertise and inconvenience for participants/patients. While to-date, it remains unclear whether these approaches are more effective than targeting methods which do not require an MRI scan, this may prove a barrier for clinical translation of novel rTMS interventions, particularly in developing countries.

3.10 PEER WORK

DESCRIPTION OF THE INTERVENTION(S) AND MODE OF ACTION

Peer support refers to a person with lived experience of mental health challenges (usually called a peer worker or peer provider) entering into a peer relationship with another person experiencing similar challenges. In this report, we focus on formal peer support as opposed to semi-formal peer support (for example, group therapy facilitated by a clinician where peer-to-peer interactions occur, but there is no peer worker present) or informal peer support (for example, the connections that people make informally). In low resources settings, peer support has been used as one form of ‘task shifting’ (training lay people to deliver interventions usually provided by qualified practitioners); however, in this report we only considered this to be peer support if the lay people had lived experience of mental health challenges.

Although there are various models of peer support, such as Intentional Peer Support (360), across all models five mechanisms have been identified that underpin peer relationships: lived experience, love labour (that is, the emotional safety and wellbeing of peers is considered and assured), the liminal position of the peer worker (that is, that they occupy the ‘liminal’ space between the boundaries of the identities of ‘patient’ and ‘clinician’), strengths-focussed social and practical support, and the helper role of the peer support worker may facilitate their own recovery (361). Unlike expert-patient relationships, peer relationships prioritise the expertise of lived experience and mutuality. Mutuality means that both the peer worker and peer (consumer) expect to learn from one another, and that they are both responsible for establishing and actively reflecting on the ‘rules’ of the relationship and power structures within the peer

relationship (362). Because peer support does not use a deficits framework, in this section we will refer to *cognition-related challenges* rather than cognitive deficits.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

There have been very few studies published in the area of peer support for cognition-related challenges in early psychosis. We did not identify any systematic reviews or meta-analyses.

One intervention that has been tested in a randomised controlled trial in the USA is the Personalised Real-time Intervention for Motivational Enhancement (PRIME) mobile app, which was developed for young people aged 16-36 diagnosed with schizophrenia spectrum disorders within the previous 5 years to improve motivation and other cognitive-related outcomes (363). The app facilitated participants to work "towards self-identified goals with the support of a virtual community of age-matched peers with schizophrenia-spectrum disorders as well as motivation coaches". In this initial trial, the motivation coaches were clinicians, meaning that the intervention involved peer-to-peer support (that is, other users of PRIME), but not the use of trained peer workers. Participants were randomised to receive either access to PRIME (n=22) or a wait-list control (n=21). The primary endpoint was change in motivated behaviour between baseline and 12-weeks as assessed by a measure of reward learning, anticipated pleasure and effort expenditure. Significant improvements were found for anticipated pleasure and effort expenditure in favour of the intervention group. Building on this work, a larger RCT is underway that involves 'super-users' (that is, people who have previously been active users of PRIME) who are trained to undertake the role of the motivation coaches (rather than clinicians as was the case in the original trial) (364).

An unpublished RCT being conducted in Hong Kong was also identified (https://clinicaltrials.gov/ct2/show/NCT04166019). The trial is recruiting individuals with recent onset psychosis to investigate the effectiveness of a peer-led self-management intervention compared with psychoeducation. Although the primary outcome includes level of recovery, secondary outcomes of functioning, problem solving, service satisfaction and focus groups from several community centres may provide valuable insight on the effectiveness of a peer support approach. Also, an open label trial of peer delivered decision coaching in individuals with early psychosis in the USA was identified (https://clinicaltrials.gov/ct2/show/NCT04532034). Although the effectiveness will not be directly compared with a control condition; acceptability/feasibility data and related qualitative insight may hold value.

A suite of interventions using the Moderated Online Social Therapy (MOST) platform in Australia have been developed and tested for early psychosis. The MOST platform combines online therapy, social networking, and general support. The platform is a combination of self-guided activities and interaction-based activities, including with clinicians, vocational workers, peer workers, and peer-to-peer interactions with other users. MOST has been developed for first-episode psychosis (called Horyzons (365)) and young people who meet the ultra-high risk criteria (called Momentum (366)). Although the MOST platform includes peer support related elements, it is not possible to differentiate the effects of peer support from other, more central parts of the intervention (for example, online therapy) and cognitive functioning is not explicitly addressed.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

There is evidence that peer support is effective in improving overall functioning and reducing hospitalisation (without an increase in overall service use) for adults diagnosed with schizophrenia (367). This study was conducted in China and was a family peer support intervention, whereby peer support was provided to both the adults diagnosed with schizophrenia and their carer (for example, parent, spouse, child). Positive effects were also found for carer functioning and support use. Consideration of how peer support for severe mental illness should be designed and implemented in low-, middle- and high-income countries is currently being investigated (ISRCTN26008944).

STRENGTH/QUALITY OF THE EVIDENCE

Not applicable.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

The main challenge is that peer support programs tend to have a generalised focus because: 1) peer workers are led by the needs and wants of the peer they are in a peer relationship with; and 2) peer support programs tend to be implemented on a small scale with limited funding, so the potential for specialisations (that is, peer workers focused solely on improving cognitive functioning) is very limited. In terms of implementing the peer workforce across mental health settings, a number of barriers have been highlighted. These include role confusion, lack of support from senior staff, lack of credibility for the role, and acculturation of the 'peerness' of the role (that is, peer workers are at risk of becoming ingrained in clinical frameworks and practices) (368-370) and these may be exacerbated for youth peer workers (371).

3.11 LIVED EXPERIENCE INVOLVEMENT

DESCRIPTION AND RATIONALE

When reviewing the literature for each section, we took note of any studies that included a lived experience perspective in the design or conduct of the study. This included the involvement of consumer researchers, consumer advisory groups or consultants, or the use of participatory methodologies such as co-design. Co-design refers to a group of methodologies for the design and development of interventions in order to ensure the outcomes of the design meet the needs of target users. A simplified differentiation between co-design and peer support lies in the respective focus on design and delivery. Co-design can take many forms, common methods include surveys, workshops, focus groups, interviews, online discussions, and polls. Key features of co-design include:

- Equal value of people with lived experience and professionals/researchers;
- The sharing of power, especially in relation to decision making;
- A design-led process; and
- Use of design methods to support active participation.

Therefore, utilising the unique perspective of individuals with lived experience can foster sharing of knowledge and power, and is particularly relevant in situations with power imbalances (for example, mental health conditions).

Consumer-focused research in adults with persistent psychosis has shown that cognitive enhancement is equally as important as addressing clinical symptoms (372). It is often assumed that people at UHR for psychosis or with FEP have similar cognitive treatment perspectives to adults with persisting psychosis; however, this perspective may be hindering development of interventions addressing cognition in youth. We know from qualitative studies that cognitive impairment is distressing and impacts functioning and quality of life in people with FEP (37); but we do not know if addressing cognitive function is a priority for individuals with emerging or first-episode psychotic illnesses, or the best methods of engagement in related therapies.

One area in which there has been increased emphasis on participatory methods over the past decade is the broader digital mental health field, with several articles written on the importance of lived experience involvement in digital intervention development, including in early psychosis. What is less clear is the best approach to user involvement. This depends on the aim and purpose of the intervention. However, in digital technology there has been some recent shifts away from pure 'co-design' approaches, which weigh the power between researcher and end user equally in making decisions about design, towards *user-centred* design or *participatory approaches*. The latter draws more heavily on methods to 'understand' the lived experience of the end user as it relates to the intervention, typically through focus groups and usability sessions (see (373)), in order to make informed choices about the design. As such, the researchers and developers retain decision-making control throughout the process. These methods have not been compared empirically, however the latter is more commonly adopted in neighbouring academic fields such as computer-human interaction, as well as in industry settings.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

No co-design or user-centred methods were identified across the themes reviewed, with the exception of digital interventions. User involvement was identified in three digital interventions for psychosis, targeting social cognition or motivation (374-376). One study implemented a virtual world for social cognition training, through collaboration between researchers and individuals who had used mental health services, the intervention was then piloted in 20 individuals with FEP (374). Another method was more aligned with co-design principles through 'design workshops' to develop the PRIME app discussed previously, and high retention, completion, and engagement rates were achieved (375). Another digital intervention discussed above (MOST platform) was developed through a series of multidisciplinary design workshops, which included the use of participatory research methods to obtain ongoing feedback from people with lived experience (FEP) and clinicians working in an early psychosis clinic (377). While co-design development involving individuals with psychosis is emerging for digital interventions, there remains a significant unmet need across all themes (378, 379), presenting an area ripe for research and development in the field of cognitive interventions for psychosis.

The lack of end-user perspectives in the design and development of all interventions is likely a key contributor to attrition rates and difficulties with engagement. Personalised and developmentally appropriate treatments are critically necessary in the context of UHR and FEP, in which many psychosocial factors play a role. Considerable efforts should be made by funders, policy makers and research leaders to encourage the involvement of individuals with lived experience in every stage of the development and implementation process.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

A scarcity of reports was also revealed through a broader search of co-design of cognitive-enhancing interventions in mental illness and neurological conditions, and the few interventions identified focused on social and functional outcomes, or e-health programs.

Specifically, development of a website for individuals with psychosis involved individuals who had experience with psychosis mental health services, and participated through consultation, content conceptualisation and writing, site design, and development of lived experience interviews (380). Two studies modified an existing program or app into a web technology targeting executive function for traumatic brain injury and psychological support for psychosis, however user involvement consisted of feedback only (381, 382).

STRENGTH/ QUALITY OF EVIDENCE

Not applicable.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

The limited interventions discussed herein implemented user engagement, consulting and informing, rather than true co-design methods. Thus, it was not possible to truly assess the effectiveness of co-design interventions in psychosis, and this is an area that requires further evidence. Potential barriers include a lack of consistency in co-design frameworks, and evaluation metrics, and more broadly, a lack of evidence on the possible impact on cognition. Thus, findings are in agreement with recent reviews of mental health technologies that identified a lack of co-design interventions for schizophrenia (383, 384). Also, a recent systematic review of co-design across global health care recommended more clear and consistent co-design terminology, better reporting of activities, and greater differentiation between the levels of co-design (385).

3.12 IMPLEMENTATION SCIENCE

DESCRIPTION AND MODE OF ACTION

It has been widely-reported that evidence-based practices take, on average, 17 years to be integrated into routine health care (386). There is also research to suggest that up to half of evidence-based practices don't make it into widespread clinical usage at all (387). This research-to-practice gap has prompted a recent expansion of the field of *implementation science*, the rigorous study of how to support and improve the adoption, application, and maintenance of evidence-based practices in routine care. Whereas clinical research concentrates on measuring clinical effectiveness outcomes, primarily reduction of symptoms, implementation research can consider any aspect of implementation, including the process of implementation, factors that influence implementation, and implementation outcomes (Table 4).

Table 4. Implementation research focuses on the process, determinants (influencers), and outcomes of implementation.

Process	Determinants	Outcomes
What was done?	**What factors influence implementation?**	**What happened?**
Strategies used for implementation (for example, training, incentives, policy change)	Barriers and enablers	Acceptability, feasibility, appropriateness
	Contextual factors (for example, system, organisational)	Adoption or intentions to use
People involved in implementation (for example, consumers, practice "champions")		Costs of implementation
	Individual factors (for example, education, prior training)	Fidelity

Importantly, implementation science tends not to focus purely on the production of academic knowledge, rather it aims to create findings for a range of stakeholders, or 'knowledge users'. This may include decision makers, such as service leaders, commissioners, or policy-makers, frontline staff who use evidence-based practices in their routine work, consumers who engage with care, or communities who can be empowered to improve their health outcomes through research (388). Implementation science also emphasises the need to understand how evidence-based interventions can benefit consumers in 'real-world' settings, outside of the highly-controlled clinical trial environment. This means that effectiveness is often considered without excluding certain people or groups to control for causal effects. Understanding the role of *context* is a key area of focus, including cultural, economic, political, social, legal, and physical environments, as well as organisational settings comprising a range of stakeholders and their relationships. The overall aim of implementation research and implementation science as a field is to build knowledge about *how* and *why* interventions work in *routine care settings*, and to develop and test approaches to improve the translation of evidence into practice.

EFFECTIVENESS ACROSS UHR/CHR AND FIRST-EPISODE PSYCHOSIS

Much of what is known about implementation of interventions for psychosis is based on findings from controlled clinical trials, which have limited generalisability across usual care settings. Little is known about contextual factors that may support readiness to implement, early uptake and engagement, or sustained use of cognitive treatment innovations in practice. Research on the implementation of interventions for cognitive impairment in FEP or UHR populations is scarce, with limited evidence related to implementation of cognitive remediation (CR) in adult mental health settings. One known study of the implementation of CR in first-

episode coordinated specialty care in the USA found evidence for feasibility including good adoption, fit, utilisation, and cost, as well as good tolerability and satisfaction (196). Overall, available findings from adult mental health settings suggest that CR is generally considered acceptable to clinicians (205, 389, 390) and consumers (391, 392). However, research on the contextual factors that support adoption and sustainability of CR in routine care is extremely limited.

For FEP and UHR populations more generally, there is growing implementation literature on specialist models of care, which focuses mostly on fidelity. Several papers provide recommendations for the implementation of early intervention specialist services, including recommendations on how to establish a service to prevent psychosis (393, 394), and one study on the development of an Australian implementation guide (395). There is growing consensus about the effective elements of early psychosis services, with fidelity scales and outcome measures available to assess quality, access, and outcomes (394, 396). Although they have shown evidence for effectiveness, barriers to implementation of specialist or standalone models of care have been identified around staffing and financial constraints, and the difficulty detecting individuals at ultra-high risk (397).They have also been critiqued for implementation-related factors such as being isolated from community mental health services and possessing highly resource-intensive characteristics (398). These factors present a particular challenge in rural and remote areas (399). A modified 'hub and spoke' model developed in Australia aims to address these challenges, though evaluation of this approach has been limited (398). Integrated care pathways, which outline services that people experiencing psychosis can expect at different phases of care, have been established in England and developed locally in Canada and Australia, with barriers to implementation suggested around system issues, such as inpatient versus community-based care and infrastructure (400, 401). It is unclear how interventions targeting cognition integrate within or outside specialist services, and whether differences in these contexts influence implementation.

ADDITIONAL EVIDENCE/INFORMATION FROM OTHER POPULATIONS

Other areas of psychosis research offer evidence about the factors that can influence implementation of evidence-based interventions. Several systematic and narrative reviews have summarised barriers and enablers to implementation of family involvement in treatment for psychosis and point to the importance of organisational culture in seeing family as part of care and the need for cultural adaptation of family-focused care (402-407). Although research on the implementation of guidelines for schizophrenia is scarce, available literature suggests barriers at the level of the organisation, as well as the consumer and clinician (408). Similarly, research on barriers to implementation of CBT for psychosis has highlighted organisational barriers as most frequently reported, followed by barriers met by staff and consumers (404). Implementation science literature beyond psychosis and cognition provides inspiration for how this field can support progress in the field of cognitive intervention for UHR and FEP populations. These include lessons from the area of child psychiatry and psychology, which have identified targets for implementation strategies beyond clinician knowledge and skills, such as organisational culture and clinician motivation (see (409, 410) for reviews).

Research on the delivery of early intervention outside specialised standalone services has been reported as heterogeneous in design and outcomes, making it difficult to draw firm conclusions about whether outcomes reported in specialist centers apply to other models (398).

STRENGTH/QUALITY OF THE EVIDENCE

Not applicable.

CHALLENGES TO PROGRESS OR IMPLEMENTATION

The scarcity of research informed by implementation science poses a significant challenge to translating evidence into practice.

OPPORTUNITIES AND RECOMMENDATIONS

Research designs and methods

Implementation science is an evolving field that provides a range of models and theories to support the design and delivery of implementation research and practice (411). These frameworks can help to describe and/or guide the process of implementing evidence into practice, build understandings about what influences implementation outcomes, and inform the evaluation of implementation.

A range of study designs and methods can support research focused on implementation (Figure 2). ***Formative evaluations*** conducted prior to implementation can offer key insights about potential barriers and enablers to uptake and sustainment, while ***summative evaluations*** can provide information about what actually happened, as well as what was seen to help or hinder implementation. ***Process evaluations*** can be conducted alongside implementation to offer insights about what was done at key stages, for instance during exploration and preparation for implementation, early implementation, and/or once an intervention has been in use for some time. Depending on the phase, research questions can focus on different aspects of implementation; for instance, who was considered most important in the preparation for implementation, or how has an evidence-based practice been modified over time and why. ***Adaptive implementation designs***, comprising a sequence of decision rules that are tailored based

on a site's uptake of a program, may produce more rapid, relevant, and generalisable results by quickly confirming or rejecting implementation strategies depending on the context (412). This approach aligns with quality improvement approaches that take measurements repeatedly and regularly over time to inform decision-making, which are often used in clinical care settings. ***Participatory action research***, carried out with and by local people rather than on them, lends itself easily to implementation research, which focuses on understanding a range of perspectives.

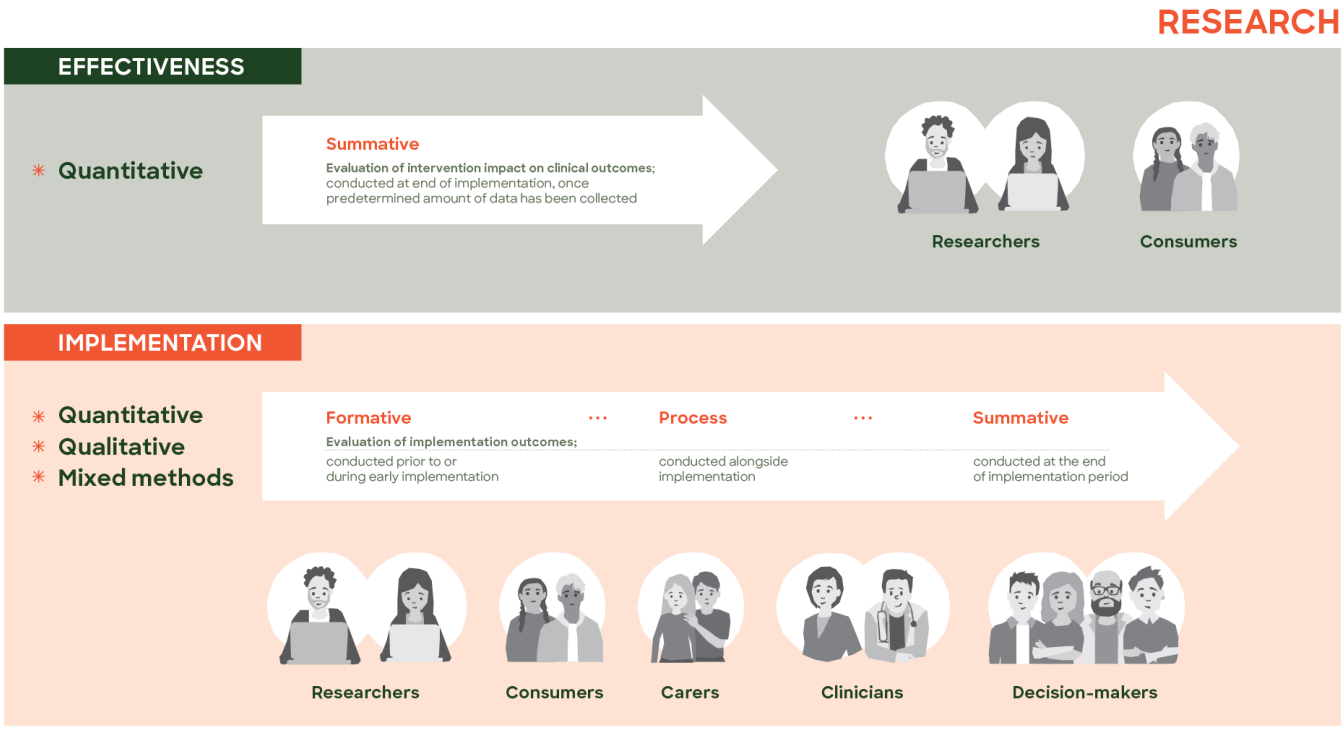

Figure 2. Research on the effectiveness and implementation of interventions differs in measurement, stages and knowledge users.

Implementation-effectiveness hybrid designs, which combine implementation research alongside clinical effectiveness research, offer a link in the research pipeline between effectiveness studies and pure implementation research, offering benefits over conducting these streams of research independently (413). By taking a blended approach, these designs have strong potential to accelerate the introduction of innovations into practice, by producing more rapid translational outcomes, including insights into effective and pragmatic implementation strategies and more relevant information for knowledge users, including decision-makers. Hybrid designs offer several options to help build the evidence for implementation alongside effectiveness, depending on a number of factors such as: face validity, existing evidence and risk associated with the intervention and implementation strategy, current implementation momentum, and feasibility of implementation. Depending on the evidence-base and face validity of the intervention, different hybrid designs may be suitable for a range of cognition-enhancing interventions for psychosis. Although hybrid research designs may be more complex and costlier to execute, the benefits are likely to outweigh the risks in terms of public health impact.

Implementation research approaches can use *qualitative, quantitative, or mixed methods* of data collection and analysis, depending on the research question and what is feasible. Mixed methods are seen as particularly suitable, as they can support data collection from multiple sources to understand a range of perspectives, causal mechanisms, and outcomes (388). Indeed, one of the key principles of implementation science is to consider the perspectives and involvement of a *range of 'knowledge users'*, that is people who will be involved in or impacted by implementation. Involving knowledge users in the design and conduct of implementation research can provide key insights that will help to support uptake and engagement with interventions in routine care. Importantly, the methods and approaches used to answer implementation-focused research questions are commonly used in clinical research, so health researchers will generally have the relevant skills to start considering implementation research questions in their work. Implementation science research and practice specialists bring expertise on theory and evidence-based implementation practice. Although there has been some research that considers the factors that may influence the implementation of cognition-enhancing interventions for psychosis (for instance the acceptability of cognitive remediation), research focused on implementation strategies and understanding the role of context is rare.

Implementation strategies

Though clinical research often focuses on a specific intervention implemented using some kind of strategy (for example, training for clinicians), both clinical and implementation research often fail to describe these in detail. Available research suggests that

implementation of cognition-enhancing interventions often includes training (391, 408); yet, there is established evidence from other areas that training and education by themselves are not usually sufficient to produce practice change (414). There is growing evidence to show that tailored implementation strategies, which specifically address determinants of practice in the local context, may help to improve uptake of evidence-based practices in routine care (415). We suggest that, at a minimum, research with UHR and FEP populations describe interventions and implementation strategies in full. Research focused on designing and testing strategies to support implementation of specific interventions is warranted where evidence for the intervention is strong and a range of other conditions are met (see section on hybrid designs). Findings of the present review suggest that these strategies are likely to benefit from targeting organisational and individual factors, which are often cited as barriers to implementation of interventions for psychosis.

Context and determinants of practice

Implementation science models and frameworks provide guidance on key contextual factors that have been found to influence implementation in health settings, for example, organisational characteristics, policy and funding landscapes, service integration and partnerships (411). Research to understand the relative importance of these factors is critical for understanding how cognition-enhancing interventions can be widely used in real-world settings. This includes research on what is already being done in routine care, which can generate "practice-based evidence" to identify the most important determinants of practice to be targeted with tailored implementation strategies. We suggest that further research is needed that considers the implementation of different models of care for UHR and FEP populations (that is, specialised vs integrated), including how interventions integrate in these different models and the relative feasibility of these approaches depending on available resources.

3.13 LOW- AND MIDDLE-INCOME RESOURCE SETTINGS

We interviewed several individuals from low- and middle-income resource settings to discuss the implementation of cognitive interventions for psychosis and associated barriers. Interviewees included mental health professionals experienced in clinical services, research, teaching, advocacy, policy, mentorship, and cultural heritage from Kenya, Nigeria, Zambia, India, and Brazil. Here, we discuss approaches to treating psychosis within major cities, thus, barriers and limitations should be considered amplified in rural areas. Although our sample is a discrete convenience sample and not representative of all low- and middle-income resource settings or the entire perspective of each of these regions, we highlight valuable insights to consider in future investigations.

Mental health care services

Across countries psychosis is initially treated with antipsychotics. Once symptoms stabilise, further investigations into aetiology, comorbidities, possible substance use and infections/ transmitted diseases are conducted. Following these initial stages, treatment approaches varied between settings.

The use of antipsychotics is variable and heavily reliant on availability and costs. In Kenya and Nigeria, haloperidol (and benzodiazepine) is generally prescribed in public settings, and newer agents may be available in private practice. In Zambia, haloperidol and chlorpromazine are prescribed in public hospitals, and olanzapine and risperidone within private clinics. In Brazil, clozapine and olanzapine are most commonly prescribed.

When mental health care workers were asked what they consider to be the top treatment priorities for psychosis, psychiatric symptoms, family relationships, substance use and finances were most commonly identified. More specifically, acceptance and support from families holds large importance and relies on de-stigmatisation, including through psychoeducation.

There are differences in the type and quality of treatment between private and public practice, for example private services allow for greater time to assess the patient, and availability of appropriate antipsychotics; *"sometimes the available treatment is not the right treatment…. the treatment you want to get is hard to get, because there are few people offering it"*.

Treatments for cognitive impairment

All interviewees agreed that cognitive impairment was an area of concern for people with psychosis. However, assessment of cognition and approaches to cognitive interventions were variable, with a notable absence of tailored treatments and limited availability of trained health care professionals in many cases.

Cognition is rarely considered in clinical practice within Zambia; at best, basic psychoeducation may be provided, often through a single session. This approach is related to the limited personnel, clinical training, and assumption that an individual with psychosis is in a cognitively impaired state. It is estimated that 1-2 individuals at each of the two mental health hospitals can complete cognitive assessments. Also, psychological support following inpatient care is rare.

The Brazilian health care system focuses on antipsychotic treatment, yet community centres provide more targeted psychosocial support through a multi-disciplinary approach including occupational, music, physical and psychotherapy. However, the only

approach to address cognition is psychoeducation. Psychiatrists will refer patients to community centres, which are easily accessible in the south of the country, but not in the north.

In contrast, in Nigeria and Kenya cognition is routinely assessed, and therapy is tailored accordingly. A comprehensive cognitive and neurological assessment is conducted, and further cognitive tests may be completed in specialised follow-up care. Also, depending on the presentation, a multi-disciplinary team including a psychiatrist, psychologist and nutritionist are often involved in applying cognitive tailored therapies. Cognitive remediation and compensation, and social cognitive training are limited to private practice.

In India, art and dance therapy, CBT, and recovery-focused care are used to target cognition, and more rarely cognitive compensation and social cognition training. Barriers to the latter two involve a lack of culturally appropriate services in native languages. Informed consent related to antipsychotic medication is not routine practice, and related terminology is only available in English.

Digital interventions were not readily available in these settings, due to limited internet services and low technology literacy, particularly in regional or rural regions. However, patients and health care workers are connected through apps, and there is opportunity for implementation of interventions through mobile apps. More complicated uses of technology (for example, VR) do not seem feasible. Nutritional agents are incorporated into management, yet unlikely to be sustained due to high costs. General exercise and sleep habits are discussed, but tailored interventions are not prescribed.

Involvement of individuals with lived experience

Peer support groups were reported in Zambia, Kenya, Nigeria, and India for general psychiatry, and psychosis on a volunteer basis, yet programs specific to cognition or paid roles were not identified. Notably, individuals are often advised against peer support programs [in Zambia], due to the severe nature of community stigma and potential mental health consequences. However, peer support programs are particularly important in breaking stigmas, for example, by translating medical terms into the local language to educate the community and enhance acceptance and inclusion of individuals with psychosis.

Co-design was not identified, although there is involvement of end users in cognitive interventions for bipolar disorder in India, and interviewees discussed the necessity to consider the perspectives of individuals with lived experience. Peer work and co-design were considered appealing and feasible in Brazil, even though they were not routinely applied. Also, task shifting was considered an impediment involving under trained workers within Kenya, Nigeria and India.

Barriers

The major barriers to cognitive interventions in these low- and middle-income resource settings were identified as:

1) limited number of adequately trained personnel;

2) lack of financial support (poverty);

3) poor mental health infrastructure;

4) lack of clinical training in cognition;

5) stigmas around mental illness; and

6) beliefs about psychosis.

A lack of skilled and accessible mental health professionals was consistently identified, particularly psychologists and psychiatrists. *"Out of a population of 18-19 million people [in Zambia], we have close to 11 psychiatrists… half of them are actually in clinical practice, and the other half are academics"*. In Zambia, mental health care clinicians are able to prescribe medication and treat psychosis following completion of a two to three-year diploma. Alternatively, in Nigeria, psychological support is available, but the costs are prohibitive for most patients.

Interviewees often acknowledged that more tailored cognitive therapies were necessary in psychosis management, yet restricted funding for first line treatment limited availability of even basic care. Use of antipsychotics is based on what is currently available at the centre, in some instances, medications are imported from overseas, and many people simply cannot afford them. Therefore, even greater financial difficulties are faced when considering tailored therapies. Although public services are free, the cost of transport may even be too burdensome for many families (reported in Brazil).

In terms of general mental health services, infrastructure is limited and exclusive to major cities. For example, referrals within Kenya and Zambia are streamlined through a single hospital, or by an outpatient and inpatient hospital, respectively. A lack of clinical spaces for psychotherapy is also hindering treatment options. When asked if there are sufficient resources, a general practitioner and professor in health replied *"If there are resources it means people should have enough… it means everyone that needs treatment*

should get it, I would say no, it is not that way". Infrastructure, particularly technology, to support clinical services is scarce and disproportionately dispersed across regions, with the lowest levels of infrastructure in rural areas.

Another major limitation within health care frameworks is the lack of focus on evidence-based cognitive interventions; *"you won't focus on something if you are not exposed to it or if you are not aware of it… education [for clinicians] is also key if you want to address cognition in psychosis"*. Thus, a bias in training is contributing to a bias in treatment; raising awareness and up-skilling the workforce may be the first steps to engaging individuals with psychosis in more cognitively tailored therapies.

Most interviewees spoke about high levels of stigma associated with mental illness, which causes difficulties for individuals accessing services, particularly women. Psychoeducation across settings is also challenging when explanations for the source of psychosis vary. In Zambia, some communities believe that an individual with psychosis is possessed, overtaken by demons, or experiencing a contagious form of epilepsy, which is at odds with the medical model of government mental health services. Individuals experiencing psychosis may therefore see a spiritual leader rather than a mental health care professional. Group therapy sessions have been implemented to facilitate understanding of psychosis, however there is often resistance and a lack of involvement.

Current evidence and recommendations

The barriers identified through the interviews are also supported in the literature of psychosis care within low- and middle-income resource settings, with an absence of cognitive interventions (416-419). Around 80% of individuals with FEP in low- and middle-income settings do not receive any mental health care, indeed 'patients with psychosis in low and middle income countries may be among the most disadvantaged on earth' (420). Also, mental health care resources are inequitably distributed between countries, regions and within communities; in some countries just one or two psychiatrists are available (421).

There is recognition that specialist services are costly to implement and resource-intensive in terms of requirements for highly-trained care teams (398). The global implementation of early intervention services for psychosis is heterogeneous and does not strictly relate to country income or health system structure. Across Europe, for instance, UK, Denmark and Norway have implemented national early intervention programs, while Germany and France have had limited uptake (422). Early intervention services in Latin America suggest that these models are feasible and adequate for the context, yet may not be appropriate for regional and rural areas (423). Adaptations have been recommended for regional and rural settings, which include access to technology and upskilling local teams; however, much of the work in this area has come from Australia and Canada, which, although facing challenges in terms of distance and isolation, have the benefit of well-resourced health systems (424, 425).

Looking beyond early intervention, available evidence from low- and middle-income resource settings supports the acceptability and feasibility of community-based psychosocial interventions for schizophrenia, although overall the volume of evidence is low (426, 427). There is a need for well-designed intervention studies that also incorporate measures of acceptability and feasibility, as well as the development of implementation outcomes measures that can be applied across diverse cultural settings. Accommodations for cultures with different beliefs about psychosis are necessary. Research and grey literature on the implementation of mental health interventions in low- and middle-income resource settings have reported a range of barriers at structural and organisational levels, related to infrastructure, policy, funding, planning and organisation, as well as individual barriers related to lack of awareness and stigma around mental illness (428, 429).

The World Psychiatric Association guideline for early intervention in psychosis in low- and middle-income resource settings recommends integration into existing services structures as community help-seeking pathways, culturally adapted interventions, free comprehensive care, and public health campaigns to reduce stigma and raise awareness (430). Cultural adaptation of cognitive interventions should include a bio-psycho-*spiritual*-social model. Western models should not be directly translocated, but principles should be. There is also a large opportunity to up-skill the workforce, by including more training in the importance of cognition and how cognition and functional recovery can be addressed in care. Many countries do not have policy frameworks for mental health, treatment, thus guidelines should be addressed at the policy level. There are several other areas for progress, such as increased infrastructure and support for families, yet these are reliant on resources and funding which are limited. There is a clear need to address cognitive interventions in psychosis care in low- and middle-income resource settings.

4. RECOMMENDATIONS

This landscape review determines that there is a **low volume of research** on interventions for cognitive impairment in early psychosis, with the exception of antipsychotics and cognitive remediation (medium volume). Furthermore, the various interventions that have been tested have generally had **inconclusive or small effects**, with the exception of social cognition interventions (medium-large effects). Most of the evidence on efficacy relates to cognitive outcomes; **functional outcomes are rarely measured** and when they have been measured the **effects are minimal** (with the exception of compensatory interventions). Below we provide general recommendations, which are applicable regardless of the type of intervention under investigation. This is followed by specific recommendations relevant to different types of intervention.

- High-quality, well-powered randomised controlled trials are needed across the board. The following sub-recommendations are critical to improving trial design:
    - Studies should only enrol participants with cognitive impairments, as would be done on a needs-based approach in clinical practice. This is absolutely key to cost-effectiveness and will increase treatment effect sizes.
    - Inclusion of people with IQ below 70 as this is an arbitrary cut-off and severely limits the investigation of the effects of interventions specifically targeting cognitive impairment, including their effectiveness at different levels of impairment.
    - Other inclusion criteria need to be *broadened* to allow the inclusion of a wider diversity of participants, facilitating a more real-world evaluation of the effectiveness of interventions, including a more powerful investigation of the heterogeneity and specificity of effects (433). For example, including the full-spectrum of psychotic disorders (non-affective and affective), including individuals who do and do not speak the local language (with inclusion of funding for interpreters), including participants in different health settings, regions, and countries.
    - Include both cognitive (objective and subjective) and functioning outcome measures.
- For some interventions, stratifying or personalising the intervention approach based on cognitive, functioning and biological factors (such as biotype) is desirable to progress personalised mental healthcare (that is, quantitative assignment designs). Adaptive trial designs could be considered (that is, modifying the intervention or combination of interventions based on response or level of engagement) (e.g., (434)).
- Longer follow-up periods are needed. This is not only important for determining the durability of treatment effects, but also for accounting for the interaction with the dynamic development occurring during adolescence and young adulthood. Careful and repeat measurement of relevant variables (cognitive, clinical, functional, and so on) is recommended to enable inference regarding mechanisms of change, if change is observed. This will facilitate the ability to maximise the engagement of these putative mechanisms in subsequent studies.
- High-quality health economic evaluations should be conducted to determine the cost-benefit of different types of interventions. Inclusion of a cost-effectiveness component in clinical and implementation trials can help to build an understanding of the resources needed for different interventions and implementation strategies across settings.
- There needs to be progress towards standardisation of cognition, social cognition and functioning outcome measures, including outcome measures that are meaningful to individuals with early psychosis. Currently, there is no agreement in the field and the measure chosen depends on the treatment target.
- Cognitive screening is not routinely conducted in early psychosis services (435, 436). Studies examining the effectiveness and implementation of cognitive screening in early psychosis are recommended. For example, one cognitive screening measure that warrants validation in youth populations is the Screen for Cognitive Impairment in Psychiatry (SCIP) (437).
- Research exploring the needs and preferences of key stakeholders, including young people with psychosis, caregivers/families, clinicians, service managers and funders in relation to cognitive impairment in psychosis, is critically missing from the literature. This work is urgently needed and could be facilitated through implementation science. Formative evaluations conducted prior to implementation can offer key insights about preferences, potential barriers and enablers to uptake and sustainment.
- Co-designed interventions for cognitive impairment in psychosis are severely lacking. Including lived-experience researchers in the design and production of interventions is recommended.
- There is a need for research on the potential and actual implementation barriers at organisational and individual levels, with a view to designing strategies that will overcome these barriers. Adoption of appropriate implementation research methodology, including formative evaluations, summative evaluations, process evaluations and adaptive implementation designs is required.
- Research is needed on what is already being done in routine care in various settings around the world, which can generate “practice-based evidence” to identify the most important determinants of practice to be targeted with tailored implementation strategies.
- Disengagement from treatment is a challenge in psychosis care, including for FEP (438-440). A number of factors have been shown to impact treatment engagement, including some factors that may be targeted by implementation strategies, for instance, involvement of family in care and model of care (439-443). We suggest the inclusion of robust and meaningful treatment and service engagement measures as part of evaluating the success of implementation strategies for cognition-enhancing interventions, along with further research on implementation strategies specifically designed to support engagement for UHR and FEP populations.
- To date, all interventions for cognition in early psychosis (and more generally in the field) are focused on addressing deficits. Development and trialling of novel cognitive *strengths-based interventions* either alone or in combination with cognitive enhancing interventions may offer a fresh, engaging and effective approach for young people with psychosis (197).
- In low- and middle-income regions education, training and development of the mental health workforce on cognitive impairment in psychosis and strategies for screening and intervention is recommended.

Pharmaceuticals

- At present the limited evidence for novel pharmaceuticals in enhancing cognition suggests that pharmaceutical interventions are a lower priority for future research trials than behavioural interventions.

- Studies addressing shared decision making in prescription of antipsychotics and other drugs are urgently needed, as this may be associated with enhanced treatment engagement and better outcomes. Cognition must be considered in these studies, including how cognitive impairment can affect decision-making capacity and how cognitive impairment can be accommodated.
- Use of alternative designs to RCTs, including large clinical cohort studies and nationwide population-based registries, as conducted in other health conditions is recommended (444).

Nutrients

- Studies on nutraceuticals need to better account for interactions with pharmaceuticals.
- There is a need to better understand the acceptability of taking supplements and various modes of administration in young people.

Cognitive Remediation and Compensation

- Evidence in chronic psychosis samples suggests that the largest effects on functional outcomes (for example, employment) are achieved when cognitive remediation is combined with a psychosocial intervention such as supported employment (for example, Individual Placement and Support) (44, 194). Cognitive remediation or compensation trialled in combination with supported education and/or employment is strongly recommended in early psychosis.
- The mechanisms of treatment effects remain poorly understood and require more research, particularly regarding the relationship between cognitive improvement and functional gains and whether cognitive improvement is a pre-requisite for functional improvement. It also remains unclear which individuals are likely to respond best to cognitive remediation (particularly in early psychosis) and when adjunctive or alternative therapies are warranted.
- Existing cognitive remediation and compensation programs are intensive, often lengthy, and require facilitation by highly skilled therapists. This is not feasible in many mental health settings. Future research should explore the development and piloting of briefer and simplified programs that can be delivered by general mental health professionals (non-expert in cognition).

Social Cognition Interventions

- Possible methods of addressing poor engagement (and possible funding shortfalls) are to conduct shorter interventions with more frequent treatment entry points, and/or eliminating or modifying (for example, online group-based exercises) the 'homework' component (221).
- It is recommended that future research evaluate the *key ingredients* of social cognitive training programs, in order to maximise benefits and enhance feasibility (230).
- The inclusion of 'bridging activities' in social cognitive training interventions has been suggested as a potential mechanism for enhancing functioning (230). While some of the current programs do use bridging activities to promote translation of social cognitive gains to everyday functioning [e.g., practice partners (211), in vivo real-world exercises (445)] the findings have been mixed. Thus, further research is needed in this area.
- Future research should examine the potential synergistic effects of combining social cognitive training with other novel interventions aimed at treating symptoms, remediating deficits and improving functioning, such as exercise programs and nutraceuticals. While a handful of RCTs in early stage illness have examined social cognitive training in combination with other treatments, including paliperidone (223), oxytocin (446), and cognitive training (221, 226, 227) with some promising results, this line of enquiry is in its infancy.
- It is unclear whether comprehensive, targeted or combined programs would be most beneficial/feasible from a cost-effectiveness perspective, particularly considering the potential for significant additional funding that may be required for clinician training, implementation and maintenance of comprehensive and combined programs. Head-to-head trials are needed.

Sleep Interventions

- Research into pre-clinical and sleep deprivation models may further our understanding of sleep and cognitive impairments in psychosis, and guide novel treatment development.
- We recommend investigating whether interventions such as zolpidem and non-invasive brain stimulation enhance and co-ordinate networks of sleep oscillations, and improve memory consolidation.
- Investigation into the modes of action linking cognitive impairment and sleep disturbance in psychosis to guide intervention development.
- Sleep interventions have been largely unexplored in relation to their potential efficacy for cognitive impairment in psychosis and should be investigated in UHR/FEP. Studies should incorporate the general recommendations provided above.

Exercise, Mind-Body and Mindfulness

- As exercise (including mind-body activities such as yoga) is a universally accepted health behaviour (regardless of illness) and practiced globally, more research should be conducted to examine the barriers and facilitators of exercise that characterise early psychosis populations in different countries, including low- and middle-income resource settings.
- Mindfulness-based interventions may need to be adapted to accommodate the cognitive impairments of participants (e.g., briefer sessions to accommodate difficulties with sustained attention).
- Opportunities exist for exercise-based interventions to be supplemented (for example, with motivational interviewing, goal setting) in order to support the motivational issues experienced by many patients. Further, Firth, Stubbs (302) found that supervision by physical activity professionals was required for significant improvements in global cognition. This may be a necessary component to manage motivation and perception of ability through supervised support and encouragement.

Digital, including virtual reality

- Many potentially effective applications of digital interventions for enhancing cognition in early psychosis have not been explored. On the basis of early evidence, areas warranting further development include smartphone and VR-based interventions, particularly for supporting cognitive and functional recovery in real world environments.
- Partnerships between industry and research to develop digital interventions to improve cognition and establish the evidence base are highly warranted. Importantly, funders should be aware that the development pipelines of digital interventions require funding models that support significant up-front development costs and evaluation frameworks that enable flexibility in adapting the technology over time. One example is the Accelerated Creation-to-Sustainment model (ACTS) (447), which is a three-phase evaluation framework covering technology development, trialling and sustainment. This research model is well suited to digital intervention development because it allows for establishing evidence within the implementation context, ultimately maximising sustainability in real-world settings.
- As drop-out rates are high and engagement often poor (315), designing digital interventions that make use of evidence-based techniques for reinforcing motivation and engagement, such as gamification, challenges, tracking and feedback, reward and competition (448), may overcome these barriers and improve the experience of treatment (334).
- Another potential opportunity is delivering digital cognitive interventions alongside other treatments. There is evidence that receiving computer-delivered cognitive remediation alongside standard therapist-delivered cognitive behavioural therapy can result in more rapid symptomatic improvement for early psychosis (449). As people with cognitive impairment tend to be more reliant on services, resulting in greater costs (450), offering access to digital forms of cognitive remediation alongside other treatments may provide opportunities to enhance the efficiency and efficacy of care (312).
- Research is recommended on telehealth as a vehicle through which treatments can be delivered remotely, reducing demand on services and improving accessibility. This is well supported by experiences of clinicians and young people in clinical services during COVID-19 (451, 452); however, more purpose-built platforms are needed that offer better functionality to support different types of interventions (e.g., (321)).

Brain Stimulation

- The evidence from multi-session interventions is limited and mixed. Large sample sizes, and hence potentially multicentre trials, will be required to determine the efficacy of multi-session non-invasive brain stimulation interventions for improving cognition and functioning.
- Home-administered treatment protocols for tDCS/tACS (e.g., (453)) can enable the evaluation of longer-term multi-session treatment protocols (i.e., longer than 1-2 weeks delivered in RCTs to date), which potentially could produce greater and/or more sustained clinical benefits.
- Cognitive effects may also be enhanced by pairing these forms of stimulation with concurrent cognitive training (454). This combined approach was recently trialled in adolescents with ADHD (455). However, to provide evidence of effectiveness for synergistic or additive effects of this combined intervention, a 2x2 factorial design clinical trial would be required.
- Support for the development of more efficient and cost-effective rTMS targeting methods for improving cognition (e.g., similar to BEAM F3 for rTMS treatment for depression (456)), which do not require an MRI scan, represents an opportunity to facilitate the translational potential of rTMS in early psychosis (UHR/FEP).
- To obtain ethics committee approval, prospective clinical trials for existing or experimental medical devices for off label or new indications often require an Investigator Brochure that provides a comprehensive review of the existing evidence for safety/risks of the treatment/intervention. For more established treatments (i.e., rTMS and tDCS), producing and making available this document to researchers would assist with conducting future clinical trials in early psychosis (UHR/FEP).

Peer Work

- As research into the effectiveness (and appropriateness) of peer support for addressing cognitive deficits in early psychosis is scarce, exploratory research (e.g., pilot testing) is indicated. Some possibilities for exploratory research have been provided in Supplementary Table 8.

- Importantly, consideration is needed of how compatible the frameworks used by peer support and interventions to address cognitive deficits are. Although there is merit in testing the effectiveness of peer-delivered cognitive interventions, it may also be worthwhile considering interventions to upskill the peer workforce to have the knowledge and skills to identify and address cognitive challenges, which has been proposed across all mental health professionals (including peer workers, see (457)).
- In low- and middle-income countries, this could be considered in the context of task shifting that trains people with lived experience to perform support tasks normally provided by trained professionals (see (458) for an example).
- Due to the theoretical underpinnings of peer support, intervention development in this area should focus on a strengths-based approach.

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6. SUPPLEMENTARY TABLES

Supplementary Table 1. Summary of AMSTAR Strength of Evidence - Antipsychotics

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Karson et al., 2016 (73)	FEP	Not reported	7	Antipsychotic Medication	Individual or composite cognitive test scores	Not reported	Not reported	Not reported
Tani et al., 2020 (90)	Psychosis	Not reported	2	Antipsychotic dose-reduction	Composite cognitive score	Not reported	*I2* = 34%	No
Désaméricq et al., 2014 (74)	FEP	Not reported	9	Antipsychotic Medication	Cognitive composite and domain scores	Small, ranging from 0.06-0.34, but metric was not reported.	*I2* of >50% were rejected	No

Supplementary Table 2. Summary of AMSTAR Strength of Evidence - Small Molecules

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Sinkeviciute et al, 2018 (91)	SZ	Not reported	93	Cognitive enhancing drugs	Global cognition	Hedge's g = 0.1	Low to moderate I2 = 29.4%	Suspected
Choi et al., 2018 (92)	SZ or schizoaffective disorder	Asia, Europe, India, Middle East, USA	26	Cognitive enhancing drugs	Cognitive domains	Small to moderate	Qw(4) = 10.45	Not reported
Kishi et al, 2018 (94)	SZ or schizophrenia-spectrum disorders	Asia, Europe, Middle East, USA	37	Cognitive enhancing drugs	Cognitive domains	Small	I2 = 0%-65% (analysis dependent)	Some
Ortiz-Orendain et al, 2019 (95)	SZ or schizophrenia-spectrum disorders	Europe, India, Middle East, USA	11	Modafinil	Cognitive domains	Small	I2 = 56%-80% (analysis dependent)	Suspected
Solmi et al , 2017 (96)	SZ or schizoaffective disorder	Asia, Middle East, USA	3	Minocycline	Executive functioning	Small, SMD = 0.22	I2 = 42%	No
Xiang et al, 2017 (97)	SZ	Asia, Middle East, USA, South America	8	Minocycline		Small, SMD = 0.15 to 0.12	I2 = 0%-70% (analysis dependent)	No
de Boer et al, 2018 (100)	SZ	Australia, Europe, Middle East	2-4 (analysis dependent)	Raloxifene	Global cognition, cognitive domains	Small	I2 = 13%-74% (analysis dependent, where more than 2 studies were included)	No

Supplementary Table 3. Summary of AMSTAR Strength of Evidence - Nutrients

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Susai et al., 2021 (168)	UHR	Vienna, Australia, Italy	19	Omega-3 PUFAs	NS	N/A	NI	NI
de Sousa et al., 2019 (109)	SZ	Korea, USA, Serbia	7	Alpha-Lipoic Acid	Attention/ Vigilance Working memory	0.65 1.50	NI	N/A
Kopelli et al., 2020 (126)	SZ	Germany, USA, Poland	3	CBD Oil	NS	N/A	Low (I^2=0%)	N/A
Yolland et al., 2020 (117)	SZ	Australia, USA, Switzerland, Iran, China	8	NAC	Processing Speed Working Memory	0.27+ 0.56+*	Low (I^2=0%) Low (I^2=0%)	N/A
Tsai & Lin, 2010 (169)	SZ	USA, Israel, Taiwan	5	D-serine	Global Functioning	0.42*	Low (I^2=0%)	NI
		USA, Israel, Canada	6	Glycine	NS	0.25	Low (I^2=0%)	NI
		USA, Taiwan	5	Sarcosine	NS	0.29	Low (I^2=0%)	NI
		USA, Israel, Netherlands	7	D-cycloserine	NI	N/A	Low (I^2=0%)	NI
Cho et al., 2019 (141)	SZ/SAD	Israel, USA	5	Pregnenolone	Attention/ Vigilance Visual Learning/ Memory	0.59* 0.72*	Low (I^2=0%)	Nil
	SZ/SAD	Australia, South Korea, Iran, Tehran	7	Estrogen	Processing Speed[1]	0.46*	Moderate (I^2=61.8)	Nil
	SZ	USA	2	Davunetide[2]	Verbal Learning/Memory	0.86*	NI	Nil
	SZ	Germany	1	Erythropoietin	NS	N/A	N/A	Nil
	SZ/SAD	Australia, Spain, Iran, Tehran	9	SERMs	Processing Speed	0.42*	Moderate (I^2=63.3)	Detected
Soria et al., 2018 (120)	SZ	Israel, USA	4	DHEA	Attention/ Vigilance	NI	NI	NI
		Israel, USA	5	Pregnenolone[3]	Verbal Learning/Memory Attention/ Vigilance Visual Learning/ Memory	NI	NI	NI
		Australia, Spain	4	Raloxifene	Verbal Learning/Memory Executive Function Processing Speed	NI	NI	NI
Firth et al., 2017 (149)	SZ	USA, Israel	7	Vitamin B	NI	N/A	High (I^2=72.3)	Nil
		USA, Israel, Norway, India, China	5	Vitamin C/E	NI	N/A	High (I^2=87.7)	Nil
Jeppesen et al., 2020 (108)	Psychosis	Australia, China, USA, Slovenia, South Africa, Iran, Poland, UK	8	Anti-inflammatories	Working memory	0.21	Moderate (I^2=54%)	Nil

*Significant outcome; +Standard Mean Difference Effect Size; [1]Based on a single study; [2]Excluded from meta-analysis as studies did not meet criteria. Included here for breadth of information; [3]Cho et al (2019) excluded one study that was included in Soria et al. (2018) due to the addition of an active control (as well as placebo). NI - No Information; N/A - Not Applicable; NS - Not Significant; SZ - Schizophrenia; SAD - schizoaffective disorder; UHR - Ultra High-Risk; SERMs - Selective Estrogen Receptor Modulators. Aspirin, Oxytocin, taurine, not presented here due to a lack of efficacy

Supplementary Table 4. Summary of AMSTAR Strength of Evidence - Cognitive Remediation and Compensation

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Vita et al., 2021 (171)	SZ	Europe, North America, Asia, Australia, South America	130	Cognitive remediation	Global cognition	*d*=0.29	Low (i.e., I^2=24%)	No
					Attention	*d*=0.17		
					Processing speed	*d*=0.20		
					Working memory	*d*=0.25		
					Verbal memory	*d*=0.33		
					Visual memory	*d*=0.25		
					Executive functions	*d*=0.28		
					Social cognition	*d*=0.24		
					Global functioning	*d*=0.22	Low-to-moderate (i.e., I^2=37%).	No
Allott et al., 2020 (172)	SZ	Europe, North America, South America	26	Compensation	Global functioning	*g*=0.46	Low-to-moderate (i.e., I^2=38%)	No
Revell et al., 2015 (177)	Early SZ / FEP	Europe, North America, Australia	11	Cognitive remediation	Global cognition	*d*=0.13	High (i.e., I^2=76%)	No
					Processing speed	*d*=0.19		
					Working memory	*d*=0.19		
					Visual learning and memory	*d*=0.09		
					Verbal learning and memory	*d*=0.23		
					Attention/vigilance	*d*=0.06		
					Reasoning/problem solving	*d*=0.21		
					Social cognition	*d*=0.30		
					Global functioning	*d*=0.18	High (i.e., I^2=79%)	No
Glenthoj et al., (2017) (186)	UHR	Europe, North America	6	Cognitive remediation	Global cognition	N/A	N/A	N/A
					Global function	N/A	N/A	N/A

Supplementary Table 5. Summary of AMSTAR Strength of Evidence - Social Cognition

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Yamada et al., 2019 (140)	FEP	UK, Australia, Spain, Canada	5	1 neurocognitive without SCT component; 1 computerised SCT; 2 pharmacological without SCT component; 1 combined Oxytocin and SCT	Emotion recognition Affect recognition Attribution bias	g = 0.330 partial η^2 = 0.167 partial η^2 = 0.17	Not assessed	Not assessed
Yeo et al., 2021 (210)	Psychotic disorders	Mostly Western countries (USA, Italy); remaining were Eastern countries (e.g., China, Egypt, Israel, Japan, South Korea, Turkey)	42	Broad-based and targeted SCT	Emotion recognition Social perception, ToM Social functioning	g = 0.55 g = 0.46 g = 0.36 Not significant	I^2 = 65.2% I^2 = 71.8% I^2 = 69.9%	Yes Yes No
Nijman et al., 2020 (223)	Psychotic disorders	Not reported	46	Broad-based SCT; Broad-based SCT + CRT Targeted SCT; Targeted SCT + CRT	Emotion processing Social processing ToM, Social functioning	Targeted SCT (d = 0.68) Broad-based SCT (d = 0.46) Targeted SCT (d = 1.36) Targeted SCT + CRT (d = 1.38) Broad-based SCT (d = 1.35) Broad-based SCT + CRT (d = 1.45) Broad-based SCT (d = 0.42) Broad-based SCT (d = 0.82) Broad-based SCT + CRT (d = 0.41)	I^2 ranged between 99.8 and 100%	No
d'Arma et al., 2021 (228)	SZ	Europe, USA, Asia	26	SCT, various	ToM (overall) ToM (cognitive) ToM (affective)	g = 0.53 g = 0.60 g = 0.42	I^2 = 49.86% I^2 = 61.19% I^2 = 34.94%	Yes - slight Yes - slight Substantial
Grant et al., 2017 (459)	SZ	USA, Europe, Australia, China, Egypt, Israel and Korea	35	SCT, various	Affect recognition Social perception ToM Attribution bias	Not reported	Not assessed	Not assessed
Tan et al., 2018 (460)	SZ	USA, Europe, Korea, Brazil	31	SCT, various	Affect recognition Social perception ToM Attribution bias	Not reported	Not assessed	Not assessed

Supplementary Table 6. Summary of AMSTAR Strength of Evidence - Exercise, Mind-Body, and Mindfulness

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Shannon et al., (2020) (290)	FEP	Sweden, Hong Kong, USA	3	Exercise	Varied by study	No meta-analysis conducted	N/A	N/A
Firth et al., (2017) (302)	SZ	USA, Germany, China, Brazil, Portugal, Netherlands, India	10	Exercise	Global cognition	g = 0.33	Q = 7.0, p = .64, I2 = 0%	None
			7		Working memory	g = 0.39	Q = 10.9, p = .09, I2 = 45.1%	
			6		Processing speed	g = 0.13	Q = 4.97, p = .42, I2 = 0%	
			6		Verbal learning & memory	g = 0.28	Q = 7.76, p = .17, I2 = 35.6%	
			4		Reasoning & problem solving	g = -0.10	Q = 1.36, p = .72, I2 = 0%	
			3		Attention & vigilance	g = 0.66	Q = 2.51, p = .07, I2 = 20.3%	
			3		Social cognition	g = 0.71	Q = 1.23, p = .54, I2 = 0%	
			3		Visual learning & memory	g = 0.00	Q = 0.67, p = .71, I2 = 0%	

Supplementary Table 7. Summary of AMSTAR Strength of Evidence - Brain Stimulation

Reference	Population	Geographical Regions	Number of included studies	Intervention	Outcome	Effect Size	Heterogeneity of findings	Evidence of publication bias
Jiang et al., 2019 (349)	SZ	Germany, France, UK, Canada, US	9	rTMS (>1Hz)	Cognitive domains	Overall: 0.16 Working memory: 0.34	NS	No
Lage et al., 2016 (350)	Healthy, psychiatric, neurological	US, Australia, UK	20	1 Hz rTMS	Cognitive domains	N/A	Yes	Unknown
Sloan et al., 2021 (351)	SZ, Schizo-affective disorder	Canada, Germany, US, Australia, France, UK, China, Israel, Republic of Korea	22	rTMS/ tES	Working memory	Accuracy: 0.11 Reaction Time 0.23	NS	No
Kostova et al., 2020 (352)	SZ	Canada, Germany, US, Australia, France, UK, China, Israel, Republic of Korea, Netherlands	32	tDCS	Cognitive domains	N/A	Yes	No
Yu et al., 2020 (353)	SZ, Schizo-affective disorder, Psychosis	China, Australia, France, Germany, Republic of Korea, US, Israel, Brazil	14	tDCS	Global cognition	Generalised cognitive functioning: 0.22	No	No
Westwood et al., 2021 (354)	Children and adults with ADHD	Iran, Germany, US, Brazil, Israel	30	rTMS/ tDCS	Cognitive domains	Attention: 0.18 Inhibition :0.21 Processing speed: 0.14	Yes	Unknown
Elyamany et al., 2021 (356)	Psychiatric	US, India, Australia, France	13	tACS	Clinical	N/A	Yes	Unknown

Supplementary Table 8. Opportunities and recommendations for peer work

Peer support specialisation	Potential application for supporting cognitive functioning*	Current practice?
Generalised youth peer support	In the context of peer support focusing on what the person wants to talk about, challenges with cognitive functioning may be raised in sessions. Peer workers may share their experiences of related challenges (for example, difficulties remembering things, finding it hard to make decisions) and strategies they used to deal with these challenges.	It is likely that if cognitive functioning is an issue for the young person that it will be discussed in a peer support session. However, how much the peer worker has experienced the same challenges, what they know about cognitive functioning, and what experience or knowledge they have of interventions to address these challenges will almost certainly vary significantly and is likely to be limited as it is not a well reported feature of empirical research or program descriptions.
Vocational peer support	Vocational peer workers (VPW) help young people to explore, obtain, and remain in education, training and employment activities. This includes sharing their own experiences of vocational challenges and strategies, and there is a clear opportunity for upskilling VPW to learn more about cognitive challenges and interventions. This may as part of the peer support provided, but also in terms of learning about how to connect and engage young people in services or interventions.	It is likely that people with cognition-related challenges would raise them in the context of looking for, commencing and remaining in education, training and employment.
Peer support for engagement and treatment decision making	Peer workers help young people think about the information they want/need to know, how to obtain and retain that information, and how to use it to make decisions. These include decisions about whether or not to engage in a service, which part/treatment option to engage in (including revisiting the decision and changing as necessary), and related decisions.	Depending on the approach of collaborative involvement used by peer support workers, it is likely that cognitive challenges are at least discussed during peer support sessions. For example, shared decision making considers the information needs of the person faced with the decision, including their preferred way to receive and understand information. It is highly likely that memory and decision-making impairments would be addressed in this process.
Family peer work	Family peer workers are family members* of people who experience mental health challenges. Given that some interventions focused on cognition may require family support, family peer workers could be useful to help implement whole-of-family approaches to supporting young people improve their cognition. Consideration of whether this would be better suited to be delivered by a family therapist is warranted. Perspectives of family peer workers, families and neuropsychologists need to be explored as a starting point.	Family peer work is less commonly available than youth peer work. Additionally, fewer sessions tend to be available to families, meaning the focus is on general support, especially if the young person has come to the service in crisis.
Peer delivered cognitive interventions	Youth peer workers could be trained to deliver interventions focused on improving cognition or developing skills and strategies to cope with cognition-related challenges, including harnessing cognitive strengths. In order for this to still be in line with the peer support model/framework and theoretical underpinnings, this would be most suitable for approaches that are flexible, client-led, and strengths-based.	We were unable to locate any programs or research studies in the grey or academic literature that were specific to cognitive functioning. As a result, it is highly unlikely that these programs currently exist. To develop a peer-delivered intervention for cognitive functioning a co-design approach is recommended in order to work through how these two frameworks could both maintain fidelity (that is, still meeting the core principles of peer support and meeting the evidence base around how to identify and improve cognition-related challenges). The co-design approach should involve key stakeholders, such as youth peer workers, neuropsychologists, young people who have experienced cognition-related challenges, and their family* members.