Selective 5HT3 antagonists and sensory processing: a systematic review

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INTRODUCTION
Serotonin (5-HT) is a biogenic monoamine with a complex role in regulation of the sleep-wake cycle, appetite, pain, body temperature, vomiting, cognitive, perceptual and affective functions [1]. The involvement of 5HT in hallucinations was first established in clinical experiments with psychedelics (5HT2A agonists such as psilocybin and lysergic acid diethylamide) which are associated with heightened and or altered sensory experiences, including visual and auditory hallucinations [2]. Subsequent research has shown a prominent role of 5HT in early sensory processing, mediated through serotonergic innervation of primary sensory cortices, and subcortical structures (including the amygdala and thalamus) that modulate neuronal responses to sensory stimuli [3, 4]. The antipsychotic potential of serotonergic agents has been of longstanding interest [5], since the discovery that clozapine, whose multi-target action includes 5HT1A, 5HT2A/C and 5HT3 receptors, was effective in reducing psychotic symptoms in patients with treatment-resistant schizophrenia. Research in this area has been largely directed towards schizophrenia, but the focus has recently shifted towards psychosis in the context of neurodegeneration, encouraged by pivotal trials of the 5HT2A receptor partial inverse agonist Pimavanserin, which showed modest benefits in the treatment of Parkinson’s disease (PD) psychosis [6, 7]. There are multiple potential serotonergic agents of interest, including the 5HT3 receptor antagonist ondansetron, that is licensed for use as an anti-emetic and under evaluation in the phase II Trial of Ondansetron as a Parkinson’s Hallucinations Treatment (TOP HAT) (Clinical trials.gov NCT04167813). 5HT3 receptors are cation selective ion channels, closely related to nicotinic acetylcholine receptors, and are highly expressed in mesocorticolimbic regions that are involved in sensory information processing, and assign context and salience to sensory inputs [8]. Distinct from other 5HT receptor subtypes, whose actions are G-protein coupled, 5HT3 receptors mediate fast synaptic neurotransmission and modulate the release of multiple neurotransmitters (dopamine, substance P, gamma-aminobutyric acid (GABA) and acetylcholine) through their expression on pre-synaptic terminals of non-serotonergic neurones [9, 10] and post-synaptic GABAergic inter-neurones [11]. Although there is no evidence of a direct involvement of 5HT3 receptors in hallucinations, preclinical studies have shown antipsychotic and pro-
cognitive effects of 5HT3 receptor antagonist ondansetron in animal models that are relevant for psychosis in humans [12]; ondansetron attenuated amphetamine-induced dopamine release in mesocorticolimbic regions without inducing parkinsonism [9, 10, 13]; and reversed impairments in sensory gating and visual processing in the DBA/2 mouse model of α7-nicotinic cholinergic receptor depletion, by increasing hippocampal acetylcholine release [14, 15]. The latter findings extend to the second-generation 5HT3 antagonist tropisetron; a selective 5HT3 antagonist with additional partial α7-nicotinic receptor agonist activity [16]. In vitro demonstration that many antidepressant and antipsychotic drugs functionally antagonise 5HT3 receptors in a non-competitive way, by inhibiting 5HT-induced ion influx, and that clozapine and olanzapine have direct 5HT3 receptor antagonist effects, provided additional, indirect evidence of the involvement of 5HT3 receptors in psychotropic drug action [17, 18].

Clinical evidence supportive of ondansetron’s potential efficacy in the treatment of Parkinson’s hallucinosis was shown in the early 1990s in a case series of 7 inpatients (5 men, aged 64–78 years) all of whom responded to ondansetron 12–20 mg/day without side effects, and with complete symptom resolution in 4 patients [19]. An open study carried out by the same research group, included 16 patients (11 men, aged 64–68 years) with Parkinson’s and severe, persistent visual hallucinations, who were titrated from 4–8 mg/day ondansetron to an optimum dose (mean 16 mg/day, range 12–24 mg/day), and evaluated after 4–8 weeks’ treatment. There were marked improvements in visual hallucinations (complete symptom resolution in 14), and associated delusions (partial to complete response in 8 of 9), with no worsening of motor symptoms or cognition, and improved global functioning [20]. Although the drug has been used off-licence by some clinicians, this line of development was not pursued by the manufacturer, and the previously high cost of ondansetron prevented further independent studies. Since coming off patent in 2006, ondansetron has been evaluated in phase II trials as an adjunctive treatment for patients with schizophrenia who were either treatment refractory or symptomatically stable on antipsychotic medication. These studies have shown evidence of efficacy in the treatment of both negative and cognitive symptoms, including some evidence of improved visual information processing [21–23], and the drug is under phase II evaluation in a Trial of Ondansetron as a Parkinson’s Hallucinations treatment (TOP HAT) (Clinical trials.gov NCT04167813). The observation that ondansetron and other 5HT3 antagonists (tropisetron, granisetron, dolasetron) improve the ability to filter (gate) irrelevant stimuli and enhance visual information processing in animal models, is of potential therapeutic relevance as sensory gating deficits are a robust neuropathophysiological marker of psychosis in humans [24–26].

We systematically reviewed human studies that had evaluated the effects of ondansetron and related compounds on sensory gating or sensory processing, in both clinical populations and in healthy participants.

METHODS

Study design

We conducted a systematic review with narrative synthesis, which followed the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27] and aimed to determine the effect of 5HT3 receptor antagonists on sensory processing.

Eligibility criteria

We included human studies of healthy participants and any clinical population to identify the impact of 5HT3 antagonists on sensory (visual, olfactory, auditory, gustatory, tactile) or sensorimotor function. Studies were included if participants were administered a 5HT3 receptor antagonist (ondansetron, palonosetron, tropisetron, dolasetron, granisetron) and compared to those not taking a 5HT3 antagonist. We included studies if their primary or secondary outcomes involved evaluation of sensory or sensorimotor functioning, comprising investigations of auditory gating deficits, visuoperceptual functioning and any neuroimaging study outcomes. Studies were excluded if they evaluated the impact of 5HT3 antagonists on pain or pruritus. We included randomized controlled trials (RCT), cohort studies and controlled clinical studies, and excluded protocols, case studies, dissertation theses, meeting abstracts, unpublished dissertations, and conference presentations. Only studies written in English were included.

Search strategy

A database search was carried out in August 2021, using Medline, Embase, PsycINFO and Web of Science (WoS). Relevant reviews and references of the included studies were searched manually to identify appropriate studies for this review. Databases were searched using the following terms:

- Ondansetron OR Zofran OR Zophren OR tropisetron OR granisetron OR Sancuso OR Kytril OR “Apo-Granisetron” OR Kevatril OR Sustol OR dolasetron OR Anzemet OR Anemet OR Zamanon OR palonosetron OR Aloxi OR Akynzeo OR Jouting OR Mitrac OR Palox OR Pal祖 OR Palzen OR Themiset OR Zirhu OR “5-h3 antagonist” OR “5-h3R”) AND (visuopercept* OR visual* OR visual memor* OR visual recog* OR sensor OR olf* OR gust* OR tact* OR propriocept* OR interocept* audit*)

The search terms were differentiated based on the variable databases and their respective search criteria, as the subject headings are different (see supplementary materials for the full search strategy). Two authors (SR and ET) independently and blindly screened all the titles and abstracts against the eligibility criteria. Full texts of the remaining studies were assessed against the eligibility criteria (SR and ET). Any disagreements were resolved through discussion between these two authors.

Data extraction

ET extracted data from all the studies, with JR, CBR and SC acting as second blind raters. Any disagreements were resolved with discussion between two raters and any unresolved differences were discussed with JAB. Effect measures were reported as recorded by the study authors. Data were extracted in regard to the relevant outcomes (any observed effects of 5HT3 receptor antagonists on sensory or sensorimotor functioning), study characteristics (design, setting, population, inclusion/exclusion criteria) and clinical characteristics (population, sample size, diagnostic criteria, age, sex). All relevant outcomes were recorded.

Risk of bias in individual studies and quality assessment

The Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project (EPHPP) was used to assess bias [28]. This tool is designed to evaluate several study designs and assesses the following: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity and analysis. The scores in the subsections were used to generate an overall rating of ‘strong’, ‘moderate’ or ‘weak’ using the EPHPP guidance, with a ‘strong’ paper defined as that with no ‘weak’ subscores, and a ‘weak’ paper having two or more ‘weak’ subscores. ET completed EPHPP for all the included studies whilst CBR, JR and SC independently and blindly rated the quality of the studies. Any differences were solved with discussion and any unresolved discrepancies were discussed with JAB.

Synthesis of results

Due to the small number and heterogeneity of the studies, we carried out a narrative synthesis. All included studies were presented in a table, listing the extracted variables.

RESULTS

Study identification

Of the 12 studies initially identified, two papers [29, 30] described an identical sample and, on further exploration, were found to report the same trial, 1 year apart (one reporting 12 weeks data; another data from the first 8 weeks). Data were extracted from the paper reporting 12 weeks of data, and the other paper [30] was excluded. The PRISMA flowchart is shown in Supplementary Fig. 1.
Study characteristics

Reviewed studies included five randomised control trials with parallel group design [29, 31–34], five randomised control trials with crossover design [35–39] and one cohort (patients versus healthy controls) study [40]. The age of participants ranged from 19 to 55 years. Studies were conducted in the UK, USA, China, Israel, Japan and Iran. Of the five crossover studies, three included healthy volunteers [36, 37, 39], one involved participants with schizophrenia stable on unspecified antipsychotics [35], and one assessed participants with schizophrenia stable on clozapine [38]. The parallel group studies all included patients with schizophrenia, whose symptoms were stable on risperidone. Six studies evaluated ondansetron [33, 35, 36, 38, 39], four evaluated tropisetron [31, 32, 34, 40] and one granisetron [37]. Characteristics and details of the included studies are described in Table 1.

Outcome measures

Outcome measures used in the included studies are described in Table 2. Eight studies were carried out in patients with schizophrenia who were symptomatically stable on antipsychotic medication. Five studies measured the impact of ondansetron on sensory gating, using the P50 electroencephalogram (EEG) event-related potential (ERP) waveform response to a repeated auditory stimulus [31, 32, 34, 35, 40]. The P50 waveform response occurs 50 ms after an auditory stimulus. In the paired-click paradigm, the initial stimulus (S1) is followed by a second stimulus (S2) 500 ms later, and evidence of ‘gating’ is shown by a reduction in amplitude of S2. In healthy participants the S2/S1 ratio is <0.5, but is larger in patients with schizophrenia [24–26]. Three of the studies included measures of visuoperceptual function (as part of a wider battery of neuropsychological tests) as co-primary outcomes [31, 32, 34]. Three studies included measures of visual processing as a primary outcome [38] or as secondary outcomes in studies whose primary aim was to investigate the effect on adjunctive ondansetron on the Positive and Negative Symptom Scale (PANSS) total and subtotal scores [29, 33]. Three studies, carried out in healthy participants, included measures of visuoperceptual [36, 37] and sensorimotor processing [39] as primary outcome measures.

Quality assessment

Three studies were assessed as being of high quality [29, 32, 34], five studies were assessed as being of moderate quality [31, 33, 35, 36, 39] and three studies were assessed as being of low quality [37, 38, 40]. Quality assessment ratings are shown in Table 3.

Findings

Findings from the included studies are described below and are also detailed in Table 1.

Sensory gating

The effect of a single 16 mg dose of ondansetron on P50 gating was investigated using a placebo-controlled crossover design in eight patients [35], seven of whom had been prescribed unspecified first generation (dopamine D2/3 selective) antipsychotics and one olanzapine (second-generation antipsychotic with 5HT3 antagonist properties). Evoked potentials were measured 1, 2 and 3 h post treatment, to coincide with peak plasma concentrations. There was a significantly high reduction in the S2/S1 ratio following ondansetron, which achieved a maximum at two post treatment, the time of peak plasma concentration (ondansetron ratio 41.4%; placebo mean = 80.2%).

Tropisetron was evaluated in four studies [31, 32, 34, 40]. The first [40] was described as a proof of principle study, which aimed to investigate the effects of a single 10 mg dose of tropisetron on sensory gating deficits in 22 patients with schizophrenia who were symptomatically stable on a range of antipsychotics, and in 15 healthy volunteers. A significant improvement in sensory gating was observed, but only in patients who were non-smokers. The authors suggested that future studies should recruit only non-smokers, to avoid the potential confounding effects of long-term nicotine exposure on α7-nicotinic receptors.

Three subsequent studies used placebo-controlled designs to evaluate the impact of tropisetron on patients who were stable on risperidone (2–6 mg daily), which was chosen because it does not target α7-nicotinic or 5HT3 receptors [31, 32, 34]. The studies differed in relation to their number of treatment arms, administered doses, treatment duration, and the inclusion or exclusion of smokers. One study [32], which was rated as high quality, compared tropisetron 10 mg/day to placebo over 8 weeks in 40 patients (20 per arm; 5 smokers in the placebo and 6 in the tropisetron arm) and found a reversal of P50 gating deficits in the tropisetron, but not placebo group, that was restricted to non-smokers. Tropisetron was also superior to placebo in improving the accuracy of performance on the Rapid Visual Information Processing (RVP) task of visual sustained attention [41], but only in non-smokers. There was no significant correlation between the degree of change in S2/S1 ratio and RVP performance which the authors attributed to the small sample size.

Two studies restricted the sample to non-smokers and compared three doses of tropisetron (5 mg, 10 mg, 20 mg) to placebo (10 in each arm), either after single-dose administration [34] or 10 days treatment [31]. There was an overall effect of tropisetron on S2/S1 ratio, which did not survive correction for multiple comparisons in the single-dose study, and showed no difference between doses. Both studies investigated cognitive function using the Repeatable Battery for Neuropsychological Status RBANS; a brief neuropsychological screening battery that includes 12 cognitive domains (language, attention, immediate memory, visuospatial/constructional and delayed memory) [42], and found a significant drug-by-time effect on RBANS total and the immediate (verbal) memory subtotal. The study that evaluated the effect of 10 days treatment observed a correlation between the extent of the reduction in P50 gating ratio and improved performance on immediate memory [31].

Visuoperceptual function

Two placebo-controlled trials, whose primary aim was to evaluate the effect of ondansetron as an adjunctive treatment for cognitive and negative symptoms in patients with chronically stable schizophrenia who were treated with risperidone, included tests of visuoperceptual function as secondary outcomes. These studies reported a reduction in PANSS total [29] and on positive and negative subscores [33], respectively, in ondansetron treated patients. There were also improvements in performance on tests of visual memory (visual reproduction, visual paired associate learning) [29] and visuoperceptual (object assembly) ability [33]. Neither study corrected for statistical effects of the multiple tests included in the respective batteries.

One placebo-controlled trial evaluated 7 days adjunctive treatment with ondansetron on co-primary outcomes (PANSS and visuoperceptual and spatial function) in patients treated with clozapine who had been in symptomatic remission for 6 months [38]. No effect was observed in PANSS scores. Visual memory performance (Rey Osterrieth complex figure test) improved in the ondansetron treated group, but no differences were found in relation to other tests (digit span, digit symbol, paired associates).

A single placebo-controlled crossover study evaluated the effects of granisetron, alone and with lorazepam, in 12 healthy participants [37]. Granisetron reduced the latency of performance on a test of visual sustained attention but did not improve performance accuracy and showed no effect on choice reaction time. No effects of ondansetron were observed on choice reaction time or simulated car tracking tests [36].
Table 1. Study characteristics and findings.

| Author, year | Country | Type of study | Population and referral setting | Intervention, sample size (N), duration | Mean age ± SD years Number (%) females | Outcome measure(s) of interest | Type of statistical analysis | Summary of findings |
|-------------|---------|---------------|----------------------------------|----------------------------------------|----------------------------------------|--------------------------------|-----------------------------|----------------------|
| Adler, 2005 | USA     | Double-blind placebo-controlled crossover trial | Diagnosis of schizophrenia, based on PANSS and BPRS scores, stable on antipsychotic medication NR | Randomised in terms of order: A. Ondansetron 16 mg + placebo B. Placebo + ondansetron 16 mg N = 8, Single dose | 42 ± 6 4/8 (50%) female | Primary Outcome: P50 auditory evoked potential, assessed using the paired-click paradigm (500 ms apart), and indexed by the T/C ratio. | Parametric and nonparametric methods. A priori comparison made for T/C ratio after 2 h (peak plasma concentration) using two-tailed Student's t test. | Ondansetron associated with improvement in P50 auditory gating (t0.2 = 2.43, p < 0.04) Seven patients who were treated with 'typical' antipsychotics showed significant change, and no improvement was observed in one olanzapine-treated patient. |
| Akhondzadeh, 2009 | Iran | Double-blind placebo-controlled parallel group trial | Diagnosis of schizophrenia (DSM-IV-TR), stable on risperidone (4–6 mg/day) for a min of 8 weeks Inpatient and community | Randomised to adjunctive treatment with: A. Ondansetron 8 mg/day (N = 15) B. Placebo (N = 15) N = 30, 12 weeks | A. 33.00 ± 5.88 B. 33.53 ± 5.95 11/30 (37%) female | Primary outcome: PANSS Mean, total and subtotal scores Secondary outcomes: WMS-R: Visual Paired Associates 1 & 2, Visual Reproduction 1 & 2, Block design | Student's t test Fisher's exact test | Significant improvement in PANSS total score at 12 weeks (t28 = 6.65, p < 0.001) Ondansetron associated with improvement on Visual Reproduction 1 (p = 0.05) and 2 (p = 0.05), Visual Paired Associates 1 (p = 0.04) and 2 (p = 0.04) |
| Hall, 1991 | UK | Double-blind placebo-controlled crossover study | Healthy male volunteers NR | Randomised in terms of order: A. Ondansetron 1 mg BD B. Ondansetron 8 mg BD C. Placebo BD D. Placebo BD for 2 days + final dose of lorazepam 2 mg N = 12, 2.5 days | 31 (range 21–40) 0/12 (0%) female | Primary outcomes: CRT Simulated car tracking Trapezoidal integration. Analysis of covariance | No effect of ondansetron on CRT or simulated car tracking |
| Koike, 2005 | Japan | Cohort study | Diagnosis of schizophrenia (DSM-IV) NR | Tropisetron 10 mg administered to: A. Patients with schizophrenia (N = 22) B. Healthy controls (N = 15) N = 37, Single dose | 39.8 ± 14 years 12/37 (32%) female | Primary outcome: P50 auditory evoked potential, assessed using the paired-click paradigm (500 ms apart), and indexed by the T/C ratio. | Paired t test | Tropisetron improved P50 auditory gating in patients with schizophrenia (t32 = 2.32, p = 0.033) *only in non-smokers Change in P50 T/C ratio correlated with the baseline value (r = 0.85, t = 6.60, df = 17, p < 0.001), |
| Leigh, 1991 | UK | Double-blind placebo-controlled crossover design | Healthy male volunteers NR | Randomised in terms of order: A. Placebo capsule + placebo infusion B. Placebo capsule + granisetron 160 mcg/kg infusion C. Lorazepam 2.5 mg capsule + placebo infusion D. Lorazepam 2.5 mg capsule + granisetron 160 mcg/kg infusion N = 12, 1 day | 32 (range 19–46) 0/12 (0%) females | Primary outcomes: CRT RVP (non-standardised) Repeated-measures ANOVA. Greenhouse-Geisser correction | Repeated-measures ANOVA. Greenhouse-Geisser correction | Granisetron associated with a reduced mean latency of correct responses on RVP (main effect, p = 0.03) No change in CRT |
| Levkovitz, 2005 | Israel | Double-blind placebo-controlled crossover trial | Diagnosis of schizophrenia (DSM-IV), who had been in remission for 6 months, and treated with fixed doses of clozapine (360 mg/day) Community | Randomised in terms of order: A. Ondansetron (8 mg OD) B. Placebo N = 21, 7 days | 31.2 ± 8.9 0/21 (0%) female | Co-primary outcomes: PANSS, Mean, total and subtotal scores WAI-S: Digit Span, Digit Symbol, Paired association, Rey–Osterrech Complex Figure | Repeated-measures ANOVA Paired Student's t tests | No change in PANSS total or subtotal scores. Ondansetron improved Rey–Osterrech performance (p = 0.002). No effect on other subtests |
Ondansetron associated with reduction in PANSS positive and negative scores (p < 0.001). Student t-test. ANOVA.
P50 auditory invoked potentials, assessed using the paired-click paradigm (500 ms apart), and indexed by the T/C ratio. ANCOVA.

Primary outcome: RBANS total, and immediate memory (F3,28 = 3.92, p = 0.05) but not visuospatial subtests. MANOVA, ANCOVA, Chi-squared. Bonferroni corrections. Controlled for confounding effects of age, education, sex, illness duration, risperidone dose, chloral hydrate use.

Tropisetron reduced P50 gating ratio (F3,28 = 7.31, p = 0.001). No differences observed between doses. Drug-by-time effect on RBANS total (F3,28 = 4.20, p = 0.01) and immediate memory (F3,28 = 3.43, p = 0.03) but not visuospatial subtests. Correlation between improved immediate memory and reduced gating ratio (r = 0.38, p < 0.001).

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**Table 1. continued**

| Author, year | Country | Type of study | Population and referral setting | Intervention, sample size (N), duration | Mean age ± SD years Number (% of females) | Outcome measure(s) of interest | Type of statistical analysis | Summary of findings |
|--------------|---------|---------------|---------------------------------|----------------------------------------|------------------------------------------|-----------------------------|----------------------------|---------------------|
| Samandi, 2017 | Iran | Double-blind placebo-controlled parallel group trial | Diagnosis of schizophrenia (DSM-IV-TR), treatment-resistant, stable on risperidone (4–6 mg/d) for at least 2 months prior to enrolment. Inpatient and community | Randomised to adjunctive treatment with: A. Ondansetron 4–8 mg/day (adjunct to risperidone 8 mg/day) (N = 18) B. Placebo (adjunct to risperidone 8 mg/day) (N = 20) | A. 40 (CI: 37.43 to 43.26) B. 37 (CI: 34.02 to 39.20) 3/38 (7.9%) female | Primary outcome: PANSS mean, total and subtotal scores Secondary outcomes: WAIS-R: Picture Completion Object assembly Comprehension | Parametric and nonparametric methods. Student’s t-test. Chi-squared. ANOVA. MANOVA, ANCOVA. MANOVA, ANCOVA, Chi-squared. Bonferroni corrections. Controlled for confounding effects of age, education, sex, illness duration, risperidone dose, chloral hydrate use. | Ondansetron associated with reduction in PANSS positive and negative scores (p < 0.001). Tropisetron improved performance on Object assembly (p < 0.001) and Comprehension (p < 0.001). |
| Shina, 2010 | Japan | Randomised placebo-controlled parallel group trial | Diagnosis of schizophrenia, (DSM-IV-TR), stable on risperidone (2–6 mg/day) for minimum 8 weeks. Community setting | Randomised to adjunctive treatment with: A. Tropisetron B. 10 mg/day (N = 20) C. Placebo (N = 20) | A. 34.96 ± 6.82 11/20 (55%) female B. 35.15 ± 8.54 10/20 (50%) female 21/40 (53%) female | Co-primary outcomes: P50 auditory invoked potentials, assessed using the paired-click paradigm (500 ms apart), and indexed by the T/C ratio. CANTAB (RVP, DMS), PANSS | Chi-squared. ANOVA. Paired t test. Bonferroni corrections for multiple CANTAB comparisons. Sensitivity analysis (whole sample and non-smokers only) | Tropisetron t13 = 3.24, p = 0.006, but no placebo (t13 = 0.570, p = 0.6), improved P50 auditory gating deficits. Tropisetron improved RVP performance accuracy but only in non-smokers, after Bonferroni correction (t11 = 5.78, p < 0.001). No change in PANSS.
| Stern, 2019 | USA | Double-blind placebo-controlled crossover trial | Healthy population Advertisements posted on the internet and university campus | Randomised in terms of dose and order: A. Ondansetron 8 mg + placebo (N = 19) B. Ondansetron 16 mg + Placebo (N = 21) C. Ondansetron 24 mg + Placebo (N = 18) N = 58, Single dose | A. 32 ± 11 10/20 (50%) female B. 29 ± 8 C. 33 ± 11 25/53 (47%) female | Primary Outcome: First-order processing following body BFV and CV tasks | Regression Analysis | Ondansetron 24 mg associated with reduced activation in insula, sensorimotor cortex premotor areas, ACC, and temporal cortex relative to placebo during CV video task. No differences observed during BFV tasks. |
| Xia, 2020 | China | Double-blind placebo-controlled parallel group trial | Diagnosis of schizophrenia (DSM-IV) schizophrenia stable on risperidone (3–6 mg/d) for at least 1 month prior to participation in the study. Inpatient | Randomised to adjunctive treatment with: A. Tropisetron 5 mg/d B. Tropisetron 10 mg/d C. Tropisetron 20 mg/d D. Placebo N = 3, 1 day | A. 29.60 ± 8.90 B. 26.30 ± 5.25 C. 31.50 ± 9.93 D. 36.50 ± 10.61 9/38 (23.7%) female | Co-primary Outcomes: P50 auditory invoked potential 1 h after taking tropisetron or placebo RBANS Tropisetron improved RVP performance accuracy but only in non-smokers, after Bonferroni correction (t11 = 5.78, p < 0.001). No change in PANSS. | MANOVA: Age, education, gender, illness duration, dose as covariates if interactive effect of drug × time was significant. ANCOVA/Dunnnett test used to compare doses. Bonferroni correction. Notice main effect of tropisetron on P50 ratio (F1,12 = 10.1, p < 0.05), but did not survive Bonferroni correction. Main effect of tropisetron on RBANS total (F1,12 = 3.81, p < 0.05), and immediate memory (F1,12 = 3.92, p < 0.05) but not visuospatial subtests. No differences observed between doses. |
| Zhang, 2012 | China | Double-blind placebo-controlled parallel group trial | Diagnosis of schizophrenia (DSM-IV), non-smoking patients stable on risperidone 3–6 mg/day at least 1 month prior to enrolment Inpatient | Randomised to adjunctive treatment with: A. Tropisetron 5 mg/day (N = 10) B. Tropisetron 10 mg/day (N = 10) C. Tropisetron 20 mg/day (N = 10) D. Placebo (N = 10) N = 40, 10 days | Range 20–55 10/40 (25%) female | Co-primary outcome: P50 auditory invoked potentials, assessed using the paired-click paradigm (500 ms apart), and indexed by the T/C ratio. RBANS | MANOVA, ANCOVA, Chi-squared. Bonferroni corrections. Controlled for confounding effects of age, education, sex, illness duration, risperidone dose, chloral hydrate use. | Tropisetron reduced P50 gating ratio (F1,12 = 7.31, p = 0.001). No differences observed between doses. Drug-by-time effect on RBANS total (F1,12 = 4.20, p < 0.05) and immediate memory (F1,12 = 3.43, p = 0.03) but not visuospatial subtests. Correlation between improved immediate memory and reduced gating ratio (r = 0.38, p < 0.001). |
Table 2. Outcome measures.

| Author, year | Test                                      | Brief description                                                                                                                                                                                                 |
|--------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adler, 2005  | P50 Sensory Gating Electroencephalogram (EEG) | Tests sensory gating using the P50 Event-related potential (ERP) waveform paired-click paradigm. The P50 waveform is an event-related potential measured on EEG, occurring 50 ms after an auditory stimulus. The participant is presented with two auditory clicks: S1 (Control, C) and S2 (Test, T), presented within 500 ms of each other. Evidence of ‘gating’ (attenuation of the wave) can be seen in the second P50 wave. Gating is calculated using a composite score which relates S1 and S2 amplitudes either as ratios (T/C ratio, suppression ratio, S2/S1 ratio) or differences (S1 – S2). |
| Koike, 2005  | Rapid Visual Information Processing        | Subtests of interest: Rapid Visual Information Processing: A white box is shown in the centre of the screen, inside which digits from 2 to 9 appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits. Outcome measures: accuracy, (number of correct responses), latency (speed of response), probability of false alarms and sensitivity. Delayed Match to Sample: An abstract and non-verbal sample is presented to the participants. After a short period of time, they are also presented four similar patterns. The participants have to choose the pattern that exactly matches the sample. Outcome measures: accuracy and latency. Choice Reaction Time: An arrow-shape appears on either side of a screen on which there are two buttons, one on either side. Participants press the appropriate button depending on where the arrow appears. Outcome measures: accuracy and latency, errors of commission and omission (late and early responses). Pattern Recognition Memory: A series of patterns are shown, and participant tasked with discriminating between new and repeated patterns. Outcome measures: accuracy and latency. Spatial Recognition Memory: A series of squares located on a screen are shown. Participant is tasked with remembering previous positions of the square. Outcome measures: accuracy and latency. Spatial Span: Participant presented with white square that changes colour. Participant tasked with remembering the order of colour change. Outcome measure: span length of order. Spatial Working Memory: Participant must use a process of elimination to uncover squares to find the target square. Outcome measure: accuracy. Stockings of Cambridge: Participant tasked with rearranging images which can be done in a discreet number of moves. Outcome measures: difficulty level reached, mean moves used and thinking time Intra-extra Dimensional Set Shifting: Participant tasked with determining a ‘rule’ that determines which of two visual stimuli consisting of shapes is ‘correct’ based on feedback. Outcome measures: errors, attempts, stages completed, latency |
| Shiina, 2010 | Cambridge Neuropsychological Test Automated Battery (CANTAB) Computerised non-verbal test battery | Five different letters of the alphabet presented on the screen in a pseudo-random sequence, and in both lower and upper cases (A, B, D, E and H); 400 presentations/rate of one per second, on display for 0.1 s. Participants were required to press a response button when they identified consecutive presentations of the same letter, irrespective of case. Outcome measures: accuracy and latency. Choice Reaction Time (non-standardised version) Computerised non-verbal test of psychomotor function | Two buttons with neighbouring LEDs (light-emitting diodes) are equally-spaced with a control button. When an LED lights, participants transfer a digit from the control button to the colourful button next to the lit LED and afterwards return the digit to the control button until one of the two LEDs lights again. During this test participants are presented with concurrent auditory misdirection. Outcome measures: accuracy (number of correct responses) and latency (reaction time and movement time). |
| Leigh, 1991  | Rapid Visual Information Processing (non-standardised version) Computerised non-verbal test of psychomotor function | Two buttons with neighbouring LEDs (light-emitting diodes) are equally-spaced with a control button. When an LED lights, participants transfer a digit from the control button to the colourful button next to the lit LED and afterwards return the digit to the control button until one of the two LEDs lights again. During this test participants are presented with concurrent auditory misdirection. Outcome measures: accuracy (number of correct responses) and latency (reaction time and movement time). |
| Leigh, 1991  | Choice Reaction Time (non-standardised version) Computerised non-verbal test of psychomotor function | Six red lights shine randomly one at the time. Participants have to turn off the light light by pressing a corresponding button. Outcome measure: time taken to respond to the red light stimulus together and total time taken to both respond and cancel the light. |
| Hall, 1991   | Simulated Car Tracking Computerised non-verbal test of psychomotor function | A computer-based test where participants had to maintain the cursor in line with a moving target using a joystick. Outcome measures: accuracy of tracking, response time to 10 peripherally presented visual stimuli recorded. |
This table describes the tests and subtests used amongst the studies. Some papers used discreet subtests from a Battery. For clarity, all subtests from a battery are listed here, and the subtests used by a given paper are then described. The subtest of interest to our review are stated explicitly.
| Author & date  | Title                                                                 | Selection bias | Study design | Confounders | Blinding | Data collection methods | Withdrawals and drop-outs | Global rating |
|---------------|-----------------------------------------------------------------------|----------------|--------------|-------------|----------|------------------------|---------------------------|---------------|
| Adler 2005    | Improved P50 Auditory Gating With Ondansetron in Medicated Schizophrenia Patients | 3              | 1            | 1           | 1        | 1                      | 1                          | 2             |
| Akhondzadeh 2009 | Added ondansetron for stable schizophrenia: a double-blind, placebo-controlled trial | 1              | 1            | 1           | 1        | 1                      | 1                          | 1             |
| Hall 1991     | A study to evaluate the effect of ondansetron on psychomotor performance after repeated oral dosing in healthy subjects | 3              | 1            | 1           | 1        | 1                      | 2                          | 2             |
| Leigh 1991    | Effects of granisetron and lorazepam, alone and in combination, on psychometric performance | 3              | 1            | 1           | 2        | 1                      | 3                          | 3             |
| Levkovitz 2005 | The effect of Ondansetron on memory in schizophrenic patients          | 3              | 1            | 3           | 3        | 1                      | 3                          | 3             |
| Koike 2005    | Tropisetron improves deficits in auditory P50 suppression in schizophrenia | 2              | 2            | 3           | 3        | 1                      | 3                          | 3             |
| Samadi 2017   | Efficacy of Risperidone Augmentation with Ondansetron in the Treatment of Negative and Depressive Symptoms in Schizophrenia: A Randomized Clinical Trial | 2              | 1            | 3           | 1        | 1                      | 1                          | 2             |
| Shiina 2010   | A randomised, double-blind, placebo-controlled trial of tropisetron in patients with schizophrenia | 1              | 1            | 1           | 1        | 1                      | 1                          | 1             |
| Stern 2009    | High-dose ondansetron reduces activation of interoceptive and sensorimotor brain regions | 3              | 1            | 1           | 2        | 2                      | 1                          | 2             |
| Xia 2020      | One-day tropisetron treatment improves cognitive deficits and P50 inhibition deficits in schizophrenia | 2              | 1            | 1           | 1        | 1                      | 1                          | 1             |
| Zhang 2012    | Short-Term Tropisetron Treatment and Cognitive and P50 Auditory Gating Deficits in Schizophrenia | 3              | 1            | 1           | 1        | 1                      | 1                          | 2             |
Interoception
One study used functional MRI to evaluate effects of ondansetron on interoception (the ability to interpret internal sensations such as satiety, respiration, heartbeat and relate them to emotions) [39]. The study was hypothesis-driven, based on ondansetron’s use to decrease pruritis and pain. Fifty-three participants were randomized (by order and dose) to receive a single dose of ondansetron or placebo before carrying out an fMRI task previously shown to engage interoceptive circuitry. The highest dose (24 mg) of ondansetron reduced activation in the interoceptive circuit (insula, sensorimotor cortex, premotor area, anterior cingulate cortex and temporal cortex), but only when participants were viewing the control video.

DISCUSSION
Previous meta-analyses of 5HT3 antagonists have reported on the efficacy of ondansetron as an adjunctive treatment for negative symptoms and general psychopathology in patients with chronic, stable schizophrenia [21]. In this review, we focused specifically on the impact of ondansetron and other 5HT3 antagonists on sensorimotor cortex, premotor area, anterior cingulate cortex and temporal cortex, using fMRI methods. The highest dose (24 mg) ondansetron reduced activation in the interoceptive circuit (insula, sensorimotor cortex, premotor area, anterior cingulate cortex and temporal cortex), but only when participants were viewing the control video.

Ondansetron has a more complex mechanism of action than tropisetron [64], which are also of interest as adjunctive treatments for schizophrenia. Tropisetron was superior to placebo in reversing impairments in visual attention in a single study. There was inconsistent evidence of an effect of ondansetron in other tests of sensorimotor processing, and no evidence that ondansetron or granisetron improved performance in general cognitive tests in healthy participants. Interpretation of the findings is limited by the small number of included studies, relatively small sample sizes, and methodological heterogeneity; including in the population studied (schizophrenia versus healthy participants); the lack of specificity of test performance measures, many of which were administered as part of larger, standardised batteries; and the confounding effects of antipsychotic or other psychotropic medication in patients with schizophrenia. It is also that possible that potential improvements in sensorimotor processing might only be detected in patient groups with impaired visuoperceptual processing. This might explain the absence of any effects in healthy participants in the studies reviewed. Perhaps the most important limitation is the lack of placebo-controlled data on patients with untreated positive symptoms, which limited interpretation of the extent of ondansetron’s ‘antipsychotic’ effects.

Despite these limitations, there was consistent and robust evidence that 5HT3 antagonists enhance sensory processing in humans, especially when assessed using neurophysiological markers. Impaired sensory gating reflects a reduced ability to filter irrelevant information [43] and is considered a robust neurophysiological marker of psychosis in schizophrenia and bipolar disorder [44]. It has been suggested that an abnormal P50 ratio represents a neurocognitive deficit and vulnerability marker that is present across the psychosis spectrum [24–26], characterised by poorer performance on tests of sustained attention and vigilance [26, 45], including greater noise-induced distractibility during attentional tasks. The S2/S1 ratio of the P50 waveform response has been associated with the ‘global inattention’ scale of the Scale for Assessment of Negative Symptoms (SANS) [46] and with trait severity of auditory hallucinations, measured by the Psychotic Symptoms Ratings Scale (PSYRATS) [47]. Auditory gating is modulated through interplay between serotonergic, cholinergic and GABAergic neurotransmission [44].

Cholinergic inputs from the septal nucleus interact with 5HT3-expressing GABAergic interneurons in the CA3–CA4 hippocampal regions during the early phases of auditory processing, leading to transient inhibition of pyramidal neurones and suppression or gating of the response to a repeated stimulus [48]. Hippocampal α7-nicotinic receptors have been implicated in this process [49], based on the finding that α7-nicotinic receptor antagonists block both ondansetron and tropisetron’s reversal of gating deficits in DBA/2 mice [14, 16, 50]. Genetic studies carried out in people with schizophrenia and their families have similarly linked gating deficits to the α7 subunit of the nicotinic cholinergic receptor gene [51, 52].

Sensory gating is a ‘bottom up’ filter but is also influenced by top down processes [53, 54]. Studies that have used invasive techniques in animal and human neuroimaging studies have implicated a widely distributed network that spans temporo-parietal and prefrontal regions [48] and emphasised the importance of synchronised neuronal firing in maintaining efficient cognitive and perceptual processing [55]. Cortical GABAergic interneurones are important in this respect, as they facilitate sensory integration and modulate functional network dynamics [11]. The thalamus acts as a gateway for sensory (feedforward) inputs and a hub for cortical feedback, which is then relayed to GABAergic inter-neurones in the primary somatosensory cortex express 5HT3-A receptors, the majority of which are located in L1; an optimal location for their role in modulating cortical sensory processes [56]. Cholinergic activation acts to further increase the precision of sensory input processing [57] by increasing the signal-to-noise ratio of cortical neuronal responses to sensory inputs [58]; with nicotinic receptors, expressed in the hippocampus, thalamic reticular nucleus, and geniculate nuclei [59] playing a key role in this process [60].

The relative importance of the contribution of α7-nicotinic partial agonist, versus 5HT3 antagonist mediated effects, on sensory gating is unclear. Research in DBA/2 mice has shown differential effects of the α7-nicotinic receptor partial agonist DXMB-A (reduced S2 amplitude), the full α7 agonist varenicline (which has no effect on sensory gating) [61], and the selective 5HT3 receptor antagonists ondansetron and tropisetron (reduced S2 and increased S1 amplitude) [12, 14]. These findings suggest that 5HT3 antagonist effects alone are sufficient to reverse gating deficits, and that full α7 receptor agonism is not beneficial, possibly due to receptor desensitisation [52].

A direct comparison of the neurophysiological effects of ondansetron and tropisetron, and their relationship with changes in neuropsychological test performance and clinical symptoms would provide a mechanistic understanding of treatment effects. Future studies should also consider including drugs such as encenicline, an α7-nicotinic receptor partial agonist with 5HT3 antagonist effects [62, 63], and CVN058, a novel selective 5HT3 antagonist [64], which are also of interest as adjunctive treatments for patients with schizophrenia.

The effects of 5HT3 antagonists on the RVP test should be further explored, as impaired test performance is viewed as an endophenotypic marker of cognitive vulnerability to psychosis [65–67] and, importantly, the test has proved sensitive to the effects of tropisetron. This area of research could also be extended to include antipsychotic naive patients with prodromal or milder psychotic symptoms, to provide additional insights into the mechanisms of any treatment effects at an early stage of the illness.

From a neurochemical perspective, the modulatory effects of 5HT3 antagonists on nicotinic cholinergic and GABAergic neurotransmission are highly relevant when considering the treatment of hallucinations in PD, as there is marked disruption of nicotinic cholinergic neurotransmission in people with PD [68], and...
magnetic resonance spectroscopy (MRS) has shown a reduction in GABAergic activity in the occipital cortex in PD patients who hallucinate compared to those without [69]. The improvement in visual sustained attention following the use of 5HT3 receptor antagonists also warrants further consideration, as integrative theories regarding the origins of misperceptions and hallucinations propose that they arise as a result of impairments in visual perception and attentional binding [70]. Aligned with this, the Activation, Input, Modulation model proposes that hallucinations occur as a result of dysregulation of gating and filtering of sensory inputs, which reduces the dominance of inputs from external sources and increases cortical responses to internally generated imagery [71]. The fact that people with PD who experience hallucinations tend to over-rely on prior knowledge compared to those who do not [72] supports these theories. Auditory gating deficits have been observed in patients with PD compared to healthy subjects; especially in patients with more severe disease (Hoehn and Stages IV–V). However, there has been no direct comparison of hallucinators versus non-hallucinators.

The TOP HAT Trial (Clinical trials.gov NCT04167813) will provide placebo-controlled data on the effectiveness of ondansetron as a treatment for hallucinations in PD. Further research is, however, needed to investigate the relationship between sensory gating, visual information processing and emergent hallucinations in PD. Interventional studies are also needed to compare the effects of ondansetron and tropisetron (or drugs with similar properties) on visual information processing and emergent hallucinations in PD. Activation, Input, Modulation model proposes that hallucinations tend to over-rely on prior knowledge compared to healthy subjects; especially in patients with more severe disease (Hoehn and Stages IV–V). However, there has been no direct comparison of hallucinators versus non-hallucinators.

REFERENCES

1. Olivier B. Serotonin: a never-ending story. Eur J Pharm. 2015;753:2–18.
2. Kumar S, Soren S, Chaudhury S. Hallucinations: etiology and clinical implications. Ind Psychiatry J. 2009;18:119–26.
3. Jacob SN, Nienborg H. Monoaminergic neuromodulation of sensory processing. Front Neural Circuits. 2018;12:51.
4. Zismore TM, Hurley LM, Dacks AM. Serotonergic modulation across sensory modalities. J Neurophysiol. 2020;123:2406–25.
5. Meltzer HY. The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 1999;21:1065–155.
6. Meltzer HY, Mills R, Revels S, Williams H, Johnson A, Bahr D, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson’s disease psychosis. Neuropsychopharmacology 2010;35:881–92.
7. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson’s disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 2014;383:533–40.
8. Barnes NM, Hales TG, Lummis SC, Peters JA. The 5-HT3 receptor and psychopathology in schizophrenia. Pharmacology and psychopharmacology 2009;56:273–84.
9. Fink KB, Gothert M. 5-HT3 receptor regulation of neurotransmitter release. Pharm Rev. 2007;59:360–417.
10. De Deurwaerdere P, Di Giovanni G. Serotonergic modulation of the activity of mesencephalic dopaminergic systems: therapeutic implications. Prog Neurobiol. 2016;151:175–6.
11. Tremblay R, Lee S, Rudy B. GABAergic interneurons in the neocortex: from cellular properties to circuits. Neuron 2016;91:260–92.
12. Smucny J, Stevens J, Olincy A, Tregellas JR. Translational utility of rodent hippocampal auditory gating in schizophrenia: a review and evaluation. Transl Psychiatry. 2015;5:e587.
13. Alex KD, Pehek EA. Pharmacologic mechanisms of serotoninergic regulation of dopamine neurotransmission. Pharm Ther. 2007;113:296–320.
14. Wildboer KM, Zheng L, Choo KS, Stevens KE. Ondansetron results in improved auditory gating in DBA/2 mice through a cholinergic mechanism. Brain Res. 2009;1300:41–50.
15. Barnes JM, Costall B, Coughlan J, Domeney AM, Gerrard PA, Kelly ME, et al. The effects of ondansetron, a 5-HT3 receptor antagonist, on cognition in rodents and primates. Pharm Biochem Behav. 1990;35:935–62.
16. Hashimoto K, Iyo M, Freedman B, Stevens KE. Tropisetron improves deficient inhibitory auditory processing in DBA/2 mice: role of alpha 7 nicotinic acetylcholine receptors. Psychopharmacology 2005;183:13–9.
17. Rammes G, Eisensamer B, Ferrari U, Shapa M, Gimpil G, Gilling K, et al. Anti-psychotic drugs antagonize human serotonin type 3 receptor currents in a noncompetitive manner. Mol Psychiatry. 2004;9:846–58. 18.
44. Atagun MI, Drukker M, Hall MH, Altun IK, Tatlí SZ, Guloküz S, et al. Meta-analysis of auditory P50 sensory gating in schizophrenia and bipolar disorder. Psychiatry Res Neuroimaging. 2020;300:111078.

45. Potter D, Summerfelt A, Gold J, Buchanan RW. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr Bull. 2006;32:692–700.

46. Smucny J, Wylie K, Rojas D, Stevens K, Olincy A, Kronberg E, et al. Evidence for gamma and beta sensory gating deficits as transitional endophenotypes for schizophrenia. Psychiatry Res. 2013;214:169–74.

47. Smith DM, Grant B, Fisher DJ, Boracci G, Labelle A, Knott VJ. Auditory verbal hallucinations in schizophrenia correlate with P50 gating. Clin Neurophysiol. 2013;124:1329–35.

48. Vlieck P, Bob P, Raboch J. sensory disturbances, inhibitory deficits, and the P50 wave in schizophrenia. Neuropsychiatr Dis Treat. 2014;10:1309–15.

49. Luntz-Leyzman V, Bickford FC. Freedman R. Cholinergic gating of response to auditory stimuli in rat hippocampus. Brain Res. 1992;587:130–6.

50. Simosky JK, Stevens KE, Adler LE, Freedman R. Clozapine improves deficient inhibitory auditory processing in DBA/2 mice, via a nicotinic cholinergic mechanism. Psychopharmacology 2003;165:386–96.

51. Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci USA. 1997;94:587–92.

52. Adler LE, Olincy A, Waldo M, Harris JG, Griffith J, Stevens K, et al. Schizophrenia, sensory gating, and nicotinic receptors. Schizophr Bull. 1996;24:189–202.

53. Lightfoot G. Summary of the N1-P2 cortical auditory evoked potential to estimate the auditory threshold in adults. Semin Hear. 2016;37:1–8.

54. Rosburg T, Trautner P, Elger CE, Kurthen M. Attention effects on sensory gating—intracranial and scalp recordings. Neuroimage 2009;48:554–63.

55. Uhilhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 2006;52:155–68.

56. Larkum A. A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex. Trends Neurosci. 2013;36:141–51.

57. Sarter M, Hasselmo ME, Bruno JP, Givens B. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res Brain Res Rev. 2005;48:98–111.

58. Gill TM, Sarter M, Givens B. Sustained visual attention performance-associated prefrontal neuronal activity: evidence for cholinergic modulation. J Neurosci. 2000;20:4745–57.

59. Tregellas JR, Wylie K, Alpha7 nicotinic receptors as therapeutic targets in schizophrenia. Nicotine Tob Res. 2019;21:349–56.

60. Gil Z, Connors BW, Amitai Y. Differential regulation of neocortical synapses by neuromodulators and activity. Neuron 1997;16:79–87.

61. Waldo MC, Woodward L, Adler LE. Varenicline and P50 auditory gating in medicated schizophrenic patients: a pilot study. Psychiatry Res. 2010;175:779–80.

62. Keefe RS, Meltzer HA, Dgetluck N, Gawryl M, Koenig G, Moebius HJ, et al. Randomized, double-blind, placebo-controlled study of encineline, an alpha7 nicotinic acetylcholine receptor agonist, as a treatment for cognitive impairment in schizophrenia. Neuropsychopharmacology 2015;40:3053–60.

63. Hashimoto K. Targeting of alpha7 nicotinic acetylcholine receptors in the treatment of schizophrenia and the use of auditory sensory gating as a translational biomarker. Curr Pharm Des. 2015;21:3797–806.

64. Sehatpour P, Javitt DC, De Baun HM, Carlson M, Beloborodova A, Margolin DJ, et al. Match negativity as an index of target engagement for excitation/inhibition-based treatment development: a double-blind, placebo-controlled, randomized, single-dose cross-over study of the serotonin type-3 receptor antagonist CVN058. Neuropsychopharmacology. 2021. (ePub ahead of print).

65. Cattapan-Ludewig K, Hilti CC, Ludewig S, Vollweider FX, Feldon J. Rapid visual information processing in medicated schizophrenic patients: the impact of cognitive load and duration of stimulus presentation. A pilot study. Neuropsychobiology 2005;52:130–4.

66. Hilti CC, Delko T, Orosz AT, Thoman K, Ludewig S, Geyer MA, et al. Sustained attention and planning deficits but intact attentional set-shifting in neuroleptic-naive first-episode schizophrenia patients. Neuropsychobiology 2010;61:79–86.

67. Hilti CC, Hilti LH, Heinemann D, Robbins T, Seifritz E, Cattapan-Ludewig K. Impaired performance on the Rapid Visual Information Processing task (RVIP) could be an endophenotype of schizophrenia. Psychiatry Res. 2010;177:60–4.

68. Forgacs PB, Bodis-Wollner I. Nicotinic receptors and cognition in Parkinson’s disease: the importance of neuronal synchrony. J Neural Transm. 2004;111:1317–31.

69. Firbank MJ, Parikh J, Murphy N, Killen A, Allan CL, Collorent D, et al. Reduced occipital GABA in Parkinson disease with visual hallucinations. Neurology 2018;91:e675–85.

70. Collorent D, Perry E, McKeith I. Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations. Behav Brain Sci. 2009;28:737–57.

71. Diederich NJ, Goetz CG, Stebbins GT. Repeated visual hallucinations in Parkinson’s disease as disturbed external/internal perceptions: focused review and a new integrative model. Mov Disord. 2005;20:130–40.

72. Zarkali A, Adams RA, Psarras S, Leyland LA, Rees G, Weir RS. Increased weighting on prior knowledge in Lewy body-associated visual hallucinations. Brain Com- mun. 2019;1:fcz007.

AUTHOR CONTRIBUTIONS
ET carried out the review as part of an MSc dissertation project, supervised by JB and SR. ET and SR screened all studies, ET extracted and rated eligible studies. JBR and SC acted as second blind raters. OZ, RW and RH contributed to the design and interpretation of the findings. All authors contributed to the writing of the manuscript.

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