Cognitive and executive impairments in Parkinson’s disease psychosis: a Bayesian meta-analysis

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INTRODUCTION

Psychotic symptoms in Parkinson’s disease (PD) are one of the most common non-motor symptoms, manifesting typically as visual hallucinations and delusions, are distressing and associated with increased risk of hospitalisation, loss of independence and mortality.2–9 Several studies have shown that participants with PD psychosis (PDP) have worse performance compared with PD participants without psychosis (PDnP) in cognitive domains such as memory, attention, visuospatial abilities and other executive skills.2–9 Cognitive deficits are associated with poor quality of life, and with the onset of dementia as PD progresses.8 A better understanding of cognitive dysfunction in PDP could thus help inform treatment for the psychosis symptoms themselves as well as progression to dementia. However, which key cognitive domains are differentially affected in PDP compared with those without (PDnP), remains unclear. Montagnese et al9 investigated this by taking a meta-analytical approach and found that across measures of episodic memory, global cognition (eg, Mini-Mental State Examination, MMSE16), language, attention, visual perception, working memory and executive functioning, PD participants with visual hallucinations performed worse compared with PD without visual hallucinations, with the greatest impairments being in executive functions and attention. They also reported that only age, but not PD medications, duration and severity of PD, gender or general cognitive status, was associated with

ABSTRACT

Background Cognitive and executive deficits lead to worsening of quality of life and are a risk factor for developing dementia in people with Parkinson’s disease (PD) with psychosis (PDP). However, which key cognitive domains are differentially affected in PDP compared with those without (PDnP), remains unclear. Here, we examined this using a Bayesian meta-analytical approach.

Methods Searches were conducted on PubMed, Web of Science, SCOPUS, Medline and PsycINFO. Hedges’ g effect-size estimates were extracted from eligible studies as a measure of standard mean differences between PDP and PDnP participants. Meta-analyses were conducted separately for each cognitive domain and subdomain, we examined the effect of age, PD medications, PD duration and severity, depression and psychosis severity for all major domains with meta-regressions.

Results Effect-size estimates suggest worse performance on all major domains (k=105 studies) in PDP compared with PDnP participants, with global cognition (k=103 studies, g=−0.57), processing speed (k=29 studies, g=−0.58), executive functions (k=33, g=−0.56), episodic memory (k=30 studies, g=−0.58) and perception (k=34 studies, g=−0.55) as the most likely affected domains. Age, depression and PD duration had moderating effects on task-related performance across most of the major nine domains.

Conclusions We report extensive deficits across nine domains as well as subdomains in PD psychosis, with global cognition, processing speed and executive functions as the most likely impaired. The presence of depression may influence task-related performance in PDP, alongside age and PD duration, but not dose of dopamine replacement treatments.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cognitive and executive processing deficits are commonly reported in patients with Parkinson’s disease (PD) with psychosis. Several studies have shown deficits in executive functions, fluency, visuospatial ability, attention and memory but only one meta-analysis has been published on this topic. This suggested a wide range of impairments across the major domains.

WHAT THIS STUDY ADDS

⇒ This meta-analysis confirmed extensive cognitive and executive impairments across major domains and subdomains in PD psychosis patients and with a Bayesian approach we observed that global cognition, perception, executive functions, episodic memory and processing speed were the most likely impacted domains. Age, PD duration and depression had a moderating effect on task performance in PD psychosis patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results further highlight the presence of general cognitive and executive impairments in the presence psychotic symptoms in patients with PD compared with patients with PD without psychosis. Of those, episodic memory may be the most robustly impaired and may also contribute to this non-motor symptoms. These should be further examined with also cognitive paradigm in neuroimaging studies.
performance on general cognitive tests, working memory and executive functions. However, which cognitive domains might be most likely to be differentially impaired in PD participants with psychosis compared with those without psychosis remains unclear. This is important for a better understanding of the relationship between neurocognitive impairments and psychotic symptoms, and their potential role in the development of these symptoms, which in turn may help develop more effective interventions, for example, targeting a particular cognitive domain to help reduce specific symptoms. Hence, we wanted to address these issues using two approaches. Instead of taking a frequentist approach such as that adopted by Montagnese et al., we have adopted a Bayesian approach to allow us to estimate the likelihood or probability of impairment in task performance above a certain threshold in each cognitive domain between participants with PD and PDP. Further, we compared the magnitude of impairment in all the domains by restricting our analyses to those studies that have reported across all cognitive domains of interest to identify domains for which the evidence of impairment is most robust. Unlike before, we also examined impairment in subdomains of broader cognitive domains, for example, working memory subtests measuring manipulation and maintenance of information, category-based or letter-based fluency, the ability of copying and drawing, verbal and non-verbal retrieval. We also updated the evidence from Montagnese et al. with additional studies including PDP with a wider range of psychotic manifestations, for example, multimodal hallucinations, hallucinations with/without insights and more severe symptoms (eg, delusions), and summarised evidence on different cognitive domains based on recommended approaches. Finally, we explored the association between age, PD medications, depression and severity of psychosis symptoms on the probability of reporting such task-related performance differences using a Bayesian meta-regression and also report pooled effect-size estimates after accounting for the confounding variables that were significantly associated with task performance.

METHODS

Search strategy

Searches were conducted on PubMed, Web of Science, SCOPUS, Medline and PsycINFO (Ovid) on 14 September 2021 (protocol registered on PROSPERO; CRD42021260475). Full search strategy can be found in online supplemental material 1. In brief, terms for the clinical condition (eg, “Parkinson”, “Parkinson psychosis”, “Parkinson disease psychosis”) and for cognitive deficits (eg, “memory impair*”, “attention*”, “language impair*”) were used. Systematic reviews and meta-analyses were used as additional resources to identify articles. We report following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Eligibility criteria

Studies were included in this review if (A) they included participants with PD psychosis and compared their performance on neuropsychological assessments with that of PD participants without psychosis (PDP) (B) participants with PD had a diagnosis of psychosis after PD onset; (C) PD participants did not have a diagnosis of PD dementia; (D) they were written in English, peer-reviewed and original pieces of research and (E) if they had available data on the neuropsychological assessments for each group. Studies that examined cognitive deficits in PD were included on the grounds that they provided subgroup analyses between participants with PD psychosis and PD without psychosis. Grey literature, reviews, books and conference abstracts were excluded. We did not include studies with PD dementia participants, and longitudinal studies were included on the grounds that they provided baseline assessments for use in the present analyses.

Data synthesis

Data extraction procedure is reported in online supplemental material 1. The nature of the cognitive assessments examined in this review measured a variety of cognitive and executive areas and were classified into separate domains as recommended. We conducted separate meta-analyses for each category and subcategory of cognitive and executive domains. First, we extracted Hedges’ g effect-size estimates and associated standard errors (SE) for each cognitive task for each study representing standardised mean differences between PD psychosis and PDP. These were computed in R (V.4.0.3) using the metafor package. Subsequently, Hedges’ g effect sizes from individual studies were synthesised in a Bayesian meta-analysis using a random-effects approach with the brms package based on the STAN probabilistic programming language, accounting for the fact that some studies contributed to multiple domains or subdomains, thus violating the requirement of independence of effect sizes. The package brms provides an estimate of between-study and within-study variance which assesses the presence of variability across different studies. We applied a normal distribution for the population-level parameter (mean=0, SD=1) with a half-t distribution as τ, known as Half Cauchy, as recommended and also the Hamiltonian Monte Carlo No-U-Turn sampling procedure. Several cognitive tasks involve multiple domains. For example, letter-based or category-based fluency tests require processing speed as well as language ability; similarly, the Stroop test call on both selective attention and it requires the ability to switch from one task instruction to a different one, and processing information in a timely manner. When such tests were employed in a study, they were included under all the applicable domains. Perception-based assessments were classified into subdomains based on the work from Montagnese et al. Publication bias was assessed by regressing the effect-size SE on the effect sizes for each analysis, and we applied cluster-robust variance estimation to control for the lack of independent effect size.

In the first instance, separate Bayesian analyses were conducted for each domain. In order to identify the cognitive domains most likely affected in PDP, we estimated the empirical cumulative distribution function (ECDF) for each domain using a threshold of effect size $=−0.3$. A negative effect-size indicates that participants with PDP performed worse compared with PDP participants. Using this threshold, the ECDF gives the probability of impairment (ie, PDP worse than PDP) equivalent to an effect-size difference of 0.3 or more. Based on the convention that effect-size estimates of 0.3 may be deemed as medium sized effect,” we reasoned that any cognitive domains affected to an extent equal to or greater than this threshold were most likely to represent the key domains that may underlie psychosis in PD, as opposed to general cognitive impairments associated with PD itself. Finally, in order to allow a systematic comparison of the magnitude of impairment across all the cognitive domains investigated thus far in the literature, we also carried out a separate analysis restricting to those studies that have reported across all cognitive domains of interest. Below, effect sizes are reported in Hedges’ g, as estimate of standard mean difference between
PDP and PDnP, and 95% credible intervals (95% CI). In all analyses, convergence was successful as represented by the potential scale reduction factor (R<1.01).

Bayesian meta-regressions were conducted where at least 10 or more studies were available to examine the effect of key confounding factors of interest such as depression, dopamine-replacement medications (expressed in levodopa equivalent daily dose, LEDD), motor symptoms (expressed with the Movement Disorder Society - Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III scores, as a measure of PD severity), severity of psychosis symptoms and global cognition on the performance on neuropsychological assessments. To summarise neuropsychiatric scores for depression and psychosis severity from different assessments, we computed standardised scores by dividing the mean with the SD reported in each study for each participant’s group, respectively, for depression and psychosis severity. Additional analyses were carried out to investigate the effect of concomitant psychotropic medications as well as the nature of psychotic symptoms. For concomitant psychotropic medications, as there were fewer than three studies for each of these treatments, we did not carry out separate subgroup analyses. Instead, we carried out sensitivity analyses excluding the relevant studies for each domain as applicable. For psychotic symptoms, based on previous research,31 we first categorised the studies based on the type of psychotic symptoms in PD participants, into studies that included PD participants who only reported hallucinations (‘hallucinators’), PD participants with delusions only (‘delusions’) and PD participants with both hallucinations and delusions (‘psychosis’). There were not enough studies in the ‘delusion’ group to conduct a meta-analysis. Therefore, we conducted additional meta-analyses for all cognitive domains comparing task-related performance between ‘hallucinators’ and PDnP participants, and between ‘psychosis’ and PDnP participants. We assessed the quality of included studies using the Effective Public Health Practice Project32 scale (see online supplemental material 1 for description).

RESULTS

Study characteristics

From an initial list of 5144 studies, we identified a total of 69 studies after removing duplicates and full-text screening, and a further 36 from systematic reviews and meta-analysis9 leading to a total of 105 studies reporting on 2912 PDP participants (mean age±SD=68.92±4.34, 48.8% male) and 6056 PDnP participants (mean age±SD=66.88±4.28, 57.1% male). Basic sample characteristics are reported in table 1 (for description of sample feature, please see online supplemental materials 2 and 3). Figure 1 reports the flow chart with the steps that led to the final study pool.

Pooled effect-size estimates of task performance in PDP versus PDnP across different cognitive domains: Bayesian meta-analysis

Figure 2A reports the forest plot with posterior probability draws for each major cognitive domain. A negative effect-size estimate indicates that PDP participants performed worse while a positive estimate indicates that they performed better compared with PDnP participants in that specific cognitive domain. All the effect-size estimates across all nine major domains indicate that task performance across all these cognitive domains tested was worse in PDP compared with PDnP participants, with the largest effect sizes observed in construction, processing speed, episodic memory, global cognition and executive functions. Overall results for domains and subdomains are reported in table 2. The presence of both between-study and within-study heterogeneity were detected across all analyses, both in the domains and subdomains related analyses. Publication bias was also present in the majority of the analyses. See online supplemental material 4 for funnel plots and posterior probability forest plots for each domain and subdomain (online supplemental eFigures 2–43).

Of the included 105 studies, only 2 studies reported including PD participants on antipsychotic medications,33,34 and one study reported including PD participants on cholinesterase inhibitors35 and they only contributed data to the domain of global cognition. Sensitivity analysis excluding these three studies did not change the reported results on global cognition (g=−0.58 (95% CI −0.69 to −0.47); between-study variability, 0.40, 95% CI 0.28 to 0.52; within-study variability 0.30, 95% CI 0.15 to 0.44)).

Cumulative probability of the most likely impaired domains

To identify the most likely domains affected in PDP, we applied the ECDF and set effect size of −0.3 as threshold to the estimates reported above. Of all the domains tested, only the domains of global cognition, processing speed, executive function, episodic memory and perception were found to have over 99.5% probability of impairment equivalent to an effect size of at least −0.3 or worse (table 2).

Task-related performance in the same sample of participants

In addition, data from four studies that assessed all nine domains were meta-analysed12 36–38 separately, so as to compare relative impairments across all the domains in the same group of participants. Figure 2B reports the posterior probability distribution across the nine domains for these four studies. PDP participants were more likely to show a worse performance on only episodic memory tests compared with PDnP (g=−0.33 (95% CI −0.55 to −0.08; between-study variability, 0.16, 95% CI 0.01 to 0.53; within-study variability 0.10, 95% CI 0.00 to 0.28)). The presence of between-study heterogeneity was detected in this analysis. There were no differences between PDP and PDnP participants included in these four studies and those included in the general study pool (k=101) (see online supplemental material 5).

Pooled effect-size estimates of task performance in PD participants with different psychosis symptoms across cognitive domains

As there were not enough studies in the ‘delusion’ group to conduct a meta-analysis, we conducted separate meta-analyses for all cognitive domains comparing task performance between ‘hallucinators’ and PDnP participants, and between ‘psychosis’ and PDnP participants. Results are reported in online supplemental material 6. In brief, the effect-size estimates for all nine domains were negative, indicating that PD participants with hallucinations likely performed worse than PDnP participants. We were only able to compare PD participants in the ‘psychosis’ group with PDnP participants on global cognition, episodic memory and language domains. The effect sizes indicate that PD participants with psychosis were likely to perform worse than PDnP participants on global cognition. The presence of both between-study and within-study heterogeneity were detected across all analyses.


3
<table>
<thead>
<tr>
<th></th>
<th>PDP (n=2912)</th>
<th>PDnP (n=6056)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>68.92±4.34</td>
<td>66.88±4.28</td>
</tr>
<tr>
<td>Education years, mean±SD</td>
<td>11.29±3.52</td>
<td>11.12±3.54</td>
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<tr>
<td>PD duration, mean±SD</td>
<td>9.08±2.94</td>
<td>7.00±2.65</td>
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<tr>
<td>Male, n (%)</td>
<td>1404 (48.8)</td>
<td>3460 (57.1)</td>
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<tr>
<td>LEDD, mean±SD</td>
<td>644.94±223.82</td>
<td>570.21±220.83</td>
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<tr>
<td>UPDRS (part III), mean±SD</td>
<td>28.19±7.79</td>
<td>23.31±6.72</td>
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</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Domain</th>
<th>PDP (n)</th>
<th>PD (n)</th>
<th>Age PDP (mean±SD)</th>
<th>Age PD (mean±SD)</th>
<th>UPDRS part III scores (PDP) (mean±SD)</th>
<th>UPDRS part III scores (PD) (mean±SD)</th>
<th>PD duration (years) (PDP) (mean±SD)</th>
<th>PD duration (years) (PD) (mean±SD)</th>
<th>LEDD mg/day (PDP) (mean±SD)</th>
<th>LEDD mg/day (PD) (mean±SD)</th>
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<tr>
<td>Attention</td>
<td>571</td>
<td>1094</td>
<td>68.00±3.92</td>
<td>66.05±4.15</td>
<td>27.4±7.9</td>
<td>22.45±6.94</td>
<td>8.01±2.68</td>
<td>6.61±2.54</td>
<td>668.91±219.2</td>
<td>574.28±185.96</td>
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<tr>
<td>Constructions</td>
<td>265</td>
<td>332</td>
<td>67.43±3.67</td>
<td>65.76±4.06</td>
<td>25.38±5.86</td>
<td>21.65±6.57</td>
<td>6.95±2.95</td>
<td>6.32±2.43</td>
<td>647.70±210.70</td>
<td>541.67±190.12</td>
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<tr>
<td>Episodic memory</td>
<td>775</td>
<td>1358</td>
<td>68.01±3.85</td>
<td>66.37±4.02</td>
<td>26.27±6.84</td>
<td>21.82±6.42</td>
<td>8.44±3.30</td>
<td>7.02±2.89</td>
<td>614.32±258.74</td>
<td>536.33±215.66</td>
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<tr>
<td>Executive functions</td>
<td>804</td>
<td>1399</td>
<td>68.55±4.17</td>
<td>66.62±4.14</td>
<td>26.82±7.71</td>
<td>22.18±6.87</td>
<td>8.46±3.31</td>
<td>7.16±3.07</td>
<td>612.86±243.97</td>
<td>536.45±232.50</td>
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<td>Global cognition</td>
<td>2673</td>
<td>5862</td>
<td>68.74±4.15</td>
<td>68.87±4.25</td>
<td>27.97±7.94</td>
<td>22.77±6.59</td>
<td>8.90±3.03</td>
<td>6.94±2.85</td>
<td>644.24±230.55</td>
<td>571.53±223.78</td>
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<td>Language</td>
<td>832</td>
<td>1619</td>
<td>68.24±3.94</td>
<td>66.48±3.81</td>
<td>25.52±6.70</td>
<td>20.59±5.62</td>
<td>8.76±3.53</td>
<td>7.42±2.96</td>
<td>618.67±249.45</td>
<td>545.05±30.75</td>
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<td>Perception</td>
<td>813</td>
<td>1607</td>
<td>68.58±3.35</td>
<td>66.90±3.21</td>
<td>27.67±8.88</td>
<td>22.21±6.89</td>
<td>8.96±2.98</td>
<td>7.20±2.64</td>
<td>643.27±77.83</td>
<td>549.47±45.73</td>
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<tr>
<td>Processing speed</td>
<td>743</td>
<td>1431</td>
<td>68.36±3.80</td>
<td>66.62±4.00</td>
<td>25.80±6.87</td>
<td>20.66±5.82</td>
<td>8.22±3.32</td>
<td>6.92±3.02</td>
<td>612.23±265.13</td>
<td>538.05±44.86</td>
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<tr>
<td>Working memory</td>
<td>474</td>
<td>921</td>
<td>68.04±4.60</td>
<td>66.34±3.99</td>
<td>27.53±5.32</td>
<td>22.97±5.90</td>
<td>7.99±3.90</td>
<td>6.67±2.29</td>
<td>574.54±325.65</td>
<td>510.02±262.71</td>
</tr>
</tbody>
</table>

Motor scores are measured using the MDS-UPDRS part III scale (and previous versions), PD medications are reported in LEDD mg per day and PD duration is reported in mean years. LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society - Unified Parkinson’s Disease Rating Scale; PD, Parkinson’s disease; PDnP, PD participants without psychosis; PDP, PD with psychosis.
Effect of potential confounding factors: Bayesian meta-regression

Meta-regression results are shown in table 3. In brief, the likelihood that LEDD may be associated with cognitive and executive deficits was negligible across all domains. Similarly, psychosis severity was unlikely to be associated with task-related performance in global cognition assessments (and it was not possible to assess this for individual cognitive domains). Age was likely associated with task-related performance on all domains, except for attention. PD duration was likely to influence performance on global cognitive assessments, construction, executive functions and working memory, although the pooled effect-size estimates for global cognition remained unaffected even when PD duration tended to zero (please see online supplemental material 7). Severity of depression likely moderated performance in global cognition, executive functions, processing speed and language though the pooled effect-size estimates for global cognition and attention remained unaffected even after the severity of depression scores tended toward zero (please see online supplemental material 7). All three moderators were inversely associated with task performance, such that, the longer the disease duration, the more severe the depression and the greater the age, the worse the performance on cognitive domains. We further conducted an additional analysis with global cognition scores as moderator and this was unlikely to be associated with task-related performance across any of the domains (table 3).

DISCUSSION

Here, we endeavoured to uncover what the probable estimate of cognitive performance might be in PDP participants using a...
Bayesian meta-analysis. Previous studies reported cognitive deficits in PDP participants on a range of cognitive or executive measures, but what the true effect is likely to be remained unanswered. We found that compared with those without psychosis, participants with PD psychosis are likely to show a worse task-related performance on all major domains, and subdomains with the largest effect sizes on measures assessing construction, episodic memory, processing speed, global cognition and executive functions. We further observed deficits in several specific subdomains such as semantic and phonemic fluency, and naming, copying, learning, verbal and nonverbal retrieval, and higher order visual processing (i.e., dorsal and ventral streams, and low-level vision apperception).

<table>
<thead>
<tr>
<th>Domain (k=)</th>
<th>SMD, g (95% CI) (cumulative probability of SMD&lt;−0.3)</th>
<th>Variability (expressed in tau, r, with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language (k=34)</td>
<td>−0.45 (−0.59 to −0.31) (98.6%)</td>
<td>Between-study: 0.29 (0.12 to 0.44) Within-study: 0.19 (0.02 to 0.36)</td>
</tr>
<tr>
<td>Reading (k=7)</td>
<td>−0.27 (−0.71 to 0.17)</td>
<td>Between-study: 0.24 (0.01 to 0.72) Within-study: 0.41 (0.08 to 0.90)</td>
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<tr>
<td>Phonemic fluency (k=17)</td>
<td>−0.47 (−0.71 to −0.25)</td>
<td>Between-study: 0.29 (0.03 to 0.58) Within-study: 0.19 (0.01 to 0.46)</td>
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<tr>
<td>Semantic fluency (k=19)</td>
<td>−0.63 (−0.89 to −0.39)</td>
<td>Between-study: 0.50 (0.24 to 0.74) Within-study: 0.05 (0.0 to 0.14)</td>
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<tr>
<td>Naming (k=10)</td>
<td>−0.28 (−0.57 to −0.03)</td>
<td>Between-study: 0.19 (0.01 to 0.53) Within-study: 0.23 (0.01 to 0.55)</td>
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<tr>
<td>Construction (k=11)</td>
<td>−0.59 (−0.93 to −0.21) (93.7%)</td>
<td>Between-study: 0.28 (0.01 to 0.70) Within-study: 0.58 (0.32 to 0.90)</td>
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<td>Drawing (k=5)</td>
<td>−0.64 (−1.53 to 0.33)</td>
<td>Between-study: 0.51 (0.02 to 1.56) Within-study: 0.97 (0.36 to 1.96)</td>
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<tr>
<td>Copying (k=7)</td>
<td>−0.74 (−1.08 to −0.41)</td>
<td>Between-study: 0.16 (0.01 to 0.51) Within-study: 0.26 (0.01 to 0.75)</td>
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<td>Working memory (k=16)</td>
<td>−0.36 (−0.61 to −0.12) (69.8%)</td>
<td>Between-study: 0.40 (0.21 to 0.67) Within-study: 0.21 (0.08 to 0.36)</td>
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<td>Manipulation (k=10)</td>
<td>−0.41 (−0.82 to 0.01)</td>
<td>Between-study: 0.59 (0.29 to 1.05) Within-study: 0.12 (0.0 to 0.36)</td>
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<tr>
<td>Maintenance (k=10)</td>
<td>−0.32 (−0.64 to 0.00)</td>
<td>Between-study: 0.39 (0.13 to 0.73) Within-study: 0.24 (0.02 to 0.50)</td>
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<tr>
<td>Episodic memory (k=30)</td>
<td>−0.57 (−0.76 to −0.39) (99.6%)</td>
<td>Between-study: 0.43 (0.21 to 0.70) Within-study: 0.17 (0.11 to 0.42)</td>
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<td>Encoding (k=12)</td>
<td>−0.78 (−1.21 to −0.37)</td>
<td>Between-study: 0.56 (0.06 to 1.08) Within-study: 0.25 (0.01 to 0.74)</td>
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<td>Non-verbal retrieval (k=12)</td>
<td>−0.61 (−0.88 to −0.34)</td>
<td>Between-study: 0.15 (0.01 to 0.44) Within-study: 0.46 (0.25 to 0.73)</td>
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<td>Verbal retrieval (k=26)</td>
<td>−0.52 (−0.78 to −0.29)</td>
<td>Between-study: 0.52 (0.22 to 0.88) Within-study: 0.17 (0.01 to 0.38)</td>
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<tr>
<td>Perception (k=34)</td>
<td>−0.54 (−0.71 to −0.37) (99.6%)</td>
<td>Between-study: 0.19 (0.01 to 0.40) Within-study: 0.63 (0.51 to 0.77)</td>
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<td>Visual acuity (k=8)</td>
<td>−0.19 (−0.64 to 0.25)</td>
<td>Between-study: 0.35 (0.02 to 0.87) Within-study: 0.31 (0.01 to 0.80)</td>
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<td>Dorsal stream (k=19)</td>
<td>−0.44 (−0.65 to −0.22)</td>
<td>Between-study: 0.21 (0.02 to 0.45) Within-study: 0.46 (0.29 to 0.66)</td>
</tr>
<tr>
<td>Ventral stream (k=8)</td>
<td>−1.03 (−1.60 to −0.43)</td>
<td>Between-study: 0.60 (0.03 to 1.40) Within-study: 0.45 (0.03 to 1.09)</td>
</tr>
<tr>
<td>Dorsal stream/ventral stream (k=7)</td>
<td>−0.59 (−1.31 to 0.17)</td>
<td>Between-study: 0.78 (0.05 to 1.81) Within-study: 0.58 (0.05 to 1.33)</td>
</tr>
<tr>
<td>Low level vision apperception (k=9)</td>
<td>−0.87 (−1.38 to −0.37)</td>
<td>Between-study: 0.30 (0.01 to 0.90) Within-study: 0.81 (0.48 to 1.26)</td>
</tr>
<tr>
<td>Imagery (k=2)</td>
<td>0.35 (−0.60 to 1.32)</td>
<td>Between-study: 0.69 (0.03 to 2.59) Within-study: 0.17 (0.01 to 0.55)</td>
</tr>
<tr>
<td>Visual contrast (k=4)</td>
<td>−0.41 (−0.87 to 0.14)</td>
<td>Between-study: 0.27 (0.01 to 0.92) Within-study: 0.28 (0.02 to 0.70)</td>
</tr>
<tr>
<td>Executive functions (k=23)</td>
<td>−0.56 (−0.70 to −0.41) (99.9%)</td>
<td>Between-study: 0.30 (0.12 to 0.47) Within-study: 0.19 (0.01 to 0.41)</td>
</tr>
<tr>
<td>Processing speed (k=29)</td>
<td>−0.58 (−0.75 to −0.41) (99.9%)</td>
<td>Between-study: 0.37 (0.25 to 0.53) Within-study: 0.8 (0.00 to 0.22)</td>
</tr>
<tr>
<td>Attention (k=24)</td>
<td>−0.39 (−0.62 to −0.17) (79.7%)</td>
<td>Between-study: 0.40 (0.11 to 0.64) Within-study: 0.26 (0.02 to 0.55)</td>
</tr>
<tr>
<td>Global cognition (k=103)</td>
<td>−0.57 (−0.68 to −0.47) (100%)</td>
<td>Between-study: 0.41 (0.29 to 0.52) Within-study: 0.28 (0.14 to 0.42)</td>
</tr>
</tbody>
</table>

Between-study and within-study variabilities is also reported with associated 95% CI.
This is in line with previous evidence, indicating extensive cognitive impairments in PD psychosis also encompassing subareas of cognitive, perceptual and executive abilities.\textsuperscript{11 12 39 40} In addition, using a threshold of impairment equivalent to an effect-size estimate of at least $-0.3$ or worse, we found that although the probability of impairment for any of the nine domains was higher than $69\%$, the domains of general cognitive abilities, executive function, processing speed, memory and perception were the most likely to be impaired in PDP with probabilities $>99.5\%$. This is in line with and extends on previous findings suggesting that although overall cognitive and executive functions may be disrupted in PDP,\textsuperscript{9} global cognitive and executive functioning, processing speed and episodic memory (and its subdomains) may be the key domains affected. We observed similar effect sizes to those reported in Montagnese\textsuperscript{et al.}\textsuperscript{9} with some discrepancy in magnitude of impairment estimated. This may be related to the fact that we applied a non-frequentist approach to this meta-analysis, which allows computation of pooled effect size (per cognitive domain) based on probability distribution drawn from a prior (based on previous established knowledge) and the data from the 105 studies.\textsuperscript{41 42} A number of cognitive subdomains appeared impacted in PDP showing a similar pattern of results favouring the presence of extensive impairments. Finally, when we restricted our analyses to those four studies that reported on all domains, we found that episodic memory was the only domain that was significantly impaired in PDP compared with PDnP. However, whether this indicates that episodic memory deficits underlie the emergence of psychotic symptoms in PD, whereas involvement of other domains reflect progression of PD in general, remains to be tested.

In addition, subgroup analyses showed that compared with PDnP participants, PD participants with hallucinations were more likely to show impairments across all nine domains while PD participants with combination of both hallucinations and delusions (ie, ‘psychosis’ group) were more likely to experience deficits in global cognition but not episodic memory and language domains. Whether the lack of significant difference in the domains of episodic memory and language for studies comparing ‘psychosis’ participants reflected the modest sample ($k=3$) of previous studies included in this analysis as opposed to the larger sample ($k=13$) of studies included in the analysis of global cognition remains to be seen.

Age was the most common moderator likely associated with impaired performance, across all major domains except for attention, progressing age being associated with worse performance, in contrast to Montagnese\textsuperscript{et al.}\textsuperscript{9} who reported an effect of age only for global cognition, executive functions and working memory. We report an effect of age on cognitive performance in participants with PD psychosis, whereby each year of increasing age, the effect size for cognitive performance on global cognition and episodic memory measures will decrease by $0.04$, similarly it will decrease by $0.05$ in executive functions assessments, by $0.06$ in processing speed and working memory tests. PD duration also moderated performance on global cognition, construction, executive functions and working memory, with longer duration associated with worse performance, although the effect-size for global cognition remained significant even when the duration of PD tended towards zero in these analyses. It is likely that with each year of PD duration, the effect size for performance on tests measuring global cognition and executive functions will decrease by $0.06$. Dopamine-replacement medications (expressed in LEDD) were unlikely to affect task-related performance in participants with PD psychosis, in accordance with previous evidence.\textsuperscript{43 44} We also observed an inverse relationship between performance on global cognition, executive functions, processing speed, and language, and depression indicating that, like with PD duration and age, the greater the depression the worse the cognitive performance. This is in agreement with previous literature,\textsuperscript{45 46} highlighting the effect of neuropsychiatric symptoms on cognitive functioning in PD as well as PD psychosis. Interestingly, including depressive symptoms as a moderator did not affect the effect-size estimate indicating worse performance on global cognitive measures in participants.
with PDP, thus suggesting that impairment in global cognition in PDP participants is not merely a reflection of more severe depression in this group. Depression and longer PD duration are generally associated with cognitive deficits and it is a risk factor for PD dementia; our findings suggest that this also applies to PD psychosis whereby participants with PDP and longer disease duration and concomitant depression may be more likely to experience overall cognitive deficits compared with those without depression and with a short PD duration. Montagnese et al did not find such association in their meta-analysis which is discrepant with our results. Our findings suggest that global cognition and working memory may be more affected in participants with PDP with depressive symptoms and longer disease duration; similarly, if they report more depressive symptoms their executive function and processing speed may also be impaired compared with other domains. This should be further explored in cohort-based studies where neuropsychiatric and PD-specific symptoms are monitored over time. Targeting depression in this clinical population may potentially help slow down the decline in specific cognitive domains, however, this remains to be tested. Moreover, we included global cognitive scores as moderator in the meta-regression analyses but found no likely association between global scores on tests, such as the MMSE, and task performance in participants with PD psychosis. This may suggest that deficits in global cognition may not account for the domain-specific impairments in various cognitive domains that we have reported here in participants with PDP. This is also in line with Montagnese et al. However, it is worth noting that the studies included in our syntheses did not control for group differences in global cognition, disease duration and depression in their analyses of group differences in cognitive domains. As the study-specific effect-size estimates pooled in our syntheses were based on these uncontrolled estimates, we cannot be absolutely certain that global cognitive deficits, disease duration and depression do not underlie domain-specific cognitive impairments in PD psychosis.

Our findings are to some extent in agreement with the attentional network dysfunction model of psychosis in PD, specifically in relation to processing speed and episodic memory. This model suggests that visual hallucinations in PD may be a by-product of dysfunctional information processing across the ventral and dorsal attentional networks, and Default Mode Network. Consistent with this, we observed possible deficits in measurements assessing processing speed, as well as general cognitive and executive functions, which are associated with these cortical networks. However, based on the present findings, it may be challenging to propose one model to explain psychosis in PD. Rather it may be related to impairment in a range of cognitive processes and structure and/or function of neural substrates subserving those processes. Nevertheless, these results suggest that future research should focus on episodic memory and its subcategories (ie, recognition, cued and free recall, false positive error in recognition tests) and its relationship with PDP. Further, studies may employ neuroimaging approaches in conjunction with memory tasks or memory-related cognitive activation paradigms to examine whether altered memory-related brain function may underlie psychosis in PD.

Psychosis in PD is burdensome and leads to deteriorating quality of life and it is particularly imperative to address all domains of impairment associated with PDP. Results presented here suggest that certain cognitive domains may be impaired in people with PDP over and above that expected by factors such as severity of psychosis, age, duration of PD and depressive symptoms, indicating that these domains may be considered legitimate targets of intervention for PDP, even in the absence of dementia. Interventions in this context could include both pharmacological and non-pharmacological strategies to address cognitive deficits in this clinical population such as cognitive training, cognitive remediation programme and physical activity, and rationalisation of psychotropic medications with anticholinergic side effects. There is also insufficient evidence on whether dementia-specific medications, for example, cholinesterase inhibitors, may be helpful in reducing cognitive and executive deficits in PD participants with psychosis who have not yet developed dementia. Our results showing cognitive deficits encompassing different domains in people with PD psychosis compared with PDnP corroborates previous findings and underlines the importance of longitudinal studies to investigate their association with the risk of developing dementia (PD dementia) and whether earlier interventions may help progression of cognitive decline to PD dementia.

**Limitations and future research**

Results reported here are to be considered in light of a range of limitations some of which are related to the specific analytical approach that we have used here, and others pertain to limitations of the meta-analytical approach in general. Focusing on the former category, first, we used a somewhat non-informative prior in our analyses. Specifically, we used a normal distribution for the population-level parameter, that is, where we would expect a potential effect size to be, and the Half-Cauchy prior for the distribution parameter, tau (t). Half-Cauchy distribution has been recommended in research where sample sizes are relatively small and for its properties. Although this population-level prior does not provide extensive information, it may be useful especially in initial investigations on a specific problem based on the belief that all probabilities are equal and can set the foundation for exploratory analyses. Using a meta-analytical approach, we were not able to examine an exhaustive list of cognitive domains. Instead, we were only able to synthesise the effect sizes of cognitive and executive domains that have been investigated in the included studies, applying recommended guidelines for the domain classification. Therefore, it is plausible that cognitive impairments other than those examined in these 105 studies may be impaired in people with PD psychosis. Nevertheless, it is worth noting that we also examined subdomains (eg, manipulation, encoding, semantic fluency), and it may be possible that deficits in the overall domain (eg, language) might be actually due to impairments in the respective subdomains such as, for example, category-based and letter-based fluency as well as naming abilities instead of difficulties in comprehension (ie, reading). Understanding where the putative impairments lie may lead to better understanding of the neurocognitive profile of PD psychosis and the extent to which each domain contributes to psychotic symptoms in PD. One other limitation relates to the task performance in the same sample across the nine cognitive domains. We found only four studies that examined all domains and due to the very small sample (PDP, n = 129; PDnP, n = 139) it may be challenging to compare these results with those from the larger group of studies (k = 101), as they may not be as representative. However, we tested for discrepancies in key characteristics, for example, age, motor symptoms, PD medications and both samples were comparable, thus suggesting that differences between the samples of the two sets of studies may not explain the discrepant result. Moreover, the presence of between-study and within-study heterogeneity and publication bias across the analyses warrant cautious
interpretation of the effect-size estimates. Such variability and publication bias were also reported in Montagnese et al. It may also be argued that PDP participants with hallucinations may be different compared with PDP participants with other kinds of psychotic symptoms. Additional analyses focusing on studies comparing ‘hallucinators’ with PDnP participants suggested that impairments were present across all major domains, consistent with the results of our main analyses, while studies comparing ‘psychosis’ participants with PDnP showed impairments in global cognition but not language or episodic memory. We did not have a sufficient number of studies to perform analysis with the ‘delusion’ group as published studies have predominantly included PD participants reporting hallucinations, in line with evidence that presence/passage hallucinations and visual hallucinations may be more prevalent than other psychotic manifestations. Given the modest number of studies that were included in the analyses that produced non-significant results in our subgroup analyses, future studies may also focus on PD participants with psychotic symptoms other than hallucinations to examine whether cognitive impairments reported here are differentially associated with certain types of psychotic symptoms. Another limitation relates to the fact that we primarily examined the effect of PD medications expressed in LEDD in the meta-regressions. LEDD is one of the most common clinical parameters to measure the amount of dopaminergic medications (ie, dopamine agonists, levodopa, levodopa intestinal gel). Participants with PDP may, however, be on different other medications including antipsychotics, anticholinergic drugs, as well as antidepressants. We observed a lack of consistent reporting, for example, studies have reported the number or percentage of people on a given medication, for example, amorphopine, donepezil, rivastigmine, while others report just the category of the medication (either in number or percentage and at times in mg per day). This limited our ability to more comprehensively account for the role of medications in cognitive impairment in PDP. Participants with PD psychosis may be on a range of different medications alongside their dopamine agonist treatment, in particular antipsychotic and antidepressant drugs, some of which have anticholinergic side effects, and cholinesterase inhibitors, which may have an effect on cognition, and therefore, arguably, may have confounded results presented here. We found only three studies that included participants with PDP taking antipsychotics or cholinesterase inhibitors and all of them contributed data to the analysis of global cognition domain. Sensitivity analysis excluding these three studies suggested that group differences in global cognition remain unchanged, indicating that they may not have confounded our results on global cognition. On this basis, it seems unlikely that concomitant psychotropic medications may have confounded results presented here. However, future studies investigating impairments in cognition in participants with PDP should consider approaches to account for potential confounding effects of concomitant psychotropic medications either at the study design or analysis stage. We examined the effect of age and disease duration, expressed as mean age and mean duration for PD participants with psychosis, on task-related performance on different domains. Although converting these two variables into categorical factors, for example, age and duration bands, may lead to statistical loss of power in such approach, it would be informative from a clinical perspective to try and apply age and disease duration as categorical factors in moderator analysis in a frequentist approach. One other factor worth considering in future research is the effect of sex on cognitive performance in PD participants with psychosis. We were not able to examine the effect of sex in meta-regression analyses in the absence of adequate reporting of sex-specific results in previous studies. Most studies included in the present work reported the number of males and/or females (or their percentages) but did not report sex-specific performance on cognitive batteries, therefore, not allowing us to examine the effect of sex. Future studies should, therefore, examine whether cognitive performance differs between male and female PDP participants. In this work, we mainly focused on cross-sectional studies that examined PDP participants at a single time point. Although this is informative, PD psychosis is a risk factor for more severe PD symptoms, worsening of quality of life, increased hospitalisations as well as PD dementia. We observed cognitive impairments in all nine domains (as categorised based on recommendations from Harvey) and it would be clinically informative to understand whether impaired performance on any of these domains may be associated with increased risk of subsequent development of dementia in PD participants. While it was not possible to address this in the context of the present work in the absence of appropriate longitudinal data in the included studies, the present results suggest that this is a worthwhile endeavour for future research. In particular, prospective longitudinal studies may help investigate whether baseline impairments in one or more specific domains of cognition may serve as prognostic markers of development of dementia in those with PD psychosis.

CONCLUSIONS

This systematic review and meta-analysis examined the probable cognitive and executive domains affected in participant with PD psychosis using a Bayesian approach. Our findings suggest extensive deficits across the major cognitive domains in PD psychosis compared with PD without psychosis, with global cognitive functions, processing speed, executive functions and memory as the most likely affected domains. Of those, episodic memory may be the most robustly impaired domain as suggested by analyses from the set of studies investigating all domains. PD medications did not affect the relationship between PDP and task-related performance; however, age, PD duration and severity of depression may also contribute to worsening of cognitive performance on the majority of these domains. These findings are to be considered preliminary and warrant replication in future studies incorporating a prospective longitudinal design to investigate whether these impairments in these cognitive domains may be causally associated with psychotic symptoms in people with PD.

Contributors

Conceptualisation: SP, DF, LV and SB; Methodology: SP and SB; Investigation: SP, DF, LV and SB; Data curation: SP, LG and RW; Formal analysis: SP, SB; Visualisation: SP and SB; Funding acquisition: SB, LV and DF; Writing (original draft): SP and SB; Writing (review and editing): All authors; Supervision: LV, DF and SB. Guarantor: SP, LV, DF and SB.

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Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. LV has collaborated with Beckley Canopy Therapeutics/Canopy Growth (investigator-initiated research) wherein they supplied study drug for free for charity (Parkinson’s UK) and NIHR (BRC) funded research.

Competing interests

None declared.
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