

**Table 1** Summary of study characteristics across included studies (n=80).

| Study Characteristics                                                                                                                                | n  | %     |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----|-------|
| <b>Publication year (Mean = 2016.6, SD=4.64)</b>                                                                                                     |    |       |
| 2006-2010                                                                                                                                            | 6  | 7.5%  |
| 2011-2015                                                                                                                                            | 12 | 15%   |
| 2016-2020                                                                                                                                            | 28 | 35%   |
| 2021-2025                                                                                                                                            | 34 | 42.5% |
| <b>Study region</b>                                                                                                                                  |    |       |
| Europe                                                                                                                                               | 37 | 46.2% |
| Asia                                                                                                                                                 | 31 | 38.8% |
| North America                                                                                                                                        | 10 | 12.5% |
| South America                                                                                                                                        | 2  | 2.5%  |
| <b>Species/Model</b>                                                                                                                                 |    |       |
| <ul style="list-style-type: none"> <li>• Rat models: Wistar, Sprague-Dawley, 6-OHDA lesion models, MCAO stroke models</li> </ul>                     | 36 | 45%   |
| <ul style="list-style-type: none"> <li>• Mouse models: APP/PS1, 5xFAD, C57BL/6J, transgenic MANF mice, TH-EGFP mice, NestinCre mice</li> </ul>       | 20 | 25%   |
| <ul style="list-style-type: none"> <li>• Invertebrates: <i>C. elegans</i>, <i>Drosophila melanogaster</i> (RNAi and PD models)</li> </ul>            | 6  | 8%    |
| <ul style="list-style-type: none"> <li>• Non-human primates: Marmoset (<i>Callithrix jacchus</i>)</li> </ul>                                         | 1  | 1.3%  |
| <ul style="list-style-type: none"> <li>• Cell lines: HEK293, INS1, midbrain neuron cultures, primary neuronal cultures</li> </ul>                    | 6  | 8%    |
| <ul style="list-style-type: none"> <li>• Mixed models: Studies that used both in vivo (rodent) and in vitro models (e.g., neurons + rats)</li> </ul> | 11 | 13.8% |
| <ul style="list-style-type: none"> <li>• Other</li> </ul>                                                                                            | 1  | 1.3%  |
| <b>Intervention types include # of studies</b>                                                                                                       |    |       |
| <ul style="list-style-type: none"> <li>• Recombinant Protein Administration (CDNF or MANF injection)</li> </ul>                                      | 31 | 38.8% |
| <ul style="list-style-type: none"> <li>• Gene Therapy (AAV-Mediated Delivery of MANF or CDNF, or Viral Protein Complex Delivery)</li> </ul>          | 10 | 12.5% |
| <ul style="list-style-type: none"> <li>• Endogenous Expression Modification (Knockout, Overexpression, or Knockdown Models)</li> </ul>               | 19 | 23.8% |
| <ul style="list-style-type: none"> <li>• Stem Cell Delivery (engineered cells expressing CDNF/MANF)</li> </ul>                                       | 2  | 2.5%  |
| <ul style="list-style-type: none"> <li>• Peptidomimetics/Synthetic Analogs</li> </ul>                                                                | 1  | 1.3%  |
| <ul style="list-style-type: none"> <li>• Exercise Intervention (Voluntary/Forced Exercise increasing endogenous MANF/CDNF)</li> </ul>                | 3  | 3.8%  |
| <ul style="list-style-type: none"> <li>• Combination Therapy (CDNF + Other Treatment Methods)</li> </ul>                                             | 7  | 8.8%  |
| <ul style="list-style-type: none"> <li>• Cell Culture Treatment (in vitro cell studies with</li> </ul>                                               | 6  | 7.5%  |

|                                                                                                  |    |      |
|--------------------------------------------------------------------------------------------------|----|------|
| recombinant proteins or gene knockdowns) <ul style="list-style-type: none"> <li>Other</li> </ul> | 1  | 1.3% |
| <b>Outcomes</b>                                                                                  |    |      |
| Dopaminergic Neuron Health                                                                       | 55 |      |
| <ul style="list-style-type: none"> <li>TH+ Neuron Survival</li> </ul>                            | 20 |      |
| <ul style="list-style-type: none"> <li>Fiber Density (TH+ fiber)</li> </ul>                      | 15 |      |
| <ul style="list-style-type: none"> <li>Dopamine Metabolite Levels</li> </ul>                     | 10 |      |
| <ul style="list-style-type: none"> <li>Morphology (soma size, branching)</li> </ul>              |    |      |
| Motor Function                                                                                   | 40 |      |
| <ul style="list-style-type: none"> <li>Rotarod Test (latency to fall)</li> </ul>                 | 25 |      |
| <ul style="list-style-type: none"> <li>Open field (locomotion, distance moved)</li> </ul>        | 10 |      |
| <ul style="list-style-type: none"> <li>Pole Test (bradykinesia)</li> </ul>                       | 5  |      |
| <ul style="list-style-type: none"> <li>Gait Analysis (stride length)</li> </ul>                  | 4  |      |
| <ul style="list-style-type: none"> <li>Wire Hang/Grip Strength</li> </ul>                        |    |      |
| Behavioural Function                                                                             | 26 |      |
| <ul style="list-style-type: none"> <li>Anxiety-like behaviour (EPM, open field)</li> </ul>       | 10 |      |
| <ul style="list-style-type: none"> <li>Depression-like Behaviour (FST, TST)</li> </ul>           | 15 |      |
| <ul style="list-style-type: none"> <li>Cognitive Performance (NOR, Morris Water)</li> </ul>      | 5  |      |
| <ul style="list-style-type: none"> <li>Social Interaction Tests</li> </ul>                       | 20 |      |
| <ul style="list-style-type: none"> <li>General Activity/ Exploration Behaviour</li> </ul>        | 55 |      |
| Combined Motor and Behavioural Outcomes                                                          |    |      |
| Cellular Stress Response                                                                         | 50 |      |
| <ul style="list-style-type: none"> <li>BIP/GRP78 Expression (ER stress chaperones)</li> </ul>    | 40 |      |
| <ul style="list-style-type: none"> <li>CHOP Expression (pro-apoptotic marker)</li> </ul>         | 30 |      |
| <ul style="list-style-type: none"> <li>Aggregate UPR Marker Expression</li> </ul>                | 15 |      |
| <ul style="list-style-type: none"> <li>XBP1 Splicing (UPR activation)</li> </ul>                 | 10 |      |
| <ul style="list-style-type: none"> <li>ATF4/ATF6 Pathway Activation</li> </ul>                   | 5  |      |
| <ul style="list-style-type: none"> <li>IRE1<math>\alpha</math> Signaling Modulation</li> </ul>   |    |      |