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# Sage Science Spotlight: SAGE-718 In-Depth

May 20, 2021

# Safe Harbor Statement

- The slides presented today and the accompanying oral presentations contain forward-looking statements, which may be identified by the use of words such as “may,” “might,” “will,” “should,” “can,”,“expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “opportunity”, “goal”, “mission”, “potential,” “target”, or “continue,” and other similar expressions.
- Forward-looking statements in this presentation include statements regarding: our clinical development plans, including expected timelines for initiation and completion of trials and reporting of results; the potential regulatory pathways and plans for our product candidates; our belief in the potential for success of our product candidates in various indications, including the potential profile and benefit of our product candidates; our estimates as to the number of patients with disorders and diseases of interest to us and that we hope to help; and the goals, opportunity, mission and vision for our programs and our Company and the potential for our business.
- These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risk that:
  - Our clinical trials may not meet their primary endpoints or key secondary endpoints. Success in non-clinical studies or in prior clinical trials of our product candidates may not be repeated or observed in ongoing, planned or future studies involving the same compound or other product candidates or in the same or different indications. Final results of studies where we reported interim results may not be consistent with the interim results. Non-clinical and clinical results from ongoing or future trials may not support further development of the product candidate or regulatory approval on the timelines we expect or at all or may require additional clinical trials or nonclinical studies.
  - We may experience slower than expected enrollment in our clinical trials or may encounter other delays or problems, including in analyzing data or requiring the need for additional analysis, data or patients, and such issues with any trial could cause delay in completion of the trial, availability of results and timing of future activities.
  - The impact of COVID-19 on our clinical development timelines may be more significant than we expect and may negatively impact expected site initiation, enrollment or conduct in our clinical trials, or cause us to pause trials or not be able to use data, in each case which may significantly impact our ability to meet our expected time-lines or may significantly impact the integrity or sufficiency of the data from our trials or cause us to have to change our plans.
  - We may encounter unexpected safety or tolerability issues with respect to our product candidates or identify other issues in clinical trials or nonclinical studies.
  - At any stage, regulatory authorities may ask for additional clinical trials, nonclinical studies or other data in order for us to proceed further in development or to file for or obtain regulatory approval. The FDA and other regulatory authorities may ultimately decide that the design or results of our completed, ongoing or planned clinical trials for any of our product candidates, even if positive, are not sufficient to file for or obtain regulatory approval in the indications that are the focus of our development plans despite prior regulatory advice. Other decisions or actions of the FDA or other regulatory authorities may affect the initiation, timing, design, size, progress and cost of clinical trials and our ability to proceed with further development;
  - Even if our products are successfully developed and approved, the number of patients with the diseases or disorders our products treat, and the actual market for such products may be smaller than our current estimates; or we may not achieve market acceptance or reimbursement at acceptable levels.
  - We may not be able to obtain and maintain adequate intellectual property protection or other forms of data and marketing exclusivity for its products, or to defend our patent portfolio against challenges from third parties.
  - We may face competition from others developing products for similar uses as those for which our product candidates are being developed.
  - We may not be able to establish and maintain key business relationships with third parties on we may encounter technical and other unexpected hurdles in the manufacture and development of our products.
  - Any of the foregoing or other factors may negatively impact our ability to achieve our goals, mission, opportunities, plans or expectations for our business.
- For additional disclosure regarding these and other risks Sage faces, see the disclosure contained in the "Risk Factors" section of our most recent report, and in our other public filings, with the Securities and Exchange Commission, available on the SEC's website at http://www.sec.gov. Any forward-looking statement represent our views only as of today, and should not be relied upon as representing our views as of any subsequent date. We undertake no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

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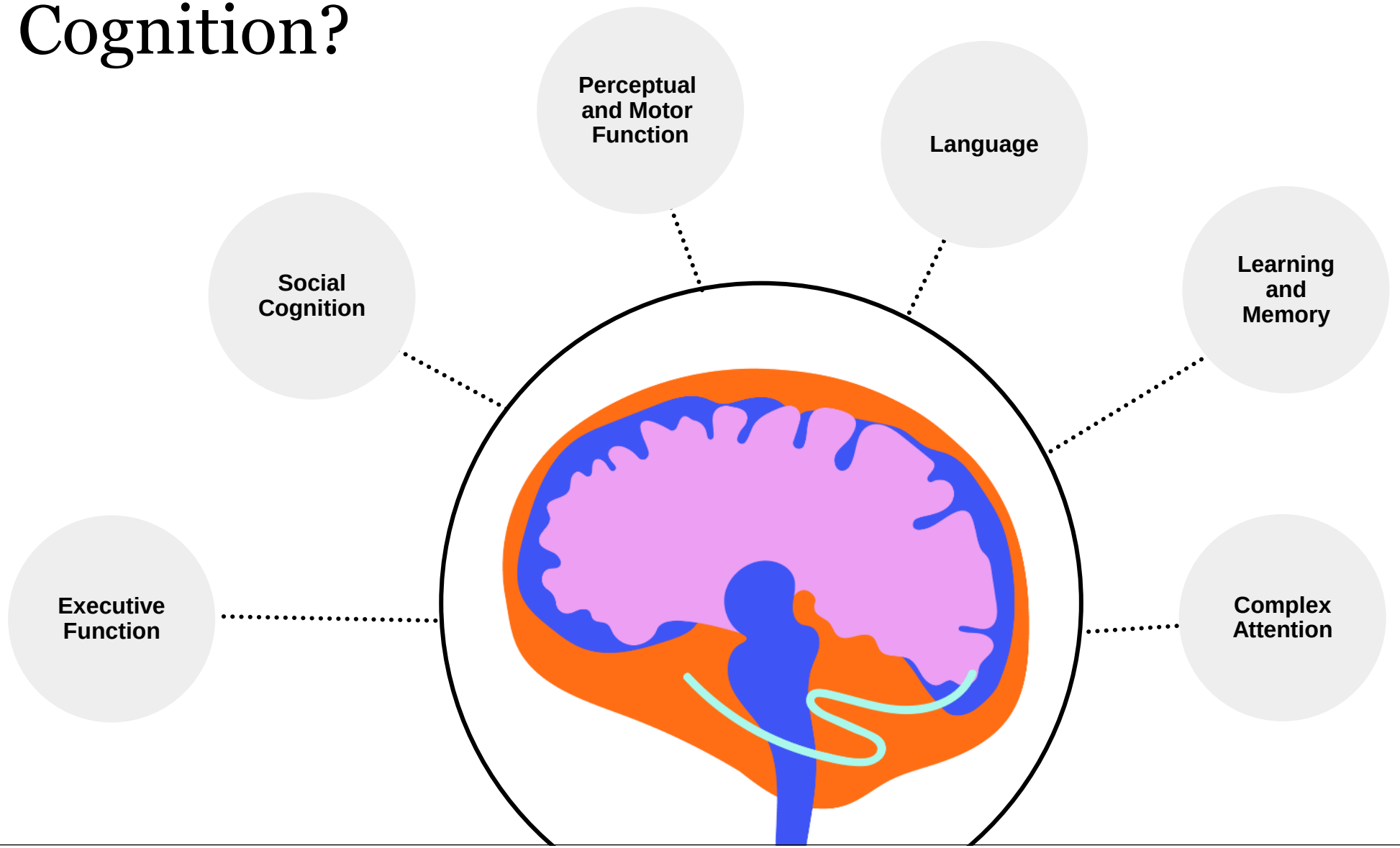
# What is Cognition?




Sachdev, P et al. (2014). Classifying neurocognitive disorders: The DSM-5 approach. Nature Reviews

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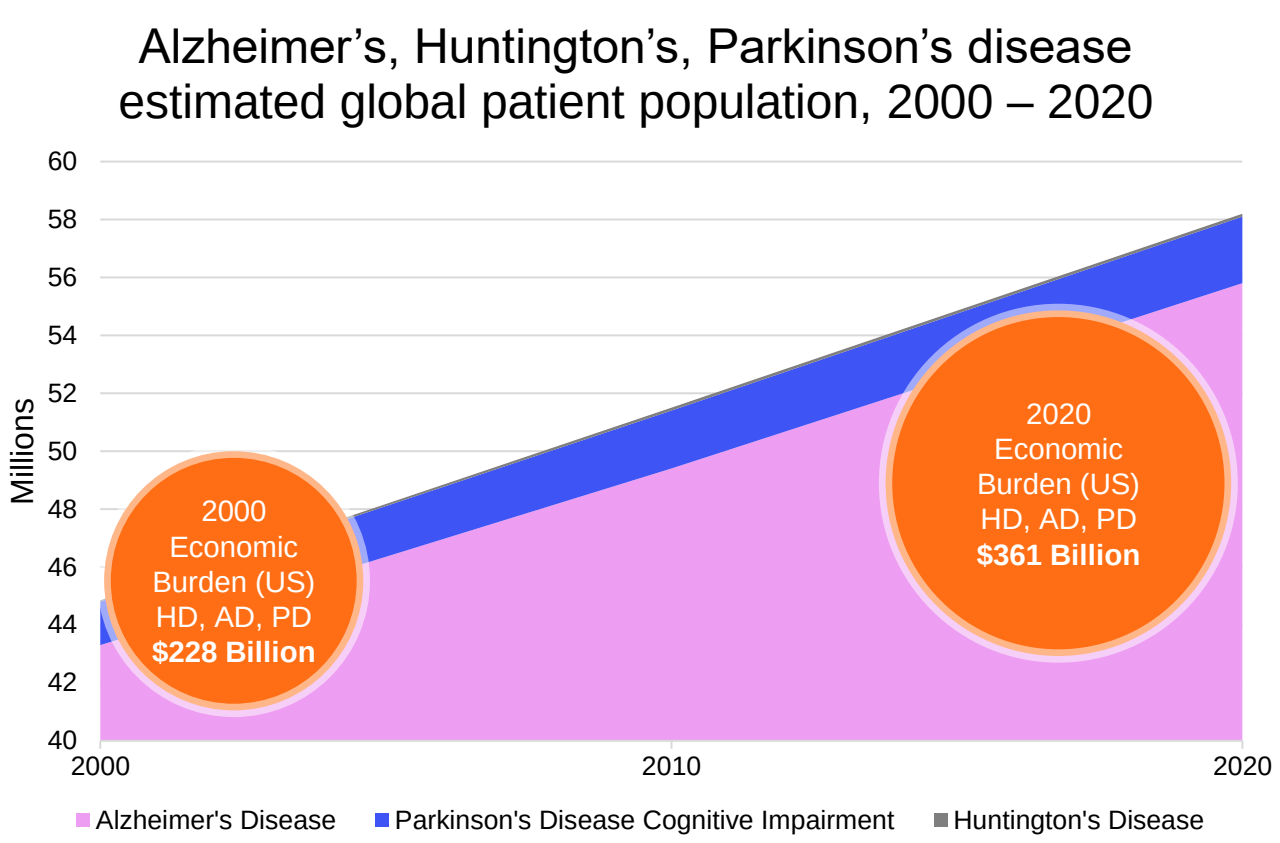
# Neuropsychiatric Disorders

*Dearth of innovative treatments approved for disorders of cognition*

- Globally, disorders involving cognitive dysfunction continue to increase and are one of the greatest areas of unmet need
  - Currently available treatments are limited in efficacy
- People with cognitive impairment report:
  - Executive deficits: multi-tasking, organization, planning, working memory
  - Difficulty concentrating
  - Memory loss
- Significant impact on patient ability to work, live independently, adhere to medical care, and interact with family




Sachdev, P et al. (2014). Classifying neurocognitive disorders: The DSM-5 approach. Nature Reviews Neurology. 10. 634-642. 10.1038/nrneurol.2014.181.

***BLS CPI (Consumer Price Index) Calculator was used to estimate 2000 and 2020 economic burden using U.S. specific studies in respect to the indications noted.***

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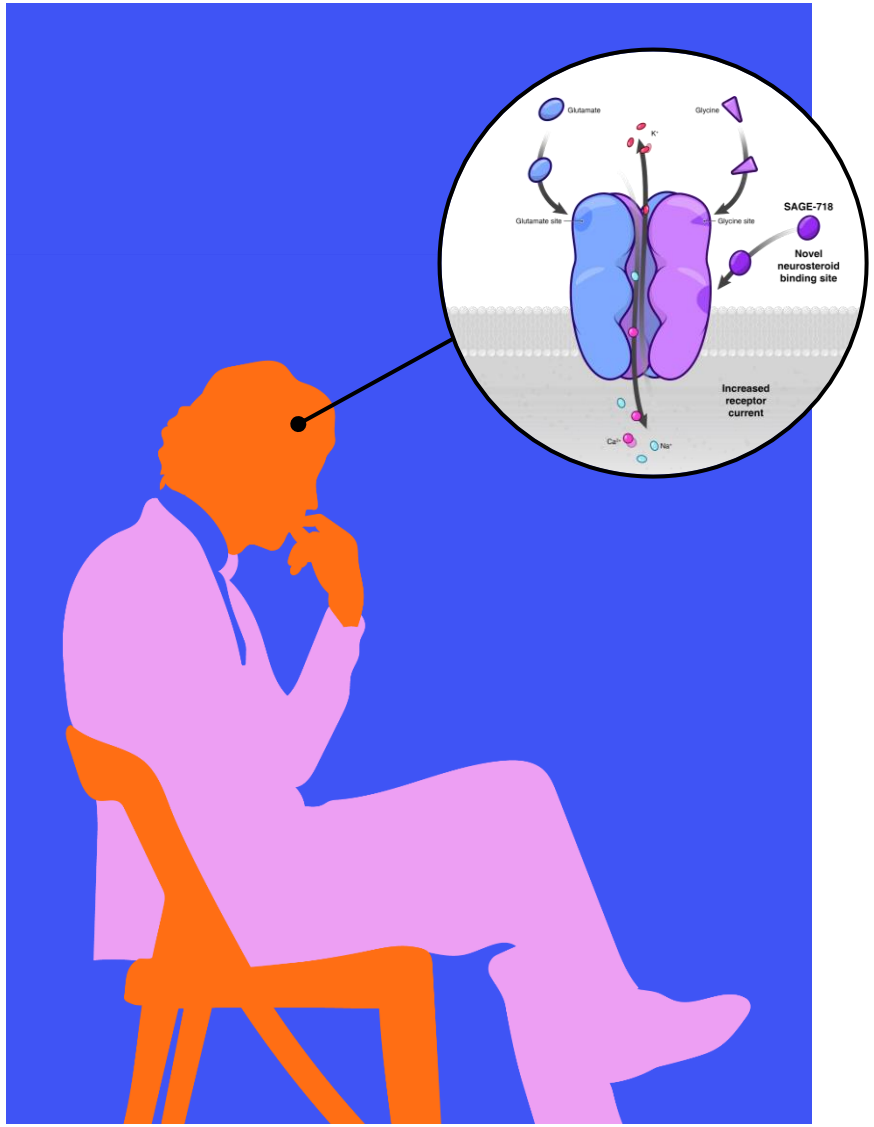
# Re-thinking Treatment of Neuropsychiatric Disorders

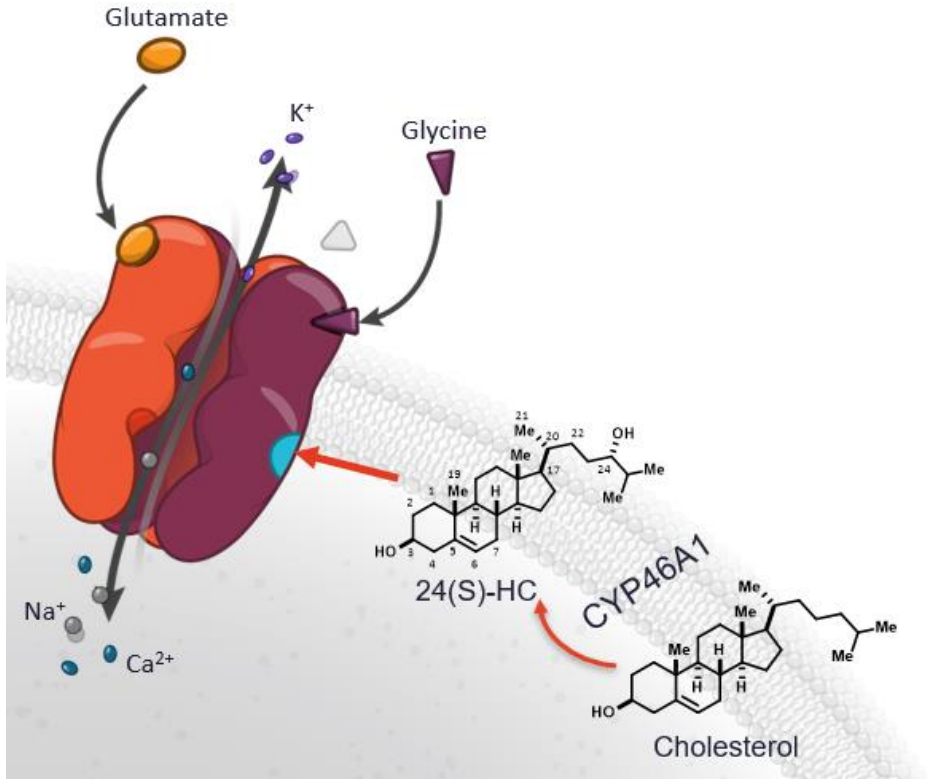
- NMDA receptors play a critical role in the process of neuroplasticity and are important in a host of cognitive, learning and behavioral processes
  - NMDA receptor function can be reduced by disease and declines during aging
- NMDA receptor modulation may have potential to address disorders of cognition & behavior across the lifespan:
  - Neurodegenerative disorders
  - Neurodevelopmental disorders
  - Disorders requiring recovery or rehabilitation of cognitive function
- Traditional approaches to modulating the NMDA receptor run the risk of causing severe side-effects associated with either excessive stimulation or complete blockade of activity



# Emerging Science Drives New Thinking

*Novel starting point for understanding NMDA receptor modulation*

- 24S-hydroxycholesterol (24S-HC) is a cholesterol metabolite produced primarily in the brain
- 24S-HC positively modulates NMDA receptors (PAM)
- Sage has developed a library of novel, wholly-owned, NMDA modulators with distinct profiles
- Strong IP strategy backs Sage's NMDA receptor modulator portfolio
- **By exploiting the pharmacology of endogenous regulatory systems, Sage's NMDA receptor modulator portfolio has potential to reduce severe consequences associated with either the excessive stimulation or complete blockade of these critical receptors**

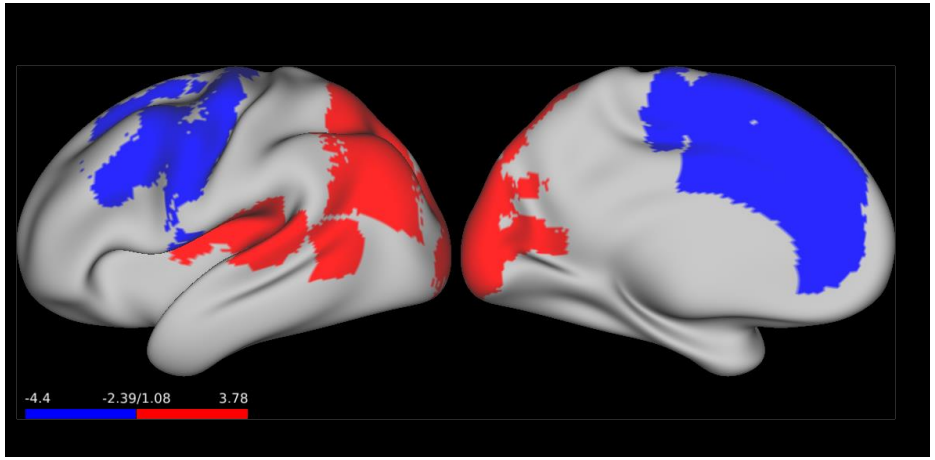


# SAGE-718 a First-in-Class NMDA Receptor PAM

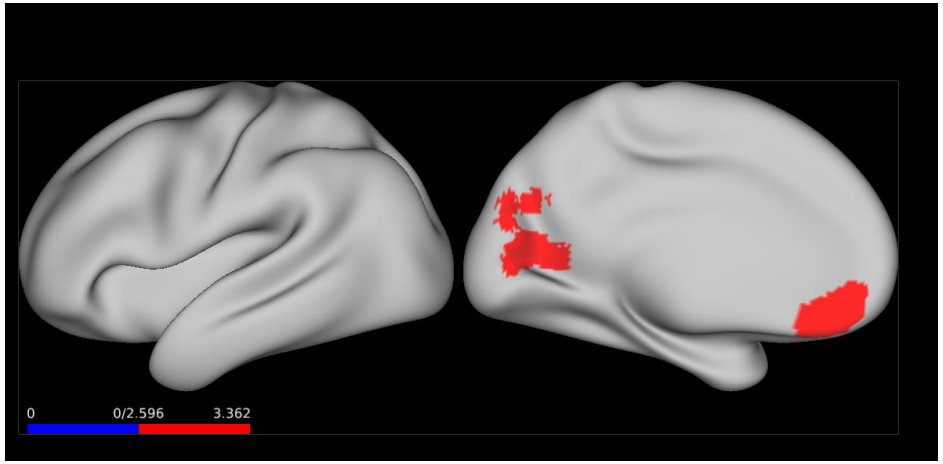
*Potential to provide unique cognitive benefits for patients with neurodegenerative disorders*

- Robust preclinical activity and improvement demonstrated in animal models associated with NMDA receptor dysfunction
- Clinical biomarker data support SAGE-718's ability to modulate key brain circuits involved in cognition and attenuate brain changes associated with NMDA receptor blockade

**NMDA receptor blocker**




**SAGE-718 + NMDA blocker**




Left: Ketamine (NMDA-receptor blocker) caused regionally localized increases (**RED**) and decreases (**BLUE**) in cerebral blood flow (BOLD-MRI)
Right: SAGE-718 blunted ketamine's induced increases and decreases in BOLD-MRI

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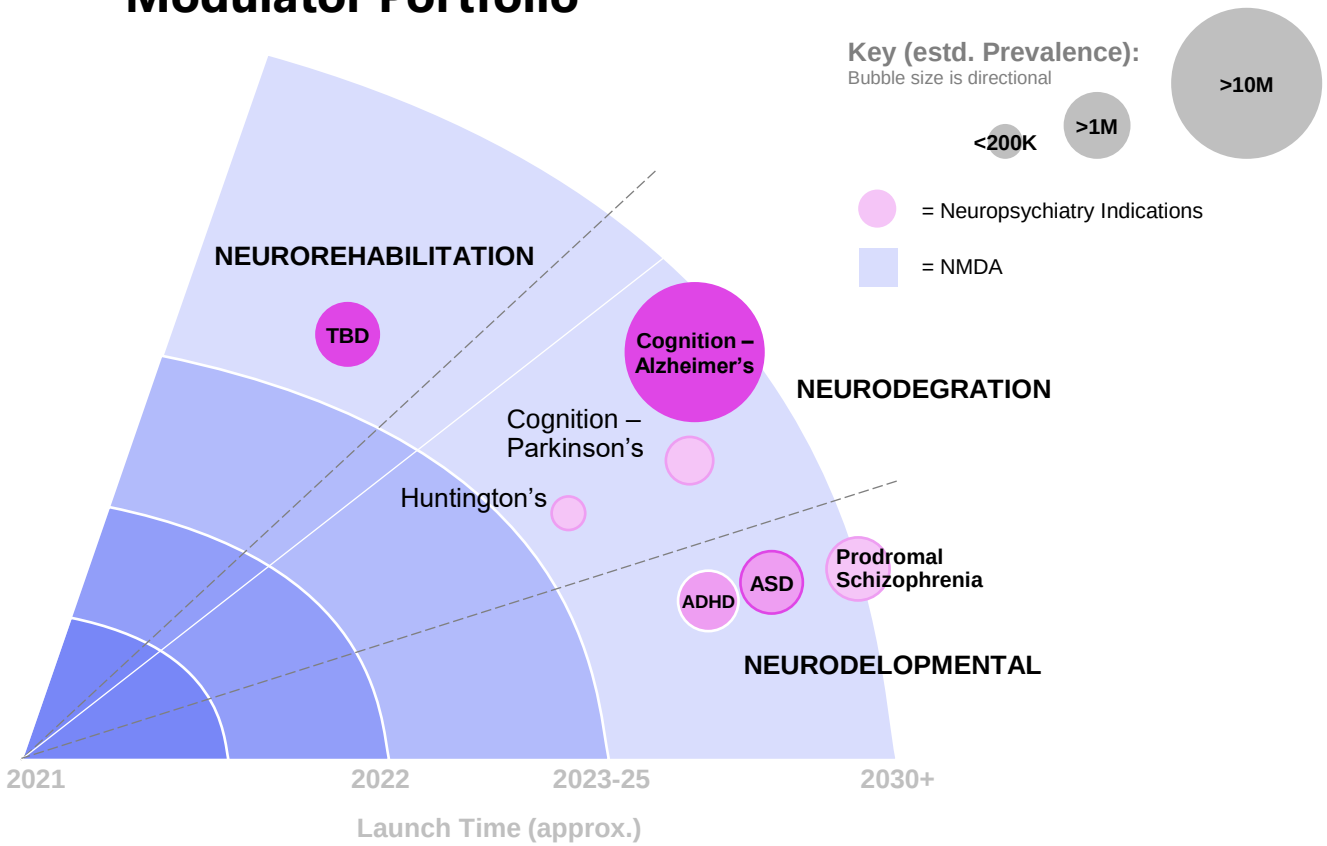
# Disciplined Approach to Building Diverse Pathways for Development

- Cognitive dysfunction is a core feature influencing disability in multiple diseases
- SAGE-718's mechanism-of-action potentially supports a broad cognitive benefit
- Leading with human data to build out a sequence of indications
  - Hypothesis targeted indications, *and*
  - Platform of open label trials in a diverse set of patient populations to allow clinical data / insights to inform decision making

## Potential Indications for Sage's NMDA Receptor Modulator Portfolio



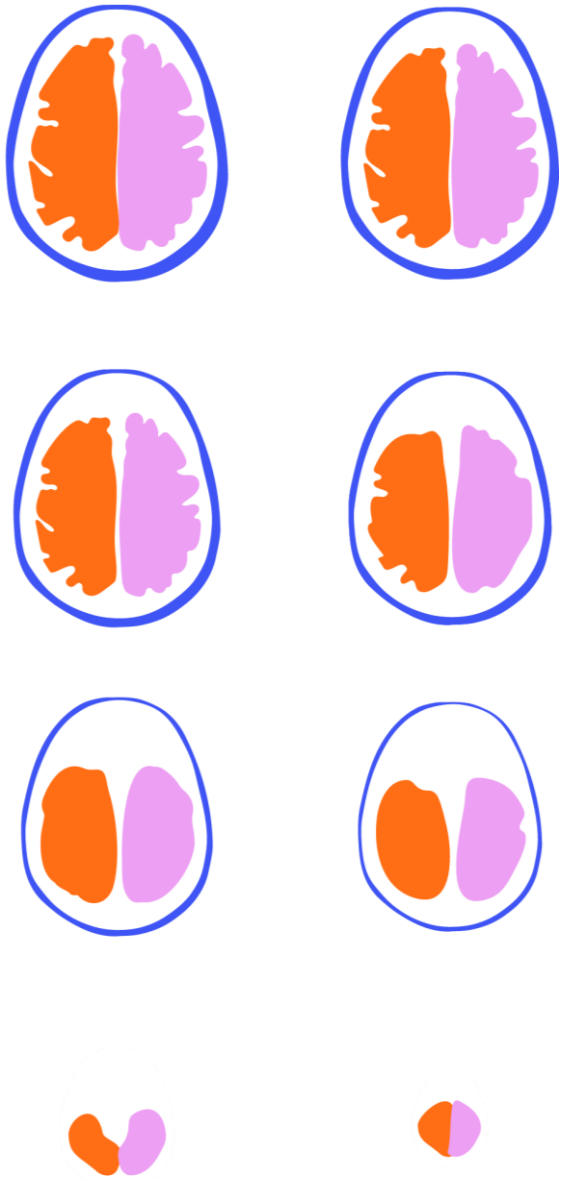
# SAGE-718: Clinical Approach

## Dr. Sam Frank

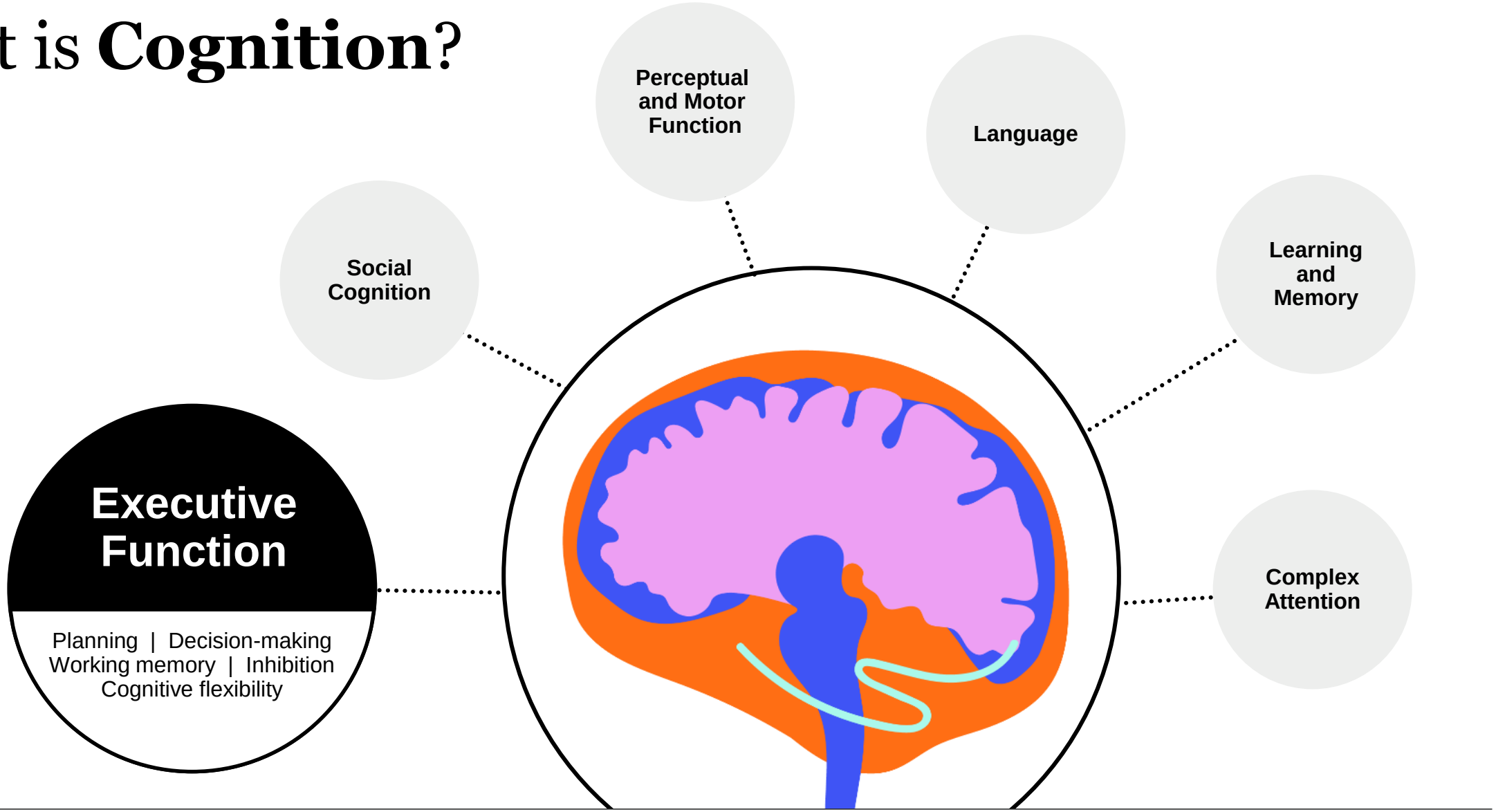
Associate Professor of Neurology,
Beth Israel Deaconess Medical Center

## Seth Rotberg

Patient Advocate (Huntington's Disease)



# What is **Cognition**?

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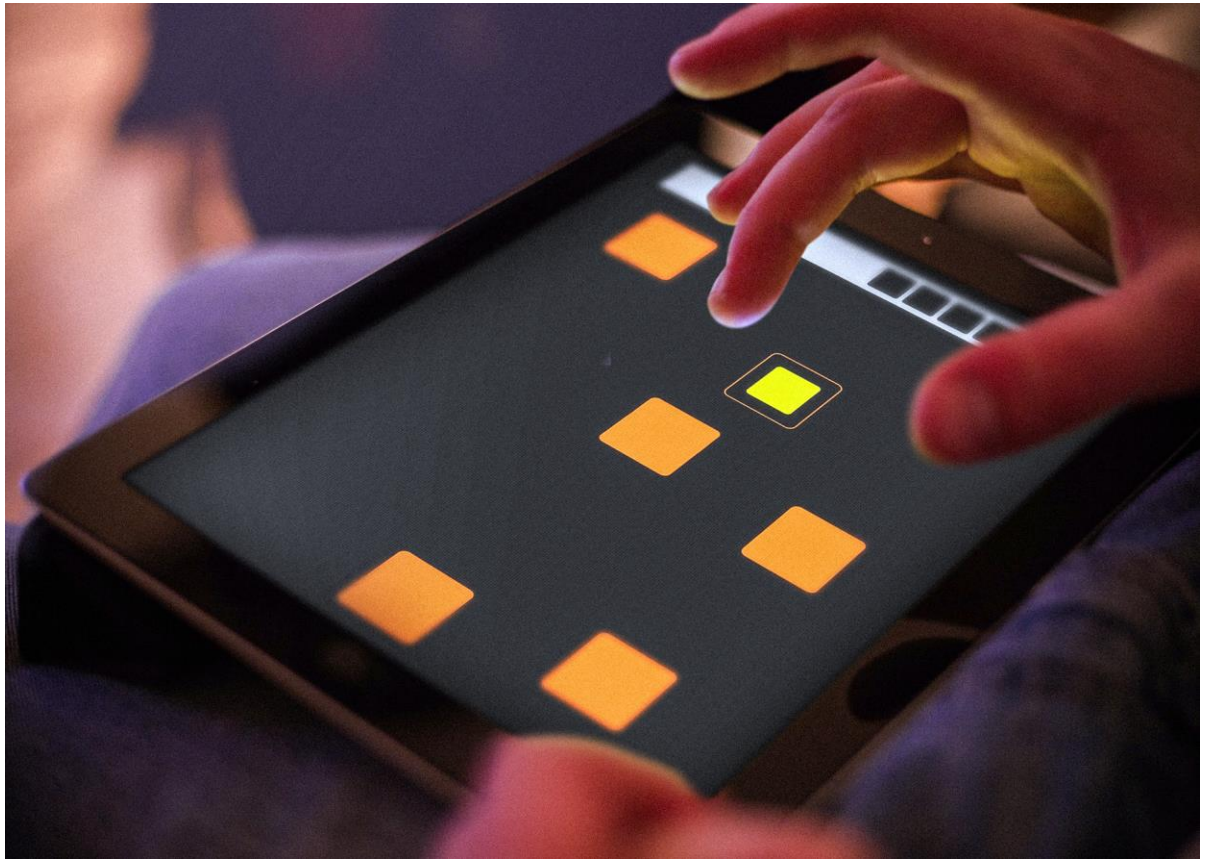
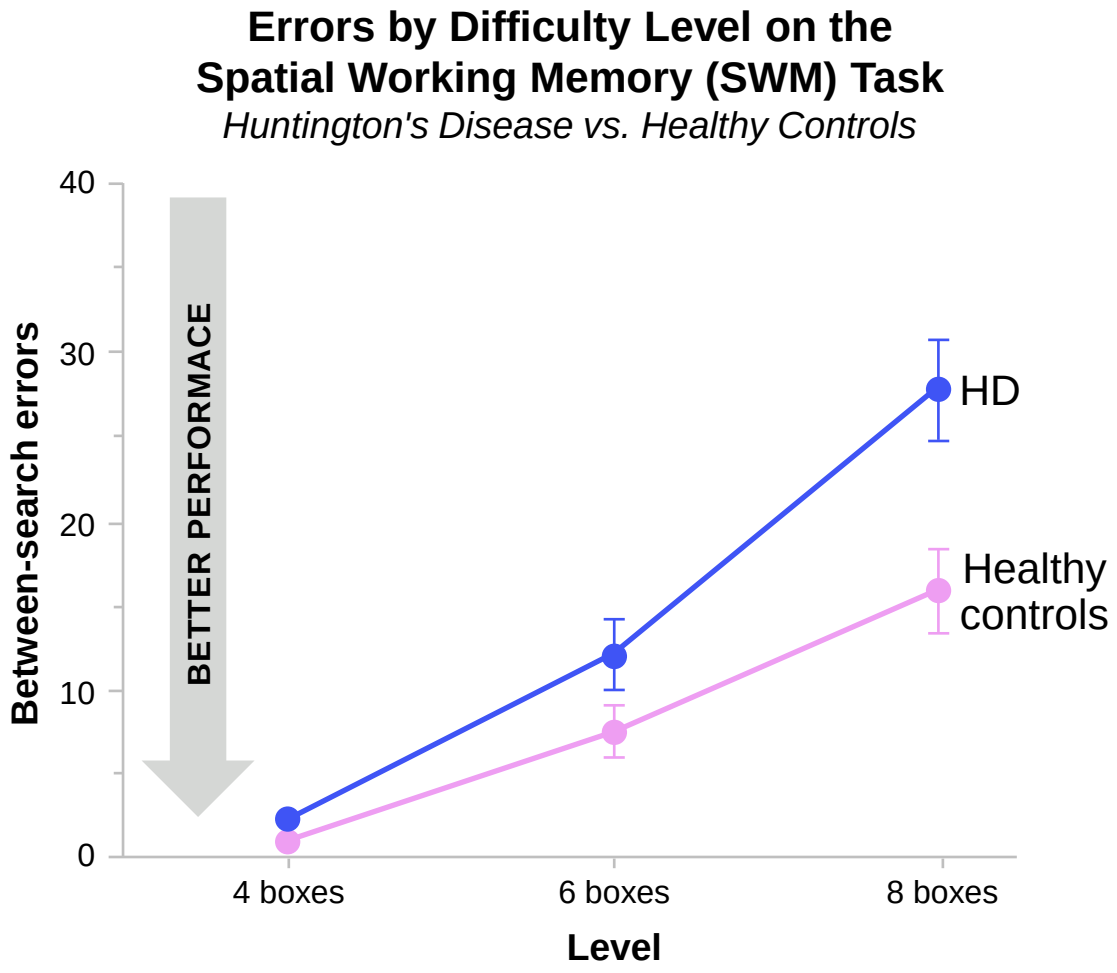
# Executive Functioning: A Closer Look

## Spatial Working Memory (SWM) Task






Lawrence et al, Visual object and visuospatial cognition in Huntington's disease: implications for information processing in corticostriatal circuits, Brain, July 2000.

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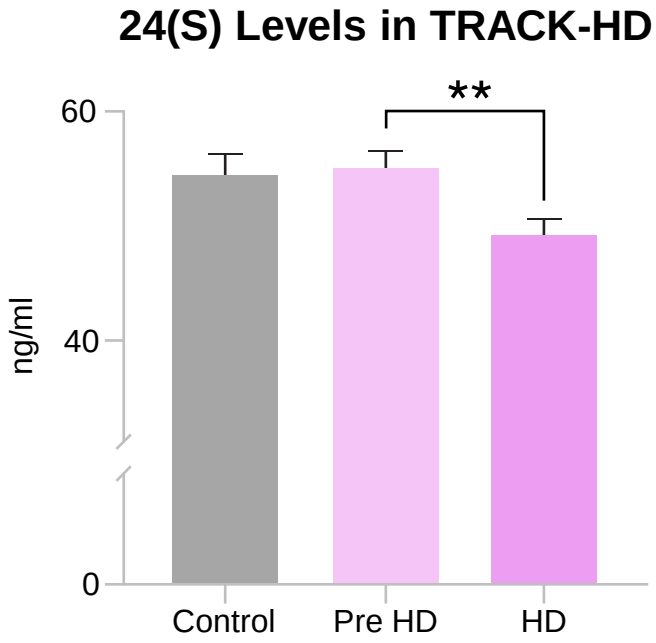
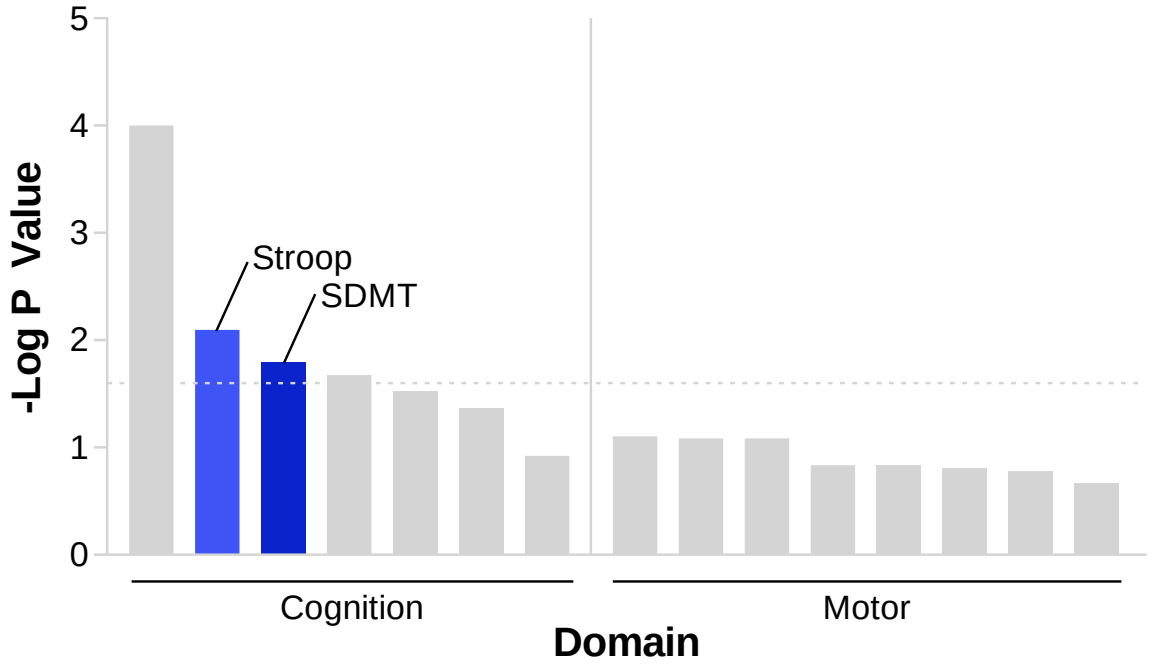
# 24(S)-HC Correlates with Cognitive Impairment in HD

24(S)-HC is significantly reduced in both the plasma and brain of patients with HD

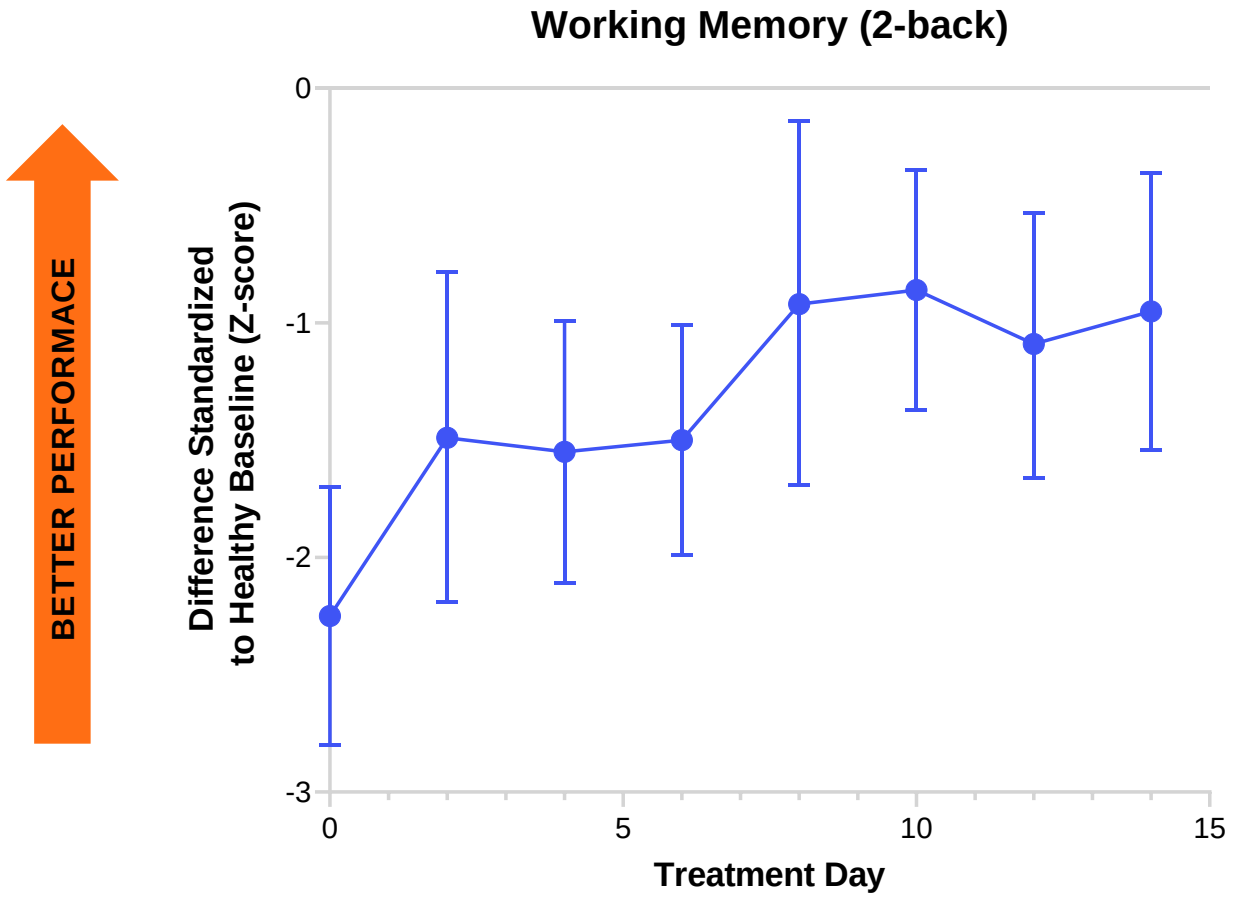



Sage collaboration with CHDI established relationship between 24(S)-HC levels and cognition, but not motor performance




*Watkins et.al., Neuropsychologia, 2000; 38: 1112-1125

# Cognitive Performance in Patients with Early HD Treated with Sage-718 Over 2 Weeks



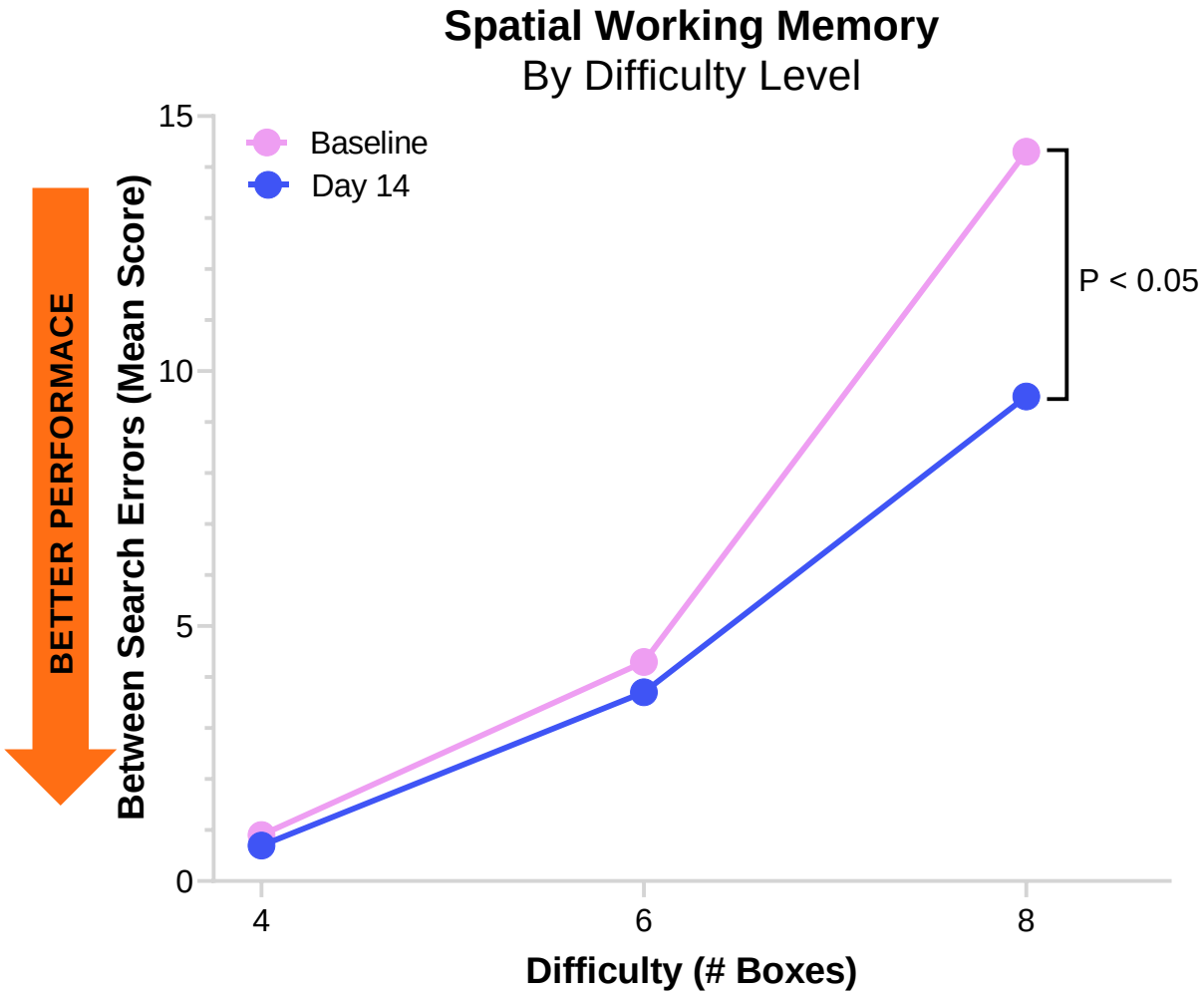

Improvement in HD subjects that approaches performance level of healthy volunteers

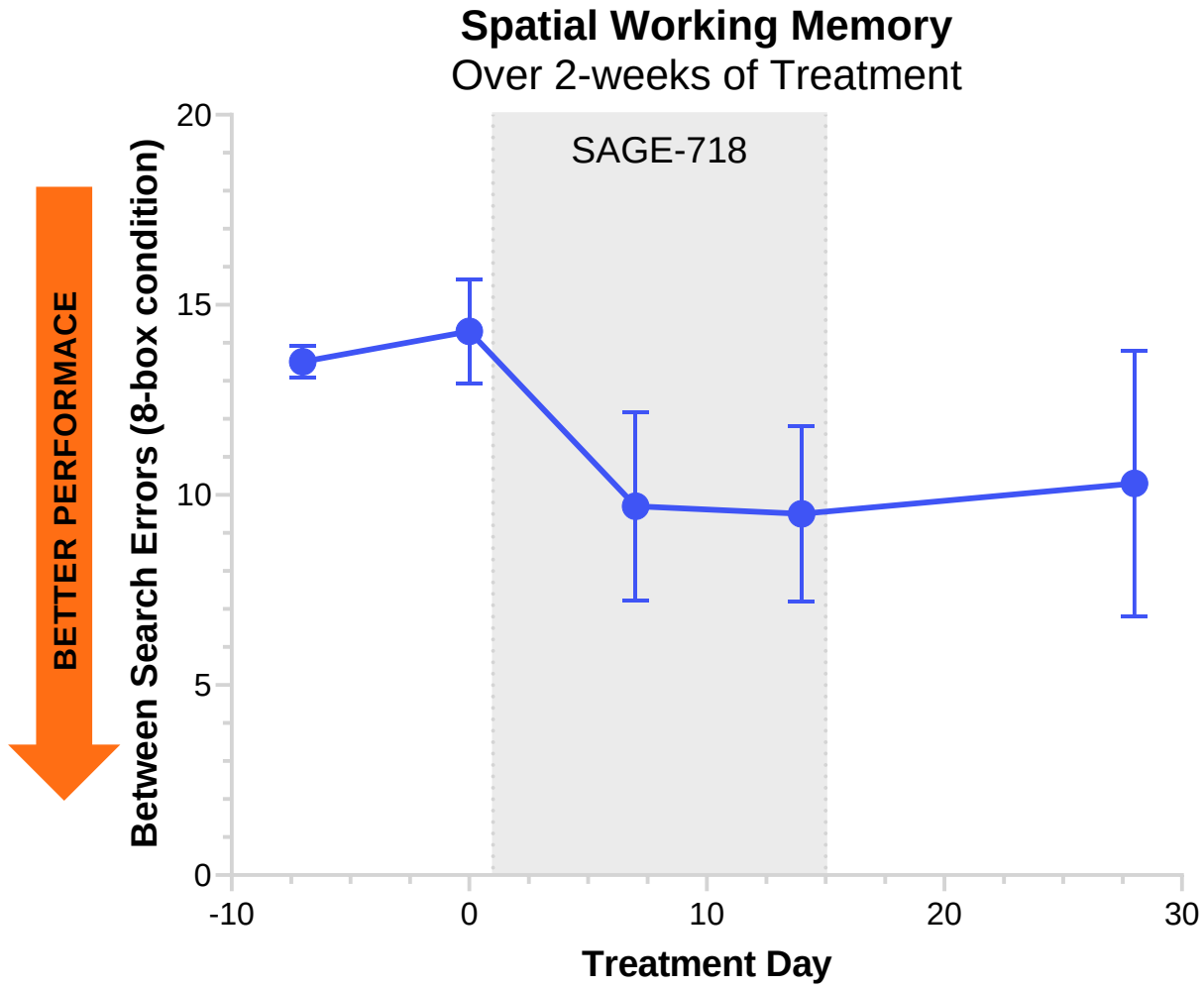
# PD-MCI Data from PARADIGM Study Reinforces and Extends Findings in a New Patient Population

5/5 unique tests of **Executive Functioning** showed improvement over 2 weeks of treatment

3/4 unique tests of **Learning & Memory** showed improvement over 2 weeks of treatment

# Spatial Working Memory (SWM) Task in PARADIGM Study



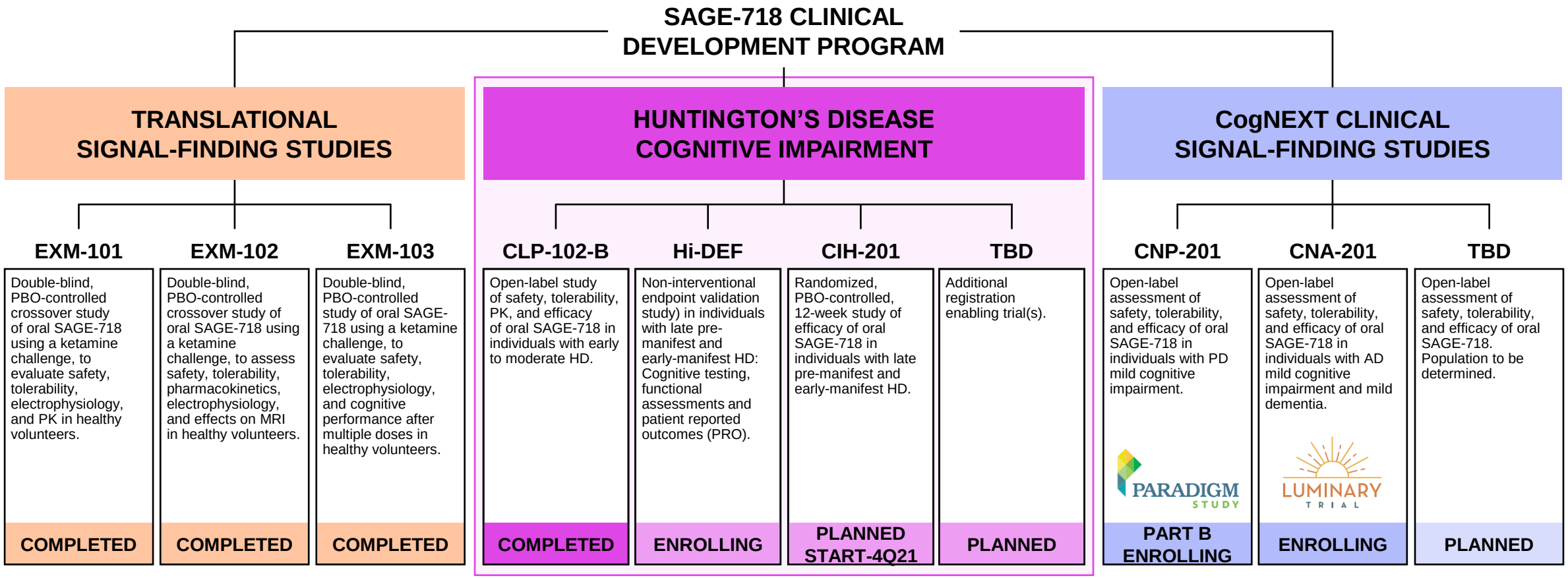



# SAGE-718 Safety Summary

- SAGE-718 was generally well-tolerated within the studies completed to date
- The overall safety data on these studies show:
  - All reported adverse events (AEs) were rated as mild or moderate in severity
    - AEs such as headache and dizziness were more commonly reported
  - No Serious AEs or deaths were reported
  - No safety signal was identified within vital signs, ECGs, or EEGs
  - No trend was noted in the evaluated C-SSRS scores

# SAGE-718's Cognition Platform

*Potential to reshape the cognition landscape*




Abbreviations: HD = Huntington's Disease, PD = Parkinson's Disease, AD = Alzheimer's Disease, PBO = Placebo, PK = Pharmacokinetics, MRI = Magnetic Resonance Imaging

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# Next Steps:

- Extensive engagement with HD community and key stake holders
  - Clear recognition that cognitive impairment is an unmet medical need
  - Understanding of data required to support various stakeholder needs
- We plan to initiate a well powered, placebo-controlled study of cognition and functioning in early HD patients in late 2021
- We have also initiated a non-interventional study to better link cognitive performance to patient reported functioning

| | Early | Mid | Late | 2022 | Expected Milestones |
|---|---|---|---|---|---|
| SAGE-718 | ✓ | | | | Report topline data from PARADIGM in Parkinson's Disease |
| | | ● | | | Initiate PARADIGM (Part B) 4-week dosing |
| | | ● | | | **Initiate non-interventional cognition / function tracking study in Huntington's Disease** |
| | | | ● | | Report topline data from LUMINARY in Alzheimer's Disease |
| | | | ● | | **Initiate placebo-controlled Phase 2 study in Huntington's Disease** |
| | | | | ● | Initiate placebo-controlled Phase 2 study in a second indication pending data from ongoing OL trials |

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# Seeing the brain differently *makes a world of difference*

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