PREFATORY NOTE

This document is the original thesis proposal submitted to the dissertation committee in 2023. The proposal outlined a research program comprising three interconnected meta-analyses examining cross-species translation of cognitive interventions:

- Meta-Analysis 1: Environmental enrichment effects on cognition (rodent and human studies)
- Meta-Analysis 2: Cognitive enhancers (modafinil, methylphenidate, D-amphetamine)
- Meta-Analysis 3: Alzheimer's disease drugs (donepezil, rivastigmine, galantamine)

Following committee review, the scope of the dissertation was refined to focus exclusively on Meta-Analysis 1 (environmental enrichment). This modification was agreed upon with the dissertation committee after the proposal was submitted, and was approved without requiring submission of a revised proposal document.

The rationale for this scope refinement was that the environmental enrichment meta-analysis was sufficiently complex for the dissertation. The development of the Resource Level Scale (RLS) coding system, the three-level meta-analytic framework with robust variance estimation, and the comprehensive moderator analyses required to test the resource mismatch hypothesis warranted a complete and rigorous treatment that would not have been possible with a broader but shallower approach across three intervention domains.

The methodology implemented in the dissertation follows this original proposal exactly. The proposal specified adherence to the analytical framework of Cait et al. (2022, 2024; see reference section of the following document), and all analyses were conducted as specified therein. No methodological deviations from the approved protocol occurred.

The original thesis proposal begins on the following page.

Meta-analytic study of the impact of environmental resources on the translational relevance of laboratory rodents

Greg Fitzgerald[1]
[1]SUNY Albany

Executive Summary

There is a high rate of translational failure in CNS drug development. Identifying the factors that contribute to translational failure is a major priority. I hypothesize that the amount of environmental resources afforded to laboratory rodents impacts their translational relevance. Since CNS drugs and environmental resources are capable of producing a shared set of therapeutic effects via a shared set of neurophysiological mechanisms, the apparent effectiveness of a CNS drug will vary based on the environmental resource level. For rodents to be translationally relevant, their resource level should match that of human clinical trial participants. I contend that the resource level of conventional laboratory housing falls well below that of humans. Preclinical tests will therefore overestimate how effective CNS drug candidates will be in humans. More highly-resourced preclinical environments may reduce the translational failure rate by preventing ineffective CNS drugs from advancing to human trials.

To test this hypothesis, I propose three meta-analyses that address relevant research questions:

1. The first meta-analysis will evaluate whether the observed effectiveness of enrichment interventions is greater in rodents compared to humans. The scope of this analysis will be cognitive outcomes due to short-term enrichment interventions in adults.
2. The second meta-analysis will evaluate whether the cognition-enhancing effects of the stimulant drugs modafinil, methylphenidate, and D-amphetamine are greater in rodents compared to humans. The scope of this analysis will be cognitive outcomes due to acute administration in adults.
3. The third meta-analysis will test whether the procognitive effects of the Alzheimer's disease (AD) drugs donepezil, rivastigmine, and galantamine are greater in rodents compared to humans. The scope of this analysis will be chronic administration in human AD patients and rodent models of AD.

If my hypothesis is supported by these analyses, it would suggest that optimizing laboratory housing conditions could improve the predictive value of preclinical CNS drug studies, ultimately leading to more efficient drug development.

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Introduction and Background

A major goal in neuroscience research is developing effective treatments for central nervous system (CNS) diseases. In service to this goal, animal models are used to characterize basic neurophysiological mechanisms, identify specific disease processes, and develop drug treatments. The most common model organisms in biology research are two rodent species, the house mouse (*Mus musculus*) and the Norway rat (*Rattus norvegicus*).[1] Due to their many neurobiological and behavioral similarities to humans, mice and rats are regarded as translationally relevant for the purpose of testing CNS drugs. Indeed, demonstrating that a drug is effective in a rodent model often presages the start of a human trial.

Despite the ostensibly high translational relevance of laboratory rodents, most of the CNS drugs reported to be effective in rodent models fail to show effectiveness in human trials. This phenomenon is called translational failure. It is costly both in economic terms and in the opportunity cost of not having investigated alternative drugs. In behavioral neuroscience, it is estimated is that ~90% of drugs fail in human trials.[2] While some of these drugs fail for reasons unrelated to their effectiveness (e.g. toxicity, low tolerability), the most common cause of translational failure for CNS drugs is ineffectiveness.[3]

Due to the immense value of effective CNS drugs, even a slight reduction in the rate of translational failure would correspond to a major gain in productivity. It is therefore worth exploring the causes of translational failure to see if any can be mitigated. The most common explanation for translational failure is intrinsic biological differences between humans and preclinical models. While this explanation is always plausible, it is rarely ever verified by follow-up studies. Pinpointing the biological mechanisms responsible for the differential drug response would be not just challenging, but not especially rewarding since the drug's value would have been depreciated by the failed clinical trial.

There is no way to correct for an intrinsic species difference apart from switching to a more translationally relevant animal model. However, this usually isn't feasible. Even though primates would be more translationally relevant than rodents when assessing the effectiveness of CNS drug candidates, rodents may still be preferable for pragmatic, financial, and ethical reasons. Given that rodents remain the primary model for preclinical testing, researchers must focus on optimizing their translational relevance by identifying and addressing any modifiable factors that might be compromising it.

I propose that the laboratory environment –specifically, the cage environment – is an underrated factor that may be negatively impacting the translational relevance of preclinical rodent models. I hypothesize that insufficient environmental resources in conventional laboratory cages compromise the translational relevance of rodents in CNS drug studies. Specifically, I predict that rodents housed in more resource-rich environments will show drug responses more similar to humans, thereby reducing the likelihood of translational failure. Furthermore, I argue that the resource-poor conditions typical of conventional laboratory housing have led to systematic overestimation of the effectiveness of both CNS drugs and environmental enrichment interventions.

Theoretical Framework

Environmental resources and Resource Level

The amount of *resources* provided in laboratory cages may significantly affect the translational relevance of rodent models. These resources include social partners, exercise opportunities, cage space, bedding material, nesting substrate, gnawable objects, and shelters. The neurocognitive effects of providing additional resources have been extensively studied in basic neuroscience through a paradigm called *environmental enrichment*. This approach compares a control group to an experimental group that receives supplementary resources. These additional resources are termed *environmental enrichment* or simply *enrichment*. Studies using this paradigm have advanced our understanding of experience-dependent learning, critical periods in neural development, as well as neurotrophic and neuroprotective signaling mechanisms.[4,5]

Enrichment studies have shown that providing additional resources (enrichment interventions) produces various therapeutic effects, including enhanced cognitive performance in both healthy animals and models of neurodegenerative disorders like Alzheimer's disease (AD).[6–9] These benefits are mediated by well-characterized endogenous mechanisms and are reflected in multiple neural biomarkers associated with brain health and cognitive function. Such biomarkers include increased regional and whole brain volume,[10] increased neuron and synapse density,[11,12] improved synaptic morphology, and elevated neurotrophic factor synthesis/expression.[13,14] These biomarkers are also implicated in the neuroprotective effect of enrichment interventions in rodent models of AD.[15] Beyond slowing cognitive decline, these interventions also reduce pathological hallmarks of AD, including beta amyloid (Aβ) accumulation and proinflammatory cytokine levels.[16]

While enrichment studies typically compare just two states --a control environment and an enriched environment --there exists a vast spectrum of possible environmental configurations, each defined by its unique combination of resources. I will use the term *resource level* to describe these different environmental states. To develop this concept fully, I will first present resource level as a theoretical construct to frame my hypothesis, then refine it into an operationalized definition suitable for quantitative analysis.

Resource level is a composite variable that quantifies the variety and abundance of environmental features available to an animal. In laboratory settings, where experimenters have complete control over cage environments, the measure encompasses both the number of distinct resource categories (e.g., nesting materials, enrichment objects, social partners) and the quantity of each resource provided.

In enrichment studies, resource level is the independent variable. The enriched cage environment has a definitively higher resource level than the control cage environment because it contains all the resources of the control cage, plus additional resources. The control group's environment is thus a strict subset of the enriched group’s environment. This paradigm allows for direct causal inferences about the effects of the added resources. However, comparing environments with different, non-overlapping resource sets is more challenging. For example, when comparing a cage containing an exercise wheel and shelter to one containing a plastic tube and nesting substrate, there is no logical basis for ranking their relative resource levels.

This ambiguity highlights why resource level must be treated differently in theoretical versus empirical contexts. While a general conception of resource level is sufficient for developing my theoretical framework, my quantitative analyses will require a more precise, operationalized definition that permits objective measurement.

CNS drugs and environmental resources and have overlapping mechanisms and therapeutic effects

There is considerable evidence that many CNS drugs share neural mechanisms and therapeutic effects with environmental enrichment. This mechanistic overlap across diverse CNS drugs is noteworthy. For example, research on cholinergic agonist drugs for AD shows that their procognitive and neuroprotective effects require upregulation of neurotrophic factors - the same factors implicated in enrichment's beneficial effects.[16,17]

This convergence suggests that some CNS drugs may achieve their therapeutic effects by recruiting mechanisms normally activated by environmental enrichment. Supporting this hypothesis is the concept of 'enviromimetic' drugs, which are specifically designed to reproduce enrichment's neurobehavioral benefits by targeting these shared mechanistic pathways.[18] Novel CNS drug candidates may similarly engage these enrichment-associated neural mechanisms.

As illustrated in **Figure 1**, both environmental resources and CNS drugs can activate common downstream effectors that mediate therapeutic effects. While CNS drugs are either administer or not, environmental resources can be available across a range of resource levels. Enrichment studies demonstrate that animals with access to more resources typically show higher baseline levels of mechanism activity and therapeutic effects compared to those in resource-poor environments. Consequently, a CNS drug's apparent effectiveness may be diminished in resource-rich conditions due to elevated baseline levels of relevant outcome measures.

Standard preclinical drug testing partially controls for this by using conventional laboratory housing as a standardized environment. However, if the resource level of this standardized environment differs substantially from that of typical human living conditions, it could lead to discrepancies between preclinical and clinical measures of drug effectiveness. A sufficiently large mismatch in resource level between humans and laboratory rodents could contribute to translational failure in CNS drug testing.

Diminishing returns on the effectiveness of additional resources

Before exploring how CNS drug effectiveness is influenced by resource level, it is necessary to discuss how resource level impacts relevant neurocognitive outcomes in the absence of drug intervention. As previously discussed, there is an overall positive relationship between resource level and neurocognitive effects. However, an important aspect of this relationship is that the effect of additional resources becomes less pronounced as more resources are added, a phenomenon called diminishing returns.

The resource-outcome relationship follows a pattern similar to that shown in **Figure 2A**, which summarizes an economic study[19] that compared a resource measure (annual income) with a relevant outcome (self-reported happiness). The effect of additional income shows diminishing returns at higher income levels, culminating in a plateau region where additional income produces a marginal effect on self-reported

happiness. It is reasonable to expect that this pattern of diminishing returns is a general feature of all resource-outcome relationships, including those involving laboratory rodents.

Figure 2B generalizes this concept to the laboratory context, plotting resource level against neurobehavioral outcomes. The x-axis represents the resource level, spanning from a theoretical minimum to a theoretical maximum. The y-axis represents neurocognitive measures, ranging from 0 (minimum possible activity/performance) to 100 (maximum possible activity/performance). The theoretical relationship shown in **Figure 2B** illustrate the diminishing returns principle. The impact of additional resources depends on the current resource level. **Figure 2C** visualizes the declining effectiveness of additional resources as resource level increases.

When analyzing outcomes across different resource levels, an interesting phenomenon can occur. Even though the overall relationship between resources and outcomes is a non-linear curve with diminishing returns, it is possible to observe linear effects.[20] This typically happens when the range of resource levels being studied represents only a small segment of the complete curve. As illustrated in **Figure 2D**, examining a narrow range of resource levels yields what appears to be a linear relationship. This has important implications for interpreting studies that examine a small range of resource levels.

Diminishing returns on drug effectiveness at higher resource levels

The pattern of diminishing returns with environmental resources is also characteristic of drug effects, as shown in the dose-response curve in **Figure 3A**. This similarity in response patterns aligns with the hypothesis that both environmental resources and CNS drugs act through overlapping mechanistic pathways.

Given that environmental resources and CNS drugs influence shared neural mechanisms and therapeutic outcomes, the effectiveness of a CNS drug is likely to vary across resource levels. **Figure 3B** illustrates this relationship using a hypothetical preclinical study of a CNS drug candidate, revealing that there are diminishing returns on the relative effect of the drug at higher resource levels.

Figure 3C quantifies this relationship at four resource levels. At the lowest of these resource levels, drug administration produces a 100% increase in the outcome measure. However, in more well-resourced environments, there is a marked decline in the relative effect of drug administration. At the highest resource level shown, the drug produces only a 1.3% improvement over baseline. This trend of declining drug effectiveness at higher resource levels is further visualized in **Figure 3D**.

Depending on the environmental conditions, the same drug can yield markedly different statistical outcomes. To demonstrate this, consider a hypothetical study comparing control and drug treatment groups (n=25/group, SD=10/group). **Figure 4A** shows statistical analyses at three different resource levels.

There is an observable decline in standardized effect size measures at higher resource levels. This is visualized in **Figure 4B**, which plots Cohen's *d* across resource levels. The negative correlation aligns with empirical observations that preclinical drug studies often report larger effect sizes than subsequent human trials,[21] though other

factors like publication bias[22] and inadequate randomization[23] also contribute to this discrepancy.

Beyond effect size, resource level can also impact the determination of statistical significance. **Figure 4C** illustrates how p-values systematically increase with resource level, eventually crossing the significance threshold. This relationship is depicted in **Figure 4D**, where a vertical line marks the resource level above which the drug effect ceases to be statistically significant.

This analysis indicates that the effectiveness of a CNS drug will vary systematically with resource level, showing larger effects at lower resource levels. It raises a concerning possibility: if humans typically live at higher resource levels than laboratory rodents, this environmental mismatch could generate false positive results in preclinical testing. Since translational failure typically manifests as false positives (drugs that work in preclinical trials but fail in humans), this model suggests that testing drugs in under-resourced laboratory environments may contribute to the problem.

Conventional laboratory housing is likely under-resourced relative to the typical human environment

Conventional laboratory housing refers to a standardized environment for conducting biomedical research involving rodents, including preclinical tests of CNS drug candidates. This environment typically consists of a shoebox-sized cage with basic necessities: bedding, food, water, cage-mates, and sometimes nesting materials. While specific laboratory housing regulations vary by country and institution, this basic resource configuration remains remarkably consistent.

Several lines of evidence suggest these conventional housing conditions may be under-resourced relative to human environments. Most notably, there is no historical evidence that these standards were ever optimized to match human resource levels. Rather, the historical record indicates that housing standards evolved primarily from economic constraints, researcher convenience, and basic animal welfare considerations. Of these factors, only welfare concerns would have motivated the inclusion of additional resources, while cost and convenience considerations would have discouraged additional inclusions.

Figure 5A presents a theoretical mapping of rodent housing conditions and human environments along the resource level axis. In this framework, conventional cages (**Figure 5B**) are located farthest left along the curve, indicating lower resource levels. The “enriched cages” typical of enrichment studies (**Figure 5C**) are placed at a higher resource level, since they contain all the resources of conventional cage along with additional inclusions.

Further right along the curve, there is a label for both "superenriched" (**Figure 5D**) and naturalistic/semi-naturalistic housing conditions (**Figure 5E**). These environments include substantially more resources than typical “enriched cages,” often incorporating features of the natural habitats.[24] While superenriched, naturalistic, and semi-naturalistic environments show considerable variation in implementation, they consistently provide far more resources than typical enrichment study conditions.[25–27] In light of how well-resourced these conditions are, I located the resource level for such environments near the plateau region of the curve. However, few studies have examined the

neurobehavioral effects of these highly-resourced environments,[11,25,27,28] and none have systematically compared all three conditions (conventional, enriched, and superenriched/naturalistic) according to neurocognitive outcomes.

The placement of humans near the superenriched/naturalistic level on this scale requires justification. The relationship between resources and outcomes typically shows a plateau region where additional resources yield only marginal returns. In the context of enrichment interventions, this manifests as reduced effectiveness of interventions at higher resource levels. This pattern aligns with human studies, in which enrichment interventions show minimal effects on key outcomes such as cognitive enhancement or attenuated cognitive decline.[29] This contrasts sharply with rodent studies, which consistently demonstrate both cognitive enhancement and attenuated cognitive decline following enrichment interventions. While the practical limitations of human experiments mean enrichment interventions are generally less intensive than those used in rodent studies, this is not generally treated as a strong argument against applying rodent enrichment findings to humans.[30,31] An alternative explanation for the greater apparent effectiveness of enrichment interventions in rodents is that most humans live at a higher resource level than their conventionally housed rodent counterparts.

The differential effectiveness of enrichment interventions across species is mirrored by the differential effectiveness of CNS drugs. Whereas the extent of pharmacological cognitive enhancement in humans is so marginal as to be debatably real, there are many rodent studies that report significantly improved cognitive performance following drug administration.[32,33] This also applies to drug studies involving rodent models of AD, which regularly show cognitive benefits well above what is observed in clinical trials of human AD patients. While there are many reasons why CNS drugs may seem to be more effective in laboratory rodents than in humans, the mismatch in baseline resource levels between laboratory rodents and humans may play an important role. This possibility motivates my investigation into whether conventional laboratory housing might compromise the translational relevance of rodent models in CNS drug development.

The Resource Level Scale is an operationalized version of the resource level variable

While the resource level concept is useful for developing a theoretical model, it isn't suitable for quantitative analysis. I will use an operationalized version called the *Resource Level Scale* (RLS), adapted from Cait et al (2024).[20] The RLS classifies cage resources into 11 distinct *resource categories*: (1) burrowing substrates, (2) chewing/gnawing materials, (3) increased environmental complexity, (4) foraging opportunities, (5) fresh plant matter or odors, (6) nesting material, (7) shelters/nest boxes/hiding places, (8) additional space, (9) sweet or high fat food, (10) wheels, and (11) social partners.

A cage's RLS score (0-11) represents the number of resource categories present. This score will serve as the independent variable in my statistical analyses. For an example of RLS scoring, consider a conventional laboratory cage (**Figure 5B**) with additional nesting material. This cage's RLS score would be 1. Now consider a cage with additional space, an exercise wheel, additional cage-mates, toys, and shelters. This cage's RLS score would be 5.

Following RLS analysis, one can undertake a more granular analysis. For each resource category, one can perform an intra-category analysis to examine how quantitative variations in that resource category affect outcomes. For instance, increasing the number of cage-mates represents an intra-category increase in social resources, even though the RLS score would remain the same. In their meta-analysis, Cait et al (2024) found that increasing the total number of resource categories (RLS score) had a greater impact on morbidity measures than increasing the quantity of an existing resource category.

Several resource categories require a benchmark comparison to determine whether the RLS score should be incremented. An example is “additional cage space” -- to determine if a cage has additional space, we need a reference point. Following Cait et al (2024), I will use the minimum housing standards for the United States --as outlined in *The Guide For the Care and Use of Laboratory Animals*[34] --as the reference point for scoring RSL. For example, any cage exceeding the minimum dimensions described in *The Guide* will be scored as having "additional space" in the RLS framework. For all intents and purposes, the minimum housing standards described in The Guide are identical to what I previously described as conventional laboratory housing.

In an earlier section, I discussed the challenge of comparing cage environments where neither cage's resources is a strict subset of the other. This issue also exists within the RLS framework, which may classify highly disparate environments using the same RLS score. Such heterogeneity can undermine the validity of a measure. However, analyzing a large number of studies mitigates this potential issue. As long as there is diversity in the combinations of resource categories that comprise each RSL score, any additional variance will be random rather than systematic. As a consequence, it is possible to undertake statistical comparisons across diverse housing conditions.

Main Hypothesis

Based on the theoretical framework developed above, I hypothesize that insufficient environmental resources in conventional laboratory housing reduces the translational relevance of rodent models in CNS drug development. Specifically, I propose that the mismatch between laboratory rodent and human resource levels leads to systematic overestimation of drug effectiveness in preclinical studies, contributing to translational failure.

Research Questions

Theoretical Validation

Before addressing my main hypothesis, I will examine a key assumption of my theoretical framework: environmental resources show diminishing cognitive benefits at higher resource levels. Hence:

> **Research Question 1**: Is there a systematic relationship between resource level and cognitive performance in laboratory rodents? If so, does this relationship indicate diminishing returns at higher resource levels? To what extent does this relationship vary by:
> A. the number of distinct resource categories (RLS score)
> B. the quantity of resources with individual resource categories (e.g. more cage-mates, more cage space).

Next, I will examine an implication of my claim that the human resource level exceeds that of conventionally housed laboratory rodents. If this claim holds true, it follows that additional resources will produce larger cognitive effects in laboratory rodents compared to humans. Hence:

> **Research Question 2**: Do comparable enrichment interventions (e.g. exercise, social engagement) show larger cognitive effects in conventionally housed laboratory rodents compared to humans?

Main Hypothesis Testing

I will then directly test my main hypothesis by comparing the effectiveness of two classes of CNS drugs on cognitive outcomes in humans and conventionally housed rodents. If my hypothesis is correct, the effectiveness of these CNS drugs will be greater in laboratory rodents.

> **Research Question 3**: Do cognition-enhancing drugs produce larger cognitive effects in conventionally housed laboratory rodents compared to humans?

> **Research Question 4**: Do AD drug treatments produce larger effects in conventionally housed laboratory rodents compared to humans?

To address these research questions, I propose three meta-analyses:

1. Meta-Analysis 1 will address Research Questions 1-2 by evaluating the cognitive effects of additional resources in both rodents and humans.

2. Meta-Analysis 2 will address Research Question 3 by comparing the effectiveness of three well-studied cognitive enhancers (modafinil, methylphenidate, D-amphetamine) on cognitive outcomes in humans and rodents.
3. Meta-Analysis 3 will address Research Question 4 by comparing the effectiveness of three AD drugs (donepezil, rivastigmine, galantamine) on cognitive outcomes in humans and rodents.

Methods and Protocols

Overview

This thesis will consist of three meta-analyses examining the relationship between environmental resources and translational relevance in CNS drug development. Each analysis will follow standardized systematic review protocols (PRISMA guidelines) and employ statistical methods adapted from Cait et al. (2024).

General Methodological Framework

The following elements apply to all three meta-analyses. In almost all cases, my proposed methodology reflects what was done in Cait et al (2024).

Pre-registration and documentation

- Once approved by the committee, all meta-analysis protocols will be pre-registered on --PROSPERO (National Institute for Health Research) and the SUNY Albany Scholar's Archive repository.
- Maintain a public log of all analytical decisions
- Document all deviations from pre-registered protocols
- Produce an annotated record of all statistical procedures using RMarkdown syntax.

Literature search strategy

- Systematic searches will use the following databases: PubMed, Scopus, and PsychNet.
- Additional citations will be sourced from relevant review article reference lists
- Search strings will be calibrated to each meta-analysis's specific scope
- No date restrictions on searches

Study selection criteria

- *Inclusion criteria*
  - Population: Adult rodents (mice/rats) and humans
  - Interventions: Environmental enrichment, cognition-enhancing drugs, or AD treatments
  - Outcomes: Validated cognitive performance measures
  - Study design: Experimental studies with sufficient data for calculating effect size
- Selection process: Records will be aggregated in Microsoft Excel, then screened using DistillerSR software. Studies that meet the aforementioned criteria will undergo data extraction.
- Maintain documented rationale for all inclusion/exclusion decisions

Data extraction

- For included studies, extract the following data:
  - Study characteristics
  - Population characteristics
  - Intervention
  - Description of environmental resources
  - Outcome measures

- Indications of study quality

Assessment of study quality

- *Risk of Bias estimate*
  - For animal studies, I will use the SYRCLE (SYstematic Review Centre for Laboratory animal Experimentation) Risk of Bias tools.[35]
  - For human studies, I will use the Cochrane risk-of-bias tool for randomized trials (RoB 2) checklist.[36]
- *GRADE assessment of study quality*[37]
- Assessment of publication bias using funnel plots Egger's test

Statistical analysis

- Primary analyses
  - Meta-analysis with random effects model
  - Effect size measurement using Hedge's g
  - Heterogeneity assessment using I^2 statistic and Q test
- Secondary analyses
  - Subgroup analyses for specific categorical variables (species, drug type, cognitive domain)
  - Moderator analysis using meta-regression for all other independent variables
  - Sensitivity analyses to test the robustness of the results against alternative assumptions, model characteristics, and study inclusion criteria.
- I will reproduce the statistical procedures of Cait et al (2024) to demonstrate my understanding of the software implementation of these meta-analyses.

Reporting

- All results will be reported according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines,[38] which are considered the gold standard for ensuring clear and comprehensive reporting of methods and results.

The specific protocols for each meta-analysis are presented in the following sections.

Meta-Analysis 1: Characterizing the effects of resource level on cognitive performance in rodents, and comparing the effectiveness of enrichment interventions in humans and laboratory rodents

Background

In modern developed nations, meaningful improvement in adult cognitive capabilities through environmental interventions is considered difficult to achieve.[39,40] While rodent studies frequently report significant cognitive enhancement from environmental enrichment, the relative magnitude of these effects across species has never been systematically compared

Hypothesis

I hypothesize that conventionally housed laboratory rodents will show larger cognitive improvements from enrichment interventions than humans receiving comparable interventions. I predict:

- Larger effect sizes in rodent studies compared to human studies.
- Overall positive correlation between resource level and cognitive performance
- Diminishing cognitive effects of additional resources at higher resource levels
- Greater cognitive improvements from providing a new resource category vs increasing the quantity of resources of an existing category.

Significance

This analysis will test two key aspects of the theoretical model. First, by comparing enrichment's effectiveness across species, we can test the prediction that conventionally-housed rodents will show greater cognitive improvements in response to enrichment interventions when compared to humans. If enrichment interventions produce systematically larger effects in laboratory rodents, this would indicate that conventionally-housed rodents may not be translationally relevant for the purpose of assessing the cognitive effects of enrichment interventions.

Second, by examining how resource levels modulate cognitive performance in rodents, we can test our model's prediction of diminishing returns. Observing this relationship would strengthen the theoretical foundation for our subsequent meta-analyses examining drug effects. Depending on whether enrichment-induced cognitive enhancement shows diminishing returns at higher resource levels, the result will inform the interpretation of the other two meta-analyses.

Population

LABORATORY RODENTS	HUMAN PARTICIPANTS
Inclusion criteria	Inclusion criteria

• SPECIES: mouse (Mus musculus) or rat (Rattus norvegicus)
  ○ Exclusion criteria: transgenic, chimeric, disease model
• STRAIN:
  ○ Exclusion criteria: strain information is absent or ambiguous
• AGE
  ○ For mice, >8 weeks old at start of intervention
  ○ For rats, >10 weeks old at start of intervention
  ○ Exclusion criteria: age of testing not documented
• SEX
  ○ male or female
  ○ Exclusion criteria: sex not specified
	• AGE
	  ○ Must be 18-65 years old
	  ○ Exclusion criteria: age of testing not documented
	• SEX
	  ○ male or female
	  ○ Exclusion criteria: sex not specified
	
	Exclusion criteria:
	• HISTORY OF DIAGNOSED COGNITIVE IMPAIRMENT

Intervention: Environmental resources

LABORATORY RODENTS	HUMAN PARTICIPANTS
1. Resource categories Inclusion criteria: • Sufficiently detailed description of each resource category implemented • Quantity of each resource category implemented • Duration of resource availability 2. Intra-category resources Inclusion criteria: • Sufficiently detailed assessment of added resources • Duration of resource availability	Enrichment interventions Inclusion criteria • Specifies type of intervention (Cognitive training/stimulation, physical activity, social engagement, etc) • Sufficiently detailed description of intervention procedures • Specifies duration of intervention • Specifies the session length, if relevant • Specifies the session frequency, if relevant

Comparator: Standard conditions

LABORATORY RODENTS	HUMAN PARTICIPANTS
Resources supplied to the to the control group/condition (if not specified, assume the resource level of conventional	Human adults in environmental contexts typical of modern developed nations.

laboratory housing)	

Outcomes: Cognitive performance on comparable tests

COGNITIVE DOMAIN	LABORATORY RODENTS	HUMAN PARTICIPANTS
	TESTS	TESTS
Learning & Memory (Spatial)	►Morris water maze ►Barnes maze	►Virtual Morris water maze ►Virtual reality navigation ►Corsi block-tapping test
Learning & Memory (Recognition)	►Novel object recognition ►Novel object location	►Face recognition tests ►Pattern recognition memory ►Paired associates learning
Working Memory	►Y-maze alternation ►T-maze alternation ►Spontaneous alternation ►Radial arm maze	►N-back task ►Digit span task ►Letter-number sequencing
Executive Function/ Attention	►5-choice serial reaction time task ►5-choice continuous performance task ►Attentional set-shift task	►Wisconsin card sorting test ►Trail making test ►Stroop test ►Continuous performance test ►Psychomotor vigilance task ►Sustained attention to response test ►Digit vigilance test
Associative Learning	►Contextual fear conditioning ►Cued fear conditioning ►Inhibitory avoidance	►Paired associate learning ►Conditional associative learning ►Probabilistic learning tasks

Search strings

LABORATORY RODENTS	HUMAN PARTICIPANTS
(murinae OR mice OR mouse OR Mus OR rodent* OR murine OR rat OR rats) AND (cage OR caging OR caged OR cages OR "enrich* environment*" OR "environmental enrichment" OR "naturalistic environment" OR "voluntary wheel running" OR "running wheel" OR "wheel running" OR "running disk" OR "physical activity") AND	("environmental enrichment" OR "cognitive enrichment" OR "cognitive training" OR "cognitive stimulation" OR "cognitive intervention" OR "cognitive activity" OR "mental activity" OR "mental stimulation" OR "mental training" OR "physical activity" OR "exercise" OR "social interaction" OR "social activity" OR "social enrichment") AND (human* OR adult* OR participant* OR subject* OR patient*)

("morris water*" OR "novel object*" OR "operant*" OR "y-maze" OR "y maze" OR "t-maze" OR "t maze" OR "alternation" OR "4-arm maze" OR "4-chamber maze" OR "plus-maze" OR "plus maze" OR "+-maze" OR "+ maze" OR "inhibitory avoidance" OR "contextual fear*" OR "cued fear*" OR "radial arm*" OR "radial maze" OR "barnes" OR "non-match*" OR "5-choice*")	AND ("virtual morris water maze" OR "virtual water maze" OR "virtual navigation" OR "virtual reality navigation" OR "corsi block" OR "corsi test" OR "corsi span" OR "block tapping" OR "face recognition" OR "pattern recognition memory" OR "paired associate*" OR "paired learning" OR "n-back" OR "nback" OR "working memory task" OR "digit span" OR "number span" OR "letter-number sequencing" OR "wisconsin card sort*" OR "wcst" OR "trail making" OR "tmt" OR "stroop" OR "continuous performance test" OR "cpt" OR "psychomotor vigilance" OR "pvt" OR "sustained attention to response" OR "sart" OR "digit vigilance" OR "conditional associative learning" OR "probabilistic learning") ("performance" OR "cognition" OR "cognitive" OR "learning" OR "memory" OR "attention" OR "executive function" OR "processing speed") NOT ("child*"[Title] OR "adolescent*"[Title] OR "infant*"[Title] OR "animal*"[Title] OR "mice"[Title] OR "mouse"[Title] OR "rat"[Title] OR "rats"[Title])

Meta-Analysis 2: Comparing the magnitude of cognitive enhancement due to acute administration of three putative cognitive enhancers (modafinil, methylphenidate, D-amphetamine) in humans and laboratory rodents

Background

Pharmacological enhancement of cognitive function in healthy adults is known to be difficult to achieve.[40] An extensive analysis by Roberts et al. (2020) found limited evidence for meaningful cognitive enhancement from the stimulant medications that are considered to be among the most potent cognitive enhancers: modafinil, methylphenidate, D-amphetamine. In contrast, rodent studies regularly report significant cognitive improvements as a result administration of these (and other) drugs. Despite this apparent discrepancy, there has yet to be a systematic comparison of the effectiveness of these drugs across species.

Hypothesis

I hypothesize that conventionally-housed laboratory rodents will show larger cognitive improvements from acute stimulant administration than humans receiving equivalent doses. I predict that there will be larger effect sizes in rodent studies compared to human studies for all three drugs, across all cognitive domains tested.

Significance

This analysis will test whether the apparent effectiveness of cognition-enhancing drugs varies systematically between species. If these stimulant drugs show consistently larger effects in rodents, this would support my hypothesis that conventional laboratory housing may be under-resourced relative to the typical human environment.

Population

LABORATORY RODENTS	HUMAN PARTICIPANTS

Inclusion criteria
• SPECIES: mouse (Mus musculus) or rat (Rattus norvegicus)
  ○ Exclusion criteria: transgenic, chimeric, disease model
• STRAIN:
  ○ Exclusion criteria: strain information is absent or ambiguous
• AGE
  ○ For mice, >8 weeks old at start of intervention
	Inclusion criteria
	• AGE
	  ○ Must be 18-65 years old
	  ○ Exclusion criteria: age of testing not documented
	• SEX
	  ○ male or female
	  ○ Exclusion criteria: sex not specified
	
	Exclusion criteria:
	• HISTORY OF DIAGNOSED COGNITIVE IMPAIRMENT

○ For rats, >10 weeks old at start of intervention ○ Exclusion criteria: age of testing not documented • SEX ○ male or female ○ Exclusion criteria: sex not specified	• PRIOR HISTORY OF DRUG EXPOSURE

Intervention: Acute drug administration

LABORATORY RODENTS	HUMAN PARTICIPANTS
Inclusion Criteria: • DRUG: Modafinil, Methylphenidate, D-Amphetamine • DOSE (Mg/Kg) • TREATMENT DURATION/FREQUENCY • ROUTE OF ADMINISTRATION • POST-ADMINISTRATION PRE-TESTING INTERVAL	Inclusion criteria: • DRUG: modafinil, methylphenidate, D-amphetamine • DOSE (mg/kg) • TREATMENT DURATION/FREQUENCY • ROUTE OF ADMINISTRATION • POST-ADMINISTRATION PRE-TESTING INTERVAL

Comparator: Placebo/vehicle treatment

The analysis will use the Comparator table from Meta-Analysis 1.

Outcomes: Cognitive performance on comparable tests

The analysis will use the Outcomes table from Meta-Analysis 1.

Search strings

LABORATORY RODENTS	HUMAN PARTICIPANTS
(murinae OR mice OR mouse OR Mus OR rodent* OR murine OR rat OR rats) AND (modafinil OR methylphenidate OR "methyl phenidate" OR ritalin OR dexamfetamine OR dextroamphetamine OR "d-amphetamine" OR "d amphetamine" OR dexamphetamine) AND ("morris water*" OR "novel object*" OR "operant*" OR "y-maze" OR "y maze" OR	(human* OR adult* OR participant* OR subject* OR patient*) AND (modafinil OR methylphenidate OR "methyl phenidate" OR ritalin OR dexamfetamine OR dextroamphetamine OR "d-amphetamine" OR "d amphetamine" OR dexamphetamine) AND

"t-maze" OR "t maze" OR "alternation" OR "4-arm maze" OR "4-chamber maze" OR "plus-maze" OR "plus maze" OR "+-maze" OR "+ maze" OR "inhibitory avoidance" OR "contextual fear*" OR "cued fear*" OR "radial arm*" OR "radial maze" OR "barnes" OR "non-match*" OR "5-choice*")	("virtual morris water maze" OR "virtual water maze" OR "virtual navigation" OR "virtual reality navigation" OR "corsi block" OR "corsi test" OR "corsi span" OR "block tapping" OR "face recognition" OR "pattern recognition memory" OR "paired associate*" OR "paired learning" OR "n-back" OR "nback" OR "working memory task" OR "digit span" OR "number span" OR "letter-number sequencing" OR "wisconsin card sort*" OR "wcst" OR "trail making" OR "tmt" OR "stroop" OR "continuous performance test" OR "cpt" OR "psychomotor vigilance" OR "pvt" OR "sustained attention to response" OR "sart" OR "digit vigilance" OR "conditional associative learning" OR "probabilistic learning") AND ("cognitive" OR "cognition" OR "performance" OR "memory" OR "attention" OR "learning") NOT ("child*"[Title] OR "adolescent*"[Title] OR "infant*"[Title] OR "adhd"[Title] OR "addiction"[Title] OR "dependence"[Title])

Meta-Analysis 3: Comparing the magnitude of cognitive enhancement due to chronic administration of Alzheimer's disease drugs (donepezil, rivastigmine, galantamine) in humans and laboratory rodents

Background

AD is the most common neurodegenerative disorder.[41] There have been many examples of drug candidates that appeared effective in rodent models but subsequently failed in clinical trials.[42] The cholinergic drugs (donepezil, rivastigmine, galantamine) are among the few approved treatments to have been tested in both human AD patients and rodent models of AD. As a result, these drugs afford an opportunity to compare therapeutic effectiveness across species. While these drugs show modest attenuation of cognitive decline in human patients, rodent studies often report not simply greater attenuation but wholesale rescue of cognitive deficits. Despite this apparent discrepancy, there has yet to be a systematic comparison of the effectiveness of these drugs across species.

Hypothesis

I hypothesize that conventionally-housed laboratory rodents will demonstrate larger cognitive benefits –both in spared cognitive losses and cognitive improvement – from chronic administration of these cholinergic AD drugs compared to human patients. I predict that there will be larger effect sizes in rodent studies compared to human studies for all three drugs, across all cognitive domains tested.

Significance

This analysis examines whether the therapeutic effectiveness of AD drugs varies systematically between species. If cholinergic drugs demonstrate consistently larger effects in rodent models, this would support my hypothesis that conventional laboratory housing may be under-resourced relative to the typical human environment.

Population

LABORATORY RODENT MODELS OF AD	**HUMAN AD PATIENTS**

Inclusion criteria
• SPECIES: mouse (Mus musculus) or rat (Rattus norvegicus)
• STRAIN:
  ○ Exclusion criteria: strain information is absent or ambiguous
• AD MODEL TYPE
  ○ If transgenic, specify genotype
• AGE
	Inclusion criteria
	• AGE
	  ○ Must be >65 years old
	  ○ Exclusion criteria: age of testing not documented
	• SEX
	  ○ male or female
	  ○ Exclusion criteria: sex not specified
	• DISEASE SEVERITY

○ For mice, >8 weeks old at start of intervention ○ For rats, >10 weeks old at start of intervention ○ Exclusion criteria: age of testing not documented • SEX ○ male or female ○ Exclusion criteria: sex not specified	• Specify the level of cognitive impairment experienced by the study population. This may be reported as a range of numerical values on a test of global cognitive function, or as a categorical designation such as cognitively normal, mild cognitive impairment (MCI), mild dementia, moderate dementia, or severe dementia • COMORBIDITIES ○ Specify the proportion of the study population with each listed comorbidity ○ Exclusion criteria: ♦ HISTORY OF NEUROLOGICAL DISEASE OR TRAUMA

Intervention: Chronic drug administration

LABORATORY RODENT MODELS OF AD	HUMAN AD PATIENTS
Inclusion criteria: • DRUG: donepezil, rivastigmine, galantamine • DOSE (mg/kg) • TREATMENT DURATION/FREQUENCY • ROUTE OF ADMINISTRATION	Inclusion criteria: • DRUG: donepezil, rivastigmine, galantamine • DOSE (mg/kg) • TREATMENT DURATION/FREQUENCY • ROUTE OF ADMINISTRATION

Comparator: Placebo/vehicle treatment

LABORATORY RODENT MODELS OF AD	HUMAN AD PATIENTS
Resources supplied to the to the control group/condition (if not specified, assume the resource level of conventional laboratory housing)	Human adults in environmental contexts typical of modern developed nations.

Outcomes: Cognitive performance on comparable tests

COGNITIVE DOMAIN	LABORATORY RODENT MODELS OF AD	HUMAN AD PATIENTS

Global cognition	n/a	►Mini-Mental State Examination (MMSE) ►Montreal Cognitive Assessment (MoCA) ►Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) ►Clinical Dementia Rating (CDR) ►Rey Auditory Verbal Learning Test (RAVLT) ►Trail Making Test (TMT) Parts A and B ►Digit Span Test (DST) (forward and backward) ►Clock Drawing Test (CDT) ►Verbal Fluency Tests (category and letter fluency) ►Boston Naming Test (BNT) ►Logical Memory Test (WMS-LMT) (part of Wechsler Memory Scale)
EPISODIC MEMORY	n/a	►MMSE (Recall) ►MoCA (Memory) ►ADAS-Cog (Word Recall Task) ►CDR (Memory) ►RAVLT (Immediate Recall Trials (I-V)) ►RAVLT (Short Delay Free Recall (VI)) ►RAVLT (Long Delay Free Recall (VII)) ►WMS-LMT (Immediate Recall) ►WMS-LMT (Delayed Recall) ►WMS-LMT (Thematic Scoring) ►WMS-LMT (Gist Scoring)
WORKING MEMORY	►Y-maze alternation ►T-maze alternation ►Spontaneous alternation ►Radial arm maze	►MMSE (Registration) ►ADAS-Cog (Commands) ►ADAS-Cog (Remembering Test Instructions) ►RAVLT (List B Interference) ►DST (Forward: Repeat digits in same order)

		►DST (Backward: Repeat digits in reverse order)
LANGUAGE PROCESSING	n/a	►MMSE (Language) ►MoCA (Naming) ►MoCA (Language) ►ADAS-Cog (Naming Objects and Fingers) ►ADAS-Cog (Language) ►ADAS-Cog (Comprehension of Spoken Language) ►ADAS-Cog (Word Finding Difficulty) ►BNT (total words named) ►BNT (spontaneous correct) ►BNT (correct with semantic cue) ►BNT (correct with phonemic cue)
RECOGNITION MEMORY	►Novel object recognition ►Novel object location	►ADAS-Cog (Word Recognition Task) ►RAVLT (Recognition) ►WMS-LMT (Recognition)
EXECUTIVE FUNCTION	►5-choice serial reaction time task ►5-choice continuous performance task ►Attentional set-shift task	►MoCA (Abstraction) ►ADAS-Cog (Ideational Praxis) ►CDR (Judgment and Problem Solving) ►TMT (Part B: Alternate between numbers and letters) ►Verbal Fluency (Category fluency) ►Verbal Fluency (Letter fluency) ►MoCA (Visuospatial/Executive)
ASSOCIATIVE LEARNING & MEMORY	►Contextual fear conditioning ►Cued fear conditioning ►Inhibitory avoidance	n/a

Search strings

LABORATORY RODENTS	HUMAN PARTICIPANTS
(murinae OR mice OR mouse OR Mus OR rodent* OR murine OR rat OR rats) AND	(human* OR adult* OR patient*) AND

(donepezil OR aricept OR rivastigmine OR exelon OR galantamine OR reminyl OR razadyne OR "cholinesterase inhibitor*" OR "acetylcholinesterase inhibitor*") AND ("alzheimer*" OR "AD model" OR "cognitive decline" OR "memory impairment" OR "APP" OR "amyloid" OR "tau" OR "transgenic") AND ("morris water*" OR "novel object*" OR "operant*" OR "y-maze" OR "y maze" OR "t-maze" OR "t maze" OR "alternation" OR "4-arm maze" OR "4-chamber maze" OR "plus-maze" OR "plus maze" OR "+-maze" OR "+ maze" OR "inhibitory avoidance" OR "contextual fear*" OR "cued fear*" OR "radial arm*" OR "radial maze" OR "barnes" OR "non-match*" OR "5-choice*")	(donepezil OR aricept OR rivastigmine OR exelon OR galantamine OR reminyl OR razadyne OR "cholinesterase inhibitor*" OR "acetylcholinesterase inhibitor*") AND ("alzheimer*" OR "AD" OR "cognitive decline" OR "dementia" OR "mild cognitive impairment" OR "MCI") AND ("MMSE" OR "Mini Mental State Examination" OR "MoCA" OR "Montreal Cognitive Assessment" OR "ADAS-Cog" OR "Alzheimer's Disease Assessment Scale" OR "Clinical Dementia Rating" OR "CDR" OR "NPI" OR “Rey Auditory” OR "RAVLT" OR "Trail Making Test" OR "TMT" OR "Digit Span" OR "Clock Drawing Test" OR "Verbal Fluency" OR "category fluency" OR "letter fluency" OR "Boston Naming Test" OR "Logical Memory Test" OR "Wechsler Memory" NOT ("review"[Publication Type] OR "meta-analysis"[Publication Type])

Additional components of the thesis

Narrative reviews of key mechanisms

To establish the theoretical foundation of this thesis, I will write three focused narrative reviews examining the overlap between:

1. The neurobehavioral correlates of environmental enrichment
2. The neural mechanisms of acute pharmacological cognitive enhancement
3. The neural mechanisms of AD pathogenesis and known neuroprotective/therapeutic processes

Historical perspective on laboratory housing

A critical component of this thesis is the claim that conventional laboratory housing may render laboratory rodents translationally invalid for the purposes of preclinical CNS drug testing. To support this potentially controversial position, I will analyze the historical development of laboratory housing standards. This analysis will demonstrate how economic constraints and researcher convenience shaped the current laboratory housing standards.

Key discussion points

Concerns about standardization

One of the frequently cited concerns regarding increasing the resource level OF laboratory rodents is that more resources will make the animals less standardized.[43] According to this argument, standardization decreases variance while increasing reproducibility. This concern can be addressed both empirically and theoretically. Empirically, large meta-analyses have reported additional resources were not associated with increased variance.[44–46] From a theoretical perspective, even if standardization was compromised by the provision of additional resources, no amount of standardization would compensate for the systematic bias toward overestimating drug effects in poorly-resourced environments.

Possible impact of domestication on resource requirements

Some suggest that laboratory rodents, through selective breeding and domestication, have reduced resource requirements compared to wild rodents or humans.[47,48] I will present evidence challenging this assumption and its implications for translational research.

Protocol for an experimental test of my main hypothesis

While the focus of this thesis is meta-analytic evidence, I will outline a definitive experimental protocol to test the main hypothesis. This experiment would select several CNS drugs that produced significant results in preclinical trials but went on to fail in human trials. Then, the experimenters would replicate those preclinical trials while only varying the resource level at which the experiment takes place. The study would evaluate a range of laboratory housing conditions, from conventional cages to naturalistic enclosures. If the studies conducted at higher resources levels produce drug

responses more similar to human clinical outcomes, it would demonstrate that testing at the higher resource levels would have prevented translational failure.

Figures

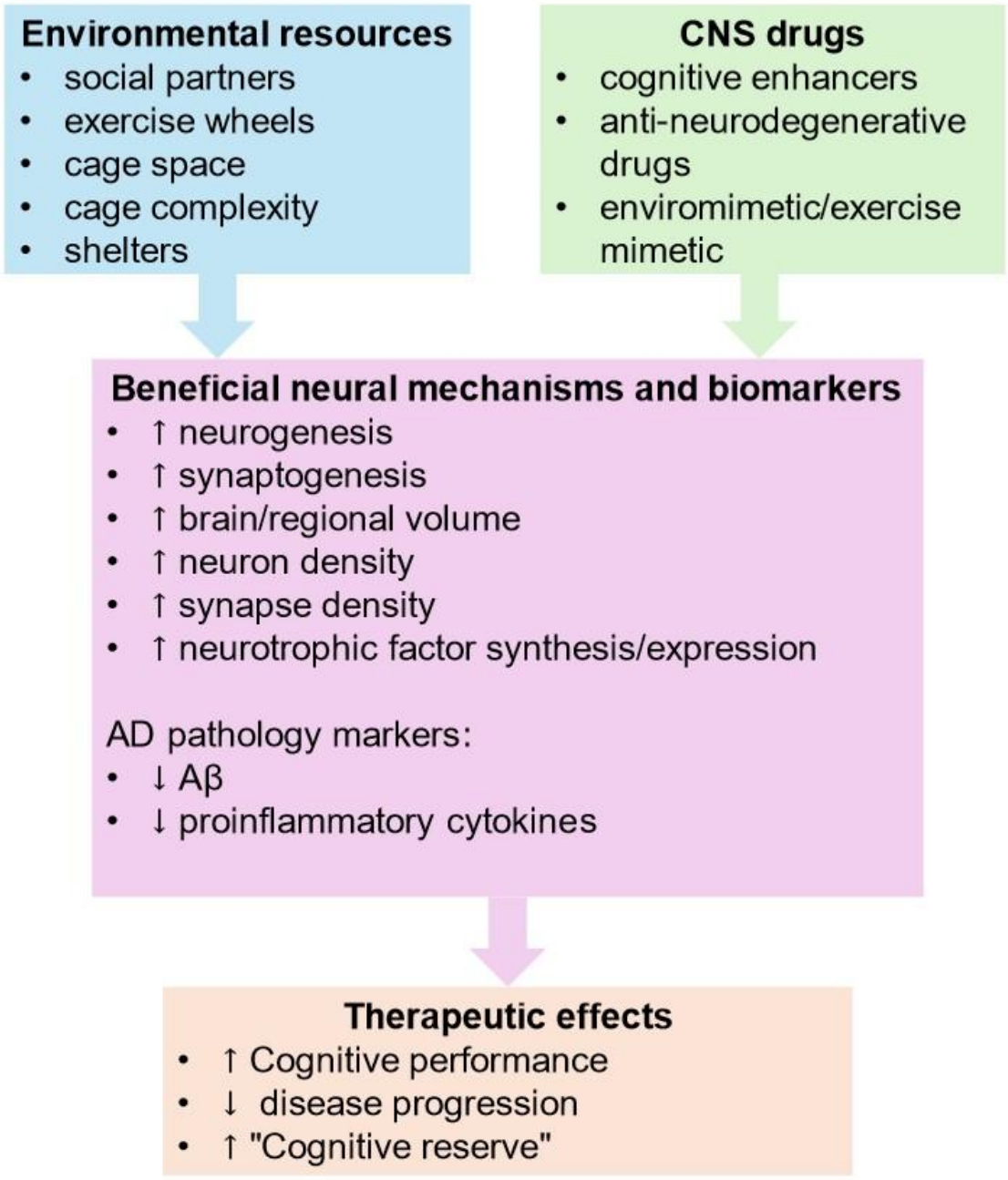

Figure 1. Convergent mechanisms of environmental resources and CNS drugs on neural mechanisms and downstream therapeutic effects

Schematic representation of how environmental resources and CNS drugs influence overlapping neural mechanisms to produce therapeutic effects. Both environmental enrichment (blue) and CNS drugs (green) upregulate beneficial neural mechanisms and biomarkers (pink), while reducing markers of neuropathology. These shared mechanistic pathways lead to similar therapeutic outcomes (orange). (Aβ: beta amyloid)

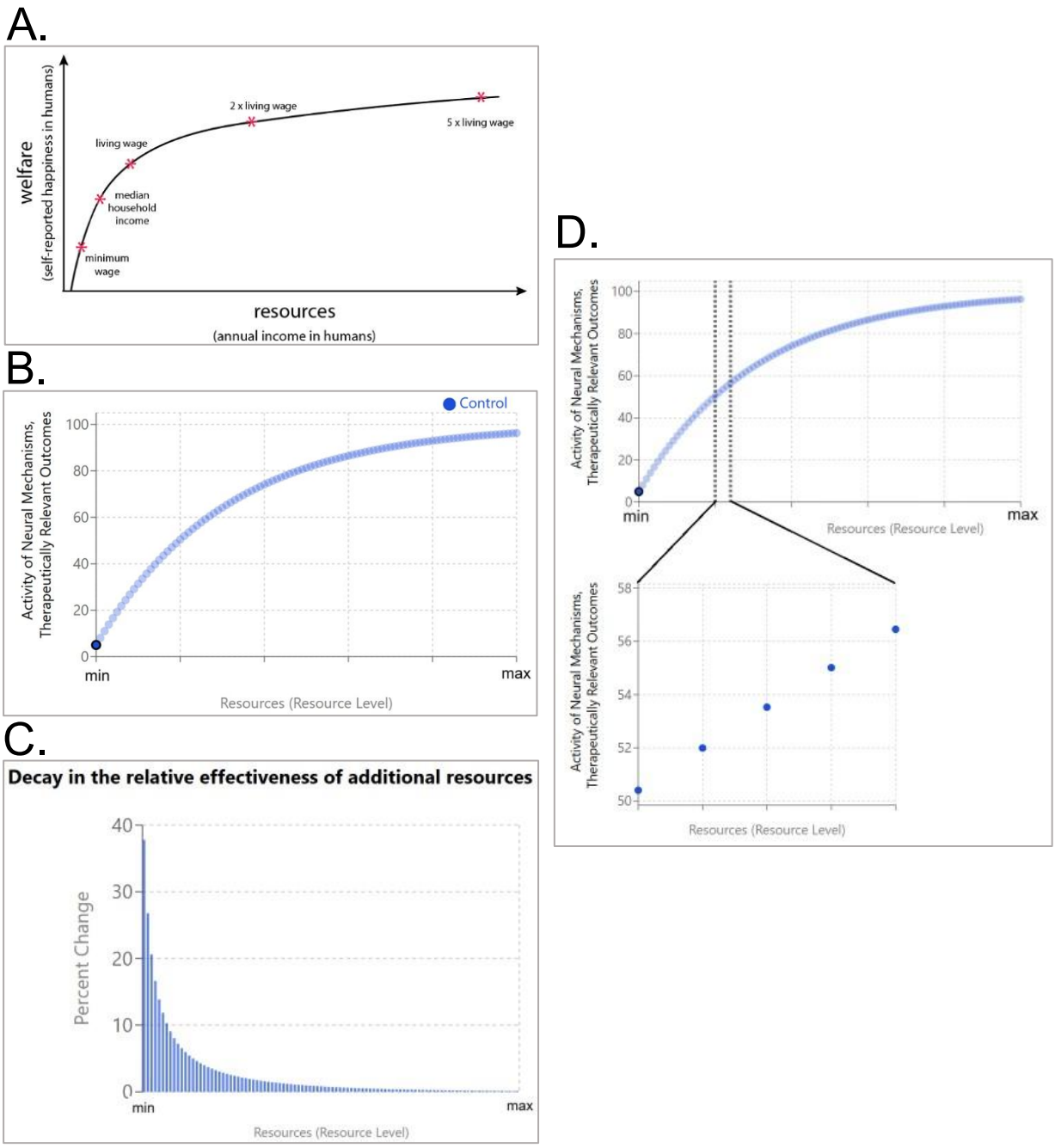

Figure 2. Resource levels show diminishing returns on neural and behavioral outcomes

Theoretical model demonstrating how increasing resource levels yield diminishing returns. (A) Economic study on the relationship between income and self-reported happiness in humans, with diminishing returns at higher income levels. (Excerpt from Cait et al, 2022[20]) (B) Predicted relationship between environmental resource levels and neurocognitive outcomes in laboratory animals, showing a similar pattern of diminishing returns at higher resource levels.* (C) Quantification of the diminishing effectiveness of additional resources for the hypothetical data in Fig. 2B. (D) Demonstration of how linear effects of additional resources may be observed despite the overall non-linear shape of the resource-outcome curve. The upper panel shows the full resource-outcome curve, with vertical dotted lines bookending a small segment. The lower panel shows a magnified view of the segment, which shows an approximately linear relationship.

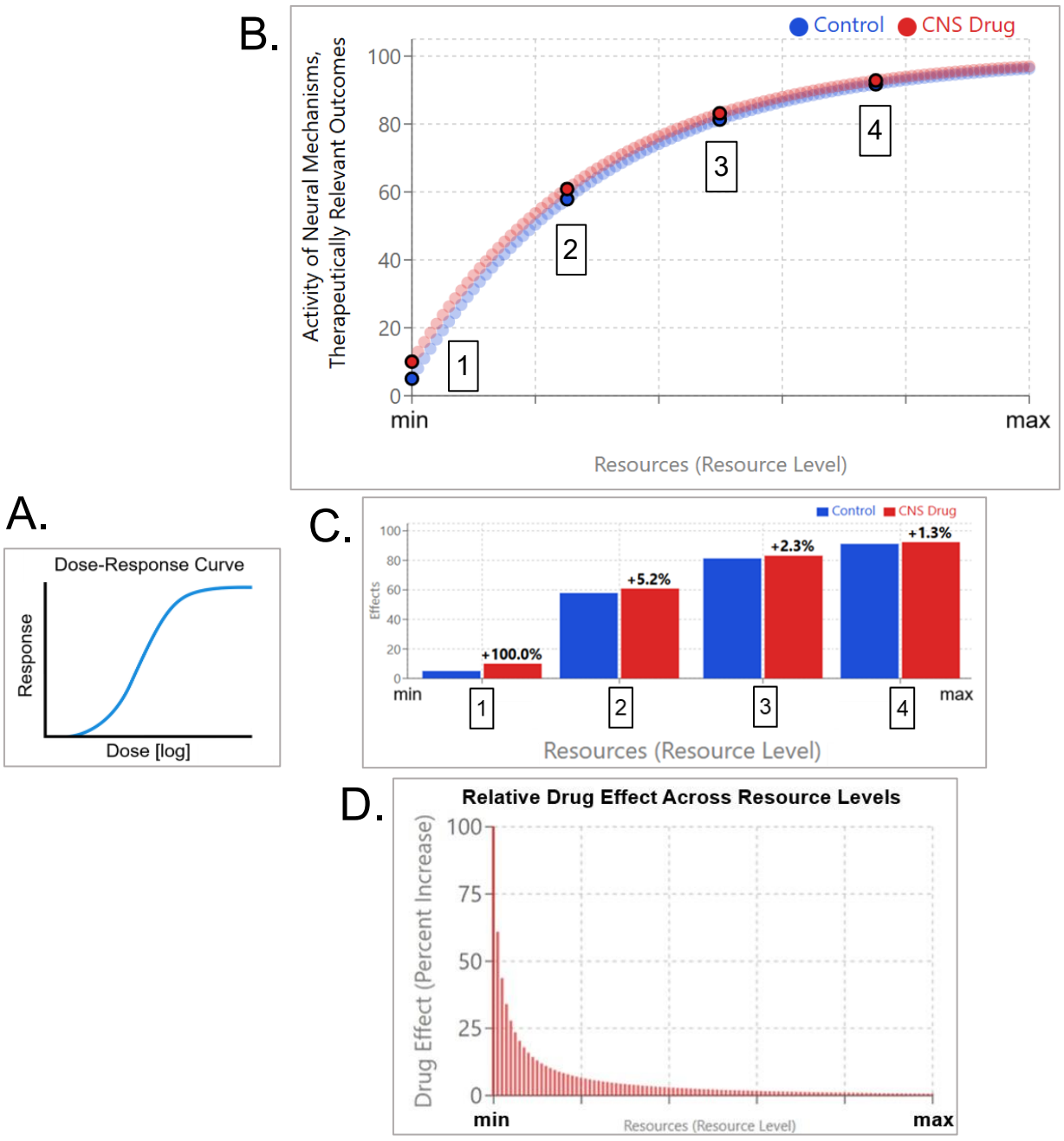

Figure 3. The apparent effectiveness of a CNS drug diminishes at higher resource levels

Theoretical model demonstrating how resource level influences the apparent effectiveness of CNS drugs. (A) Representative dose-response relationship for most drugs. (B) Theoretical curves for a hypothetical CNS drug study, showing the control (blue) and drug-treated (red) conditions. (C) Bar graph showing outcome measures for the control and drug treatment conditions at four different resource levels using the hypothetical data in Fig. 3B. The percent improvement due to the drug is also shown, revealing a decline in the relative effect of the drug at higher resource levels. (D) Quantification of the diminishing effectiveness of the drug for the hypothetical data in Fig. 3B.

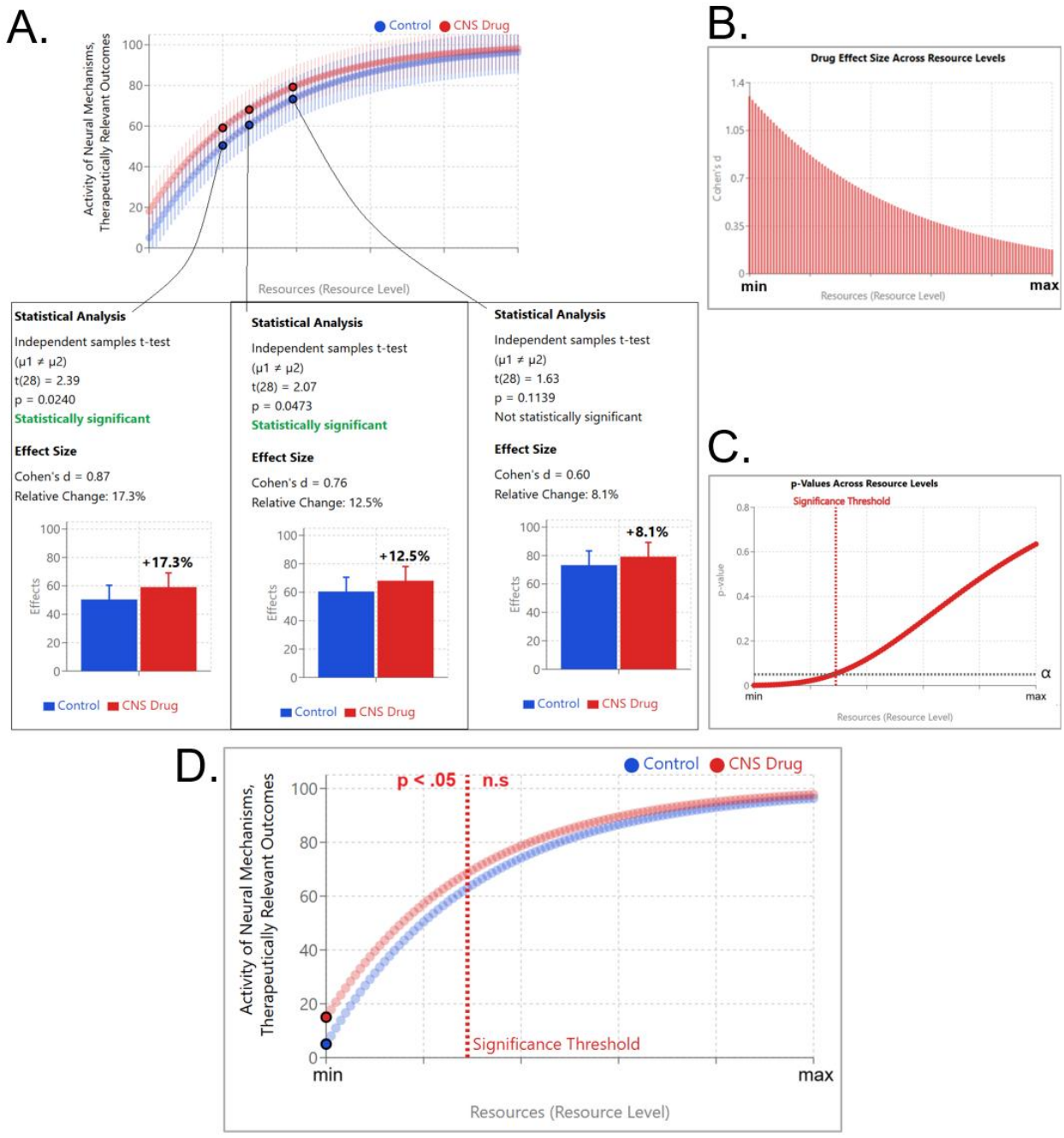

Figure 4. Resource level systematically influences statistical outcomes in CNS drug testing

Analysis of how resource level affects statistical detection of drug effects (hypothetical dataset). (A) Statistical analyses at three different resource levels, indicating that the same drug can produce different statistical outcomes depending on the resource level at which the study is undertaken. At lower resource levels, the standardized effect size (Cohen's d) is larger and there is a greater likelihood of detecting a statistically significant result (p<.05). (B) Quantification of the decay in standardized effect size across resource levels. (C) Relationship between resource level and p-value, with the horizontal dotted line indicating the significance threshold (α=0.05) and the vertical dotted line indicating the cutoff resource level below which that drug's effect will be deemed statistically significant. (D) Visualization of how resource level can determine whether a drug effect reaches statistical significance. At lower resource levels, drugs show greater apparent effectiveness.

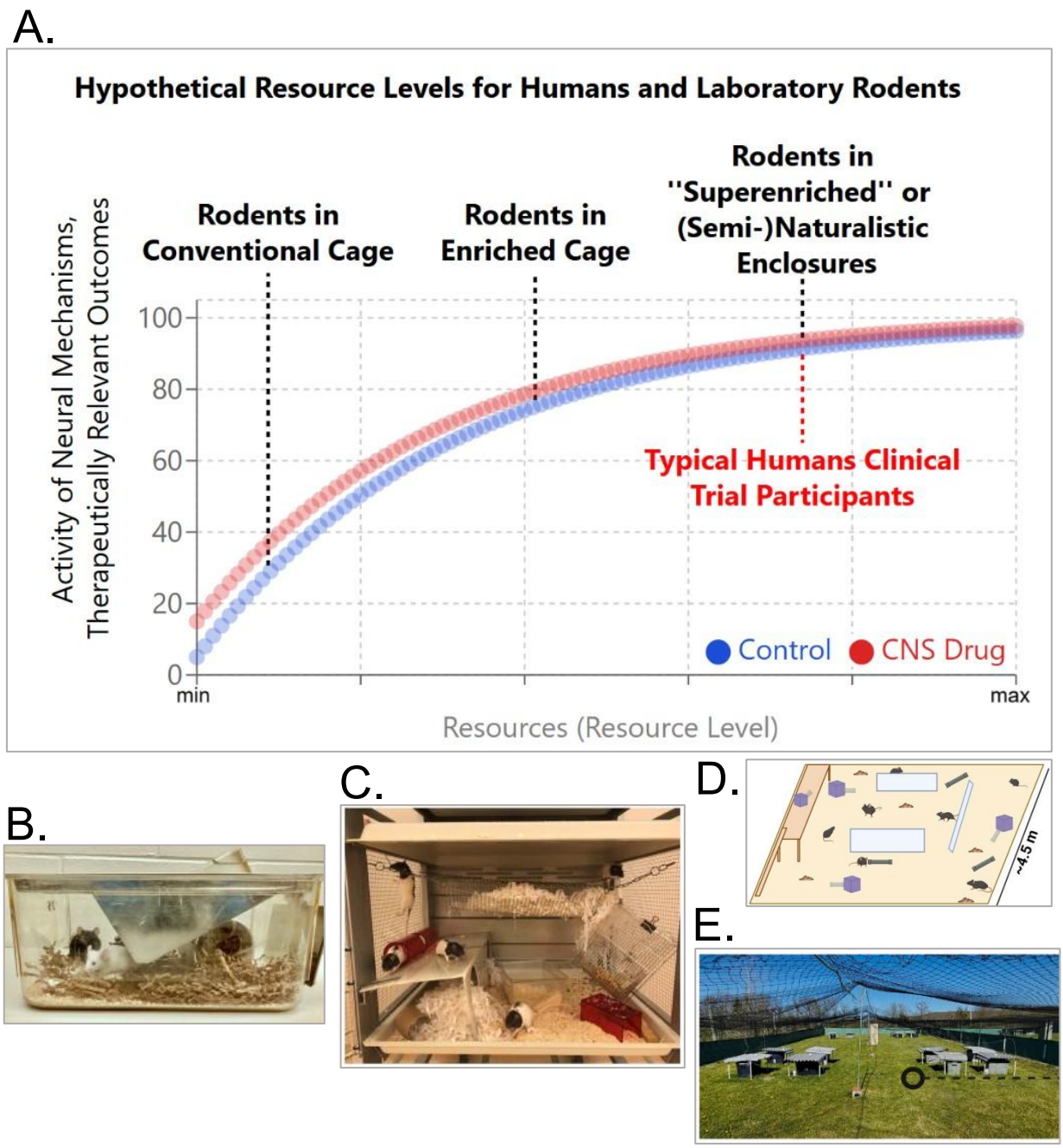

Figure 5. Resource levels across laboratory housing conditions and human environments

(A) Theoretical model comparing resource levels of laboratory rodents and humans, with hypothesized positions of different environmental conditions superimposed onto the graph from Fig. 4D. (B-E) Representative examples of laboratory rodent housing conditions at different resource levels: (B) conventional laboratory cage[1], (C) enriched cage featuring additional resources[2], (D) schematic of a "superenriched" cage, with resources provisioned at a wider scale[3], and (E) semi-naturalistic outdoor enclosure providing natural features.[4]

[1]Mason & Cait (2022),[2]Mazhary & Hawkins (2019), [3]Zipple et al (2023), [4] Zipple et al (2023)

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