Specific Aims

There are two distinct issues that this grant proposal hopes to address 1) most of the experiments used for human neuroscientific research while being psychological sound lack ecological validity, often measuring behavioral constructs[1], and 2) there is a critical lack of objective ways to measure the negative and cognitive symptoms of schizophrenia.[2] Therefore, this proposal aims to create a psychologically controlled and ecologically informed immersive virtual environment (IVE) to act as an objective diagnostic tool for assessing motivational impairments typical of schizophrenia.

Human neuroscience research relies almost exclusively on rigid psychology experiments, that from an ecological standpoint, fall short of representing behavior's holistic nature. Conversely, psychology's cognitive science sister field, ethology (the study of animal behavior), facilitates the interactive and extend duration qualities that psychological tasks lack. Most importantly, ethological observation utilizes **objective** space-time representations of behavior. In neuroscientific research, graphical behavior paths are objective measures of behavior correlating with assumed internal states. One staple example is the patterns produced during a Morris water maze experiment.[3,4,5] However, due to both warranted ethical concerns and technological limitations, incorporating this objective method in human research is nearly absent. Thus, given the immense benefits that layering mathematical graphing onto human behavior might provide, the proposed solution is experimentation using IVEs, specifically virtual reality (VR). As VR is safe, it offers more ecological validity to tasks, and with the emergence of fMRI-compatible head-mounted display (fcHMD) technologies, it can facilitate simultaneous neural imaging.[1,6,7]

Therefore, this proposal's central goal is to combine the following five components to create one coherent experiment: 1) A psychologically controlled and ethologically informed effort-based decision-making task game. 2) A collection of objective measures of cognitive effort. 3) A collection of subjective measures of motivation. 4) The fMRI blood-oxygen-level-dependent (BOLD) activation in several brain regions of interest (ROI) that are associated with effort-based decision-making during time points of interest, mainly the ventral striatum (VS) but also the anterior cingulate cortex (ACC) and prefrontal cortex (PFC).[8,9,10,11,12,13] 5) An ethological evaluation of virtual paths produced during the IVE task.

The hypotheses are (1) objective measures of effort/performance will be statistically similar for participants between counterbalanced real-world and IVE tasks and will correlate with subjective survey results, validating the IVE task. (2) Averaged BOLD activation within the VS will differ between healthy control and schizophrenia groups during IVE task like results in previously established effort-based decision studies, adding to current motivation literature. (3) The statistically significant differences in hypotheses one and two will present as noticeable path differences groups. We will test these hypotheses with the following aims:

Aim 1: To create a psychologically controlled and ecologically informed IVE effort-based decision task. Participants will play an effort-based foraging IVE game for monetary gain. The game's parameters will a psychologically validated task component, an effort expenditure for rewards task (EEfRT), and an ethological, resource expenditure for movement optimal foraging theory.

Aim 2: To validate the IVE effort-based decision task using a within-subject comparison to real-world EEfRT performance and negative symptom surveys. Both healthy controls (HC) and participants with schizophrenia (SCZ) will participate in a counterbalanced evaluation of similarly designed real-world and IVE effort-based tasks, and the SCZ results will be compared to the two negative symptoms in an attempt to validate the IVE task.

Aim 3: To assess the IVE performance and average VS BOLD activation between groups and separately evaluate individual in-game pathing. SCZ should engage in less high effort berry collection and high effort button clicking for monetary reward, will show less VS activation in the time window after completing a berry collection and before moving to another one, and that they will path past high effort berry patches to a greater degree than their HC counterparts.

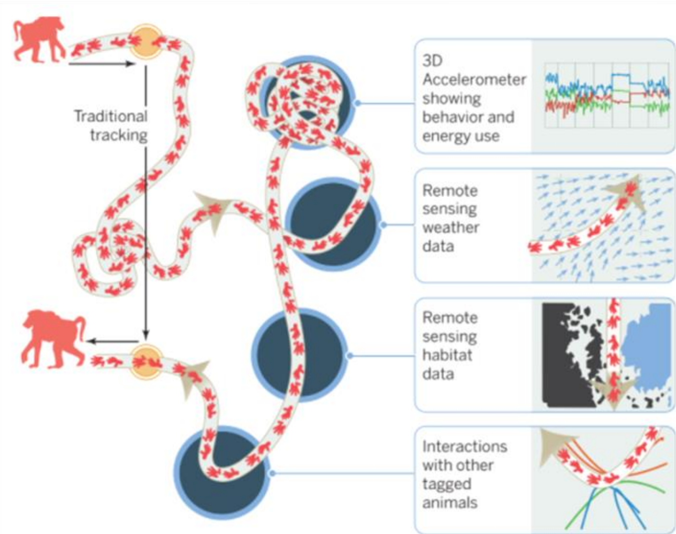
Significance 1: Combination of IVEs, fcHMD, and Animal Behavior Modeling

Virtual reality paths created by human participants interacting within standardized IVEs may serve as an objective and ecologically valid mental illness diagnostic tool. Two distinct pieces of evidence directly support this theory. The first piece of evidence comes from a human motility study that evaluated path differences between agoraphobics and HC during a city walk, finding the patient population behaved like high anxiety animal models by avoiding the center of the market and staying along the edges.[14] The second piece of evidence comes in the form of an explosion of presence/immersion literature from the field of applied cognitive psychology. This collection of work establishes that real-world and IVE tasks produce similar biomarkers. With the rise of next-generation virtual reality (VR) systems like Oculus Rift and HTC Vive, the immersive capability (the technological component of user presence) of VR has improved to the point that this media can instill the subjective feeling of being present in the virtual world, which correlates with objective measures like heart rate and skin conductance alterations.[15,16,17,18,19] Together evidentially establishing the likelihood of IVE human path differences and the feasibility of these environments as proxies for real-world cognitive science research.

Central to integrating IVEs into neuroscience research is the recent invention of the VR fcHMD, an advancement that allows researchers to engross stationary participants in dynamic environments. In 2008 a research team established its proof of concept, which coincided with the manufacture and distribution of the immersive next-generation virtual reality systems mentioned above.[7] However, the neuroscientific community has not widely adopted this technique, as it has only been utilized in a handful of studies since. A 2015 neuropsychology review pushing for the inclusion of VR into neuroscience claims this media stand to create more ecologically valid tasks as it can measure "functional" behavior and not merely cognitive "constructs." [1] The same review also notes a common rebuttal to the inclusion of behavioral ecology into neuroscience, a lack of standardizable stimuli, does not apply to this media as it is reproducible and manipulatable.

Additionally, a 2018 mini-review assessing the usefulness of the fcHMD in evaluating human memory brain correlates outlines two ways that the combination of VE and fcHMD can inform neuroscientific research, stating it may help identify time points of interest through path analysis and aid in the identification of the structural and functional correlations of behavior through analysis of these time points.[6] This same group lends credence to the idea that this system combination may be a practical means for studying human ethology. Claiming VR can facilitate the ethical and technical translation of extensively used animal research paradigms, such as the Morris water maze, to human participants. With these technologies', psychology tasks and ethological movement theories can be evaluated conjunctively, providing virtual paths that coalign with extended duration decision-making and brain activity!

The origin of such paths comes from rudimentary animal migration patterns, as animals from Arctic terns to whale sharks have had their macro geopositioning decisions evaluated over year-round treks to and from breeding and feeding regions.[21] While global macro positioning is interesting; it fails to capture an organism's real-time experience. Therefore, much of the more recent research has begun using similar paths to track animals' micromovements. Studies using rodent and zebrafish locomotion have been vital players, showing that toxin exposure, predatory proclivity, and brain lesioning alter animal behavior, which critically corresponds to changes in the physical path associated with their movement.[22,23,24]



Big-data animal tracking. The red trajectory shows how studies can now track animals with unprecedented detail, allowing researchers to predict the causes and consequences of movements, and animals to become environmental sensors. Multisensor tracking tags monitor movement, behavior, physiology, and environmental context. Geo- and biosciences merge now using a multitude of remote-sensing data. Understanding how social and interspecific interactions affect movement is the next big frontier.

Figure 1. Reproduced from Kays R, Crofoot MC, Jetz W, Wikelski M. ECOLOGY. Terrestrial animal tracking as an eye on life and planet. Science (New York, N.Y.). 2015;348(6240):aaa2478. Showing macro and micro animal movements, as well as examples of ecophysiological evaluation (top right) and social behavior/collective movement evaluation (bottom right).

As figure 1. shows, researchers are now capable of collecting both macro and micro motility types simultaneously during the real-world activity of animals because of improvements to tracking technologies.[6] This group suggests that the "golden age of animal tracking science has begun" if analytical technologies can keep pace. They highlight three types of physical movement patterns transferable to this grant: ecophysiology, social behavior, and collective motion. In addition to this group's proposed uses, a large body of ethological literature explores the well-established optimal foraging theory. The overarching idea of optimal foraging theory is that natural selection produced animals that will take the most direct path while collecting "resources" to maximize productivity while minimizing energy expenditure.[5,25,26,27] Notably, the 2018 neuropsychology review from above explicitly recommended a foraging task to increase fMRI studies' ecological validity using VR, which will be the task this grant proposal implements.[6]

Although there is much research interest in combining neuroscience with VR IVEs, this proposal hopes to depict the feasibility of the overall IVE methodology and eventually turn this technology toward the brains of healthy participants partaking in a subset of the IVE umbrella, a real-time strategy (RTS) video game. This game type presents players with complex and dynamic human vs. human real-time abstract mazes where **naturalistic** human behavior and brain activity occurs. One research group has gone as far as to claim that the RTS virtual arenas acting as "standard task environments" stand to serve cognitive science to the same degree that the drosophila has served biology.[29] A claim bolstered by the successful measurement of expertise, executive control, and emotional regulation using this complex platform.[28,29,30] RTS games are also being evaluated through the lens of sports analytics, allowing one group of researchers to remotely collect millions of comparable game files, vastly outperform typical psychological participant pool sizes by over four orders of magnitude as well as the standard laboratory dependence.[31] However, with current data collection laws the way they are, the players were unaware that they were taking place in this data collection. The significance of this proposed methodology is that it more accurately mirrors the real world. Although it feels like we are three-dimensional beings, behavior and our lives occur over time. These IVE paths create a four-dimension picture, likely making them more valuable than real-world neuroscientific research in many ways. For instance, exact movement patterns that correspond to behavioral processes like learning, decision making, or spatial representation can be captured and evaluated alongside the corresponding evolving brain states, informing systems-level analysis of neurological function.

Significance 2: Objective Psychological Measure – Effort Expenditure for Reward Task (EEfRT)

Excitingly, this IVE pathing evaluation combined with preexisting evaluative psychological techniques may fulfill an urgent need better to assess the negative and cognitive symptoms of schizophrenia. Underneath the category of negative symptoms, people with schizophrenia tend to lack motivation and be less communicative. An issue that stems from a lack of motivation is the inability to initiate the motivation to perform everyday tasks. A 2015 review suggests that all studies evaluating these negative symptoms of schizophrenia depend heavily on clinician-conducted interviews, asserting that this subjective assessment had obvious clinical limitations. So, because this typical behavioral pattern dramatically affects an individual's ability to function in society and the highly subjective nature of diagnostic measures, there is a need to develop objective techniques. One solution put forward is the use of payment-motivated, effort-based decision-making tasks to assess motivation decreases typically of schizophrenia to fill this gap. While this paradigm usings decision-making as the task, the experimental design of these tasks looks more at effort exertion for a reward.

A 2009 review examining the modulation of dopamine on neural networks implicated in effort-based decision-making describes decision making "as a cycle of two general processes, namely, evaluation and execution."[13] The execution portion arises from the interplay of motivation and action. Thus, as motivation is a critical component of every decision, these effort-based decision tasks are likely to reveal brain states critical to motivation. The group also delineates the temporal aspect of decisions stating that decisions address problems either in the moment or in the future. During effort-based decision-making tasks, participants engage with repeated similar high effort vs. low effort choices, presenting researchers the opportunity to measure the differences in brain activity during in-the-moment motivational decisions. Negative symptom research is necessary because, currently, antipsychotic treatments fail to adjust this aspect of the disorder.[2] Additionally, the task can be stripped off the IVE foraging game and replaced with another psychological paradigm, like the IOWA gamblers task, where SCZ also show distinctive patterns of impairments during this decision-making task—potentially adding a layer of objectivity to many established tasks.[32]

In the effort-based decision-making literature, three task types show promise, cognitive, perceptive, and physical effort tasks. One study takes the initiative to run a comparative analysis battery on a large group of SCZ and HC to assess the strengths and weakness of five developed effort-based decision-making task paradigms that fall within these three broad categories.[33] Their results indicate that physical task types, particularly the effort expenditure for rewards tasks (EEfRT) and grip effort tasks, show the group's most robust psychometric viability. Overall, EEfRT creates the "best reliability and utility as a repeated measure" when assessing the statistical significance of intra-class correlation coefficients. The EEfRT task is a button-pressing task that utilizes functionality differences between peoples non-dominant and dominant hands and displayed the likelihood of success to create a high effort versus low effort decision paradigm, which is explained in aims one and two of the approach section.[2,34,35,36] An additional primary literature study evaluating the neural correlates of schizophrenia effort impairments states the "unwillingness to expend more effort to pursue high-value rewards has been associated with motivational anhedonia in schizophrenia and abnormal dopamine activity in the nucleus accumbens (NAcc)," which along with a series of other studies effectively implicates the ventral striatum (VS) as the main ROI.[8,9,10,11,12,13] The other areas associated with this pathway that do not appear to differ between groups are the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC). These pathways sit on the fence between established and understudied. Therefore, if this IVE game differentially activates these pathways between SCZ and HC and mirrors the real-world task results, the VR game itself could be used as a cheap and engaging diagnostic tool. Pairing this tool with future negative symptom medications could provide insight into drug trial effectiveness. Overall, placing researchers in a spot to explore this tricky side of the disorder more thoroughly.

Approach

Aim 1: To create a psychologically controlled/ecologically informed IVE EEfRT game.

Rationale: An EEfRT IVE foraging game should provide the same objectivity level for measuring the motivational impairments that a real-world EEfRT provides with two valuable additions. First, the game format will enhance across study task repeatability. A function of any well-made game environment is that it creates a repeating provenance state.[38] Allowing future research groups to perform the same task using the same standardized conditions, enabling an accumulation of results. Second, it will produce motility pattern metrics, such as overall distance, likely showing that SCZ choose to partake in fewer high-effort tasks, increasing their pathing distance due to avoidance, adding another layer of objectivity to this established task paradigm. This IVE paradigm may fall short in the area of SCZ motor control, as there are motor impairments that accompany this disorder, but as the only motor differences between a real-world and IVE task will be finger movements, it is likely that this issue is a nonfactor, but is still worth considering as a potential pitfall.

Experimental Design/Strategy: The creation of this IVE will be done using Unity's free online VR software. The physical parameters of the IVE will be a one-hundred and fifty-meter radius circular field, housing two hundred berry bushes populated using a one-time procedural generation method. This generation process ensures that randomization but can also be held constant across all participants. There will be an equal number of one-hundred blue (low-effort) and orange (high-effort) berries bushes. The only restriction placed on the randomization will be that each berry bush must be no more than five meters separating a bush from either bush type. A vertical wall will surround the IVE, but other than the wall, the bushes, and the participant's avatar, no other objects will be included. All participants will spawn in the same spot at the center of this IVE and be facing the cardinal direction of North or zero degrees, ensuring all participants start off looking at the same environmental layout.

The game/task design will follow the exact parameters of an EEfRT but will incorporate resource depletion as plenty for movement from optimal foraging theory. The participants will collect berries from 75 bushes with no time limit, but they will lose half a berry for every second of walking in the IVE. In line with the EEfRT parameters, after completing an effort task (collecting berries), a UI display will inform the participants of the new collection success rate. The subsequent attempt will hold a 20%, 50%, or 80% chance of producing berries. The overall objective is to collect as many berries as possible. The number of berries they collect will be divided by twenty, and that number will be the participant's additional payout on top of a fifteen dollar an hour base pay. The collection of the easy berries (blue) will net of five and will require ten dominant hand index finger trigger pulls in four seconds. The hard berries (orange) will net between five and twenty berries but require twenty non-dominant hand trigger pulls in four seconds. However, unlike the real-world task, <u>there will no strictly segmented time windows throughout the task</u>. Instead, the fMRI BOLD activation will be measured starting from when each effort task (berry collection) ends and ending when the participant begins moving to the next berry bush. A five-second count-down timer attached to the half berry per second stationary penalty will prompt movement initiation and hopefully produce a tiny (5s) repeating window that requires environmental decision-making (where to go next, rather than the binary high vs. low in the real-world EEfRT). <u>Significantly increase ecological task validity</u>.

Expected Results and Potential Pitfalls: Creating an IVE foraging game is not outside that realm of possibility for a graduate-level project. A team in NCSU's applied cognitive psychology laboratory has created a similar IVE, which has allowed a research team to measure participant arousal during virtual falls.[16] Suggesting the feasibility of turning this tool towards neuroscientific endeavors.

There are many potential pitfalls to the transition of any task to a new media. The most glaring issue is that the EEfRT was initially designed for use in animal models, so as there are typically only two transitions from animals to people and HC studies to clinical trials. However, this study adds a third transition from real-world to IVE, further adding to the probability of design failure, which may appear as poor-retest reliability or ceiling and floor effects. It is also possible that the choice to remove the time windows will be a factor in null findings of fMRI. Two VR-specific challenges could surface the likelihood of head movement due to being engrossed in the task and simulation sickness. While technology is progressively getting better to combat this second issue, it still poses a significant challenge for any research study looking to implement VR.

Aim 2: Validation of IVE EEfRT using a counterbalanced Real-world EEfRT and negative symptom surveys

Rationale: As this methodology is untested, there must be a process of validation. Because of individual differences, this study will not use previous results to validate our task but instead perform a counterbalanced within-subject experiment comparing individuals' results looking for a similar frequency of effortful task avoidance by the SCZ individuals in both tasks. Researchers will also perform two negative symptoms surveys. The combination of the tasks and survey will help researchers determine if the IVE can produce reliable results.

Experimental Design/Strategy: All participants will sign an informed consent form and be aware that the researchers are looking at the neuroimaging correlates of motivation. The male-to-female ratio of SCZ is 1.4:1. Therefore, this proposal will aim to match that ratio.[39] The projected number of participants will be 60 SCZ and 60 HC, twenty from each group will be female participants, forty in total. Between-group differences in age, education, Intelligence quotient, socioeconomic status, gaming experience, and antipsychotic type/dosage within the SCZ population will also be controlled. Participants will take an Abnormal Involuntary Movement Scale, a screen for tardive dyskinesia, to prevent inconsistent fMRI results during recruitment. Before the tasks but after the recruitment phase, the researchers will administer to the SCZ two negative symptom surveys. First, the Clinical Assessment Interview for Negative Symptoms (CAINS) and second, the Positive and Negative Syndrome Scale (PANSS). Next, participates will then perform the two tasks in a counterbalanced fashion. Besides the inclusion of the timing window, the real-world task will only differ in a few ways: it will be performed on a computer, the participants will use their non-dominant pinky instead of trigger finger to issue key inputs, and berry colors will be replaced with text boxes

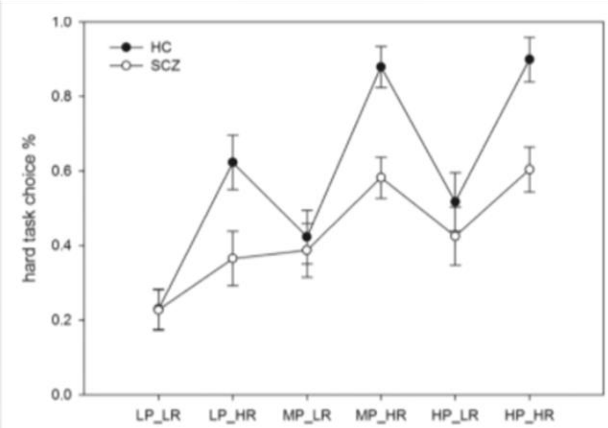


Figure 2. Behavioral effects of the rt-expenditure for reward task task in each condition. Hard task choices% = the percentage of hard task choice; LP = low probability (20%); MP = medium probability (50%); HP = high probability (80%); LR = low reward magnitude (0.8 yuan); HR = high reward magnitude (5 yuan); HC = healthy controls; SCZ = patients with schizophrenia. The error bars represent the standard deviation.

Figure 2. Reproduced from Huang J, Yang X-H, Lan Y, Zhu C-Y, Liu X-Q, Wang Y-F, Cheung EFC, Xie G-R, Chan RCK. Neural substrates of the impaired effort expenditure decision making in schizophrenia. Neuropsychology. 2016;30(6):685–696. Shows EEfRT behavioral trends between HC and SCZ populations. Showing statistically significant differences in willingness to partake in high-effort high-reward tasksbetween HC and SCZ. Interrupted as motivational decreases in SCZ population.

asking participants which difficultly version they would like to accomplish. Berries will be swapped for 'points,' and the real-world task will not be fMRI monitored.

Expected Results and Potential Pitfalls: For hypothesis one, the IVE EEfRT results should mirror the real-world EEfRT results displayed in Figure 2., as the SCZ will likely avoid effortful tasks to a greater degree than HC, even given the heightened reward that high-effort tasks provide. Additionally, SCZ, who score in the bottom 20% on the two subjective rating surveys, will probably show a greater degree of decreased motivation (fewer attempts at the high effort tasks) than the other 80% of the same population, as severe negative symptoms ratings coincide with a dramatic effort decrease during the EEfRT.

In terms of limitations, the general EEfRT shows a small to medium effect size, possibly meaning that either the IVE or real-world results could produce null findings. There is also the possibility that SCZ antipsychotic medication could affect task performance, although most EEfRT studies do not see impacts on data due to medication. IVEs might be disorienting for SCZ and may exacerbate positive symptoms in some participants.

Aim 3: To assess the IVE performance and average VS BOLD activation between groups and separately evaluate individual in-game pathing.

Rationale: If within-subject validation occurs, the next logical step is to assess if there are significant differences between groups that would lend credence to the idea that this methodology may be an objective diagnostic tool. Performance metrics, like pathing distance and berry count, and VS/NAcc BOLD activation, will be averaged and compared. The paths will also be analyzed, looking specifically at latency patterns between berry collections.

Experimental Design/Strategy: Performance metrics measured will be berry/point amount, IVE completion time, IVE path distance, and the number of skipped high effort bushes/tasks. This collection will be done using in-game statistical collection methods. The VS, PFC, and ACC BOLD activation difference, all of which have been implicated previously in EEfRT, will be collected using the fcHMD. Hypothesis two asserts that similar to previous studies, there will be hypoactivity of the VS during the study's decision-making portion. As previously mentioned, the measurement of this activation will be based on real-time in-game movement. The measurement period will be the five-second window following the previously finished effort task. When the participant goes over five s

Expected Results and Potential Pitfalls: The SCZ will likely have decreased berry/point amounts, increased IVE time, increased path distances, and more high-effort tasks skipped could be considered measures of lower motivation, as these all suggest the avoidance of the high-effort tasks. As for hypothesis two, VS BOLD activation will likely be lower in SCZ than HC group. There may also be activation decreases observed in the ACC and the PFC.[9] As for hypothesis three, some individual path differences that may arise might be longer latency between task completion and movement, more frequent intersections, possible even less direct pathing. If any of these do occur consistently and significantly in the SCZ but not HC, these findings might point researchers to investigate timepoints of interest to determine under-researched neural mechanisms of cognitive deficits in SCZ. If this is the case, there will likely be hypoactivity of the orbitofrontal cortex, similar to that of the IOWA gambling task, indicating that EEfRT measure more than simply the motivational deficits of schizophrenia.

The most glaring limitation is that removing the set time windows of the real-world task may impact the fMRI results, but as neuroscience moves to more ecologically informed experiments, there will likely be failures. It is also possible that moving an avatar around in the IVE will alter the fMRI in some way, possibly increasing the activity in the striatum associated with the basal ganglia, a critical structure for regulating movement. Another issue is that the individual variation of the virtual reality paths overlap between groups to an extent where no objective inferences can be made using them, making this experiment an extra costly step in an already tricky experimental process.

Summary: Connecting the internal with the external

Like all organisms, humans are intimately connected to, if not one with, their physical environments, which is why I believe in understanding an actual mind, neuroscience must evaluate the brain under natural conditions.[40] While IVEs are not the real-world and the virtual reality paths are not representations of movement in what we would generally consider objective reality, this combination, if done correctly, may serve as an excellent proxy for exploring a range of behavioral neuroscience questions, possibly laying another plank in the metaphorical bridge between the mind and the physical world.

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