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Human neuroimaging reveals that agency in a video game boosts functional connectivity within and between networks

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Abstract

In naturalistic settings, brains continuously interface with a dynamic and interactive external environment. The inclusion of such an environment in an fMRI study is difficult, given the practical constraints imposed by the machine itself. This study sought to test whether the ecological validity of fMRI could be enhanced by testing a new paradigm that incorporated a dynamic and interactive virtual environment (DIVE). To determine the viability of this paradigm, functional connectivity was assessed during a DIVE condition and compared to functional connectivity patterns acquired in conditions with equally dynamic stimuli but that lacked interactivity with the environment. This study found significant differences in functional connectivity between the DIVE condition and non-interactive conditions, suggesting that control within an environment may have a major impact on patterns of brain activation. Further, this may also suggest that DIVE paradigms could be viable candidates for increasing the ecological validity of fMRI experiments.

Keywords

Naturalistic neuroimaging, Anti-correlation, Dynamic environment, Interactive environment, Video-games

Summary for Lay Audience

Environments, in the real-world, are in constant flux. They change and shift based on events occurring not only external to us, but also as a result of actions we take within them. But when we interact with objects in our environment, the external world isn't the only thing that changes. Perceptions of our world change in response to the effects within our environment. These changes affect how our brain functions, which in turn, can change the way we interface with our environment. One of the major difficulties in neuroimaging is trying to balance controlled experimentation with real-world conditions. If the conditions of an experiment are too far removed from those found in real-world conditions, it can be difficult to create substantive models of how the brain functions. Functional magnetic resonance imaging (fMRI) is a type of neuroimaging in which incorporating environments and interactive agency is particularly difficult, given the practical constraints of the technology; subjects must remain motionless, supine and confined within a narrow tube. The goal of this study was to bring some fundamental elements of a natural environment—dynamism and agency—into the fMRI setting to see whether the brain acts differently than it does when compared to the conditions normally found in these studies. To circumvent the practical barriers of fMRI, I used a video game—Pac-man—as a dynamic and interactive virtual environment (DIVE). This study found significant differences in functional connectivity between the DIVE condition and non-interactive conditions, suggesting that control within an environment may have a major impact on the way the brain functions when in contexts closer to real-world conditions. My hope is that this study illustrates the utility of using the DIVE paradigm in the neuroimaging space—in particular, fMRI—to bring more real-world conditions into the toolkit for studying brains and how they operate.

Acknowledgments

This project would not have been possible without the hard work and dedication of all those who poured their time, energy and, in some cases, sanity, into making it a reality. I would first like to thank my incredible supervisors, **Dr. Jody Culham** and **Dr. Michael Anderson** for their direction, insight and patience on this endeavor. Their courage to challenge the firmly held convictions within neuroscience was bolstered by their creativity in providing bold solutions to these challenges to edify not only the field but all those researchers in it.

I would also like to thank the Herculean efforts of **Karsten Babin**. The phrase 'instrumental' does not begin to capture the debt of gratitude this project owes you. From designing the game itself, to late-night troubleshooting, to getting me started on my coding journey, through which much of the data analysis was made possible, you have been truly essential. I would also like to give special acknowledgement to **Chelsea Ekstrand** for providing the foundations for success on this project in the initial phases of its inception. **Eric Yu** also deserves special mention as the enthusiastic and curious research assistant on this project, whose hard work and 'can-do' attitude made completion of this project *on time* possible.

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Chapter 1

1 Introduction

1.1 Dynamic & Interactive Environments (DIVEs)

External environments are more than just one's physical surroundings to be perceived through our senses; they are arenas for continuously flowing action. In a very real sense, both a 'static environment'—an environment impervious to change—and a 'passive environment'—an environment impervious to change *by an agent*—are deeply unnatural phenomena. In the real world, nearly all environments are both *dynamic* and *interactive* with a near-infinite number of ways in which they change based on how we interact with them. A dynamic and interactive environment offers an important dimension in studying what brains do because it allows perceptions and actions to be fluidly updated through the feedback of actions and effects *within* that environment (Chiel & Beer, 1997; Wolpert & Flanagan, 2001). This type of environment facilitates what has been called *enactment*—cognition as generated through the interactive and fully engaged agent using perceptually guided action—which is what brains do naturally (Varela et al., 1991). Given the universal tendency for brains to operate within the context of these environments, this raises the question of whether it is even possible to understand what the brain is actually doing when enactment is removed from the equation. This study tackled this question by incorporating video games as a form of dynamic and interactive *virtual* environment (DIVE). DIVEs facilitate dynamic and contiguous perception while also incorporating a (virtual) environment in which dynamic actions and environmental effects can feed back onto perceptions for a 'closed-loop', cyclical effect. In this sense, closed-loop experiments can be viewed as enactive by incorporating environmental feedback in a continuous cycle, as opposed to 'open-loop', which examine only feedforward processes with minimal feedback (see *Figure 1*).

The term 'closed-loop' has been used in the description of systems for a wide variety of contexts and disciplines from circuits to chemical bonds, each with subtle differences meaning. I wish, therefore, to clear up any ambiguity in meaning at the outset. For the purposes here, when referring to a closed-loop system, I am speaking explicitly about systems with two main criteria. First, feedback must occur between all components of agent perception, agent action and the environment in which the agent is situated. Second, the state of the environment must be amenable to changes by a situated agent. This latter component would thereby imply that agency—a state of control over one's actions within an environment—is a necessary element in this type of closed-loop system. Agency should, therefore, be considered necessary to closed-loop perception-action-effect systems. Given its importance to closed-loop, agency's role as a key component in this study will be discussed more in depth.

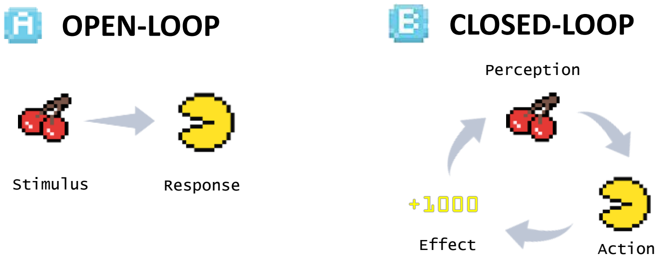


Figure 1: Illustration of Open vs. Closed Loop Systems

This illustrates the difference between 'open-loop' and 'closed-loop' paradigms; A) depicts an 'open-loop' paradigm in which stimulus-response is isolated as a feedforward process. In this example, the stimulus (cherry) elicits a response (approach); B) depicts a 'closed-loop' paradigm in which perception-action-effect are integrated as contiguous feedback cycle. In this example, the perception (cherry) elicits an action (approach), which, in turn, elicits an effect (points popup). The points popup is then perceived, and the cycle continues.

1.2 Current Practices in fMRI

The methods used in fMRI have improved dramatically since its initial development only thirty years ago. It began with a highly reductionist approach, using subtractions between rigidly constrained stimuli or tasks to isolate perceptual, cognitive or motor processes (Poldrack, 2010; Roland, 1993). Although this approach has been powerful, it is also often limited by the need for tightly controlled comparisons between conditions, difficulties with the underlying assumptions (Friston et al., 1996), and the need for an endless range of condition contrasts to study the full gamut of brain processes. As technology and techniques alike have improved, so too have the approaches of researchers. Neuroscience has begun to shift towards embracing complexity, both in the way we view cognition as an integrative system and the kinds of inferences we can make when measuring it.

Steps towards an appreciation of the dynamic and interdependent nature of cognition have followed the rise and success of resting state scans, which have been largely influential in highlighting the interplay of functional networks (Deco et al., 2011). Due to the inherent lack of external stimuli, resting state scans initially had only one task that could be reliably correlated with brain activity: rest. Rather than discovering a specific region for rest, researchers discovered a network of regions that underpinned this purportedly ‘default’ state, which came to be canonized as the default mode network, or DMN (Raichle et al., 2001). This discovery of the DMN helped to transition the field away from a modular approach to the brain—a view in which there is a one-to-one mapping of neural real-estate and external event—and towards the view that the brain is a many-to-many system (also known as the principle of *degeneracy* (Tononi et al., 1999)). The shift highlighted a major new development in assessing brain-event relationships: intrinsic functional connectivity (Raichle & Snyder, 2007). Functional connectivity, in its simplest form, is a statistical method in which temporal correlations are made between prescribed regions or networks in the brain to determine whether a relationship exists (Eickhoff S.B. & Müller V.I, 2015). It is important to note the caveat that functional connectivity, unlike *effective connectivity*, is purely correlative in nature and thus, on its own, cannot be used to establish causal influence of neural coupling (Friston, 2011).

Despite the success of resting state, the lack of interactions with the external environment limits real-world applicability (Finn, 2021). Acknowledgement of the limitations in using over-simplified or purely internal stimuli has led to a call for more naturalistic methods when looking at functional connectivity, with more researchers beginning to answer it. The resulting forays into the frontier of naturalistic paradigms have been impressive, offering unique insights within domains inaccessible to most of the common experimental models thus far (Jääskeläinen et al., 2021; Sonkusare et al., 2019). One type of naturalistic method involves the use of narratives in the scanner. Participants are told stories while undergoing fMRI, which afford participants the opportunity to self-generate the accompanying imagery. It has also yielded distinct patterns of connectivity, differentiating it from resting-state (Jääskeläinen et al., 2021). Of course, these narratives are still pre-determined by an external agent, precluding them from being truly enactive in nature (Tikka & Kaipainen, 2014).

Another major type of naturalistic paradigm gaining traction involves having subjects passively watch movies while undergoing fMRI. These so-called “movie paradigms” have shown great promise in providing reproducible, region-specific functional activation patterns without the need for an overly complicated design (Hasson, 2004; Hasson et al., 2008; Naci et al., 2014; Sun et al., 2012). More important, however, they have succeeded in capturing different functional connectivity patterns from those found in more traditional paradigms, like stimulus-response and resting-state approaches (Aliko et al., 2020; Meer et al., 2020). Further still, they demonstrate greater predictive power with respect to both behavior and trait assessment (Finn & Bandettini, 2021). This suggests that by eliminating the rigid boundaries around ‘stimuli’ and allowing perception to continuously flow through a dynamic external environment, the brain is functioning in ways we have historically failed to capture. Although movies have served as a step in the right direction for naturalistic studies, they are limited by being fundamentally passive. Task-based designs involving cognitive control have shown that functional networks communicate differently than they do under passive conditions that lack this same element of cognitive control (Cocchi et al., 2013; Moraschi et al., 2020). If this is the case, we might *also* suspect that by eliminating the rigid boundaries around ‘responses’ and instead allowing perception *and action* to continuously flow through an *interactive* dynamic environment, there may be *considerable* differences in the patterns of brain activity that are not typically reflected in traditional paradigms.

1.3 Ecological Validity & Embodiment

A core assumption of a functional magnetic resonance imaging (fMRI) experiment is that the results obtained are indicative of what brains do in real-world environments. This allows researchers to translate their findings into neurological, psychological and cognitive models that can spur new treatments, technologies and techniques that work well, even outside of the laboratory. If a tightly-controlled, experimental model fails to replicate an effect under more naturalistic conditions, such a model ought to, at best, be considered limited. In this way, the inclusion of naturalistic conditions can serve as a standard to measure the completeness of a model derived from more traditional stimulus-response paradigms (Felsen & Dan, 2005); the more naturalistic elements incorporated, the more robust the standard. But fMRI experiments contend with unique difficulties, given the natural restrictions the machine itself places upon perception, action and the environment. These difficulties impact the ecological validity of experiments, which, in turn, can hamper the efficacy of our models to foster new discoveries. A great deal of creativity on part of researchers has begun to address this problem with an effort in bringing more naturalistic paradigms into the scanner. As mentioned, one of these major developments in this pursuit has been the introduction of movie-watching paradigms.

Movie paradigms have been boasting many advantages when combined with fMRI neuroimaging. One of the major drawbacks of classic experiments is the lack of multimodal integration with dynamic contexts that unfold over time, which makes the inferences drawn from them difficult to extrapolate to real-world scenarios (Sonkusare et al., 2019). Moreover, as fMRI techniques become more advanced, the ability to assess temporal dynamics of brain activity has begun to improve (Lindquist et al., 2014), thereby widening the kit of researchers seeking new breakthroughs in neuroimaging. This makes studies involving dynamic stimuli, like movie-watching paradigms, all the more valuable.

The quest for increasingly naturalistic paradigms has been greatly served by movie-watching paradigms, but there are a few key ways in which their ecological validity may fall somewhat short. First, though movies offer naturalistic stimuli, these stimuli are *highly* curated in ways that simply do not occur in real-world environments. Camera angles, editing and style of direction are some of the tools used to evoke highly specific reactions and experiences for viewers (Hasson et al., 2008). If one of the major contributions of movie-watching paradigms towards ecological validity is the dynamism of the stimuli, it ought to be considered that many of the transitions between events, scenes and shots are artificially inducing patterns of activation to serve the portrayal of a narrative, rather than arising as organic phenomena in their own right. It may be that the latter case produces something fundamentally different from the former.

The second feature to consider about movie-watching paradigms is that they are intrinsically passive activities; there is no interactivity or agency of any kind. The degree to which this is a difficulty is still controversial, but there is some evidence to suggest that, in light of the brain's evolutionary history, "[it] should be understood as an actionoriented system," embodied within the context of an interactive environment (Anderson & Chemero, 2016). This may be especially important when considering the role of the cerebellum, which has been argued as a key player in facilitating an embodied cognition, through which thought is made possible (Koziol et al., 2012). While this debate is far from settled, we still must contend with the fact that a large proportion of what the brain does is facilitate action. Ignoring this aspect of cognitive function is likely to, at the very least, make our models of the brain incomplete. Indeed, the results of the present study also seem to suggest that perhaps something different is occurring with the inclusion of action and environment in closed-loop fashion. This is an avenue worth exploring, and DIVE paradigms might be the way to further our empirical toolkit in combining this philosophical approach with practical neuroscience methods.

1.4 Current Experiment

The goal of this project was to sustain the gains achieved through movie-paradigms while also pushing them a major step further to close the loop through the addition of agency in an interactive environment. I chose to use a form of DIVE in which a video game—Pac-man—served as the external environment while subjects underwent fMRI. While it is certainly the case that there are other, more realistic games on the market, the simplicity of Pac-man is a major asset in this initial stage of exploration; events and game states are more easily defined and objectives are clear, simple and straightforward for participants to engage with. Nevertheless, despite this simplicity, Pac-man still offers up a wide assortment of engagement opportunities, with participants navigating mazes, claiming rewards, fleeing hostile foes and climbing their way up the leaderboard. The diversity of task types provided ample opportunity for feedback through perception, action and environmental effects from a wide variety of functional networks. If even a game as simple as Pac-man were to show that the introduction of dynamic and interactive components evoke substantial changes in brain processes, this proof-of-concept demonstration would open the DIVE approach to be extended to more realistic games that tap into an even broader range of cognitive functions.

Given the sheer size and scope of this data set, there are innumerable ways in which to analyze it. These include: investigation of specific regions for differences in activation levels, examination of how in-game events evoke changes in activation patterns, or the incorporation of different types of connectivity to examine how brain states temporally impact each other or shift over time. Ultimately, my hope is that the results herein spark sufficient interest and curiosity that these avenues may constitute exciting follow-up projects, but for this project, in particular, I chose to analyze intrinsic, network-level functional connectivity between conditions for several major reasons. First, the case I am attempting to make is that active control within an immersive environment changes the way in which functional activity unfolds when compared to passive perception of an environment. A study of functional connectivity provides a data-driven way to examine large-scale differences in brain processes without needing prior hypotheses about specific regions or interactions (for which there are many possibilities but limited theoretical context). Second, this study aims to be a stepping stone in ushering neuroscience towards viewing the dynamic interaction of perception, action and environment as a key determinant of brain activity. It is necessary to first demonstrate *that* a fundamental difference exists in a DIVE through *intrinsic* functional connectivity, before examining *how* the differences unfold through *dynamic* functional connectivity.

This study began with a broad but simple hypothesis: brains will act differently in the context of a dynamic, interactive environment than when in a dynamic, passive environment. Indeed, I predicted that the variable of active control would be sufficiently robust that an effect would be evident even in virtual environments, where action is indirect. In order to assess whether the inclusion of a DIVE had an impact on patterns of brain activity, I examined functional connectivity under three different conditions: Play, Reactive Replay and Passive Replay. The Play condition allowed participants to exert control over their environment (using a controller) through the Pac-man avatar in a closed-loop way; effects within the environment were based upon participant actions within that environment. The Passive Replay condition acted as a proxy for movie-paradigms in which participants passively observed actions occurring in a non-interactive environment. To ensure that any differences observed were not due to the difference in motor movement from using the controller, I also included the Reactive Replay condition. In Reactive Replay, participants watch an identical replay, but in this case, participants retroactively follow Pac-man’s movements using the controller. The major benefit of

Reactive Replay is that it provides a condition in which both visual input and motor responses are matched to play. The primary difference between these two conditions is the order of action and effect: in play, motor actions precede environmental effects, whereas in Reactive Replay, environmental effects precede motor actions—in Play, participants had control in an interactive environment and in Reactive Replay, they did not. By comparing the Play condition with the Reactive Replay condition, I was able to assess whether the variable of environmental interactivity had an effect on functional connectivity while controlling for both sensory stimulation and motor responses.

Chapter 2

2 Materials and Methods

2.1 Experimental Design

In this study, participants both played, and watched replays of, a customized version of the classic arcade game “Pac-man” while they underwent fMRI. Each session was broken up into three separate run types: Play, Reactive Replay, and Passive Replay (*Figure 2*).

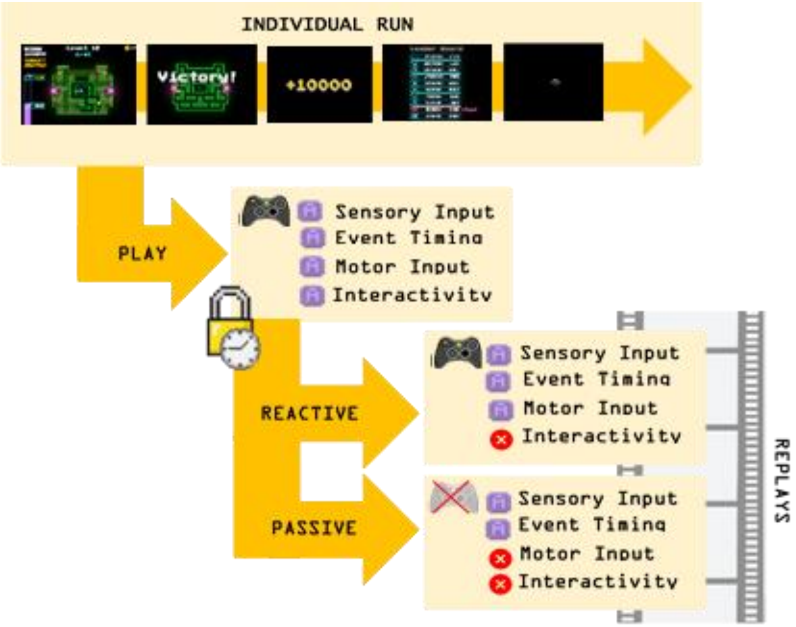


Figure 2: Illustration Showing Variable Comparisons for Each Condition

Individual runs (top) consisted of participants either playing a full run of Pac-man, or watching a replay of a full Pac-man run. The Play condition is always first, followed by both replay conditions in alternating, sequential order. These replays are time-locked to Play, as indicated by the lock icon. The controller icon depicts the conditions in which the controller is used. The ‘A’ depicts whether the variable adjacent to it is both present and matched with the Play condition.

Play: Participants controlled a circular yellow avatar (Pac-man) through which they navigated mazes and gained points to attain the highest score possible by completing levels, and eating pellets, ghosts, and cherries. During play runs, participants had full control over game events. For example, if a participants moved the trackball to the right, the Pac-man avatar would move to the right.

Reactive Replay: Participants watched the replay of their most recent play run and used the controller to reactively follow the movements of the Pac-man avatar; in this case, *without* any control over in-game events. For example, if the participant saw Pac-man turn right, they moved the trackball to the right.

Passive Replay: Participants watched the replay of their most recent play run without any interactivity with *either* the game controller *or* the in-game events. Participants did not make movements with the controller.

By necessity, play runs always came before both types of replay runs. Reactive replay and passive replay condition runs were presented in counterbalanced order. All replay conditions were time-locked to their most recent play run, creating a triplet of runs, with each run in a triplet containing the same number of volumes (see *Figure 3*). Upon completion of a run triplet, players began a new triplet in which they started with the play condition (see *Figure 3*). Sessions lasted up to three hours and were comprised of two to four triplets (with the variation based on player performance).

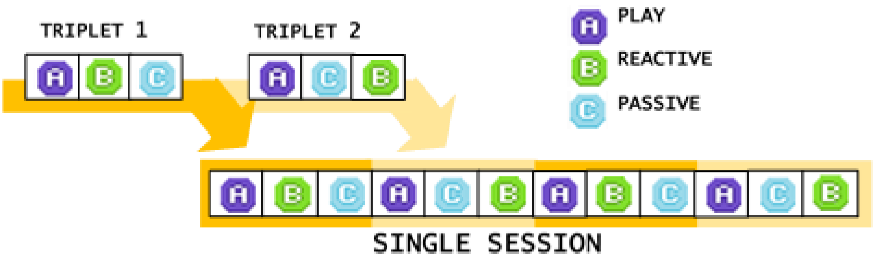


Figure 3: Illustration Demonstrating Condition Counterbalancing

This figure illustrates the counterbalancing of the three run types. Play, as represented in purple, is first in each triplet. Reactive and Passive Replay (represented in green and blue, respectively) we presented in alternating order during a single session.

Each run began and ended with a 30-s fixation period in which participants were instructed to maintain their gaze on a central cross on a fixed screen. Total run time was variable and based on player performance during play time. Play time, by contrast, constituted only time in which the participant was *in control* of the Pac-man avatar, and was capped at eight minutes per run. Play time was paused (or prematurely terminated, in the case of a ‘Game Over’ event) based on any of the four potential event sequences:

Level Completion: A *level-completion event* was initiated the moment Pac-man consumed the last pellet on the map. As soon as a level was completed, play time was paused until the subsequent level began. Upon completing a level, participants viewed a 'Victory!' screen, received 10,000 points and viewed the game screens in the first sequence as shown in Appendix A. After the final frame of this event sequence completed, the play sequence began again for the next level, beginning with the fixation cross and subsequent ready screen.

Death: A *death event* was triggered when a participant's Pac-man avatar collided with a ghost in the Scatter/Chase state (see *Figure 4* below). As soon as a death event was triggered, play time was paused until the subsequent level began. Participants began each game with five lives and lost one each time a death event occurred. If a death event occurred with lives remaining, the play sequence began again after display of a leaderboard. Player score, level, number of ghosts, number of pellets carried over to the next attempt, but Pac-man's position and ghost positions were reset to their defaults.

Figure 4: **Ghost Status Images**

This illustrates the different sprites used for the ghosts in different mode types; Scatter/Chase indicates the ghost is moving around the map and can initiate a death event. Frightened indicates the ghost can be eaten and temporarily removed from play. Retreat indicates the ghost has just recently been eaten and is temporarily removed from play.

Time's Up: Players began each Play run with an eight minute play-time timer. A '*time's up*' *event* was be triggered once the play-time timer at the top of the screen reached zero. At the end of this sequence, the fixation cross appeared for 30 seconds instead of 10, and game time was terminated. Participants picked up where the *time's up* event occurred during the next play run (provided it was not the final play run of the session). Player score, level, number of ghosts, number of pellets carried over to the next play session; only Pac-man's position and ghost positions were reset to their defaults upon resuming the game.

Game Over: A *game over* event was triggered when a participant's remaining lives reached zero. A game over event prematurely terminated the play time, resulting in the end of a run after the last frame of the *game over* sequence finished. Participants would begin a brand new game of Pac-man on the next play run, starting from level one with five lives and zero points.

2.2 Pacman Simulation

The Pac-man simulation was designed in Unity version 2019.4.19, which was used as both the game engine and the development tool. An image capture of the game screen can be seen in *Figure 5* below:

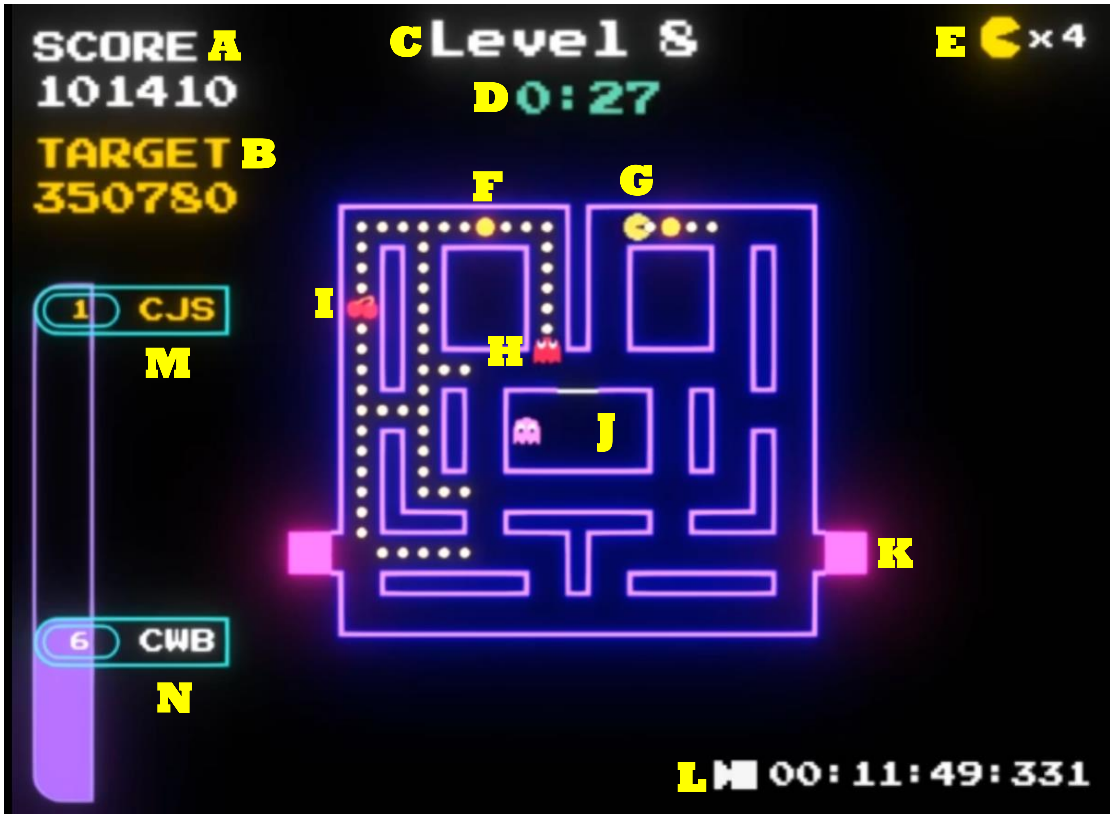


Figure 5: Screen Capture of Pac-man Simulation

A) *The players current score accumulated throughout the play session;* ***B)*** *The current high score at the top of the leaderboard. This score is the same for every participant and does not change. It was selected to be extremely difficult to surpass in the amount of time allotted;* ***C)*** *The current displayed level the player is on;* ***D)*** *The play time remaining in the current play session in minutes and seconds;* ***E)*** *The number of lives remaining for the player; each player starts the game with 5 lives;* ***F)*** *A power pellet, which causes ghosts to switch to the' frightened' state temporarily;* ***G)*** *The Pac-man avatar controlled by a player;* ***H)*** *A ghost currently in the 'scatter' state;* ***J)*** *The 'ghost house'. Ghosts remain here for a short duration at the beginning of the level and after they are eaten. While in the ghost house, ghosts remain in the 'stop' state;* ***K)*** *Warp gates in which Pac-man can enter into one side and be teleported out of the other warp gate. The gates are bidirectional;* ***L)*** *The amount of total time that has elapsed since the game session began;* ***M&N)*** *A model showing where the current player is in relation to the top score on the leaderboard. Each player chooses a 3-letter username which is demonstrated in* ***N)****.*

Game data acquisition consisted of 98 separate variables, including game state information such as ghost positions (separate variables for each ghost), Pac-man positions, cherry appearance times, etc. The recording of each variable was synchronized such that each was recorded during the exact same moment of a cycle or *game state*. These game states were captured at a refresh rate of 60 Hz such that each second contained 60 game state captures at roughly consistent intervals (with a 0.01-ms fluctuation occasionally found at some intervals). The variables involved in monitoring controller direction and pressure were collected through the use of the *Current Designs* Trackball 2 fiber optic trackball mouse which uses a two axis encoder for moving the mouse pointer. Input from the encoder came in the form of a two-dimensional vector (x,y) where x was the horizontal input from the user, and y was the vertical input. The input was manipulated such that the raw values from the track ball were interpolated to cover a small amount of time. This interpolation was necessary to avoid jittery changes in the direction, allowing for more intentional input. The processed input from the trackball was also clamped on each axis to a range of -1.0 to 1.0

The goal of the game was complete levels and attain the highest score possible in the allotted time. The simulation included a ‘Leaderboard’ comprised of artificial scores and usernames; the information that these were artificial scores was withheld from participants. The difficulty of the game was determined largely by the skill of the participant. Difficulty would increase with each level, and variables such as number of ghosts, ghost speed and size of map were modified based on how quickly a participant completed levels and avoided death events. The artificial scores and attenuation of game difficulty, based on player skill, was determined such that participants would typically end the session in the second position of the leaderboard, relatively close to the first. This was done to maintain motivation to increase participant score, irrespective of skill level. No players surpassed the second position on the leaderboard. Only one participant failed to reach the second position by the end of the session.

During the play condition, participants interacted with various elements within the game screen. The key variables that underwent real-time changes based on user input were as follows:

Pac-man: A player-controlled avatar, which moved along either the x or y axis of the map (provided no walls impeded the path).The speed of Pac-man remained fixed and, once the game began, movement was continuous unless Pac-man encountered an obstacle. This movement was generated through player interface with the mouse trackball.

Ghosts: Up to four ghosts that moved along either the x or y axis of the map. Movement speed of the ghosts increased slightly with difficulty. The game began with only one ghost active (red) with the number of ghosts increasing, based on level and difficulty, to a maximum of four (adding pink, blue and orange, in that order).

Cherries: Rewards appeared as cherries at random time intervals and at random, navigable locations on the map. Only one cherry was present at a time. Cherries remained on the map until eaten or until the level ended. When eaten, they disappeared and text demonstrating the value of points obtained (1000) briefly appeared at the site in which they were eaten.

Power Pellets: Each map initially began with four power pellets in total; one in each corner of the game map. If Pac-man consumed one of these power pellets, ghosts immediately entered the ‘Frightened’ state (see *Figure 4*) and the power pellet disappeared. Each power pellet eaten by Pac-man yielded 50 points.

Pellets: These appeared as small white dots throughout the corridors of the game map. When Pac-man ate these pellets, they disappeared. Each pellet eaten by Pac-man yielded 10 points. A level was completed when all pellets were cleared from the map.

2.3 Participants & Data Collection

Data was acquired from 24 healthy, right-handed participants ranging in age from 19-38 (median age 24; 14 female) with no known underlying, preexisting neurological conditions and with normal or corrected-to-normal vision. Participants were recruited through both Western University's Our BrainsCAN participant registry and word-of-mouth recruitment. Each participant provided informed consent and was compensated for their time. All experimental procedures used within this study were approved by the Western University Non-Medical Research Ethics Board.

Upon arrival, each participant was given an information letter describing the experiment and consent form to be signed; the information letter described, in general terms, what they would be doing during the session and address potential risks of MRI. Participants then completed the Edinburgh Handedness Questionnaire to assess handedness, with all participants scoring as unequivocally right-handed (>300). Next, participants were asked to complete a Pre-Scan Questionnaire with six questions using Qualitrics^{XM} software to gather preliminary data on prior video game experience and habitual engagement in gaming activities; the full survey is included in the supplemental materials. After completion of the Pre-Scan Questionnaire, participants were given a brief explanation of the experiment, what to do during each of the three condition types (Play condition, Reactive Replay condition and Passive Replay condition) and were given a brief explanation on how to play the modified version of Pac-man (described in detail below). Instructions included only game mechanics; no strategic information was provided. Finally, a short practice session was performed outside of the scanner, with the in-game timer set to five minutes. This five-minute practice time gave participants the opportunity to familiarize themselves with the controller and game-mechanics. After exiting the scanner, participants were given a Post-Scan Questionnaire with 12 questions based on subjective evaluations of in-game events and were compensated for their time.

2.4 fMRI Data Acquisition

Scanning utilized a 3-Tesla Siemens Prisma Fit scanner at the Centre for Functional and Metabolic Mapping at the University of Western Ontario. Structural scans used T1-weighted imaging (TE = 2.93ms; MP2RAGE, 1-mm isotropic resolution; 4° flip angle; Slices = 176). Functional scans, based on the blood oxygenation level-dependent signal used T2*-weighted scans, which were acquired using a multi-echo (ME) gradient-echo echo-planar imaging sequence (TR = 1000 ms; TE_1 = 13.2 ms, TE_2 = 30.1 ms, TE_3 = 47.2

ms; 2-mm isotropic resolution; 40° flip angle; Slices = 52). Data was collected using a 28-channel head coil (modified from a 32-channel by removing coils over the eyes) adapted to reduce visual occlusion of the screen. Participants lay supine and viewed a projection screen (26.6 cm wide, 20 cm high) through a 45° mirror at a viewing distance of 70 cm for a visual angle of 21.5° wide x 16° high. Heart rate and respiration rate were acquired continuously during scan sessions through the use of an integrated pulse oximeter (affixed to the right index finger) and respiratory belt.

2.5 fMRI Data Preprocessing & Quality Assurance

Preprocessing utilized open-source pipelines: fMRIPrep (Esteban et al., 2019), Tedana (Kundu et al., 2012) and the CONN Toolbox (based out of SPM12, Whitfield-Gabrieli & Nieto-Castanon, 2012). Quality assurance was performed at all stages. Data exclusion was determined on fully preprocessed data through the use of MRIQC (Esteban et al., 2017).

During pilot testing, some participants became so immersed in game play that abrupt motion artifacts occurred; as such, for the experiment participants, I took additional steps to minimize the effect of head motion on data quality and to quantify and compare motion across the three game states. Most notably, I implemented multi-echo imaging and applied a multi-echo independent component analysis (ME-ICA) pipeline using the Tedana, TE-Dependent Analysis, Python library (tedpca algorithm, aic; Kundu et al., 2012) in order to minimize the impact of motion artifacts on data. In one pilot participant, we confirmed that this pipeline was effective in greatly reducing the impact of head motion on data quality (Buur et al., 2009).

The preprocessing pipeline used on this data set is was follows: first, data was minimally preprocessed using fMRIPrep version 21.0.0 for standard motion correction, slice timing correction and susceptibility correction; motion was estimated using the first echo of the time series. Motion parameters and their derivatives were calculated by fMRIPrep and recorded in the list of confounds to be used to testing correlation of motion artifacts with functional connectivity correlation strength. No participants or runs were excluded due to motion.

The next stage of the preprocessing pipeline was the multi-echo ICA denoising (ME-ICA) using Tedana version 0.0.11 (Kundu et al., 2012). Tedana's approach combines both a principal component analysis and independent component analysis and then ascertains whether these components are TE-dependent or TE-independent. The former are considered to be BOLD components and are retained whereas the latter are classified as non-BOLD and the timecourses are cleaned from the data (Kundu et al., 2012). The denoising process for Tedana involves three steps: decomposition, metric calculation and component selection. In decomposition, PCA is used to reduce the dimensionality of the data to prepare it for ICA. Components from Tedana's principal component analysis (tedpca) components were selected with a seed of 42 using the Tedana '*aic*' tedpca component selection, which. The tedpca algorithm is used for classifying components as 'accepted' or 'rejected' based on the kappa and rho distributions that characterize multi-echo datasets) algorithm. 'Aic' is a balanced approach without being too liberal or conservative in selecting components. After the tedpca step, ICA is performed and metric selection begins such that BOLD and non-BOLD components are classified. Finally, in component selection, the non-BOLD timecourses are removed from the data. For the small number of unclassifiable components that were classified as 'ignored', Rica was used for manual classification; 'ignored' components within the 30th percentile for kappa and rho variables were manually included and excluded, respectively. This manual classification was incorporated into the categorization output for Tedana with which the multi-echo data was optimally combined and denoised. The structural and anatomical data was then converted into 2-mm MNI template space and segmented using SPM12. The final denoising phase was done through the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), in which the timecourses of the cerebrospinal fluid regions were regressed out, and a band-pass filter of 0.008-0.09 Hz (preserving fluctuations between 11 and 125 s/cycle) was applied after regression.

2.6 fMRI Data Analysis

ROI-to-ROI Functional Connectivity: Functional connectivity was assessed using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). I segmented the cortical, subcortical and cerebellar areas into 133 regions-of-interest (ROIs) and networks-of-interest (NOIs) through the use of three separate atlases: the Schaeffer 100-parcellation, 2-mm cortical parcellation (Schaefer et al., 2018), the Melbourne SI 16-parcellation subcortical, 2-mm subcortical atlas (Tian et al., 2020) and the Buckner 17-parcellation, 2-mm cerebellar atlas (Buckner et al., 2011). The average timecourse of each region was used to calculate the Pearson correlation coefficients between each pair of ROIs. These correlation coefficients were Fisher *z*-transformed (to make them normally distributed). For the correlation between each pair of ROIs, a one correlation coefficient of each individual ROI when compared to each other ROI. A one-sample *t*-test was used to determine whether the correlation different significantly from zero, with a false-discovery rate (FDR) correction applied based on the number of comparisons within a given condition as outlined in Benjamini & Hochberg (1995).These thresholded correlation coefficients were organized into one correlation matrix per condition with the diagonal—comprised of perfect, self-correlations which necessarily had a perfect correlation—excluded.

***Subtraction Matrices*:** To better highlight the differences between conditions, subtraction matrices were generated using the Fisher z-transformed correlation coefficients obtained for each ROI in the ROI-to-ROI Functional Connectivity calculation. The additional step of subtracting the correlation coefficients of one condition matrix from another condition matrix was performed to control for the similarities in connectivity between conditions. Thresholding for significance was conducted using a paired-samples t-test at $p < 0.05$ (FDR-corrected for the number of comparisons within the contrast).

Network-Level Functional Connectivity: Functional connectivity for the cortical atlas was also conducted at the network level. Each ROI in the cortical parcellation corresponded to one of 17 resting-state networks, as outlined in Yeo et al. (2011). For a full list of all ROIs and, where applicable, their correspondent networks, see Appendix A. The correlation coefficient of each ROI was grouped with other ROIs within the same network and an average of these correlation coefficients was obtained for each network. The 17 cortical networks chosen were the same 17 networks delineated in the cerebellar atlas (Buckner et al., 2011). Further, the subcortical atlas ROIs (originally differentiated by left/right hemisphere), were each combined with their corresponding homotopic partner and an average of their correlation coefficients was calculated. A matrix with cortical and subcortical ROIs grouped into networks, and existing cerebellar networks, was generated and was thresholded for significance using a one-sample *t*-test at $p < 0.05$.

2.7 Eye-Tracking

One possible explanation for any differences between conditions is a difference in eye-movement patterns. In order to rule this out, I conducted a behavioral study to test for these differences. Ten healthy, right-handed participants (5 female, median age 37; four of the ten participants were also included in the fMRI study) with normal vision and no underlying neurological issues had their eye movements tracked while playing Pac-man. Data collection and stimuli conformed exactly to the procedures outlined in section 2.1 and 2.3 with the only difference being session length. Eye-tracking sessions were limited to one hour and two runs of each condition type were collected for each participant, irrespective of participant performance. To facilitate this, play time was limited to eight minutes total. Participants were seated in front of a screen with a viewing distance of 40 cm. An EyeLink 1000 (SR Research) was used to collect eye-position (both eyes) data at 1000 Hz. I analyzed data for several forms of eye movement: number of saccades, number of blinks and x/y coordinates. One participant was excluded as an outlier from the data analysis for number of blinks because they demonstrated a blink rate 400% above average. Calibration was done using the built-in nine-point calibration script, and subsequently verified using the same nine-point script. The experiment was conducted once a rating of ‘good’ was obtained according the EyeLink software.. Data analysis of eye tracking data was done through the Edf2Mat Matlab Toolbox v.1.6 (Adrian Etter, 2013).

Chapter 3

3 Results

3.1 ROI-to-ROI Connectivity

I began the data analysis with an ROI-to-ROI comparison in order to examine the intra-network functional connectivity patterns, and how they might be related to inter-network connectivity overall. *Figure 6* shows the results of the ROI-to-ROI comparison in a correlation matrix, with each cell representing a correlation coefficient between two regions and thresholded for statistical significance ($p < 0.05$, FDR-corrected). All three conditions exhibit overlap in functional connectivity patterns, but these results also demonstrate two major differences when comparing Play against Reactive Replay and Passive Replay. First, intra-network connectivity appears to be significantly more robust in Play. Those clusters which are bisected by the diagonal represent regions within the same networks and indicate intra-regional connectivity. Those clusters which are bisected by the diagonal represent regions within the same networks. Second, inter-network connectivity also appears more robust in Play. This can be most plainly observed in the strength and pervasiveness of the anti-correlations between networks.

One particularly interesting relationship is the anti-correlation between the regions within the DAN and DMN. This relationship has been highlighted, with DMN regions contained within the purple dashed lines and DAN regions contained within the green dashed lines. Note the conjunction of these networks demonstrates some degree of anti-correlation in all three conditions but that the strength of this anti-correlation differs markedly in the play condition when compared with both replay conditions. In play, anti-correlations between the DMN and DAN regions appear to be more robust. Indeed, this robustness of anti-correlation in play is not limited to ROIs within the DMN/DAN conjunction and can be seen in most of the negatively correlated clusters across conditions. This effect also appears particularly striking within the cerebellar comparisons.

The visible difference in the degree of intra-network connectivity is highly evident for ROIs *within* the default mode network. This appears paradoxical in light of early studies that found a reduction of activity in the DMN during tasks, and, thereby affording it the familiar term, “task-negative network” (Raichle et al., 2001; Shulman et al., 1997). More recently, however, some studies have been demonstrating an increase in intra-network connectivity of the DMN during a variety of tasks including motor, executive function and narrative comprehension tasks (Chai et al., 2012; Crittenden et al., 2015; Vatansever et al., 2015). The increased intra-network connectivity of the DMN during Play further corroborates the idea that the DMN may play an active role during complex tasks requiring external attention.

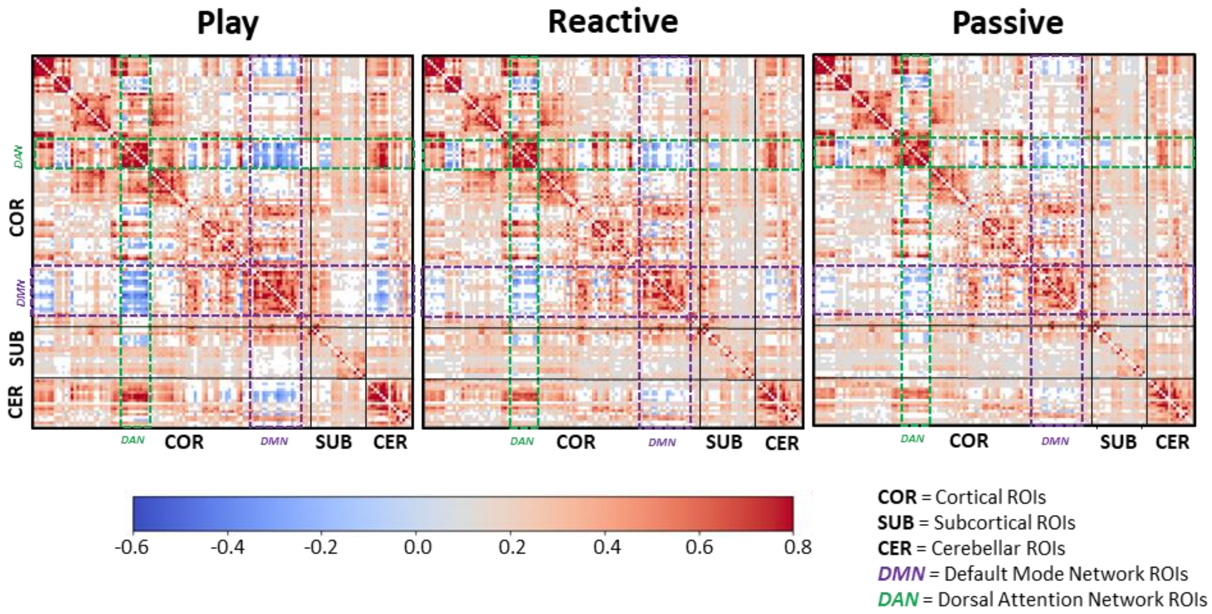


Figure 6: ROI Correlation Matrices for Play, Reactive Replay and Passive Replay

*Each cell in the matrix represents a single correlation coefficient indicating the time-course similarity between two regions, thresholded to indicate correlations significantly differ from zero. Each region is located within one of three anatomical domains: cortex (**COR,** n=100), subcortex (**SUB**, n=16) and cerebellum (**CER**, n=17). The black lines within the matrix indicate boundaries between anatomical domains with adjacent labels indicating which anatomical domain the regions correspond to**.** The colour scale indicates correlation strength and direction; dark red indicates a strong positive correlation between two regions and dark blue indicates a strong negative correlation between two regions. Green dashed lines indicate regions within the Dorsal Attention Network (DAN) and purple dashed lines indicate regions within the Default Mode Network*

To highlight the differences between conditions, I have included subtraction matrices which were generated by subtracting the correlation coefficients from the original correlation matrix (*Figure 6*) of a single condition from the correlation matrix of another condition and thresholding for significance ($p < 0.05$, FDR-corrected) (see *Figure 7*). A large discrepancy in the number of significant relationships both within and between networks can be observed between Passive vs. Reactive Replay. Strikingly, Play shows prevalent differences when compared to both Reactive Replay and Passive Replay conditions across many regions and networks, demonstrating a unique clustering pattern indicating enhanced connectivity at both intra- and inter-network level.

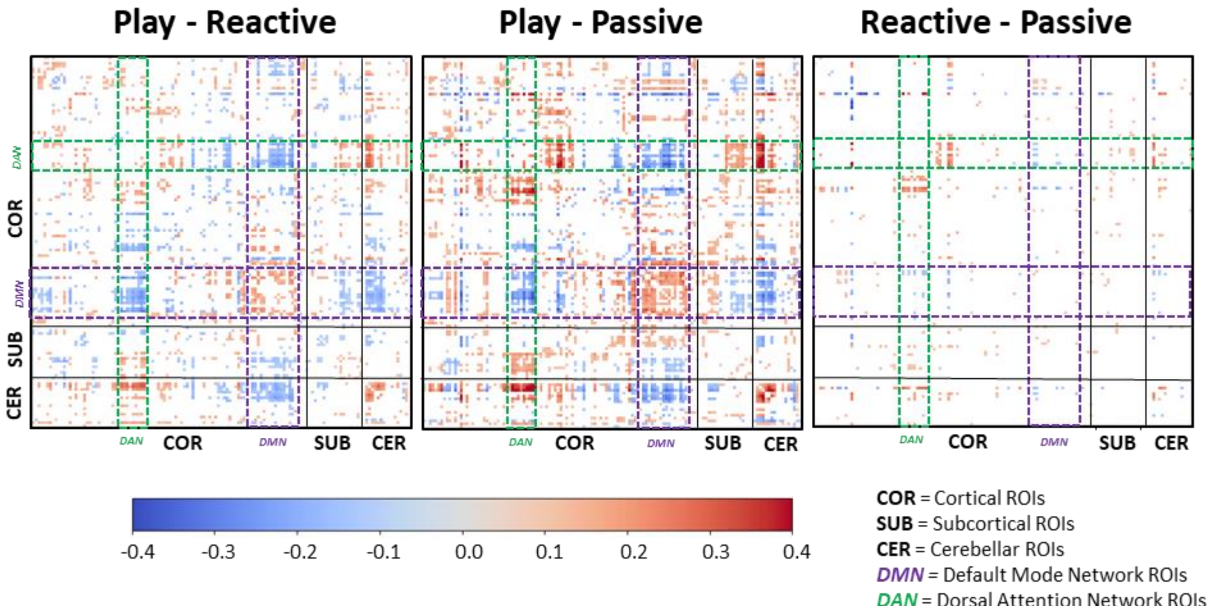
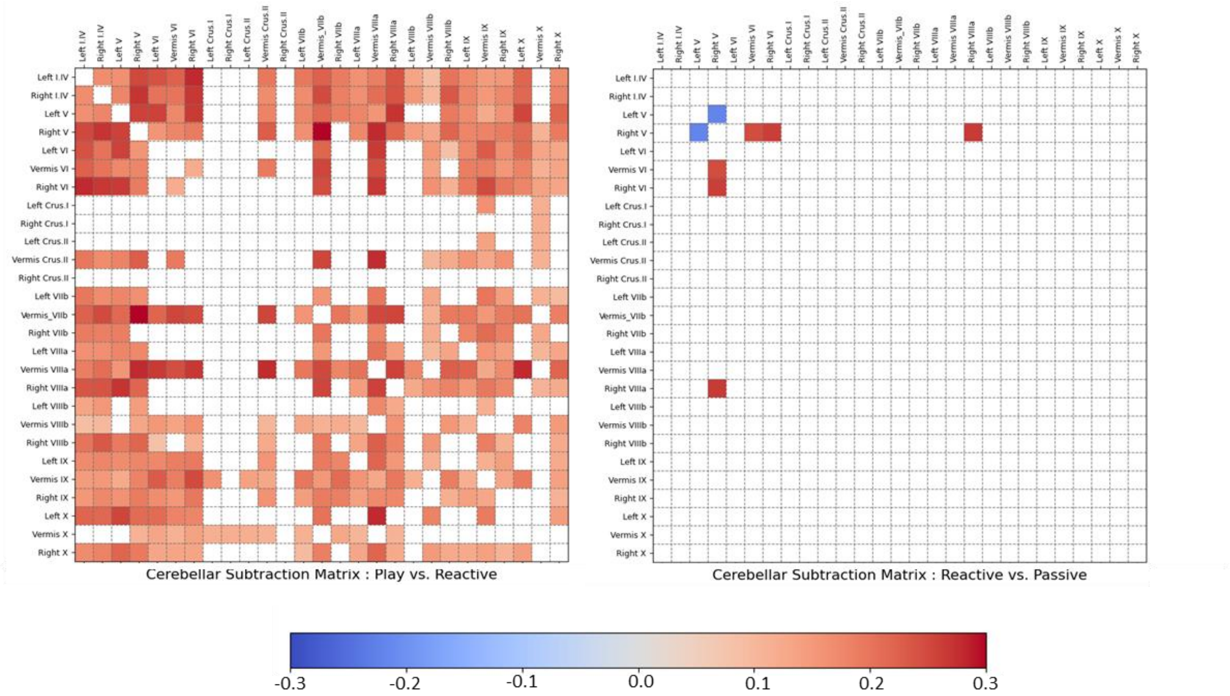


Figure 7: ROI Subtraction Matrices for Play, Reactive Replay and Passive Replay

Subtraction matrices for each condition pairing: [Play – Reactive], [Play – Passive] and [Reactive – Passive], thresholded for statistical significance. Each cell in the matrix represents the remaining correlation coefficient of two regions after subtracting the corresponding correlation coefficient from another condition.

One interesting finding that arose upon examination of the ROI-to-ROI correlation matrices was the differences in cerebellar activation patterns when comparing [Play – Reactive] and [Reactive – Passive]; there appeared to be much greater inter-network functional connectivity. I wanted to determine whether there was also greater intra-regional functional connectivity within the cerebellum, so I ran a separate parcellation analysis on only cerebellar regions with a higher degree of resolution using a probabilistic atlas of the major lobules, shown in *Figure 8* (Diedrichsen et al., 2009). These results show that, when comparing Play vs. Reactive Replay, there is a widespread difference in inter-regional connectivity that is absent when comparing Reactive Replay vs. Passive Replay.



Cerebellar Subtraction Matrix : Play vs. Reactive

Cerebellar Subtraction Matrix : Reactive vs. Passive

Figure 8: Subtraction Matrices for Cerebellar Regions

Subtraction matrices at the cerebellar level using a probabilistic atlas of the major cerebellar lobules. Each cell represents a correlation between two regions. These matrices illustrate intra-regional connectivity and are thresholded for significance. Left: [Play – Reactive]; Right: [Reactive – Passive].

3.2 Network Connectivity

Figure 9 shows a correlation matrix in which cortical ROIs were clustered according to the Yeo-17 resting-state functional network model. This model identified seven large-scale cerebral networks, which were fractionated into a more fine-grained resolution, yielding 17 networks (Thomas Yeo et al., 2011). The same pattern of inter-network correlation enhancement evident in the ROI-to-ROI comparisons is preserved after averaging the ROIs to examine network-level connectivity. This holds true both for both positive and negative correlations between networks (*Figure 10*). Many of the same cortical relationships found at the ROI level (like the DMN and DAN anti-correlation, *Figure 9*) are also preserved at the network level.

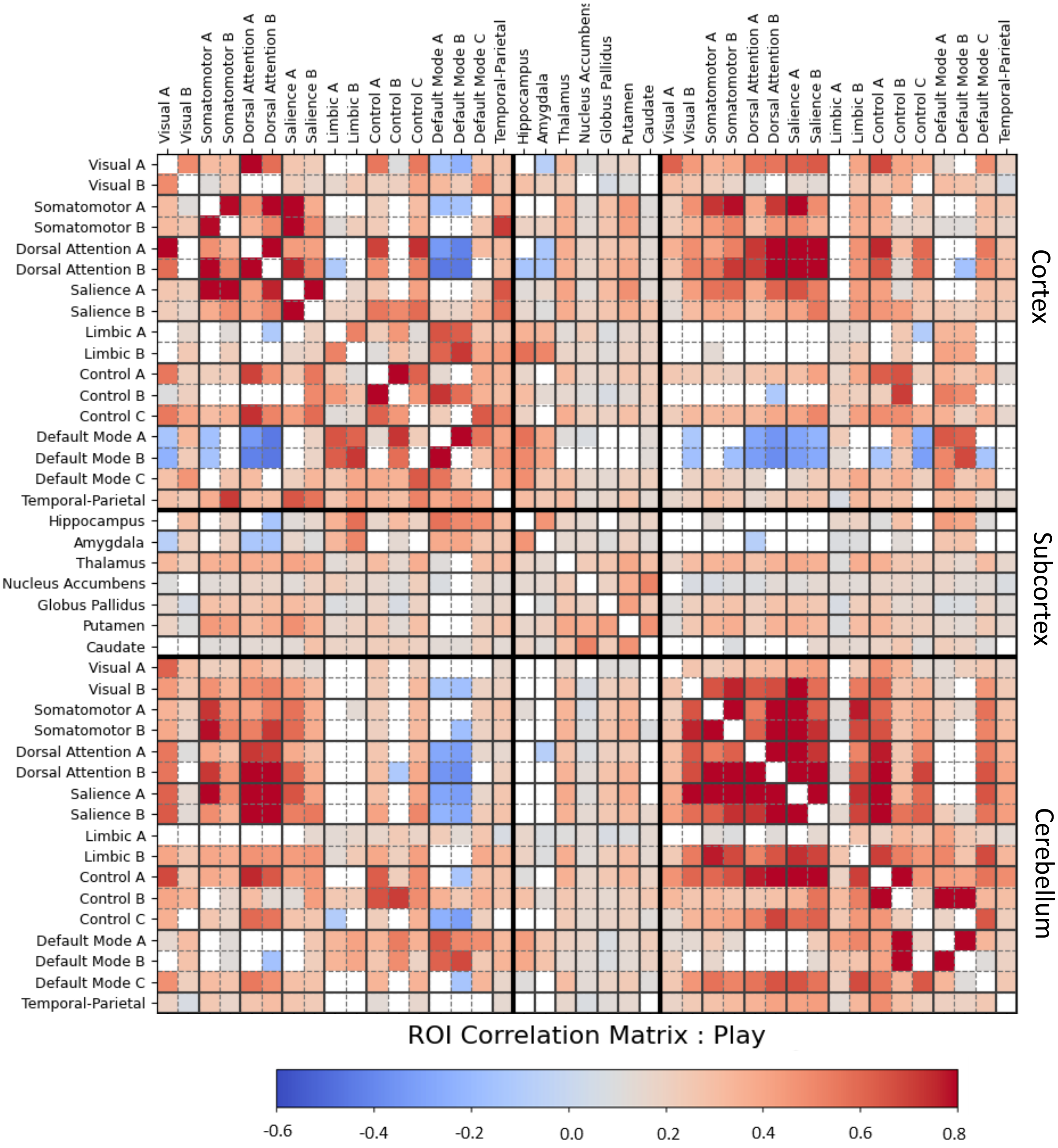


Figure 9: Network Correlation Matrix for Play at the Network Level

A network-level correlation matrix for Play that includes labels at the network level. Thick black lines indicate boundaries between brain areas (cortex, subcortex and cerebellum). Thin black lines indicate boundaries between networks at the 7-network level. Dashed grey lines indicate boundaries between networks at the 17-network level.

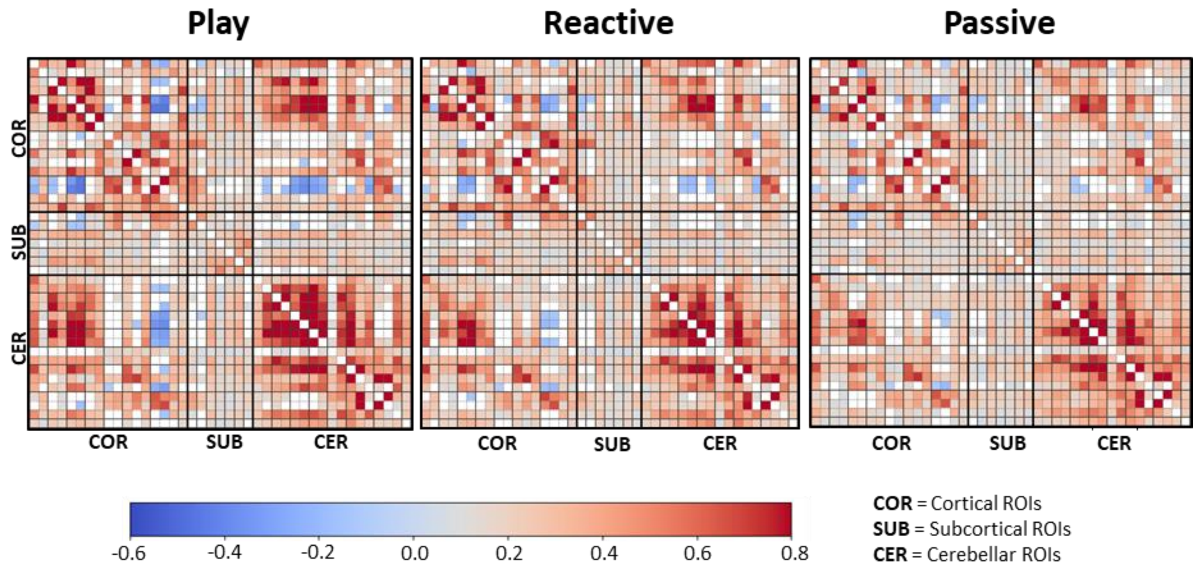


Figure 10: Network Connectivity Matrices for Play, Reactive Replay and Passive Replay

Connectivity matrices for each condition at the network level, thresholded for significance. Thick black lines indicate boundaries between brain areas (cortex, subcortex and cerebellum). Thin black lines indicate boundaries at the 7-network level.

One of the most striking differences evident when examining network level connectivity is the difference in cerebellar connectivity between Play and Replay conditions. This difference is highlighted in *Figure 8* and *Figure 11*, through the use of a subtraction matrix. Some of the greatest functional connectivity differences between Play and Passive Replay can be found in the functional relationships with cerebellar networks. This is consistent with the notion that the key role of the cerebellum is motor control and motor learning (Wolpert et al., 1998). After all, there is motor movement and learning involved in the use of a trackball which is present in Play, whereas in Passive Replay, motor movement is not involved at all. Both Play and Reactive Replay involve the same motor movements (down to consistency of directionality and timing), and, again, consistent with the cerebellar motor-control model, much of the cerebellar functional connectivity in Play can be explained by controlling for the network activation in Reactive Replay.

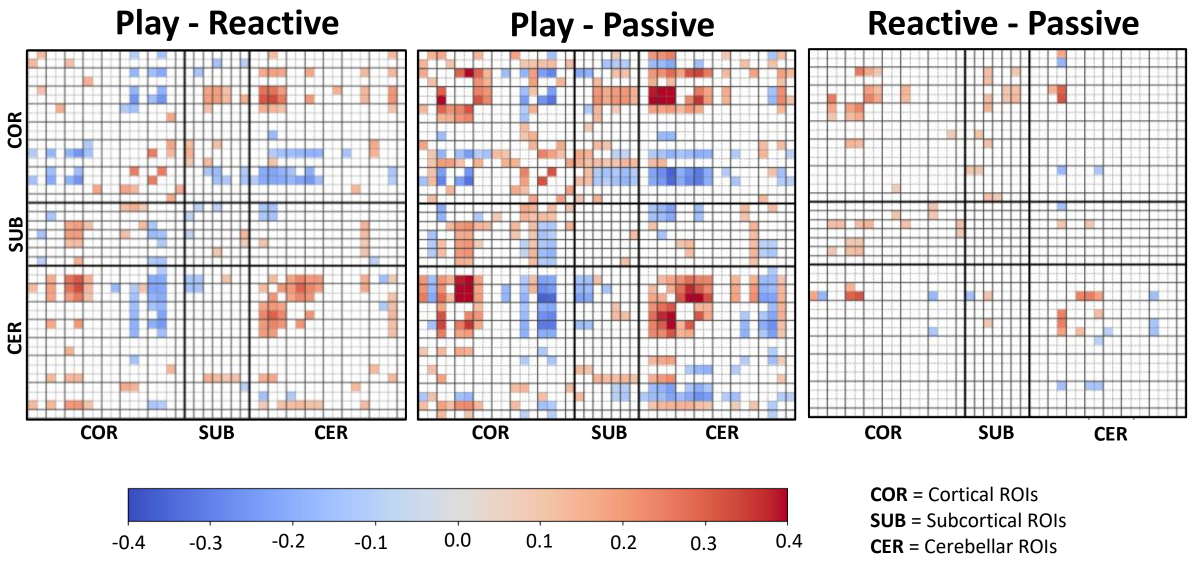


Figure 11: Network Subtraction Matrices Comparing Play, Reactive Replay and Passive Replay

Subtraction matrices for each condition at the network level, thresholded for significance. Thick black lines indicate boundaries between brain areas (cortex, subcortex and cerebellum). Thin black lines indicate boundaries at the 7-network level.

In order to break down the condition-specific differences in network connectivity, I conducted paired-sample t-tests on each of the 861 possible NOI pairings between each pair of conditions (*Figure 12*). I then characterized which NOI pairings showed a statistically significant difference (p < .05, uncorrected) for one condition compared to the other two. For example, Play-specific differences would need to show (Play ≠ Reactive Replay) AND (Play ≠ Passive Replay). Moreover, I then classified each instance of a statistically significant difference based on the correlation effect as one of six possible categories: Enhanced Positive Correlation, Enhanced Negative Correlation, Reduced Positive Correlation, Reduced Negative Correlation, Induced Anti-correlation, or Eliminated Anti-correlation. An Induced Anti-correlation indicates that the direction of correlation changed from positive to negative in the different condition, whereas an Eliminated Anti-correlation indicates that the direction of correlation changed from negative to positive in the different condition. I then performed a Chi-Square Goodness of Fit Test to test whether the number of condition-specific differences was equivalent for the three conditions. By the null hypothesis, each of the three conditions would yield an equal number of condition-specific differences. Alternatively, if one of the conditions evoked qualitatively different networks, it would produce a disproportionately large number of differences in comparison to the other two conditions. Note that although the *p* values in the first stage of this analysis were not corrected for multiple comparisons, the main goal was not to evaluate individual NOI pairings but rather to set an arbitrary threshold for the number of condition-specific differences. The crucial statistical test was the second stage of the analysis in which a single chi square test was performed and thus no correction for multiple comparisons was necessary. The Chi-Square Goodness of Fit Test was performed to determine whether the condition-specific functional connectivity patterns were equal between conditions. The proportion of these differences was found to differ by condition X^2 (2, N = 3) = 157, p = <.001. This indicates that the number of differences between conditions is different from what would be expected if the condition-specific functional connectivity pattern distributions were the same.

Table 1a, Table 1b and *Figure 13* characterize the nature of these condition-specific differences in NOI-pairings. The results showed that 163 of these NOI pairings were significantly different in Play (significant at $p < 0.05$ when compared to both Reactive Replay and Passive Replay). Of these 163 play-specific differences, 75% of those were in the form of enhanced connectivity strength (56% were increased positive correlations and 19% were increased negative correlations) with only 25% demonstrating a reduction in connectivity strength. Connectivity strength, in this case, indicates the absolute value of *r*. Conversely, there were only 58 NOI pairings that were unique to Passive Replay and 76% of these were in the form of reduced connectivity strength. Further, of the 24% of NOIs that were characterized by enhanced connectivity, 64% of those involved an increase in DMN connectivity. None of the increases in connectivity strength involved anti-correlations. Finally, there were only 11 significant NOI correlations unique to Reactive Replay and 82% of these were characterized by an increase in connectivity strength, none of which involved anti-correlations.

Figure 12: Condition-Specific Network Connectivity

A matrix depicting condition-specific network connectivity. Condition-specific coloured squares indicate that a particular NOI-to-NOI in one condition is significantly different when compared to ***both*** *of the other conditions. Scalar connectivity indicates that all conditions are significantly different from each other and exhibiting a directional effect on correlations that coincides with level of activity of the condition. If an NOI-to-NOI pairing is not condition-specific, this indicates that either none of the conditions were significantly different from one another, or that significant differences were limited to one condition comparison only. Thick black lines indicate boundaries between different brain areas (cortex, Subcortex and cerebellum).*

	Play	Reactive	Passive
Total Condition-Specific Differences	163	11	58
Enhanced Positive Correlations	91	9	12
Reduced Positive Correlations	40	2	44
Enhanced Negative Correlations	8	0	0
Reduced Negative Correlations	0	0	0
Eliminated Anti-correlations	1	0	2
Induced Anti-correlations	23	0	0

Table 1: Condition-Specific Pattern Breakdown by Correlation Effects

Table 1 *demonstrates the number of condition-specific differences in NOI-to-NOI connectivity based on correlational effect. Enhancements to correlations indicate that correlation strength increased; reductions to correlations indicate that correlation strength decreased. An induced anti-correlation indicates that correlation direction changed from positive to negative; an eliminated anti-correlation indicates that correlation direction changed from negative to positive.*

Area-to-Area Comparison	# Possible	Play	Reactive	Passive
Cortical-Cortical	272	23 (8%)	4 (1%)	16 (6%)
Cortical-Subcortical	136	19 (14%)	2 (1%)	14 (10%)
Cortical-Cerebellar	289	58 (20%)	1 (0%)	13 (5%)
Subcortical-Subcortical	56	8 (14%)	1 (2%)	2 (4%)
Subcortical-Cerebellar	289	17 (6%)	0 (0%)	4 (1%)
Cerebellar-Cerebellar	272	38 (14%)	3 (1%)	9 (3%)

Table 2: Condition-Specific Pattern Breakdown by Brain Area

Table 2 *demonstrates the number of condition-specific differences in NOI-to-NOI connectivity based on connectivity of brain area across the cortex, Subcortex and cerebellum. The '# Possible' column indicates the maximum number of unique connections possible based on the number of NOIs used (this excludes network correlations with themselves in within-area pairings). For each condition column, the number listed indicates the number of significant connections within the areas compared and the bracketed percentage indicates the proportion of total possible unique connections listed in the '# Possible' column.*

There were also 48 NOI pairings in which each condition was significantly different from another, demonstrating a scalar effect with level activity of the condition (Play > Reactive Replay > Passive Replay). Out of these, 83% were characterized by an enhancement in functional connectivity (65% were in the form of increased positive correlations and 19% were increased negative correlations).

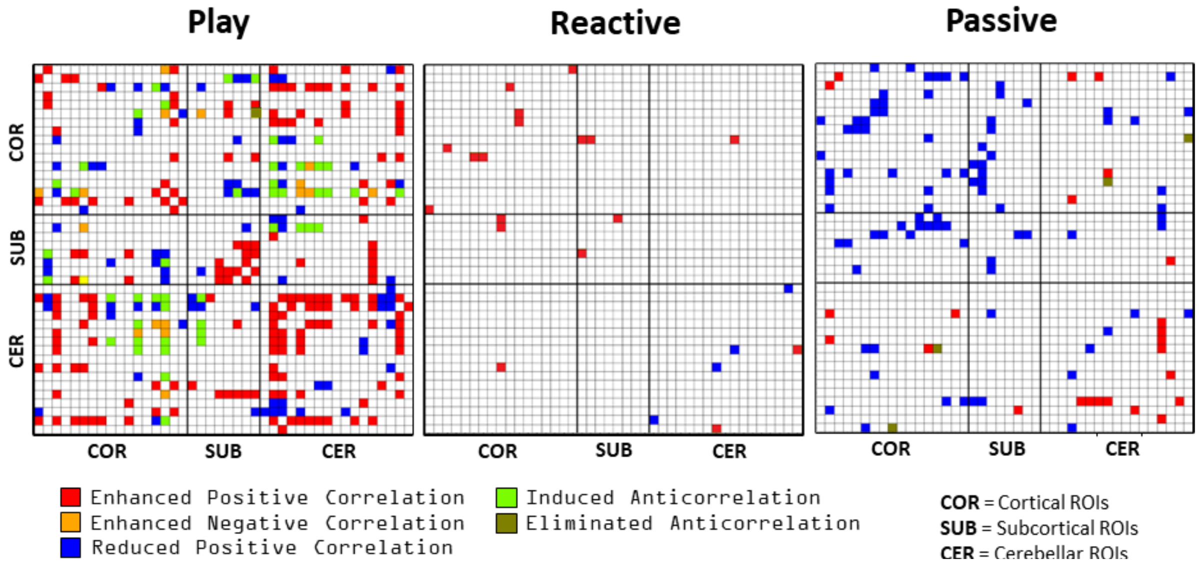


Figure 13: Condition-Specific Directional Effects for NOI-Pairings

Matrix depicting the information contained in Table 1 within the NOI-to-NOI matrices for each condition. Coloured squares indicate a condition-specific significant difference in functional connectivity pattern for the corresponding NOI-pairing. White squares indicate that the NOI-pairing was not significantly different in one condition over the others.

The connectivity both within and between brain areas (cortex, subcortex and cerebellum) are not only more numerous in Play, but it also boasts a striking difference in cerebellar activity in particular. Of the 163 Play-specific differences in connectivity, 69% of these involved cerebellar networks, a proportion substantially higher than that found in Reactive at 36% and Passive at 45%. Play – 27%

3.3 Confound Assessments

Head Motion: Based on the findings from movie-viewing studies, functional connectivity strength is unlikely to be a result of head motion artifacts. In fact, movie-viewing studies have, overall, far lower level of head motion (Vanderwal et al., 2019), while also having been shown to *enhance* network differentiation and anti-correlations in comparison to resting state (Emerson et al., 2015; Meer et al., 2020). This may suggest that less motion leads to strong patterns of functional connectivity. Nevertheless, due to the greater degree of motion in play runs discovered in the pilot phase, I wanted to assess motion for two major reasons. First, I wanted to make sure that strength of correlations was not related to level of motion. Second, I wanted to ensure that motion was not an excessive problem for this dataset, and that the multi-echo denoising had been successful.

I correlated motion timecourses for each run with all ROI and NOI timecourses in the corresponding run. The head-motion timecourses were comprised of both translation and rotation parameters and their first order derivatives for the x, y and z planes (in mm). Out of 133 ROIs and 17 networks, only one ROI time-course, a region in the left visual striate, was significantly correlated with head motion at an FDR-corrected threshold of p = 0.009). No other correlations between motion parameters and ROIs or NOIs were significant. This suggests that head motion is not the underlying cause of the differences seen between conditions.

Heart Rate: The measure of heart rate could potentially play two different roles in this data set. First, it could be construed as an indirect measure of arousal (Wang et al., 2018). Second, it could also be viewed as a potential artifact that affects blood flow and thereby, inadvertently, affects the BOLD response (Chang et al., 2009). I have included a section in the discussion to address both of these possibilities and how they might be framed, given these results. The average heart rate for Play was 77.4 bpm, for Reactive Replay 73.9 bpm, and for Passive replay 73.3 bpm. There was a significant difference in average heart rate between Play vs. Reactive Replay ($p = 0.0001$), and Play vs. Passive Replay conditions ($p = 0.0004$) in which average heart rate in Play was higher than in Reactive and Passive Replays. No significant difference in average heart rate was found between Reactive Replay vs. Passive Replay ($p = 0.4443$). In order to get a better understanding of what these differences meant, I correlated heart rate timecourses with cortical and cerebellar network timecourses, and subcortical region timecourses. The results of this correlation are shown in *Figure 14* below.

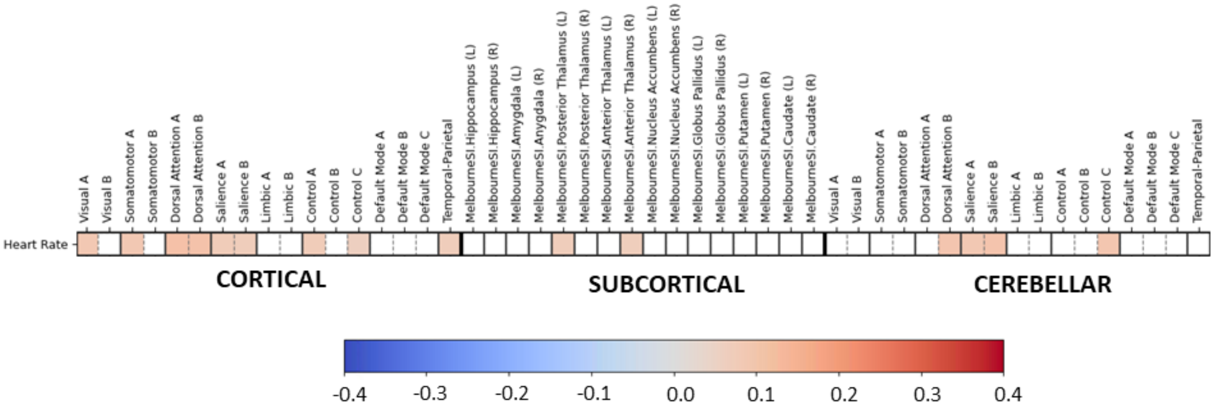


Figure 14: A Subtraction Matrix for Play vs. Reactive Including Heart Rate

A subtraction matrix comparing Play and Reactive Replay conditions that includes all cortical networks, cerebellar networks and subcortical ROIs correlated against heart rate, thresholded for significance.

Out of the 40 networks listed, 15 were significant ($p < 0.05$) with the highest correlations being in DAN A and DAN B ($r = 0.109$ and $r = 0.106$, respectively).

Other Confounds: There were no significant differences with respect to age or sex. There were also no significant within-subject differences across runs of the same condition.

3.4 Eye-Tracking

The results of the eye tracking data suggest that differences seen between conditions are not a result of either eye movements or looking behaviors. There were no significant differences found for number of saccades, number of blinks, pupil dilation or gaze position between any of the conditions (*Table 3*):

	Play vs. Reactive	Play vs. Passive	Reactive vs. Passive
# Saccades	p = 0.41	p = 0.18	p = 0.46
# Blinks	p = 0.57	p = 0.35	p = 0.35
Pupil Dilation	p = 0.35	p = 0.99	p = 0.22
Gaze Position	p = 0.72	p = 0.83	p = 0.93

Table 3: P-Values for Blinks, Saccades, Pupil Dilation and Gaze Position When Comparing Conditions

Gaze position was determined based on the difference in Euclidean distance (in pixels) and the position of Pac-man to evaluate whether looking behaviors were different between conditions. *Figure 15* illustrates the similarities in eye gaze between conditions. Gaze position was similar across conditions, with Play and Reactive Replay being the most closely aligned. Participants were found to be looking just in front of Pac-man in the direction of movement. In Passive Replay, this was also typically the case, but with a tendency to be even further ahead in the direction of movements than was seen in Play and Reactive Replay. In this sense, Passive replay could often be used to predict Pac-man's future coordinates a few seconds earlier, but somewhat less accurately than the other two conditions.

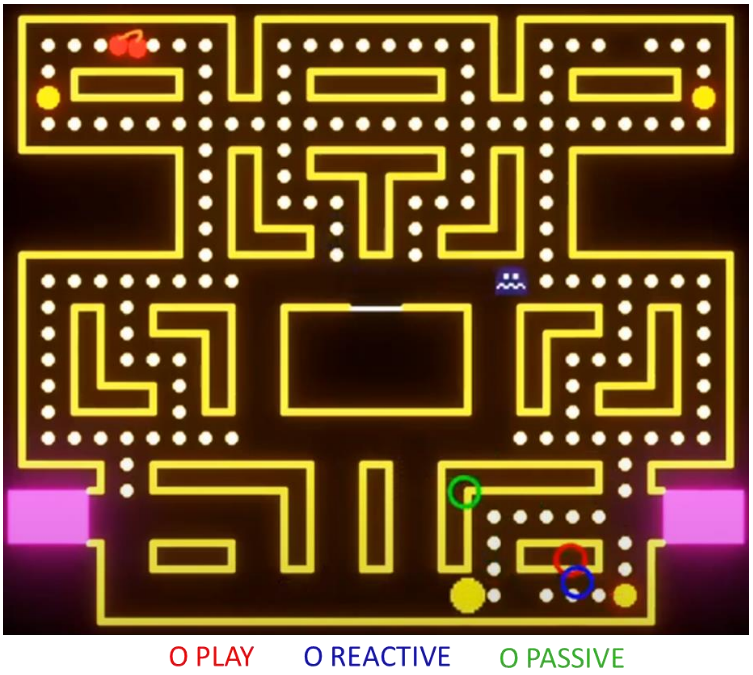


Figure 15: Screen Capture with Eye-Tracking Superimposed

A screen capture of a participant playing Pac-man with the x/y eye position coordinates for each condition superimposed. The red ring corresponds to eye position in the Play condition, the blue ring corresponds to eye position in Reactive Replay and the green ring corresponds to Passive Replay.

Chapter 4

4 Discussion

The overarching result of this study has been to show that there *are* major differences in functional connectivity during the Play condition when compared to both Replay conditions, both in number of significant connections and the enhanced strength of functional connectivity. This suggests that the incorporation of active control within an environment could be a critical component to support ecological validity in neuroimaging. Moreover, this paradigm can be instantiated through the use of low-cost tools already available, such as video games, virtual environments and dynamic narratives.

4.1 The Difference of Closed-Loop?

The most salient result of this study has undoubtedly been the difference in functional connectivity patterns between Play and both Replay conditions. Previous video game studies have demonstrated differences in amygdala activation in response to violent actions (Mathiak & Weber, 2006) and differences in key reward structures when game difficulty outpaces competence (Huskey et al., 2018). It has even been shown, for example, that levels of activation in orbitofrontal and striatal areas are significantly different in participants winning or losing a game than they are in participants simply watching someone else win or lose a game (Kätsyri et al., 2013) which echoes the results obtained in the present study here. This is, however, the first study to use video games to examine the difference in widespread functional connectivity when comparing a closed-loop paradigm with an open-loop paradigm. The results of the present study are a preliminary step in making the case that the incorporation of video games can yield results in functional connectivity research that differ from those using passive stimuli.

The large differences between Play and Replay conditions support the possibility that a closed-loop paradigm is fundamentally different. Play boasted roughly three times as many significant functional connections when compared to Passive Replay. Moreover, the composition of these condition-specific connectivity differences is strikingly different. A substantial proportion of the differences in Passive Replay involve functional connectivity of the DMN, whereas Play exhibits changes in a diverse array of functional network connections not limited to any domain or locale, but drawing substantially more on cerebellar networks than the other conditions.

Moreover, the differences do not appear to be attributable to motor effects, given that these differences continue to exist even when compared to Reactive Replay, a condition that shares motor demands with Play. One point to be addressed is whether Reactive Replay ought to be considered a unique condition in its own right. Given that the task is different from that of Play and Passive Replay, there may be a concern that Reactive Replay is recruiting a unique set of functional connectivity pairings. The results here seem to indicate, however, that this is not the case, given the very small number of network connections uniquely different in differenthis condition. Further, the results show that most of these are limited to subcortical and limbic structures. While the role of these structures in Reactive Replay is an interesting question, the limited number of unique connections and their rigid localization suggests that Reactive Replay is not engaging largely different functional connections across the brain. This further supports its role as a control condition for Play to ensure differences are not related to motor activity.

It is worth noting that this study did not examine activity levels within particular regions with known associations, but rather, it examined functional connectivity within and between networks. These large differences were found in the fundamental relationships regions and networks have with each other. This might suggest that differences in activity levels might be missing a major part of the story. If regions are circumscribed particular functions through the use of isolated and decontextualized stimuli, how can we be sure these functions hold when their functional relationships change with context? (Gibson, 1979; Willems & Peelen, 2021). This is not to say that examinations of activity levels are not valuable. Rather, it is to say that an exploration between regional activity levels and their functional connectivity may help to paint a broader picture about dynamics. The large functional connectivity differences here may be inadvertently signaling that there are interesting discoveries to be made with a shift in attention from localization of function and towards dynamic relationships between brain, body and environmental context.

4.2 Anti-correlations

One of the most conspicuous effects between conditions is the shift in inter-network strength, the greatest marker of which is seemingly found in the anti-correlations present in all conditions, and the degree to which they differ. The anti-correlation between the DMN and DAN has been widely demonstrated in both resting-state and task-paradigms alike (Fox et al., 2005; Golland et al., 2007; Uddin et al., 2009), but it has nevertheless remained controversial. Some research has suggested that these anti-correlations can be artificially induced in the preprocessing stage with certain types of regression methods, primarily global-signal regression (Murphy et al., 2009). Through the use of alternative regression methods for dealing with motion and physiological noise, researchers have found these same anti-correlations, even in the absence of global signal regression (Chai et al., 2012; Li et al., 2021). The results of this study corroborate this research in demonstrating these anti-correlations in all three conditions in the absence of global-signal regression and, indeed, minimal regression altogether. This suggests that these anti-correlations are not merely artifacts of fMRI preprocessing techniques but instead, real patterns of brain activation in need of explanation.

More importantly, however, is the difference in apparent robustness of these anti-correlations between conditions. The results of the present study appear to suggest that in many cases, the more immersive the context, the greater the anti-correlation effect. Crucially, however, is the result showing that Play was unique in being able to showcase anti-correlations that were either not present, or not sufficiently detectable, in the other conditions. One of the major difficulties of not only establishing anti-correlations, but also studying them, is that in the absence of global-signal regression, negative correlations suffer from smaller effects (Dixon et al., 2017). Functional network activation is biased towards positive activation patterns, possibly as a result of anatomical differences (Hayasaka, 2013) or differences in time-lag responses (Goelman et al., 2014). Whatever the reason, Dixon et al. (2017) found that the exclusion of global signal regression decreased the effect of the anti-correlation between the DMN and DAN by 75%, from 0.24 to 0.06. The skew towards positive correlations in the absence of global signal regression can overshadow negative correlations, making it not only more difficult to ascertain statistical significance, but to then subsequently replicate these findings. It is worth noting, however, that a preponderance of studies examining anti-correlations are doing so on *resting-state* data. Task-based data, on the other hand, appear to have an impact on anti-correlation strength, showing connectivity patterns more similar to resting state with global signal regression (Li et al., 2021). Given that Play was able to both induce and enhance anti-correlations in a significant way, it is perhaps the case that DIVEs may provide new insights about anti-correlations and their role in network connectivity. This is an interesting finding that may be fertile ground for subsequent study.

With new methods to facilitate their study, anti-correlations may be the next opportunity for functional connectivity research. Exploration of *what* anti-correlations mean for the brain has been stalled by the effort required to establish *whether* they even exist as empirically valid phenomena in the first place. The DMN-DAN anti-correlation has already begun to suggest to researchers that brain function may be more readily discoverable in the dynamic coordination through cooperation and competition within and between regions, rather than within the regions themselves (Bressler & Kelso, 2016; Cocchi et al., 2013). Indeed, some research suggests that perhaps the DMN may be the key hub that determines wide-scale degrees of connectivity throughout the brain based upon competitive cross-network couplings with other networks (Wens et al., 2019). The results of the present study reveal a strong set of anti-correlations, most of which are found in the between the DMN and other networks which would corroborate this view. It may well be the case that the DMN is simply acting differently in an immersive environment, causing a whole cascade of downstream network connectivity effects. It seems likely that proper network-thinking will likely involve the incorporation of not merely a single, network interaction, but rather, a holistic approach to the brain as a *system* of dynamic and interactive networks (Anderson, 2014). Indeed, there appears to be some evidence suggesting higher degrees of intra-network connectivity corresponds to stronger inter-network anti-correlations (Brier et al., 2012). The results of the slope analysis show that Play enhances both intra-network *and* inter-network connectivity to a larger degree than Reactive or Passive Replay. This may suggest that, at the very least, anti-correlations might be more readily discoverable using a closed-loop paradigm. This is an interesting finding that may be fertile ground for subsequent study.

4.3 Cerebellum

There has been a long history identifying the cerebellum as being mainly devoted to the coordination and facilitation of motor functions (Glickstein & Doron, 2008; West & Gelderd, 2003). The winds, however, have begun to shift and more researchers have now come to recognize that the cerebellum perhaps plays a larger role in higher order cognitive functions that what was previously believed (Buckner, 2013; Rapoport et al., 2000; Schmahmann & Caplan, 2006). Much of this emphasis on motor control and coordination has been the result of a myriad of cerebellar lesion studies in which a variety of motor coordination and learning deficits arise in consequence of such lesions (Jeljeli et al., 2003; Joyal et al., 1996). This link between lesion location and deficit of motor function makes good sense if one is to take a modular approach to the cerebellum. If a lesion to region X, for example, results in an oculomotor movement abnormalities, then region X must be responsible for oculomotor movement coordination. Indeed, a modular structure has been proposed as the proper way to think about the cerebellum, even at a functional level (Apps et al., 2018).

Presupposing a modular view of cerebellar structure responsible primarily for motor control, one might hypothesize a greater degree of connectivity would be found within networks in the cerebellum when comparing the Reactive and Passive Replay conditions than when comparing Play and Reactive Replay conditions. In the former pairing, the substantive difference is the coordination of motor movements whereas, in the latter condition, motor movements are matched. This is not what is observed in the results, however. At the modular level, there are substantial significant differences when comparing Play versus Reactive Replay and very few when comparing Reactive Replay with passive Replay. These differences are then also found at the network level, both within the cerebellum and between the cerebellum and cortex. Even after controlling for motor movements in this way, many significant functional relationships within the cerebellum remain. Further, the differences between Reactive and Passive Replay show some significant relationships in the cerebellum, but these are minimal in comparison to the Play condition. This suggests that functional connectivity, both within the cerebellum and between the cerebellum and cortical networks, extends beyond the purview of motor control and motor movement alone.

This study further corroborates the growing body of evidence suggesting the cerebellum is involved in far more cognitive tasks than what was once appreciated, but even these findings may not be telling the whole story. For example, the cerebellum has been implicated in cognitive tasks involving the generation of forward models which have been argued to be instrumental in task performance monitoring (Ben-Yehudah et al., 2007; Popa & Ebner, 2019). Indeed, Popa & Ebner (2019) found neuronal spiking patterns consistent with prediction error and optimization in motor commands. However the results of the present study do not appear to demonstrate such a role for the cerebellum. In the Reactive Replay condition, participants are asked to follow the movements of Pac-man using the controller and error feedback is obvious and immediate (if the direction of Pac-man does not match controller direction). Nevertheless, the minimal differences between Passive Replay (where such error prediction feedback and correction occurs) and Reactive Replay (where such error prediction feedback and correction does occur) may suggest that it is more than simple forward modelling occurring, at least in this particular case.

This study does not purport to solve the mystery of the cerebellum and its functionality. Rather, this study suggests that novel contexts may provide interesting questions not fully answerable by our current understanding of the cerebellum. Further, framing the cerebellum in terms of forward modelling may also be insufficient on its own. What the results of this study suggest is that there may be some kind of interaction between these variables and the external context occupied by an agent. Feedback from the environment, and agency within it, may be important components to consider when studying the cerebellum and its functions. If this is the case, DIVE paradigms may be useful tools in furthering our understanding of this unique brain structure.

4.4 Artifact, Arousal or Agency?

The statistical analysis showing Play as evoking significantly faster heart rate than both Replay conditions has an impact on the way in which functional connectivity differences in Play ought to be interpreted. There are three main ways the effect of heart rate might be construed: as an indicator of possible cardiovascular artifacts contaminating the BOLD response, as a proxy for a confound approximating arousal, or as an essential, modulatory component of the brain in a closed-loop framework.

At the outset, it is important to ascertain whether the effects seen in this study are the result of cardiac-induced artifacts given the correlation of heart rate with blood flow, as this can have an effect on the BOLD response and fMRI signal (Dagli et al., 1999). There a few reasons to suspect that is not what is driving the effects in this study, however. First, while ME-ICA denoising does not eliminate all cardiovascular artifacts, it has been shown to do an adequate job of removing physiological noise (Beckers et al., 2022). Further, the subsequent use of RICA to exclude missed components with clustered activation in locations near major arteries and blood vessels as outlined in Dagli (1998) further enhances this cardiovascular artifact regression. Finally, the upper limit of the band-pass filter used was fairly conservative at 0.09 Hz so as to eliminate even lower-frequency cardiac artifacts that can be found around 0.1 Hz (Shmueli et al., 2007). Taken together, these methods deal with the issue of cardiovascular artifacts so as minimize the possibility that they are the driving force behind the effects.

The next question that might be addressed is the degree to which heart rate should be viewed as a proxy for arousal, two variables shown to be highly correlated (Azarbarzin et al., 2014). Previous studies have also indicated that heart rate variability has an impact on the BOLD signal which can, in turn, affect patterns of functional connectivity (Chang et al., 2013). Thus, arousal might be reasonably flagged as a confound that needs to be controlled for, and indeed, there are some who have called for more care when interpreting results in these cases (Gu et al., 2020). While this is certainly true, it is worth underscoring the point that arousal is a term (and a physiological response) that is used to explain a great many different types of phenomenon that occur in the brain and body. Delineating which components of arousal are signal, noise, or modulatory factors could be misleading when trying to evaluate the system more holistically. As such, while arousal cannot be ruled out as a confouder, the extent to which it should be entirely viewed as such is still an open question in need of further research.

Arousal might be better viewed as one of the main variables linking brain, body and environment. The default mode network has been shown to have an incredible degree of overlap with changes in sympathetic nervous system activity (and, thereby, autonomic arousal), which likely indicates that these systems are related in a fundamental way (Fan et al., 2012; Nagai et al., 2004). Rather than consider that the changes in functional connectivity are confounded by the relationship with arousal, it might instead be worth considering how arousal of the brain and body modulate each other as component parts of a closed-loop system. Certainly, more research will need to be done to disentangle such a relationship, but it is one that might be better explored when the system is taxed and arousal varies naturally through self-generated action and feedback, as occurs in real-world settings. The immersive nature of DIVE paradigms might, for this reason, provide a tool to study the relationship between functional activation and arousal in unique contexts.

4.5 Limitations & Directions for Further Investigation

This study has examined the virtues of a DIVE paradigm and has discussed some of the ways in which such a paradigm might be useful in exploring a wide variety of scientific questions. It is worth remembering, however, that this study is highly exploratory. For this reason, it goes without saying that more research will need to be done in order to draw any substantive conclusions on what the results here might mean.

One potential limitation to consider is that this study lacks concrete corroboration that the motor movements between Play and Reactive Replay are the same. While it is possible that participants moved the controller in significantly different ways during Reactive Replay, this seems unlikely for four reasons. First, the task was extremely simple. Participants were required to repeat condition task instructions back to the researcher after they were explained in order to ensure participants understood. All participants were able to successfully reiterate the task instructions for all three conditions. Second, researchers used an interface that clearly showed when the controller was being moved and when it was not. There were no cases in which participants did not continually use the controller during the Reactive Replay condition. This eliminates the possibility that participants were confused as to whether it was a Passive or Reactive Replay condition. Third, there was no incentive for participants to deviate from the task and move the controller at random. Fourth, while it is the case that participants may have been prone to errors due to inaccurate prediction of Pacman's trajectory, the lack of unique, Reactive Replay-specific network connections would suggest that this was no sufficient to impact the results in a meaningful way. The similarity between both Reactive and Passive connectivity matrices appears to corroborate this as well.

A more difficult limitation of this study is the large degree of variability between individual subjects. Both average connectivity strength and significant patterns of functional connectivity varied largely across individuals. These individual differences in functional connectivity and the degree to which they may exhibit interaction effects with closed-loop contexts is a fascinating topic. Given the individual variability of network connection patterns, it should be considered likely that individuals will have different responses to their environmental contexts. It is unclear how these individual differences in environmental response may be impacting the results of this study.

4.6 DIVE into the Future

There are a many potential avenues through which DIVE paradigms might be advantageous in opening new vanguards for cognitive neuroscience, computing and artificial intelligence and clinical medicine. The exploration of the brain as a closed-loop system need not be limited to theoretical model building and, by its very nature, is poised to bring a wider array of practical tools for cognitive neuroscience to build upon. The very concept of DIVE is about building models based on the real world, rather than building models that must be adapted to fit the real world. This makes it an excellent way to combine a new, bottom-up approach with tried and tested top-down approaches. By integrating bottom-up and top-down approaches into a more holistic dynamic systems one, many of the roadblocks that arise from either technique in isolation could be ameliorated to some degree (Egan & Matthews, 2006). It is unlikely that most modern researchers actually believe that the brain operates in *complete* isolation from the body and environment, and yet, it is often the case that research is executed so as to implicitly treat brains as though this were the case. The integration of dynamical systems theory (DST)—a method of studying complex interactions of dynamic systems—has led to some concrete applications. One DST examines how evolutionary principles can be used within an environment to produce autonomous agents that walk around successfully in such an environment (Beer, 1995). Indeed, this is precisely what researchers like Rodney Brooks did to revolutionize the ability for robots to navigate and interface with real-world environments in a way that had previously not been possible (Brooks, 1989). In a world seeking ever more intelligent machines, it may well be that this principle of embodiment holds. DIVEs could, thus, be more than tools for learning more about real-world cognitive agents, but also tools for artificial cognitive agents to learn how to act in the real world.

The results of this study may also have some useful implications for psychiatric medicine, through the enhancement of functional connectivity patterns. The field is constantly searching for more empirical methods of treating and characterizing mental health and brain disorders, but the number of individual differences in brains and the diversity of contexts in which they operate make it challenging to find robust, universal biomarkers. One potential limitation of resting-state, however, is that these paradigms do not tax the system sufficiently to demonstrate robust variations. Movie studies, as previously mentioned, have been able to evoke more robust patterns of functional activation, and this has already found some success in clinical studies when assessing the conscious experiences of coma patients (Naci et al., 2014). The potential advances in clinical settings of using movies for their ability to enhance functional connectivity patterns for finding biomarkers has been well-articulated by Eickhoff and Müller (2015). DIVEs might act in a similar capacity to movie studies here due to the increase in functional connectivity pattern enhancement of immersive conditions, but, of course, more research is needed to explore whether movies or DIVEs can be successfully used in this way.

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Appendices

Appendix A: Pac-man Event Tree

These figures represent the trajectory of the event screen sequences during a play run. The play sequence occurs before active play begins and starts with a fixation cross screen (at the very beginning of a run, the first fixation cross lasts 20 seconds with all subsequent fixations lasting 10). It is then followed by a ready screen and countdown, during which game time is paused. The pause on the game timer ends with the 'Go!' screen and participant interaction begins. Active gameplay ends under one of four circumstances: level completion, death, time's up or game over. In the case of the former two, upon completion of the event sequence frames, the play sequence begins again. In the case of the latter two, the run is terminated. The numbers on the side of each screen represent the amount of time the screen is displayed before transitioning to the next screen.

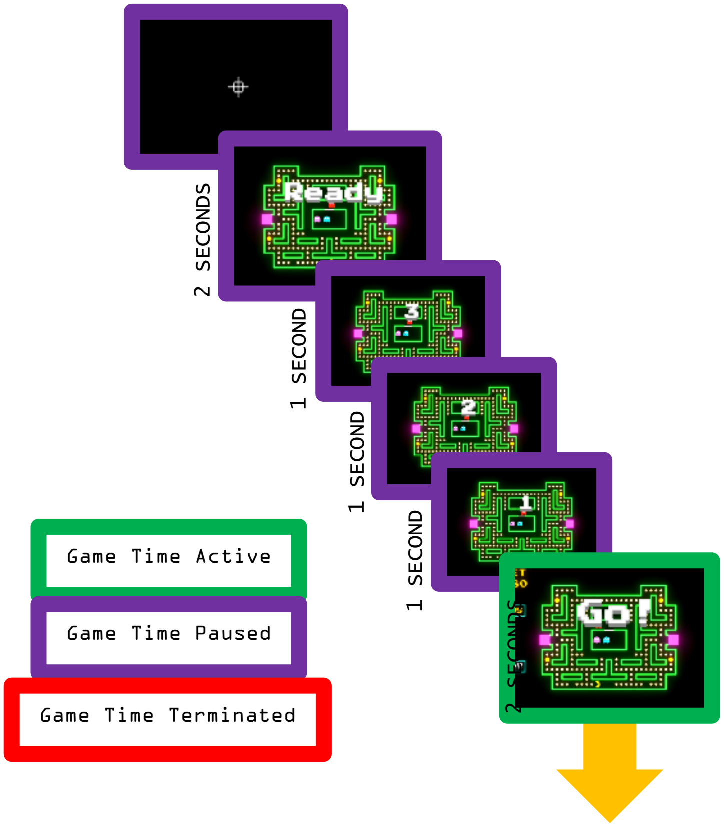

Figure 16: Screen Captures of Frames Preceding Play Time

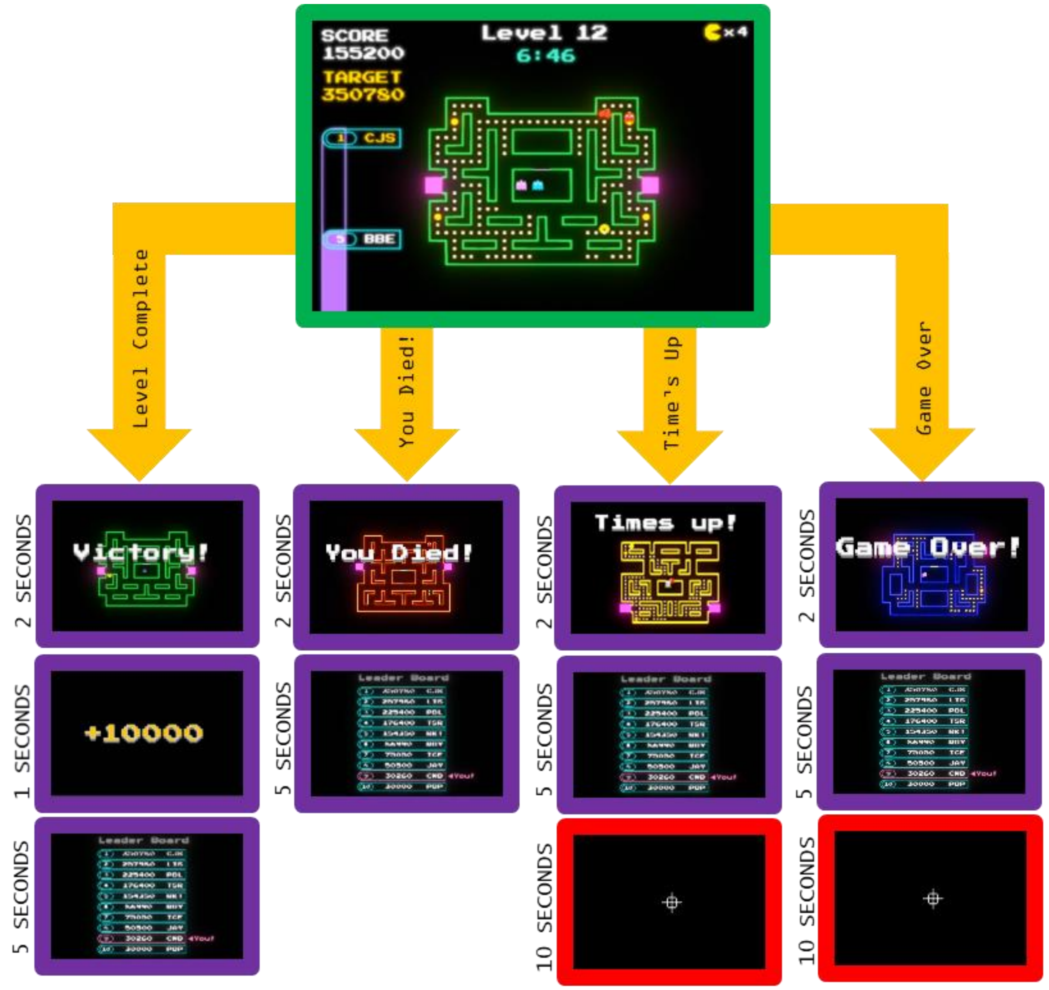

Figure 17: Possible Sequences of Play Time Termination Events

Appendix B: List of ROIs and Networks

A full list of the regions of interest (ROIs) featured in ROI matrices (see *Figure 6* and *Figure 7*):

VISUAL

VISUAL A:

1. Extrastriate 1 (L)
2. Extrastriate 1 (R)
3. Extrastriate 2 (L)
4. Extrastriate 2 (R)
5. Striate 1 (L)
6. Extrastriate 3 (L)
7. Extrastriate 3 (R)

VISUAL B:

20. Extrastriate Inferior 1 (L)
21. Extrastriate Inferior 1 (R)
22. Striate Cal. 1 (L)
23. Striate Cal. 1 (R)
24. Extrastriate Superior 1 (L)
25. Extrastriate Superior 1 (R)

SOMATOMOTOR

SOMATOMOTOR A:

14. Somatomotor A 1 (L)
15. Somatomotor A 1 (R)
16. Somatomotor A 2 (L)
17. Somatomotor A 2 (R)
18. Somatomotor A 3 (R)
19. Somatomotor A 4 (R)

SOMATOMOTOR B:

20. Somatomotor B Auditory 1 (L)
21. Somatomotor B Auditory 1 (R)
22. Somatomotor B S2 1 (L)
23. Somatomotor B S2 1 (R)
24. Somatomotor B S2 2 (L)
25. Somatomotor B S2 2 (R)
26. Somatomotor B Center 1 (L)
27. Somatomotor B Center 1 (R)

DORSAL ATTENTION

DORSAL ATTENTION A:

28. Temporal-Occipital 1 (L)
29. Temporal-Occipital 1 (R)
30. Parietal-Occipital 1 (L)
31. Parietal-Occipital 1 (R)
32. Superior Parietal Lobule 1 (L)
33. Superior Parietal Lobule 1 (R)

DORSAL ATTENTION B:

34. Posterior Commissure 1 (L)
35. Posterior Commissure 1(R)
36. Posterior Commissure 2 (L)
37. Posterior Commissure 2 (R)
38. Posterior Commissure 3 (L)
39. Frontal Eye Fields 1 (L)
40. Frontal Eye Fields 1 (R)

SALIENCE

SALIENCE A:

41. Parietal Cortex 1 (L)
42. Parietal Cortex 1 (R)
43. Insula 1 (L)
44. Insula 1 (R)
45. Insula 2 (L)
46. Parietal-Medial Cortex 1 (R)
47. Parietal-Medial Cortex 1 (L)
48. Frontomedial Cortex 1 (L)
49. Frontomedial Cortex 1 (R)

SALIENCE B:

50. Prefrontal Cortex 1 (L)
51. Inferior Parietal Lobule (R)
52. Prefrontal Cortex MP 1 (L)
53. Prefrontal Cortex L 1 (R)
54. Prefrontal Cortex MP 1 (R)

LIMBIC

LIMBIC A:

55. Temporal Pole 1 (L)
56. Temporal Pole 1 (R)
57. Temporal Pole 2 (L)

LIMBIC B:

58. Orbitofrontal Cortex 1 (L)
59. Orbitofrontal Cortex 1 (R)

CONTROL

CONTROL A:

60. Intraparietal Sulcus 1 (L)
61. Intraparietal Sulcus 1 (R)
62. Prefrontal Cortex L 1 (L)
63. Prefrontal Cortex L 1 (R)
64. Prefrontal Cortex L 2 (L)
65. Prefrontal Cortex L 2 (R)

CONTROL B:

61. Prefrontal Cortex LV 1 (L)
62. Prefrontal Cortex LV 1 (R)
63. Temporal Cortex 1 (R)
64. Intraparietal Lobule 1 (R)
65. Prefrontal Cortex LD 1 (R)

CONTROL C:

71. Precuneus 1 (L)
72. Precuneus 1 (R)
73. Precuneus 2 (L)
74. Central Cingulate P 1 (L)
75. Central Cingulate P 1 (R)

DEFAULT MODE

DEFAULT MODE A:

76. Prefrontal Cortex D 1 (L)
77. Prefrontal Cortex D 1 (R)
78. Precuneus PCC 1 (L)
79. Precuneus PCC 1 (R)
80. Intraparietal Lobule 1 (R)
81. Prefrontal Cortex M 1 (L)
82. Prefrontal Cortex M 1 (R)

DEFAULT MODE B:

83. Temporal Cortex 1 (L)
84. Temporal Cortex 2 (L)
85. Intraparietal Lobule 1 (L)
86. Prefrontal Cortex D 1 (L)
87. Prefrontal Cortex D 1 (R)
88. Prefrontal Cortex L 1 (L)
89. Prefrontal Cortex V 1 (R)
90. Prefrontal Cortex V 1 (L)
91. Prefrontal Cortex V 2 (L)
92. Prefrontal Cortex V 2 (R)

DEFAULT MODE C:

93. Retrosplinial Cortex 1 (L)
94. Retrosplinial Cortex 1 (R)
95. Parahippocampal Cortex 1 (L)
96. Parahippocampal Cortex 1 (R)

TEMPORAL-PARIETAL

Temporal-Parietal:

97. Temporal-Parietal 1 (L)
98. Temporal-Parietal 1 (R)
99. Temporal-Parietal 2 (R)
100. Temporal-Parietal 3 (R)

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