Video Games for Neuro-Cognitive Optimization

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Sophisticated video games that integrate engaging cognitive training with real-time biosensing and neurostimulation have the potential to optimize cognitive performance in health and disease. We argue that technology development must be paired with rigorous scientific validation and discuss academic and industry opportunities in this field.

Humans of all ages engage deeply in game play. Game-based interactive environments provide a rich source of enjoyment, but also generate powerful experiences that promote learning and behavioral change (Pellegrini, 2009). In the modern era, software-based video games have become ubiquitous. The degree of interactivity and immersion in these video games can now be further enhanced like never before with the advent of consumer-accessible technologies like virtual reality, augmented reality, wearable physiological devices, and motion capture, all of which can be readily integrated using accessible game engines. This technological revolution presents a huge opportunity for neuroscientists to design targeted, novel game-based tools that drive positive neuroplasticity, accelerate learning, and strengthen cognitive function, and thereby promote mental wellbeing in both healthy and impaired brains.

In fact, there is now a burgeoning brain-training industry that already claims to have achieved this goal. However, many commercial claims are unsubstantiated and dismissed by the scientific community (Max Planck Institute for Human Development/Stanford Center on Longevity, 2014; Underwood, 2016). It seems prudent for us to slow down and approach this opportunity with scientific rigor and conservative optimism. Enhancing brain function should not be viewed as a clever, profitable start-up idea that can be conquered with a large marketing budget. If the field continues to be led by overinflated claims, we will jeopardize the careful and iterative process of evidence-based innovations in brain training and thereby risk throwing out the baby with the bathwater.

To strike the right balance, the path to commercialization needs to be accomplished via cutting-edge, neuroscientifically informed video game development tightly coupled with refinement and validation of the software in well-controlled empirical studies. Additionally, to separate the grain from the chaff, these studies and the claims based on them need verification and approval by independent regulatory agencies and the broader scientific community. High-level video game development and rigorous scientific validation need to become the twin pillar foundations of the next generation of closed-loop video games (CLVGs). Here, we define CLVGs as interactive video games that incorporate rapid, real-time, performance-driven, adaptive game challenges and performance feedback. The time is ideal for intensified effort in this important endeavor; CLVGs that are methodically developed and validated have the potential to benefit a broad array of disciplines in need of effective tools to enhance brain function, including education, medicine, and wellness.

The First Pillar: High-Level Development

Scientists are not typically the most proficient video game developers. ''Games'' developed to accomplish cognitive training goals are frequently limited to the layering on of simple graphic skins and low-level reward to standard cognitive task paradigms. This gamification approach often involves sprinkling game elements on top of low-engaging cognitive tasks, creating slightly less boring exercises, which may be a factor driving the negative findings that have dominated the field. The creation of high-quality video games that generate immersive game play in the moment and repeated engagement for weeks or months requires sophisticated game design to be baked into the development process from the very beginning. Immersive interactivity is likely necessary to maximally harness plasticity and overcome homeostasis, to drive improvement on progressively more difficult tasks (Chen, 2007). Building effective immersive video games necessitates the involvement of experienced video game designers, multimedia engineers, UI experts, and graphic artists, all working together to generate rich interactivity via complex reward cycles, art, music, and story.

Scientists play a critical role in CLVG development by informing decisions that direct video game mechanics at targeted neuro-cognitive systems. Just as game design should be planned up front, neuro-cognitive targets need to be considered from the onset, not as an afterthought. This consideration is essential for designing the core closed-loop mechanics of a CLVG—rapid performance-based challenge adaptivity and performance feedback—that establish the dynamic interactivity between the player and the game environment. Challenge adaptivity is often implemented using psychophysics algorithms to dynamically scale the difficulty of game play, ideally based on real-time data of user performance. This allows the game to be played by individuals of widely varying baseline abilities. Even more importantly, it creates appropriate and personalized levels of difficulty that apply continuous pressure on the neural system activated by game play, thus

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harnessing inherent neuroplasticity processes and driving the desired neural changes (Anguera et al., 2013; Mishra et al., 2014). Performance feedback, via the delivery of reward, is a primary source of motivation for the player (Corbalan et al., 2009). It can be provided across different timescales in continuous or punctuated forms. Continuous feedback is delivered in real time, locked to each response made by the game player, and drives depth of engagement in the moment. Punctuated feedback, often presented as a player's performance summary at end of each session and across multiple sessions of game play (e.g., personalized growth curves or comparisons with other players), supports sustained commitment over long periods of time.

Cognitive scientists and neuroscientists can inform how, where, and when to focus adaptivity and feedback in CLVGs based on the objectives of the training. For instance, games that target enhanced speed of processing may focus these closed-loop mechanics on accelerating stimulus presentation times and shortening response time windows as a player's speed increases (Ball et al., 2007). Games aimed at improving interference resolution may challenge a player to adaptively resolve greater levels of interference over time. We have recently demonstrated neural and cognitive evidence for the effectiveness of this approach in studies elaborated in the next section (Anguera et al., 2013; Mishra et al., 2014). Hence, we propose that the ideal situation for the development of impactful CLVGs is one where neuroscientists work closely with video game professionals to inform the core mechanics of game play, while game engineers lead the design of overt elements of engagement and fun.

The Second Pillar: High-Level Validation

Akin to the clinical trials pathway for drug development, high-level scientific validation is an essential aspect of both the iterative process of game development as well as its translation as a tool of positive impact in the public domain. As an example of the former, two of our recent studies have informed the principles of scientific game design. Anguera et al. (2013) showed that an adaptive multitasking video game that demanded users to simultaneously improve performance on two distinct tasks generated a transfer of benefits to untrained cognitive tasks in older adults. Game play also resulted in enhanced midline frontal theta activity—an electroencephalography (EEG)-based marker of cognitive control (Cavanagh and Frank, 2014)—which correlated with observed cognitive gains. In another study, Mishra et al. (2014) performed cross-species experiments to show that poor interference resolution in older adults can be ameliorated by an adaptive game that specifically challenges users with increasing levels of distraction. To ascertain that the observed benefits were specifically driven by the game interactions, both of these studies were carefully controlled using both a no-contact control group and an active control group.

A no-contact control group facilitates an understanding of how the outcome measures are influenced by practice effects of performing repeat assessments. An active control group advances the interpretability of a study because it generates both practice effects and non-specific placebo effects. A placebo active control group involves a study cohort that plays another game that matches a player's expectations of positive outcomes. The appropriateness of a placebo control group, i.e., ensuring that it is well matched to the main study game, can be formalized with a pre-study assessment comparing expectations of naive players on the main game versus active placebo (Boot et al., 2013). In our previous studies, the active control games went beyond conventional placebo controls that contain no active ingredients. We used active control games that were very closely matched to the main study game with only a single factor varied. We refer to these as "mechanistic active controls" because they allow an assessment of the mechanism of action of a successful game by isolating the active ingredient of the effects. For example, Anguera et al. (2013) hypothesized that a multitasking challenge would lead to generalizable cognitive control benefits, and so a singletasking version of the same game served as a mechanistic active control. Mishra et al. (2014) hypothesized that interference resolution would be specifically improved by adaptive distraction challenges while the difficulty of the attention target is held constant, so we used a mechanistic active control that flipped the adaptive elements, i.e., implemented adaptive target challenge while holding distractor challenge constant. These studies establish game design principles that guide future development projects and larger-scale validation studies.

It is important to note that the validation process should not be viewed as the purview of a single study. The laboratory studies described above accomplish the goal of proof-of-principle feasibility and a first-pass understanding of active game ingredients as well as neural mechanisms of action. Studies of this type can detect the presence of a "signal," i.e., significant change on relevant outcome measures, which in turn may generate interest and guide the design of future versions of the game, as well as other stages of validation research. This involves larger numbers of study participants of different ages and various baseline abilities, as well as manipulation of intervention design and duration of game play; e.g., a comparison of dosing schedules. Prescriptive claims need to be based on large randomized controlled studies, and those claims cannot be generalized from one population to another. Once a CLVG shows promise in initial laboratory studies, validation needs to be scaled in a manner similar to clinical drug and device pathways, incorporating large sample sizes; double-blinded, randomized, placebo-controlled testing; intent-to-treat methodology; and multi-site consortium trials. This is the stepwise pathway to generate convincing evidence of efficacy and ultimately regulatory approval from agencies such as the FDA. High-level validation is a necessary process if CLVGs are to advance as a component of personalized digital medicine. Indeed, several companies are in the process of supporting multi-site randomized trials of their products with the goal of FDA approval for clinical neuropsychiatric disorders. These large-scale efficacy trials with academic university partners are performed after initial laboratory studies have detected a signal and established feasibility. Partnerships such as these reflect successful industry-academic collaborations that will engender the translation of laboratory discoveries into positive impact on people's lives.

Even beyond the domain of clinical indications, it is important that companies creating CLVGs to enhance human performance in healthy individuals conduct rigorous scientific validation studies. These studies are especially challenging given the lack of quantitative real-world outcome measures that inform brain health. As the ''Internet of Things''—devices/appliances/vehicles with embedded sensors that learn and respond to human preferences and decisions—become ubiquitous, researchers will be able to access these data to track real-world behavior in validation studies.

The art and science of CLVGs is still in its infancy. We have demonstrated initial evidence of how the closed-loop mechanics of challenge adaptivity and performance feedback can incorporate real-time individual performance metrics to guide interactivity in video games and consequently yield benefits in specifically targeted cognitive domains. But how do we ensure that individuals in the real world, beyond being participants in research studies, adhere to these game training regimens? How do we assure that the benefits are meaningful and sustainable over time? What, if any, negative side effects arise from participating in such training? How do we tune CLVGs to be specifically tailored to the neural and cognitive needs of each individual? Much future development and research needs to happen to achieve these goals.

The Future, Part 1: Personalized Game Training Programs

Adherence to a training schedule is a critical element for learning, as deep, repetitive, and consistent engagement in a game regimen is likely essential for positive outcomes. While having fun during the training process itself may indeed be a factor in why video games may be more impactful than gamified cognitive exercises (Anguera and Gazzaley, 2015), even engagement with very fun games wanes over time. Moreover, the incorporation of a new regimen into a person's life, which may replace another activity and create demands on family and career, is a challenging undertaking. A review of the literature suggests that researchers in the field of cognitive training hardly ever consider this factor, perhaps contributing to negative findings. We need to involve motivation frameworks, goal-setting, and habit formation practices in the design of training regimens. For instance, someone training for a marathon has a clear understanding of their baseline performance and the end goal they are trying to achieve. Based on this foundation, individually tailored training schedules with timelines and milestones move a runner from baseline to accomplishing a marathon. The total training period is naturally longer for those with no running history versus those with a habit of running several miles per week. The main takeaway is that during marathon training, the individual is fully aware of his/her baseline, the final goal, and their progress toward the goal in any given week. Further, the social network of the trainee—family and friends—often provides support to help them stay on track. We need to think deeply about such real-world factors if the field of cognitive training is going to advance into people's lives.

To achieve high degrees of adherence and depth of engagement over the course of training, CLVGs need to engage the user in personalized programs, not one-size-fits-all, isolated game play training sessions. These programs should include a baseline assessment of the individual's neural and cognitive status that is shared with them, along with personalized training goals and a schedule. Throughout the training period, the program needs to regularly inform the user of their current neural and cognitive status relative to their baseline and end goal. Such a personalized performance-tracking dashboard can also be shared with the user's social network to create a supportive training community. Although no technology currently provides real-world, real-time, comprehensive, and accurate tracking of neural and cognitive performance, we are rapidly moving in that direction. This will be especially useful in clinical translational settings to serve mentally impaired patients who at present receive suboptimal, subjective diagnostic updates as ''snapshots'' during doctor visits every few months.

Baseline assessment measures of neural and cognitive health will need to be systematically developed using empirically obtained large population databases. Predictive modeling approaches can then be applied to customize the initial training regimen to the individual's neural and cognitive profile. Further, it is unlikely that a single CLVG will be used in training; instead, game packages will be delivered as ''neuro-crossfit'' training programs with several CLVG weights (for dosing, intensity, etc.) customized to the individual's needs. Enabled by scalable mobile technologies and supported by remote cloud database servers to monitor performance progress, these customized CLVG programs can be validated on a large scale as part of global studies. Such research efforts have already begun in healthy (McNab et al., 2015) and impaired populations (Anguera et al., 2016; Mishra et al., 2016). As CLVG training programs become more personalized, very large sample studies and clinical trials will become necessary to investigate how specifically customized combinations of CLVGs best suit a subset of the population. This is in line with new directions in clinical medicine to systematically study the outcomes of personalized, combinatorial pharmacological treatments that meet the individual patient's needs (Schork, 2015). In summary, future CLVG research will emphasize creation and validation of rich, personalized training programs that integrate in an individual's life and deeply engage them for maximal neural and cognitive benefit.

The Future, Part 2: Multimodal, Integrated, Closed-Loop Systems

The ultimate goal of CLVGs is to drive meaningful and sustainable transfer of benefit to general neuro-cognitive functioning and overall mental health. It is becoming clear that the current, unimodal, siloed approach of training an isolated cognitive function or even a set of cognitive functions will not achieve these

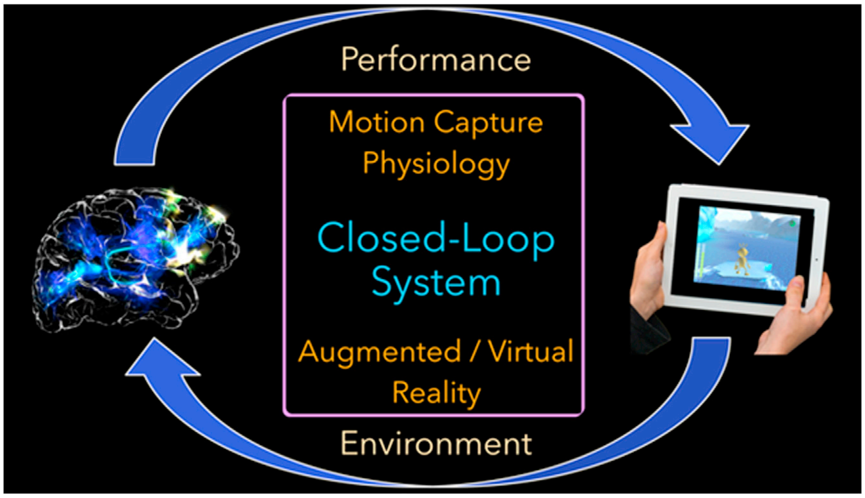

Figure 1. A High-Tech Closed-Loop Video Game
Schematic of a future, multimodal, closed-loop system that is informed by integrated neural inputs, motion capture, and physiological sensor data and that outputs a highly immersive environment experience for the user enhanced by augmented/virtual reality technologies and is tied together with sophisticated machine learning algorithms.

highest of goals. Innovations in CLVG research are necessary to refine both the input and output arm of the closed loop (Figure 1).

In the future, the input arm of the closed loop will be informed by modern wearable sensor technologies that gather real-time data on the individual's interactions during game play, including motion capture, eye movements, and physiological data from EEG, EMG (electromyography), HRV (heart rate variability), and GSR (galvanic skin responses). All of these technologies are becoming more accessible and capable of providing high-quality, research-grade data to drive the video game mechanics. Thus, in addition to performance-driven feedback and adaptivity, next-generation CLVGs will provide real-time feedback based on neural network dynamics (neurofeedback) and/or other body physiology (biofeedback) and will in turn adapt game challenge based on these physiological inputs. Note that here we are not referring to the isolated neurofeedback and biofeedback approaches that exist today, but rather we envision synergistic multimodal gaming that involves closed-loop integration of real-time behavioral and physiological data. We predict that these combinations will generate more robust, sustainable, and deficit-targeted neural and cognitive gains. The output arm of the closed loop will also be enhanced by modern and emerging engagement technologies: virtual and augmented reality (VR/AR), which generate more real-world gaming environments with enriched feedback and adaptive stimulus displays. We are in the process of creating the first prototypes of these multimodal, integrated CLVGs, which will require careful validation in multi-arm studies to tease apart gains driven by synergistic versus isolated closed loops.

Parallel to advances in hardware that feed the input/output arms of next-generation CLVGs, advanced software algorithms will bridge the intersection between these arms. These sophisticated algorithms will draw from artificial intelligence/machine learning and Bayesian modeling approaches, which jointly model physiology and behavior to reveal the critical parameters that determine embodied cognition (Turner et al., 2016). These algorithms will then precisely tailor the challenge adaptivity and performance feedback in the output arm to have the CLVG evolve with the learning capacity of the individual and thereby drive maximal neural and cognitive benefit.

Finally, we will also integrate approaches such as non-invasive electrical neurostimulation to boost the effects of CLVGs on specific neural networks (Hsu et al., 2015). Again, technological innovation will focus on multimodal closed loops that integrate real-time electrical stimulation based on active recordings of neural and/or cognitive performance status. Spectrotemporal EEG dynamics during game play can also be used to guide neurostimulation parameters at a specific frequency using real-time tACS (transcranial alternating-current stimulation).

Next-generation CLVGs promise to be sophisticated, multimodal, targeted, and personalized. Currently, commercial video games built for pure entertainment, which simultaneously and non-selectively challenge many cognitive processes, have shown beneficial transfer to general cognitive abilities (Bavelier et al., 2012; Clemenson and Stark, 2015; but for null findings see Boot et al., 2011). But unlike CLVGs, these commercial games are imprecise and cannot be used to selectively modulate specific neural processes and cognitive domains. We remain optimistic that CLVG initiatives that are based on high-level development paired with rigorous validation studies will create a new category of closed-loop technologies for neural optimization in both healthy individuals and those suffering from neural impairments, and thereby greatly advance the fields of basic cognitive and translational neuroscience research.

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