Addictive Behaviors 131 (2022) 107297

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

# Chronic use of cannabis might impair sensory error processing in the cerebellum through endocannabinoid dysregulation

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ARTICLE INFO

*Keywords:*
Chronic cannabis use
Cerebellum
Error processing
Endocannabinoid system
Motor learning

ABSTRACT

Chronic use of cannabis leads to both motor deficits and the downregulation of $CB_1$ receptors ($CB_1R$) in the cerebellum. In turn, cerebellar damage is often related to impairments in motor learning and control. Further, a recent motor learning task that measures cerebellar-dependent adaptation has been shown to distinguish well between healthy subjects and chronic cannabis users. Thus, the deteriorating effects of chronic cannabis use in motor performance point to cerebellar adaptation as a key process to explain such deficits. We review the literature relating chronic cannabis use, the endocannabinoid system in the cerebellum, and different forms of cerebellar-dependent motor learning, to suggest that $CB_1R$ downregulation leads to a generalized underestimation and misprocessing of the sensory errors driving synaptic updates in the cerebellar cortex. Further, we test our hypothesis with a computational model performing a motor adaptation task and reproduce the behavioral effect of decreased implicit adaptation that appears to be a sign of chronic cannabis use. Finally, we discuss the potential of our hypothesis to explain similar phenomena related to motor impairments following chronic alcohol dependency.

## 1. Introduction

### 1.1. Cerebellum and drug-related behavior

There is emerging evidence from pre-clinical and neuroimaging studies that the cerebellum is critically involved in addictive processes, and that cerebellar structural and functional changes emerge in relation to addictive substance abuse (Moulton, Elman, Becerra, Goldstein, & Borsook, 2014). For instance, in their review, Moulton et al. summarized the existing evidence for structural and functional alterations in the cerebellum, caused by exposure or long-term addictive substance abuse, such as cannabis, alcohol, nicotine, and cocaine. In specific, they revealed that the posterior cerebellar hemispheres appear to differ in addicted subjects versus healthy controls. However, there is no consensus yet regarding the structural and functional effects of cannabis abuse. It remains also an open question, whether the differences imply a predisposition for addiction, or are simply the result of drug use (Moulton et al., 2014).

The cerebellar modulatory function has been associated not only with motor coordination and motor learning, but as well cognitive functioning and emotional processing, all of which play a crucial part in addictive behavior (Miquel, Toledo, García, Coria-Avila, & Manzo, 2009). It appears that acute drug abuse enhances sensory processing of drug-related cues and the development of motor skills involved in the drug-taking procedure and paraphernalia. Prolonged drug-taking behavior shapes the development of value and experience-based sensory and motor representations, leading to action schemata of substance acquisition and consumption. More specifically, the repeated pairing of intrinsically neutral stimuli with the rewarding effect of taking a drug renders these stimuli incentive salient, thereby biasing attention (Berridge, Robinson, & Aldridge, 2009; Robinson & Berridge, 2000). These schemata are then easily activated by drug-related cues, leading to automated action and motor representations, which possibly underlie the addictive behavior and could account for relapses even after long abstinence (Yalachkov, Kaiser, & Naumer, 2010). On the other hand, prolonged drug-abuse is associated with impairment in cognitive control. Impaired frontal-cortico-cerebellar functional networks in alcohol use disorders due to structural damage have been associated with

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https://doi.org/10.1016/j.addbeh.2022.107297
Received 2 December 2020; Received in revised form 8 September 2021; Accepted 25 February 2022
Available online 4 March 2022

deficits in inhibitory actions. Hence, it has been suggested that the automatized actions and motor responses associated with drug-related cues become not only less amenable to cognitive interference but that the lack of cognitive control impairs the individual to inhibit drug consumption (Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014). This notion has given rise to the dual-process model of addictive behavior, in that drug-use emerges due to acquired automatic, impulsive processes which start to dominate the decision-making processes within addiction (for a review, see Stacy & Wiers, 2010). However, it has been recently argued, whether the addicted individual indeed exhibits total loss of choice or whether volitional choice is present but decision-making biased towards the drug consumption (Wiers & Verschure, 2020). It is known that the cerebellum plays a crucial role in decision-making through habit formation, reward and error processing, and motor learning (see for instance (Rosenbloom, Schmahmann, & Price, 2012)). However, it is unclear how a potential cerebellar damage due to chronic substance abuse would affect these processes leading to maladaptive and addictive behavior. In addition, investigating the role of the cerebellum in addiction might also aid in understanding, whether biased decision-making underlying addiction could be reversed through rehabilitation that is capitalizing on the learning mechanism that led to the addiction in the first place. For instance, it has been shown that by manipulating the attentional bias and action towards alcohol-related stimuli addicted individuals were able to form new, healthier habits, which reduced relapse post-treatment (Rinck, Wiers, Becker, & Lindenmeyer, 2018).

The present paper brings forward a possible explanation regarding the effects of chronic cannabis (and alcohol) use and its hypothetical molecular mechanisms (i.e., the $CB_1R$ downregulation in the cerebellum), focusing on motor learning deficits, which have been arguably overlooked until now (Blithikioti et al., 2019; Prashad & Filbey, 2017). The aim is to establish a mechanistic explanation of motor impairment due to chronic drug use –mainly cannabis and alcohol—, that is grounded on the known physiology of the cerebellum, the endocannabinoid regulatory system, and the molecular effects of chronic use. Further, we aim to account for a specific motor impairment observed in a recent clinical study (Herreros et al., 2019), which might shed light on the general principle underlying the aforementioned motor and cognitive deficits. Understanding the involvement of the cerebellum in addiction aids on the one hand to get a clearer view of the consequences of long-term drug use and to establish common diagnostic and therapeutic tools.

### 1.2. Cerebellar impairments in chronic cannabis use

There is no consensus about the specific effects of chronic cannabis use on human neurocognition. While the literature has consistently linked it to alterations in verbal learning, memory, and attention (Broyd, Van Hell, Beale, Yücel, & Solowij, 2016), there is mixed evidence pointing to impairments in psychomotor function (i.e., finger tapping, critical tracking, choice reaction time tasks, and digit-symbol substitution tasks) and executive function (i.e., tasks of planning, reasoning, interference control, and problem-solving). The inconsistency of these results may be due to the heterogeneity and the complexity of the selected tasks. Motivated by these limitations, a recent systematic review screened 248 unique articles exploring cerebellar alterations in

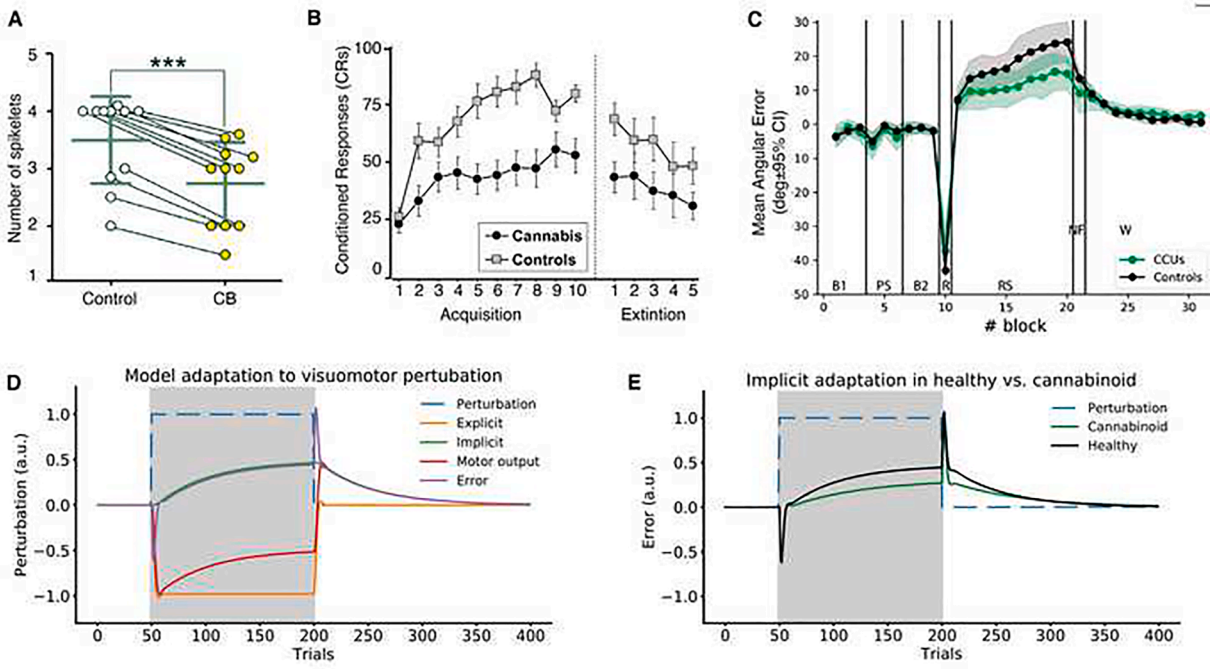


**Fig. 1. The $CB_1R$ downregulation due to chronic cannabis use leads to impaired cerebellar-based motor learning. A.** Number of spikelets in mice exposed to synthetic exogenous cannabinoids (CB) and controls. Adapted from (Irie et al., 2015). **B.** Acquisition of eye-blinking conditioned responses in cannabis users after 24 h of abstinence (Cannabis group) and controls. Adapted from (Skosnik et al., 2008). **C.** Evolution of the average directional error in a motor adaptation task. Vertical lines separate different phases of the experiment: B1, first baseline period; PS: practice strategy; B2: second baseline period; R: rotation; RS: rotation plus strategy; NF: no feedback washout; W: regular washout. Adapted from (Herreros et al., 2019). **D.** Outputs of the different components of our computational model of motor adaptation during a visuomotor perturbation task (see Methods). The shaded area indicates the perturbation period (like the RS period in (Herreros et al., 2019)), where a disturbed mapping between motor output and visual trajectory is introduced with respect to a target (in this case represented by $y = 0$, while the perturbation is represented by $y = 1$). The explicit component reflects the prefrontal-based strategy. The implicit component corresponds to the cerebellar-based slow learning process. The motor output is the sum of both the explicit and implicit components. The error is the difference between the perturbation and the motor output. Outputs are normalized to arbitrary units (a.u.) by setting the perturbation to 1 during the RS period. **E.** Error of the computational model during the visuomotor perturbation task, under two conditions: healthy and cannabinoid. The cannabinoid condition was implemented by decreasing the learning rate of the cerebellar slow adaptation process from 0.01 to 0.005, thus reflecting the $CB_1R$ downregulation hypothesis on deficient synaptic plasticity.

cannabis users (Blithikioti et al., 2019). The authors concluded that chronic cannabis intake leads to deficits in eyeblink conditioning, memory, and decision making. At a more mechanistic level, all of these behavioral paradigms are highly dependent on the endocannabinoid system. Therefore, the dysregulation of the endocannabinoid system might be key for the understanding of the motor deficits associated with this type of addiction (Prashad & Filbey, 2017). Indeed, animal studies suggest that the intake of synthetic exogenous cannabinoids reduces the number of spikelets in the complex spikes of cerebellar Purkinje cells (Fig. 1A; (Irie et al., 2015)) and slows-down the acquisition of conditioned responses (Fig. 1B; (Skosnik et al., 2008)). Grounding on these observations and the widely accepted role of Purkinje cells in the coding of sensory errors and motor control (Herzfeld, Kojima, Soetedjo, & Shadmehr, 2015, 2018), Herreros, et al. hypothesized that THC, acting as an exogenous agonist of the cannabinoid receptors, may diminish cerebellar plasticity (Herreros et al., 2019). The authors exposed 17 chronic cannabis users (CCUs) and 18 healthy age-matched controls to a visuomotor rotation task that probes a putatively-cerebellar implicit motor adaptation process together with the learning and execution of an explicit aiming rule (Taylor, Krakauer, & Ivry, 2014). The results showed impaired implicit motor adaptation in CCUs when compared to controls (Fig. 1C), thus uncovering a behavioral marker of cerebellar alterations that could have potential clinical applications.

### 1.3. Synaptic plasticity in the cerebellum and the endocannabinoid regulatory system

The endocannabinoid system is critical for synaptic plasticity regulation across many brain areas (Chevaleyre, Takahashi, & Castillo, 2006). One of the structures with the highest density of $CB_1$ receptors ($CB_1R$) is indeed the cerebellum (Herkenham et al., 1990). Learning of well-timed motor responses in the cerebellum is thought to largely rely on long-term depression (LTD) at parallel fiber-Purkinje cell (PF-PC) synapses (Ito, 2000; Koekkoek et al., 2003; Steuber et al., 2007). In turn, LTD in the cerebellar cortex relies on retrograde signaling from endocannabinoids, which downregulate the presynaptic transmitter release into Purkinje cells (Safo & Regehr, 2005), thus providing a homeostatic mechanism that protects Purkinje cells from excessive synaptic activity (Marcaggi & Attwell, 2005). Endocannabinoids regulating LTD can be released by complex spikes (Rancz & Häusser, 2006). More specifically, multivesicular release from climbing fibers into Purkinje cells (Wadiche & Jahr, 2001) generates dendritic-constrained glutamate spillover (Duguid, Pankratov, Moss, & Smart, 2007; Takayasu, Iino, Shimamoto, Tanaka, & Ozawa, 2006) and thus could mediate synaptic crosstalk-triggered endocannabinoid release (Marcaggi & Attwell, 2005) and hence postsynaptic LTD in PF-PC synapses. Furthermore, $CB_1R$ antagonists reduce the average number of spikelets in Purkinje cells' complex spikes elicited by climbing fiber inputs (Irie et al., 2015). Importantly, complex spikes have been shown to encode sensory prediction errors (Herzfeld, Kojima, Soetedjo, & Shadmehr, 2018), with the number of spikelets determining the direction and magnitude of synaptic plasticity at PF-PC synapses (Rasmussen, 2020). Hence, downregulation of $CB_1R$, as caused by chronic cannabis intake (Chevaleyre et al., 2006; Sim-Selley, 2003), would functionally lead to an underestimation of the error magnitude conveyed by the climbing fibers to the cerebellar cortex, thus explaining the deficient synaptic updates in PF-PC synapses (Tonini et al., 2006). In turn, this effect would be reflected in behavioral studies with chronic cannabis patients, that indeed show an impairment in motor learning (Prashad & Filbey, 2017), and more importantly, it points to a reduced learning speed during motor adaptation tasks as a potential behavioral marker.

To test the hypothesis that motor impairments in CCUs are due to a misprocessing of sensory errors in the cerebellum, we tested a computational model of motor learning –based on (Smith, Ghazizadeh, & Shadmehr, 2006), see Methods— in a visuomotor rotation task that assesses cerebellar-based implicit learning (Taylor et al., 2014). In this motor reaching task, a counterclockwise perturbation in the mapping between the arm and cursor movements is introduced so that subjects have to counteract it by changing their aiming point in the clockwise direction in order to reach the target. Our model incorporates a fast and slow learning process, corresponding to prefrontal-based explicit strategy switching (i.e., aiming point) and implicit cerebellar adaptation, respectively (McDougle, Bond, & Taylor, 2015). On the one hand, the explicit process receives the counterclockwise perturbation itself as an error signal (i.e., perceives the introduction of the perturbation in the mapping between arm and cursor movement) and counteracts it by rapidly changing the aiming point in the clockwise direction so that the motor output is equal in magnitude but opposite in sign (Fig. 1D, "Explicit"). On the other hand, the implicit cerebellar process receives a sensory error as the difference between the motor output and the target, thus trying to slowly bring the motor output back to the target (Fig. 1D, "Implicit"). Importantly, the rapid clockwise change of the aiming point driven by the explicit process to counteract the mapping perturbation generates a discrepancy between the actual motor command (now clockwise to the target) and the target itself, that is received by the implicit process as an error signal. This error signal then drives the implicit cerebellar-like process, which tries to bring the motor command back to the target (counterclockwise). Hence, since both systems receive different error signals but contribute equally to the final motor output (Fig. 1D, "Motor output") and have opposing effects, the net result yields a cerebellar-driven progressive overcompensation (Fig. 1D, "Error") of the motor adaptation as shown in previous behavioral studies (Herreros et al., 2019; Taylor et al., 2014). Notably, this overcompensation, which is a signature of implicit cerebellar learning, is reduced in CCUs (Fig. 1C; (Herreros et al., 2019)).

Given our hypothesis of impaired synaptic plasticity and error underestimation due to $CB_1R$ downregulation, we tested the effect of reducing the learning rate of the slow cerebellar learning process in our model. Indeed, the results show that a decreased learning rate leads not only to a smaller adaptation slope but to convergence on lower adaptation values (Fig. 1E), thus reproducing the behavioral effect seen in CCUs (Fig. 1C). This suggests that a reduced learning rate in the cerebellar cortex underlies the impaired implicit adaptation in CCUs as shown in the visuomotor rotation task (Herreros et al., 2019). Furthermore, we predict that this synaptic plasticity impairment would also prevent CCUs to rapidly acquire cerebellar-dependent sensory-to-sensory predictions that are needed for building hierarchical generative models (Maffei, Herreros, Sanchez-Fibla, Friston, & Verschure, 2017), suggesting that more nuanced behavioral tests might be needed to evaluate the full extent of chronic cannabis use on cognitive abilities beyond motor learning.

### 1.4. Chronic alcohol use and its relation to endocannabinoid dysregulation

Alcohol use disorder is associated with a wide range of neuropsychological impairments, including memory, fluid cognitive abilities, and executive function deficits (Bates, Bowden, & Barry, 2002). Excessive alcohol abuse can lead to lasting structural and functional alteration in the cerebellum (Cheng et al., 2015; Sullivan, Deshmukh, Desmond, Lim, & Pfefferbaum, 2000), and presents the third common cause for sporadic ataxia, a rare but detrimental cerebellar dysfunction that is characterized by gait instability, limb incoordination, slurred speech and nystagmus (Hadjivassiliou et al., 2017). It is hence not surprising that chronic alcohol could lead to deficits in cerebellar learning. Animals and humans show alcohol-related deficits in classical eyeblink conditioning (Cheng et al., 2015). However, little is known about whether alcoholism impairs motor adaptation, despite studies that found that individuals with cerebellar ataxia exhibit pronounced deficits in visuomotor and force-field adaptation tasks (Maschke, Gomez, Ebner, & Konczak, 2004; Schlerf, Xu, Klemfuss, Griffiths, & Ivry, 2013).

Studies in animals showed that chronic ethanol intake leads to

impaired learning of a new motor coordination task, but does not affect the performance of an already mastered task. Moreover, chronic ethanol consumption led to a decrease in complex and simple spike firing rates of Purkinje cells, with longer spike duration and pauses in complex spikes (Servais et al., 2005). The most likely candidate for these changes is the endocannabinoid system, which has been shown to regulate the reinforcing properties of ethanol and hence propagating alcohol dependence (Basavarajappa, 2019). In humans, positron emission tomography (PET) demonstrated that chronic long-term excessive alcohol consumption leads to a decreased $CB_1R$ availability in the cerebellum and parieto-occipital cortex, which appears not to resolve with abstinence (Ceccarini et al., 2014). It is hypothesized that the downregulation might be a compensatory mechanism of $CB_1R$ in reaction to the increased endocannabinoid activity due to chronic alcohol consumption (Basavarajappa & Hungund, 1999).

Although ethanol and cannabis have distinct impacts, both drugs can cause similar cognitive, psychomotor, and attention deficits independent of chronicity, as they appear to interact synergistically and create cross-tolerance effects (Basavarajappa, 2019). However, in contrast to cannabis use, alcohol-dependency leads to more lasting neuroadaptive changes in $CB_1R$ (Ceccarini et al., 2014).

### 1.5. Concluding remarks

The similarity of the behavioral and cerebellar effects of alcohol and cannabis use might open the possibility to use similar diagnostic tools to assess the cerebellar impairments caused by chronic substance abuse. The visuomotor rotation task proposed by Herreros, et al. might be a suitable tool to explore the implicit motor adaptation processes in chronic alcoholics too. To date, the implications of long-term alcohol-use on the cerebellum and motor adaptation are unclear, despite it is known that chronic use can lead to profound motor impairment. Impaired implicit motor adaptation due to deficient synaptic plasticity in the cerebellar cortex might point to a common molecular mechanism that is not only altered by chronic cannabis consumption but by alcohol use as well. This insight might help to assess better the long-term deficits and behavioral consequences of chronic substance abuse and aid in finding novel ways to provide treatments.

## 2. Methods

### 2.1. Computational model

Given that our reference task (i.e., the visuomotor rotation task used in (Herreros et al., 2019)) has been hypothesize to involve slow and fast adaptation components (McDougle et al., 2015), we implement motor learning as a two-state, gain-independent system, whereby fast ("explicit") and slow ("implicit") learning processes interact to counteract a perturbation –as in (Smith et al., 2006). The discrete-time ordinary differential equations of the model read as follows:.

$$x_f(n+1) = A_f x_f(n) + B_f e_f(n)$$
$$e_f(n) = -p(n) - x_f(n)$$
$$x_s(n+1) = A_s x_s(n) + B_s e_s(n)$$
$$e_s(n) = T - x(n)$$
$$x(n) = x_f(n) + x_s(n)$$
$$e(n) = -p(n) - x_f(n) + x_s(n)$$
$$A_f = 0.99,\ B_f = 0.5,\ A_s = 0.99,\ B_s = 0.01\ or\ 0.005,\ T = 0$$

Where $x_{f,s}$ are the internal state variables, $A_{f,s}$ are the retention factors, $B_{f,s}$ are the learning rates, $T$ is the target point, $p(t)$ is the perturbation applied to the system with respect to$T$, and $e$ is the error, with subscripts $f$ and $s$ standing for fast and slow processes, respectively. Time is defined here by the trial number ($n$), and thus all variables are updated in a trial-by-trial manner.

Importantly, the main difference between Smith et al. and our model is that the explicit and the implicit processes do not share the same error signal. The evolution of the explicit process, which has fast dynamics, represents the change in the aiming point by the prefrontal cortex following the experiment instructions –as in (Herreros et al., 2019)—, and thus, the error is defined as the difference between the negative perturbation and the current aiming point. This error term forces the explicit system to converge to the opposite point defined by the perturbation, $-p(n)$, in order to rapidly counteract it. In contrast, the implicit cerebellar process, which has slow dynamics, receives a sensory error defined as the difference between the motor output and the target reference. Notably, since the motor output $x(n)$ is the result of adding the contributions of both systems, the cerebellar process is affected by the change in the aiming point made by the explicit prefrontal-like process.

We modified the original model in this way to adapt it to the task and paradigm under study –i.e., a visuomotor rotation task with a predefined explicit strategy consisting of an opposing clockwise aiming point after the counterclockwise perturbation is introduced (Herreros et al., 2019). The parameters shown in the above equations were used for the main task (Fig. 1D) –following the results shown in (Smith et al., 2006)—, with a reduction by half of the learning rate of the implicit cerebellar process ($B_s$) in the "cannabinoid" condition (Fig. 1E). This latter reduction of the learning rate in the "cannabinoid" condition represents the downregulation of the $CB_1R$ –that control plasticity in the Purkinje cells— caused by chronic cannabis use, and thus serves to probe our hypothesis that chronic cannabis use leads to an underestimation of sensory errors in the cerebellum, which in turn would cause the related motor adaptation deficits.

### 2.2. Literature review

A general review of the recent literature (from 1990 onwards) regarding the effects of cannabis and alcohol use on cerebellar function and the endocannabinoid system –both in humans and other animals, e.g., rats and mice— was done via the search engines Scopus and PubMed, using different combinations of the keywords: "cerebellum", "endocannabinoid", "$CB_1$ receptors", "$CB_1R$", "cannabis", "cannabis chronic use", "alcohol", "alcohol chronic use", "addiction", "complex spikes", "plasticity", "impairment", "cognitive impairment", "human", and "motor adaptation". After reading the abstracts (and methods, when needed), only the papers with relevant experimental data or other systematic reviews were selected for further reading. Then, the main results of the selected papers (15) were summarized by systematically comparing cannabis and alcohol use conditions in a number of functional domains, or categories, including "effects on motor performance or adaptation" (for humans and other animals, separately), "cognitive effects" (separating between acute and chronic conditions), "drug-related cues, or craving behaviors" (only humans), "CB1R and other cerebellar effects and damage" (humans and other animals, separately; also discriminating between acute and chronic conditions), and "interaction cannabis-alcohol" (humans and other animals, separately). The results of such comparisons were then brought together and further summarized throughout the different sections of the paper.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Paul FMJ Verschure is the founder and interim CEO of Eodyne S L, which aims at bringing scientifically validated neurorehabilitation technology to society. All other authors declare that they have no conflicts of interest.

## Funding

Funding for this study was provided by cRGS ERC (PoC) H2020-EU,

ID: 840052, Virtual Brain Cloud H2020-EU, ID: 826421 and from RGS@HOME H2020-EU. EIT Health, ID: 19277. NIAAA had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

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