

SCREEN DEPENDENCY DISORDERS:

A NEW CHALLENGE FOR CHILD NEUROLOGY

DR ARIC SIGMAN



The Journal of the International Child Neurology Association (JICNA) is published by the International Child Neurology Association (ICNA), representing the Association's official Journal, providing teaching, practical and professional support for clinicians dealing with neurological disorders in childhood. It publishes, after peer-review process, papers concerning both clinical and basic research.

Citation: Sigman, A. (2017). Screen Dependency Disorders: a new challenge for child neurology. JICNA. ISSN 2410-6410. Available at:
<http://jicna.org/index.php/journal/article/view/67>



Screen Dependency Disorders: a new challenge for child neurology

Aric Sigman

Correspondence to Dr A Sigman, Office 444, 91 Western Road, Brighton BN1 2NW, UK; aric@aricsigman.com

ABSTRACT

Children's neurological development is influenced by their experiences. Early experiences and the environments in which they occur can alter gene expression and affect long-term neural development. Today, discretionary screen time, often involving multiple devices, is the single main experience and environment of children. Various screen activities are reported to induce structural and functional brain plasticity in adults. However, childhood is a time of significantly greater changes in brain anatomical structure and connectivity. There is empirical evidence that extensive exposure to videogame playing during childhood may lead to neuroadaptation and structural changes in neural regions associated with addiction. Digital natives exhibit a higher prevalence of screen-related 'addictive' behaviour that reflect impaired neurological reward-processing and impulse-control mechanisms. Associations are emerging between screen dependency disorders such as Internet Addiction Disorder and specific neurogenetic polymorphisms, abnormal neural tissue and neural function. Although abnormal neural structural and functional characteristics may be a precondition rather than a consequence of addiction, there may also be a bidirectional relationship. As is the case with substance addictions, it is possible that intensive routine exposure to certain screen activities during critical stages of neural development may alter gene expression resulting in structural, synaptic and functional changes in the developing brain leading to screen dependency disorders, particularly in children with predisposing neurogenetic profiles. There may also be compound/secondary effects on neural development. Screen dependency disorders, even at subclinical levels, involve high levels of discretionary screen time, inducing greater child sedentary behaviour thereby reducing vital aerobic fitness, which plays an important role in the neurological health of children, particularly in brain structure and function. Child health policy must therefore adhere to the principle of precaution as a prudent approach to protecting child neurological integrity and well-being. This paper explains the basis of current paediatric neurological concerns surrounding screen dependency disorders and proposes preventive strategies for child neurology and allied professions.

Keywords: Internet addiction; Internet Gaming Disorder; Addictive behaviour; Neuronal Plasticity; Public Health; Screen Time; Bidirectional Causation

© 2017 Aric Sigman; licensee JICNA

BACKGROUND

Screen viewing now begins in infancy with new research finding that the prevalence of screen viewing in children aged under two years 'is high and appears to increase steadily across age groups' [1]. Early screen exposure has been facilitated by the advent of infant/toddler products such as the 'Newborn-to-Toddler Apptivity Seat for iPad ®' [baby cradle with iPad placed directly in infant's face] and the '2-in-1 iPotty®' – a combination of iPad and potty designed to help young children with potty training which 'features a special stand to securely hold the iPad and safely entertain kids while they play with apps ... and watch videos on the iPad at any time' [2]. Ofcom (The Office of Communications, United Kingdom) recently reported 'a third (34%) of preschoolers (aged 3-4) own their own media device – such as a tablet or games console.' [3]. According to Ofcom the average UK 16 -24 year old is now 'spending more time on media and communications than on sleeping' [4].

While elevated levels of discretionary (non-homework) screen time (DST) have raised significant concerns over children's cardiometabolic, psychosocial and other medical outcomes, there is a rapidly emerging neurological dimension to this growing public health issue: the prevalence of screen-related 'addictive' behaviour, which will generally

be referred to as screen dependency disorders (SDD), that reflect impaired neurological reward-processing and impulse-control mechanisms [5,6,7,8,9,10]. Associations are emerging between SDD such as Internet Addiction Disorder (IAD) and specific neurogenetic polymorphisms, abnormal neural tissue and neural function.

This contribution is a narrative review addressing the association between SDD and abnormal neural tissue and neural function that may indicate potential risk to children's neurological development and well-being. It expands upon a plenary lecture given at the 14th International Child Neurology Congress held in Amsterdam, The Netherlands, May 1-5, 2016 [11]. This paper reflects the ideas and concerns of the author based on his literature search and experiences. The author searched four databases for relevant articles: PubMed, Medline, Embase and PsycInfo, using the terms: 'Internet addiction', 'video game addiction', 'computer game addiction', 'online game addiction', 'Internet Gaming Disorder', 'compulsive Internet use'. Each of the terms was combined with each of the terms 'neuroimaging', 'functional brain imaging', 'brain', 'limbic system' 'striatum', 'dopamine', 'reward system' using the conjunction 'AND'. The function 'find similar' was also used. Searches focused on articles published since 2012. This paper also includes some

articles from other related areas (e.g., risk factors, neuro-genetics, pathological gambling, substance dependency), where appropriate. The studies and reviews were then selected on the most important findings and views that focus on the association between SDD and abnormal neural tissue and neural function that may indicate a risk to children.

The aims of the paper are to raise awareness of screen-related dependency as a problem no longer confined to child and adolescent psychiatry. And in considering future child health policy, the paper will propose preventive strategies for child neurology and allied professions to adopt to promote the well-being of children and their neurological development. The basis of paediatric neurological concerns is outlined below.

SCREEN DEPENDENCY DISORDERS

'Addiction' is a term increasingly used to describe the growing number of children engaging in a variety of different screen activities in a dependent, problematic manner. The concept and diagnostic criteria derive from pathological gambling and substance-related addictions and are often based on the amount of time spent engaging in a screen activity, such as playing computer games, and the extent to which this compromises the individual's overall functioning.

Diagnostic criteria typically include the following features:

- preoccupation
- withdrawal symptoms
- increasing tolerance
- failure to reduce or stop screen activities
- loss of outside interests
- continuation despite negative consequences
- lying about extent of use
- use to escape adverse moods

The main neurobiological interest has centered on the problematic use of the Internet and computer games. Although there is currently a degree of interchangeability and overlap between some diagnostic terms, there are moves underway to reach a greater consensus over terminology as the lack of standardisation in the concept and terminology are considered a major impediment to advancing this area of research and treatment [12]. For that reason, the term screen dependency disorders (SDD) previously introduced by the author will be used when referring to the general range of screen-related dependencies referred to in this paper, while specific terms such as Internet Addiction Disorder (IAD), Mobile phone dependence (MPD) Internet Gaming Disorder (IGD) will be used as required when referring to specific studies cited which have used those terms [8] (see Table 1).

Table 1. Screen Dependency Disorders (SDD): Diagnostic terms commonly used in the classification of screen-related dependencies

- Internet addiction disorder
- Internet Gaming Disorder
- Problematic internet use
- Compulsive internet use
- Pathological video game use
- Video game addiction
- Pathological technology use
- Online game addiction
- Mobile phone dependence
- Social network site addiction
- Facebook addiction
- Internet pornography addiction

Although the current clinical and investigative focus surrounding SDD is on computer gaming, other forms of screen use can also become highly problematic and are of interest to neurologists. Frequent, excessive, and compulsive social network activity has become the subject of research into 'social network site addiction' and 'Facebook addiction' [13,14]. Increasing Internet pornography consumption and 'pornography addiction' has prompted research finding significant associations between internet pornography consumption and neural structure and functional connectivity [15,16,17].

There are striking behavioural and neurobiological similarities reported between SDD such as internet gaming disorder and disordered gambling, and similarities between SDD and drug and alcohol addictions [18,19,20]. The American Psychiatric Association's DSM-5 now includes Internet Gaming Disorder for future consideration as a formal 'mental disorder'; stating 'studies suggest that when these individuals are engrossed in Internet games, certain pathways in their brains are triggered in the same direct and intense way that a drug addict's brain is affected by a particular substance.' [21]

The development and maintenance of SDD are increasingly seen as a maladaptive interaction between the neurological structures and functions which underlie the central components of addiction: reward, pleasure, craving and reinforcement processing; learning and memory; impaired executive functioning, inhibitory control, decision-making and emotion management [22].

Much of the neurological investigation of SDD focuses on a dysfunctional interaction between neural structures involved in executive control and reward-seeking. Structural differences between subjects with and without SDD have been reported in both gray and white matter in prefrontal and additional brain regions, such as limbic structures. Functional brain correlates of SDD are also found in the prefrontal cortex and limbic structures. Typical characteristics in addiction of impaired executive functioning and inhibitory control are related to lower functional connectivity in fronto-striatal circuits. Alterations in dopaminergic systems involved in reinforcement/reward processing have also been suggested.

As neurological dysfunction is increasingly seen as a fundamental component of SDD it has the potential to serve as a future biomarker for diagnosis. This may help resolve diagnostic inconsistencies ultimately unifying differences in diagnostic approaches and terminology used [20,23,24].

PREVALENCE

Prevalence of SDD varies according to the screen activity, the diagnostic tool used, world region, and age of subjects. Studies of 8 – 14 yr. old computer game players in different parts of the world have reported that 8 – 9 % fulfilled diagnostic criteria for 'pathological video game use' [25,26]. A recent US study found that among young adolescent gamers, 12% were considered 'pathological video-gamers' [27]. Recent international collaborative research on South Korean young adults/adults reported that 13.8% were identified and labelled as the 'Internet Gaming Disorder risk group' [28]. Research in the European Union on Internet Addictive Behaviour among European Adolescents reported 'IGD is a frequently occurring phenomenon among European adolescents ... 1.6% of the adolescents meet full criteria for IGD, with further 5.1% being at risk' [29].

NEUROADAPTATION

Various screen activities are reported to induce structural and functional brain plasticity in adults [30,31,32]. However, childhood is a time of significantly greater changes in brain anatomical structure and connectivity [33]. It has been suggested that SDD and even extensive exposure to videogame playing during childhood can lead to neuroadaptation and structural changes in neural regions associated with addiction [34,35,36]

In a study of 248 healthy children aged 5 – 17 years Takeuchi et al. (2016) reported highly significant correlations between daily average hours of videogame play and microstructural changes over a 3-year period in diffusion tensor imaging mean diffusivity thought to reflect a reduction in tissue density [37]. They noted that such changes are uniquely sensitive to neural plasticity, particularly within the dopaminergic system. ‘In conclusion, increased video game play is directly or indirectly associated with delayed development of the microstructure in extensive brain regions ... the conditions in which children play videogames for long periods of time may lead to unfavorable neurocognitive development’ [37]. Many of the regions in which longitudinal changes were reported are those routinely implicated in studies of SDD, gambling disorders and substance addiction. (see Figure 1)

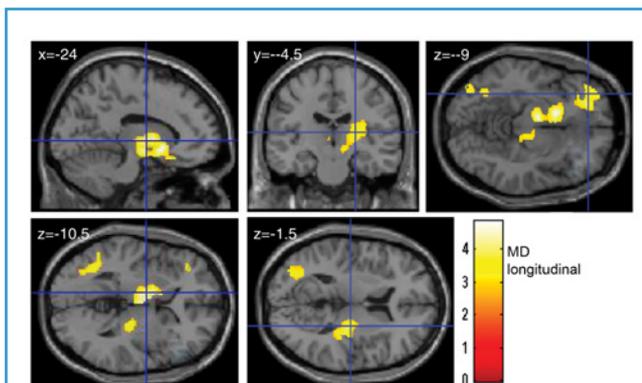


Figure 1. Longitudinal changes in Mean Diffusivity (MD) related to amount of time (hours) children played video games. Regions with significant correlations between time spent playing video games and longitudinal changes in MD are overlaid on a ‘single subject’ T1 image. Changes in MD over 3 years were observed in clusters spread throughout gray and white matter areas of the left basal ganglia, left medial temporal, bilateral thalamus, ventral parts of the prefrontal cortex, right insula, left middle and inferior temporal, fusiform and left occipital lobe. The color represents the strength of the T value for pre and post test MD difference. (Takeuchi et al 2016)

There is also new evidence indicating that changes in functional connectivity occur in the brain in response to treatment for SDD. A longitudinal study published in *Addiction Biology* reported that IGD subjects who received a psychobehavioural intervention showed a highly significant decrease in functional connectivity between the ventral striatum and inferior parietal lobule, along with amelioration in addiction severity, compared to matched IGD subjects not receiving treatment which showed no changes [38].

DOPAMINERGIC DYSFUNCTION

Dopamine is implicated in reward processing and addiction. Hypodopaminergic functioning and a resultant overall re-

ward deficiency characterize SDD. Videogame playing has been associated with dopamine release similar in magnitude to that of drugs of abuse [39]. Nuclear imaging research indicates that SDD is associated with dysfunction of dopaminergic systems. Abnormal dopamine regulation of the prefrontal cortex [PFC] is also thought to underlie the enhanced motivational value and loss of control over screen activity such as gaming, typical of ‘addicted’ subjects [40].

NEURORECEPTOR ABNORMALITIES

Individuals with IAD are reported to exhibit reduced dopamine D2 receptor availability in the striatum compared to controls. The greater the severity of IAD, the lower dopamine receptor availability was found to be [41]. Potential presynaptic abnormalities are also observed in subjects with IAD, who exhibit a significantly lower dopamine transporter expression level [35].

Dysregulation of dopamine D2 receptors has been found to be correlated with years of problematic Internet gaming. Among subjects with IGD, a low level of dopamine D2 receptor in the striatum was correlated with decreased glucose metabolism in the orbitofrontal cortex. It is suggested that this reflects D2 receptor-mediated dysregulation of the orbitofrontal cortex, which could be a key mechanism for loss of control and compulsive behavior typical of IGD [42].

The above studies are leading some researchers to speculate that these neuroreceptor abnormalities may reflect ‘neuropathologic damage to the dopaminergic neural system caused by IAD’ [35]. It is known that increased levels of endogenous dopamine enhance neurotoxicity in the striatum induced by other agents and processes [43,44]. Also, exposing either younger or older cultured striatal neurons to dopamine has been found to induce ‘dose-dependent cell death’ [45].

Neuroreceptor abnormality may also be a case of a bidirectional causal relationship where neural abnormalities exist before screen activities are initiated. In substance addictions, there is molecular neurogenetic evidence for a predisposition to ‘reward deficiency’ through hypodopaminergic function, discussed below [46]. In SDD, subsequent early, intensive and prolonged exposure to certain screen activities during critical stages of neural development may cause further dopaminergic dysfunction and neuroreceptor abnormalities, possibly through routine exposure to increased levels of endogenous dopamine leading to SDD which may, in turn, cause further dopaminergic dysfunction and neuroreceptor abnormalities. However, the associations between the SDD and neuroreceptor abnormalities could represent effect rather than cause, and longitudinal studies are needed to clarify this relationship.

In gambling disorder, evidence has recently emerged for GABA-A receptor dysregulation and associated lowered impulse control which may prove highly relevant to understanding and developing treatments for SDD [47].

CHANGES IN MESOLIMBIC SYSTEM

Longitudinal studies have found functional changes in the ventral striatum reward system among healthy non-addicted subjects engaged in video game training. In contrast to control subjects, those undergoing training exhibited strong activation of the ventral striatum which was maintained for 2 months in response to a non-video game reward task. The authors believe the video game training has an influence on

dopamine-related striatal reward processing during gaming which then persists in rewarding situations not related to video games [31]. Takeuchi et al (2016) reported that longitudinal changes within key areas of the dopaminergic system strongly related to children's daily average hours of videogame play [37].

It has been established that repeated exposure to non-drug rewards can induce neural plasticity in addiction-related circuitry. In some children, this may contribute to compulsive engagement in screen-related activities that resembles substance addiction. As with substance addiction, there is a transition period from moderate to compulsive use [48]. In the case of other non-drug rewards, this epigenetic process is achieved by acting on common molecular and cellular mechanisms of plasticity that influence vulnerability to addiction. It is mediated by the gene transcription factor Δ FosB (FBJ murine osteosarcoma viral oncogene homolog B) upregulating or downregulating relevant addiction-related genes in the nucleus accumbens which plays a central role in reward and addiction [49].

STRUCTURAL ABNORMALITIES

Extensive research is increasingly finding that adolescents and young adults with SDD exhibit microstructural and volumetric differences in, or abnormalities of, both grey and white matter compared to healthy controls [50,51,52,53,54,55,56,57,58,59]. Differences in brain structure and function are observed in many of the same regions implicated in drug addiction. Regions identified include dopamine-rich areas of the basal ganglia such as the ventral tegmental area, nucleus accumbens, caudate nucleus, putamen, thalamus and amygdala, as well as cortical projection areas such as the prefrontal cortex (PFC), orbitofrontal cortex, anterior cingulate cortex and insula [60,61,62].

A recent study involving Harvard Medical School has reported 'the first morphological evidence of altered brain structure ... in college students with mobile phone dependence' [61]. Microstructural variations were examined using fMRI involving four indices of brain morphometry and fibre integrity. In this cross-sectional study, lower grey matter volume was reported in subjects classified as mobile phone dependent relative to controls in regions such as the right superior frontal gyrus, right inferior frontal gyrus, and bilateral thalamus. GMVs were negatively correlated with subjects' scores on the Mobile Phone Addiction Index. Lower measures of white matter integrity were reported in bilateral hippocampal cingulum bundle fibers which were also negatively correlated with phone addiction index scores. The authors believe this may be due to subtle axonal injury rather than demyelination reflecting an 'underlying structural basis for functional deficits that leads to a solidification of addiction-related memories' (see Figure 2).

As SDD are increasingly associated with structural and functional differences, particularly in prefrontal regions involved in impulse control, a key aspect of addiction, recent research by Cai et al. (2016) sheds light on the lesser-known relationship between striatal nuclei volumes, SDD, and impaired impulse control. Compared to healthy controls, IGD adolescents/young adults exhibited greater volumes of the right caudate and nucleus accumbens which were in turn both associated with reduced cognitive control and more severe internet addiction scores respectively [60]. Similar research on frontostriatal circuits and IGD has found a greater volume of right caudate and nucleus accumbens as well as



Figure 2: Lower measures of WM integrity in bilateral hippocampal cingulum bundle fibers in mobile phone dependent subjects compared with controls. Regions highlighted in yellow/orange indicate significantly less Fractional Anisotropy and Axial Diffusivity measures of WM integrity of cingulum bundle fibers in the hippocampus of subjects classified as mobile phone dependent. (Wang, Zou, Song et al. 2016)

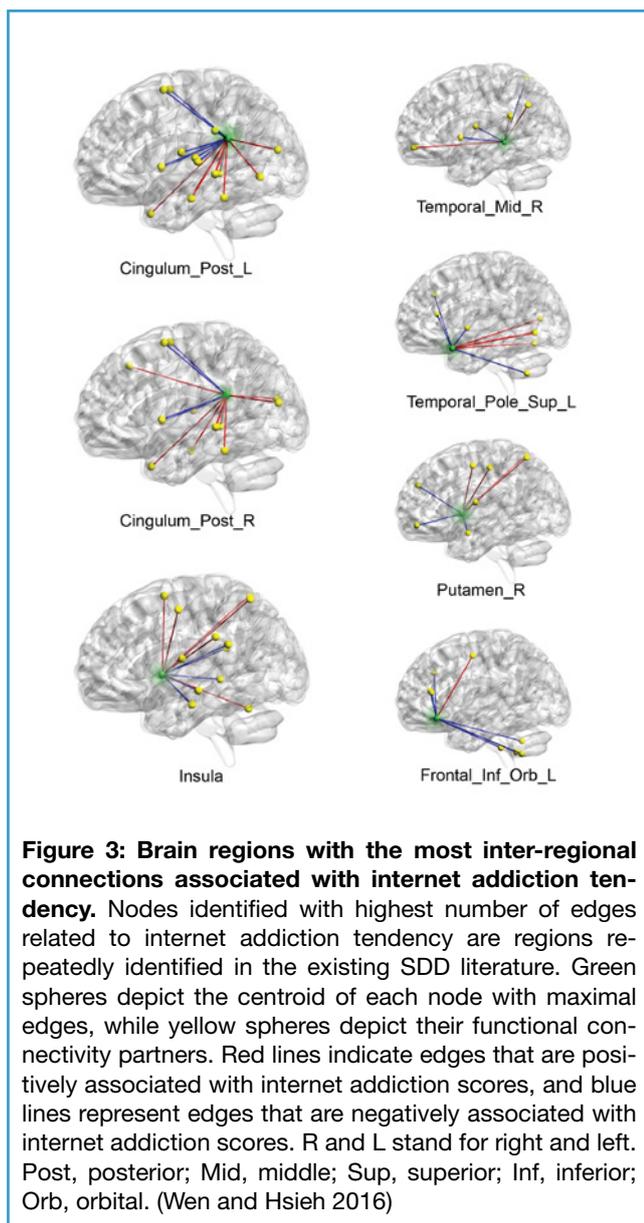
lower resting state functional connectivity strength of dorsal prefrontal cortex –caudate and orbitofrontal cortex - nucleus accumbens. Nucleus accumbens volumes were positively correlated with internet addiction test scores. The caudate volume and dorsal prefrontal cortex –caudate resting state functional connectivity strength was correlated with the impaired cognitive control. The authors stated the results were 'consistent with substance use disorder findings' [62]. Reduced fibre integrity in key areas of the salience network, which modulates self-control, are also observed in adolescents with IGD compared to controls [63,64].

Other studies are reporting 'altered correlations' between measures of impulsivity and GMV in the right dorsomedial prefrontal cortex, the bilateral insula/orbitofrontal cortex, the right amygdala and the left fusiform gyrus in adolescents with IGD compared to healthy controls. Many researchers believe that this reflects a dysregulation in neural networks involved in impulse inhibition, attention and emotion regulation which may contribute to the high impulsivity observed in IGD adolescents [23].

FUNCTIONAL ABNORMALITIES

A recent systematic review of fMRI studies involving older adolescents/young IAD adults, without any comorbid psychiatric condition concluded that in the task-related fMRI studies 'all of them found significant differences in cortical and subcortical brain regions involved in cognitive control and reward processing: Orbitofrontal cortex, insula, anterior and posterior cingulate cortex, temporal and parietal regions, brain stem and caudate nucleus ...In the resting state studies, the more relevant abnormalities were localized in the superior temporal gyrus, limbic, medial frontal and parietal regions.' [24]

New, whole-brain analyses of functional connectivity in SDD subjects have identified two topologically significant large-scale networks, one with connections that are positively and another negatively correlated with the degree of 'internet addiction tendency'. The two networks are predominantly interconnected in frontal areas, which might represent alterations in the area underlying different aspects of cognitive control. Interestingly, pre-clinical levels of Internet addiction were associated with similar regions and connections as clinical cases of addiction. The authors note 'the inter-regional connections associated with internet addiction tendency replicate those often seen in [substance] addiction literature.' [20] (see Figure 3).



Examining white matter networks in adolescents with IGD, Zhai et al. (2016) reported 'abnormal topological organization of white matter network in IGD and the association with the severity of IGD'. They observed decreased global efficiency, local efficiency and increased shortest path length in IGD adolescents compared to controls. In addition, the global efficiency of the white matter network was correlated with subjects' internet addiction test scores [65]. Yuan et al. (2016) observed abnormal functional connectivity within central executive networks and effective connectivity within salience network along with inefficient interactions between the two in IGD adolescents [64]. Wang et al. (2016) found that IGD subjects showed reduced regional centralities in the prefrontal cortex, left posterior cingulate cortex, right amygdala, and bilateral lingual gyrus, and increased functional connectivity in sensory-motor-related brain networks compared to the controls. The authors concluded 'these results imply that people with IGD may be associated with functional network dysfunction, including impaired executive control and emotional management' [66].

Other fMRI studies have reported 'deficits' in prefrontal lobe interhemispheric functional connectivity in adolescents

with IGD compared to healthy controls, interpreted as a 'neuropsychological mechanism of IGD' [67].

REGIONS OF INTEREST

Reduced functional connectivity between the ventral tegmental area and nucleus accumbens has been shown in internet gaming addiction as is the case in substance use which is thought to play an important role in the development of substance addiction [68].

The insula has been implicated in salience processing, craving, and interoception, all of which are fundamental to substance and behavioral addiction. Zhang et al. (2016) found that the severity of IGD was positively associated with connectivity between the anterior insula and angular gyrus, and superior temporal gyrus, and with connectivity between the posterior insula and superior temporal gyrus. Furthermore, the duration of Internet gaming was positively associated with connectivity between the anterior insula and anterior cingulate cortex [69]. A similar study found decreased functional connectivity between the left posterior insula and bilateral supplementary motor area and middle cingulate cortex, between right posterior insula and right superior frontal gyrus, and decreased functional integration between insular subregions. The authors concluded this is 'interpreted to reflect reduced ability to inhibit motor responses to internet gaming or diminished executive control over craving for internet gaming in IGD ... IGD is associated with altered insula-based network, similar to substance addiction such as smoking.' [70]

Lin et al. (2015) examined circuits assumed to be involved in the processing of mood and motivation along with impulse control, reporting 'aberrant corticostriatal functional circuits in adolescents with Internet addiction disorder.' 'Reduced connectivity' was observed between the inferior ventral striatum and bilateral caudate head, subgenual anterior cingulate cortex, and posterior cingulate cortex, and between the superior ventral striatum and bilateral dorsal/rostral anterior cingulate cortex, ventral anterior thalamus, and putamen/pallidum/insula/ inferior frontal gyrus, and between the dorsal caudate and dorsal/rostral anterior cingulate cortex, thalamus, and inferior frontal gyrus, and between the left ventral rostral putamen and right inferior frontal gyrus. Adolescents with IAD also exhibited increased connectivity between the left dorsal caudal putamen and bilateral caudal cingulate motor area [50].

Event-related potential studies have reinforced many of the above findings [71]. Duven et al. (2015) found that while winning reward tokens during computer game playing, subjects with IGD exhibited 'altered' reward processing, an attenuated P300 component which should instead increase with reward magnitude, indicating tolerance effects similar to substance addiction [72].

SECONDARY EFFECTS

There may also be compound/secondary effects of SDD on paediatric neural development. Screen dependency disorders, even at subclinical levels, involve high levels of discretionary screen time, inducing child sedentary behaviour for more hours per day thereby reducing aerobic fitness [73,74]. Yet, aerobic fitness plays an important role in the neurological health of children, particularly in brain structure and function. For example, Chaddock-Heyman et al. (2014) report-

ed 'aerobic fitness is associated with greater white matter integrity in children' especially in areas related to cognitive control and is thought to improve structural and functional connectivity [75]. Research on the effects of out of school physical activity on 7 – 9 year olds found that it 'enhanced cognitive performance and brain function during tasks requiring greater executive control ... a causal effect' [76]. The Lancet Physical Activity Series 2 Executive Committee recently reported a 'global pandemic of physical inactivity' [77]. The Global Matrix of Grades 2016 for children's Overall Physical Activity for example, awarded England a grade of 'D Minus' and Scotland, China and the United States an 'F' for child 'Overall Physical Activity' emphasising 'these grades identify a serious and widespread problem of excess screen viewing' [78].

PREDISPOSING RISK FACTORS

All children are not equally vulnerable to substance or behavioural addiction and this includes SDD. A study by Vink et al. (2016) of 5247 monozygotic and dizygotic adolescent twins reported that the heritability of compulsive Internet use in adolescents (48 percent) was almost identical to that of alcohol use disorders concluding that 'liability to compulsive Internet use is largely driven by genetic factors' [79,80]. Prenatal exposure to higher levels of androgens and a resultant 'hyper-male brain organization' are associated with 'problematic video gaming behavior' and 'video game addiction' [81]. The type and amount of media children consume (violent) has recently been associated with a specific gene, the long variant in the serotonin-transporter-linked polymorphic region 5-HTTLPR polymorphism, in 5 to 9 year olds and it is thought that due to their genetic disposition, children may actively seek specific media content [82].

MOLECULAR NEUROGENETICS

Genetic variation influences corticostriatal structure, function, and connectivity [83]. Addictions, including disordered gambling are considered to have robust heritability (approximately 50%). Han et al. (2007) investigated the genetic polymorphisms of the dopaminergic system in a group of excessive internet game players. They reported that individuals with increased genetic polymorphisms in genes coding for the dopamine D2 receptor and dopamine degradation enzyme were more susceptible to excessive internet gaming and have a 'higher reward dependency' compared with age-matched controls [84]. IAD subjects including those with problematic social media use are also significantly more likely to be carriers of a variation of the cholinergic receptor nicotinic alpha 4 subunit (CHRNA4) gene that also plays a major role in nicotine addiction [85]. Blum et al. (2014) and Febo et al. (2017) have proposed molecular neurogenetic evidence for a predisposition to 'reward deficiency syndrome' - hypodopaminergic function - 'a pathological condition in brain reward circuitry'. It is thought that the primary mechanism of reward deficiency syndrome is a hypodopaminergic trait [genes] as well as the impact of neuroepigenetic markers due to environmental experiences [86,46].

NEUROEPIGENETIC [DYS]REGULATION

As mentioned above, repeated exposure to non-drug rewards can alter neural plasticity in regions of the brain that are affected by drugs of abuse via epigenetic processes.

It is conceivable that intensive routine exposure to certain screen activities during critical stages of neural development may alter gene expression leading to structural, synaptic and functional changes in the developing brain. While many reward gene polymorphisms are involved in impulsive behaviors, a polymorphism in isolation may not lead to the development of a particular behavioural disorder unless it is influenced by neuroepigenetic effects. Neuroepigenetic mechanisms associated with a variety of environmental factors alter the developmental trajectories for several neuropsychiatric disorders. These mechanisms affect brain development and integrity at several levels that determine neural structure and function and resultant behavioral expressions [87]. Neuroepigenetic mechanisms have recently been found to underlie substance-induced structural, synaptic, and behavioral plasticity by coordinating the expression of neurogenetic networks within the brain [88].

Environmental exposure

In the development of substance addiction, several aspects of exposure change the pattern of altered gene expression. This in turn may render the brain more vulnerable to the addiction process [89,90]. Robison and Nestler (2011) suggest that in addition to altering the expression of genes, neuroepigenetic modifications may in turn cause gene priming and desensitization - altering the inducibility of many additional genes in response to some subsequent stimulus. These types of latent neuroepigenetic 'changes can be viewed as "neuromolecular scars" that dramatically alter an individual's adaptability and contribute importantly to the addicted state.' A neuroepigenetic model of exposure may ultimately offer a credible mechanism underlying the way environmental exposures during development can increase or reduce the risk of later addiction including SDD [90].

GENE-ENVIRONMENT INTERPLAY

While environmental factors may potentiate neurogenetic risk for addictions and adolescent impulse control disorders, they may also be harnessed to reduce neurogenetic risk. Even individuals with a family history of substance addiction may circumvent their neurogenetic vulnerability by limiting substance exposure [91]. In more supervised and restricted environments, there is less opportunity to express neurogenetic predispositions to alcohol use. In assessing the importance of genetic and environmental influences on adolescent smoking researchers reported 'dramatic moderation effects associated with parental monitoring' [92].

The association of gamma-aminobutyric acid type A receptor alpha2 (GABRA2) and cholinergic receptor muscarinic 2 (CHRM2) variant genes with children later developing externalizing trajectories [impulse control disorders] are found to diminish with high levels of parental monitoring [93,94]. Marceau et al. (2015) reported 'accounting for genetic influences of parents and adolescents ... parents' knowledge about their adolescents' activities and whereabouts exerts an environmental influence serving to reduce adolescent externalizing. This finding is particularly important for prevention' [95].

With regard to neurogenetic risk for SDD there is evidence that similar protective measures must be considered. In China, crude indirect noninvasive psychometric measures of 'neurotransmitter deficiency of internet addicted urban left-behind children' (cared for by others because their par-

ents or parent works or studies away from home) have been developed to assess speculated deficiencies in dopamine and GABA. Such children have a high prevalence of SDD. Neurotransmitter deficiency scores of internet-addicted urban left-behind children are significantly higher than that of non-internet-addicted urban left-behind children. Neurotransmitter deficiency scores for children where both parents worked away were significantly higher than for children where one parent worked away. The findings were partly attributed to 'improper guidance during internet usage' [96]. A study by Lin et al. (2009) concluded 'overall evidence suggests that parental monitoring is a major inhibitor of Internet addiction.' [97]

DISCUSSION

Understanding the neurological features of SDD continues to be bedevilled in the literature using terms such as structural or functional 'alterations', 'changes', 'reduced' and 'decreased' to describe observed abnormalities or differences between groups in a cross-sectional study as opposed to resultant changes/causal effects over time. However, many researchers do suspect that SDD leads to neuroadaptation. Kuss and Griffiths (2012) suggested 'that the brain itself actually changes as a consequence of excessive engagement with the Internet and gaming' [34].

BIDIRECTIONAL CAUSATION

Whether or not abnormalities in neural structure and function presented above either precede or are a consequence of SDD, it may also be a case of a bidirectional causal relationship. Bidirectional relationships exist between other pathologies in psychiatric and physical medicine, for example between cognitive dysfunction and pneumonia [98]. Moreover, where neural abnormalities exist before screen activities are initiated, subsequent early, intensive and prolonged exposure to certain screen activities during critical stages of neural development may cause further neurological alterations which lead to SDD which may in turn cause further neural alterations - achieved through neuroepigenetic alterations, neuroplastic changes, with an imposing backdrop of neurogenetic dispositions and prenatal influences.

PREVENTING SCREEN DEPENDENCY DISORDERS

Children are more susceptible to developing a long-term problematic dependency, pathological or not, on technology. Earlier age of initiation and higher levels of exposure to, for example, computer gaming may increase this risk. New studies find that the prevalence of screen viewing in children aged less than 2 years 'is high and appears to increase steadily across age groups' [1]. Screen habits are established early and last for decades. For example, a study of 'Life course and long-term influences on health' involving 6188 subjects concluded that 'childhood TV viewing time tracks into adulthood.... TV viewing time [at 10 yrs.] ... associated with high TV viewing time at aged 42 years.' [99] Parental monitoring along with families establishing DST limits can reduce early exposure, alter long-term media consumption habits and may prove a major inhibitor of SDD [100,101]. Recognition of the influence of parental role modeling is another important factor. Parents who engage in high DST

have children who are many times more likely to consume high DST [102].

Given the relatively high prevalence of SDD reported among children and adolescents during important stages of neural development, coupled with emerging evidence of longitudinal changes in neural structure (tissue density) related to the amount of time they spend playing video games, decisive interventions are necessary and paediatric neurologists can play a role [37].

The United States Department of Health has issued 'recommended limits for screen time' as one of its national 'health improvement priorities' and a key 'disease prevention objective' in which 'children aged 0 to 2 years' should be exposed to 'no television, videos or play video games' while those over 2 years should 'view television, videos, or play video games ... use a computer or play computer games outside of school [for non-school work] for no more than 2 hours a day' [103]. The American Academy of Pediatrics recently issued a policy statement, which 'addresses the influence of media on the health and development of children from 0 to 5 years of age, a time of critical brain development ... for children 2 to 5 years of age, limit screen use to 1 hour per day'. This is a 50 percent reduction in the Academy's previous recommended screen limits and the policy now advises paediatricians to 'educate parents about brain development in the early years' [104].

In preventing or treating substance addictions, exercise is reported to have protective effects. Individuals who engage in regular aerobic exercise are reported to be less likely to use and abuse drugs [105]. Exercise produces neuroadaptations that may influence an individual's vulnerability to initiate drug use through acting as a non-drug reward that competes with the drug and decreases the likelihood of its use [106]. This may occur by altering immediately early genes in the striatal reward system known to influence the addiction process, thereby protecting against later or previous drug use [107]. Park (2014) has reported 'a negative association between level of physical activity and risk of problematic Internet use' concluding 'physical activity may be helpful to improve adolescent mental health.' [108] Research by the Centers for Disease Control and Prevention [CDC] found a negative dose-response relationship between weekly physical activity and the risk of exceeding recommended screen time limits, recommending that 'programs that encourage limit-setting by parents and promote physical activity may reduce screen time among youth.' [109] There may be a sound neurological basis to these findings.

Exercise-induced increases in striatal dopamine D2 receptor expression have been reported suggesting that exercise can lead to neuroplasticity in dopaminergic signaling [110]. Animal research has found exercise leads to increased dendritic spine density and arborization in striatal medium spiny neurons and increased the expression of key synaptic proteins, suggesting a potential effect of exercise in modifying synaptic connectivity within a DA-depleted striatum [111]. Physical activity may also improve structural integrity and functional connectivity in children within brain areas related to cognitive control, a key element in addiction [75].

OBSTACLES TO PREVENTION

As discretionary screen time continues as the main experience and environment of children, schools and families are courted and bedazzled, child development research is fund-

ed, and governments and medical bodies are lobbied, by a prosperous, highly influential technology industry. The global entertainment and media market is currently valued at just over two trillion U.S. dollars [112]. Revenue earned in 2016 by the international computer game industry is estimated to be \$100 billion, more than double that of the international film industry [113]. Revenue from advertising alone on social media networks such as Facebook and Twitter will be \$22.5 billion [114]. As the child screen marketing ethos suggests, 'the money's where the eyeballs are' – staring at screens.

In an attempt to reduce the growing prevalence of SDD the Cyberspace Administration of China has recently issued draft legislation requiring Internet game developers to block minors from playing online games from midnight to 8am. The Internet game industry immediately expressed concerns over a reduction in revenue [115].

Public discussion of discretionary screen time and problematic screen use is a socially, economically, politically charged topic. And neurological reservations about SDD and high levels of DST are highly inconvenient. The overriding imperative has been to prevent parents from feeling uncomfortable about the age at which their children begin consumption of discretionary screen time and the children's degree of routine discretionary screen exposure. Moreover, technology advocates often steer the focus of concern away from the high level of child discretionary screen time and associated risks of SDD - to the content of what is being viewed: 'educational vs inappropriate', implying that adhering to a position of precaution on child screen time may in some way deprive children educationally and result in them being 'left behind in the digital revolution'.

Interestingly, a comprehensive review of 132 brain-training, working-memory training and video-game-training studies was recently conducted by a collaboration between the Medical Research Council Cognition and Brain Sciences Unit, the School of Clinical Medicine at University of Cambridge, and US universities. They examined the claimed benefits of such brain training and computer games for a wide variety of cognitive and everyday activities and found 'little evidence that training enhances performance on distantly related tasks or that training improves everyday cognitive performance ... evidence that such training generalizes to other tasks or to real-world performance is not compelling' [116]. Wang et al. (2016) reported an obvious outcome possibility for high computer game exposure: costs and benefits incurred at the same time. 'IGD may be associated with functional network dysfunction, including impaired executive control and emotional management, but enhanced coordination among visual, sensorimotor, visuospatial systems' [66].

A contemporary discussion of screen exposure for infants and toddlers is accompanied by reassuring positive exhortations such as 'babies are born into and rapidly adapting to an overwhelmingly digital world' which parents and health professionals should therefore embrace. However, it could equally be argued that babies are born into and rapidly adapting to a sugar-laden world (by later acquiring excessive body fat and developing insulin resistance) therefore health professionals should embrace modernity, instead of fulfilling their role which is to advance the principle of precaution even if it is at odds with the present Zeitgeist.

And so, it appears that one person's idea of screen-related neuroadaptation is another's idea of neuropathology resulting from environmental insult. In considering the findings presented in this paper and the implications for paediatric

public health, it could be argued that although correlation is not causation, as the Yale statistician Edward Tufte states 'but it sure is a hint' [117]. When concerns are raised over potential neurological risks of high discretionary screen consumption they are often dismissed as scientifically unfounded, speculative 'scare mongering'. However, the time has come for health professionals to begin to scrutinize the motives of those attempting to obstruct the sensible adoption of the traditional principle of precaution. To be clear, the burden of 'proof' must now be on those who advocate the status quo to demonstrate that high and/or premature exposure to discretionary screen time poses no health and development risks to children. Until then, child health policy must adhere to the principle of precaution as a prudent approach to protecting child wellbeing and neurological integrity.

Table 2. Recommendations

- Child neurology may be seen by some as a refined, elite, non-front-line specialty, however, paediatric neurologists are in a strong position to elevate SDD to that of a neurological public health issue. Child neurology organisations should adopt a public health position addressing children's age of initiation to screen activities, along with the amount and time of day of exposure to discretionary screen viewing as a prudent approach to paediatric public health until more is known. Formal public health positions on discretionary screen exposure are important. A European-wide study recently concluded that 'Children's and parents' perception of the screen time recommendations was related to children's television and computer time in all countries ... the more hours parents thought it was recommended for children to watch television or use a computer, the more time their child engaged in watching television and/or using the computer'. The authors therefore proposed 'a generic European intervention' to increase parental awareness [118].
- Clinicians should, where relevant, take a 'media history' from patients and discuss connections between a child's health, behaviour and screen use, educate parents about brain development in the early years, provide guidance to families about child media consumption, including limiting media use: raising the age of initiation to screen activities, reducing the degree of exposure and discouraging screens in children's bedrooms. A Systematic Review and Meta-analysis recently published in JAMA Pediatrics concluded that 'media device access and use at bedtime are significantly associated with detrimental sleep outcomes and lead to poor health outcomes ... an integrated approach among teachers, health care professionals, and parents is required to minimize device access at bedtime'[10]
- Paediatric neurology should play a more active role in research on SDD and prolonged and/or infant/toddler screen exposure. The potential development of diagnostic biomarkers for SDD would be a significant adjunct to existing diagnostic instruments. Research and development of non-invasive techniques such as transcranial magnetic or direct current stimulation targeting the ventral striatum and inferior parietal lobule circuitry is being suggested for the future treatment of Internet gaming disorders [38]. Liaising with neuropharmacologists in the testing of potential neuropharmacotherapeutic approaches for treatment of severe SDD in adults should also be considered.

- Given the commercial screen industry interests at stake, child neurologists must familiarize themselves with the influence of the technology industry in funding research and influencing media depiction of DST and SDD and be vigilant in detecting conflicts of interest. They should question the motives of those attempting to obstruct the adoption of a principle of precaution for children and screen media.

Competing interests

The author has declared that no competing interest exists. The author has received fees for occasional health education lecturing at schools, medical schools.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

REFERENCES

- Goh SN, Teh LH, Tay WR, et al. Sociodemographic, home environment and parental influences on total and device-specific screen viewing in children aged 2 years and below: an observational study. *BMJ Open*. 2016;6:e009113. doi:10.1136/bmjopen-2015-009113
- CTA Digital. 2-In-1 iPotty with Activity Seat for iPad. PART # PAD-POTTY, UPC:656777012977 <http://www.ctadigital.com/item.asp?item=3016> (Accessed May 24 2016)
- Ofcom.Children and parents: media use and attitudes report. Research document Publication. November 2016. https://www.ofcom.org.uk/__data/assets/pdf_file/0034/93976/Children-Parents-Media-Use-Attitudes-Report-2016.pdf
- Ofcom.The Communications Market Report. P18. 2016 (4 August) <https://www.ofcom.org.uk/research-and-data/cmr/cmr16>
- Sigman A. Time for a view on screen time. *Arch Dis Child* 2012;97(11):935-942. doi:10.1136/archdischild-2012-302196
- Henderson M, Benedetti A, Barnett TA, (et al). Influence of Adiposity, Physical Activity, Fitness, and Screen Time on Insulin Dynamics Over 2 Years in Children. *JAMA Pediatr*. 2016;170(3):227-235. doi:10.1001/jamapediatrics.2015.3909.
- Lin L Y, Sidani J E, Shensa A, et al. Association Between Social Media Use And Depression Among U.S. Young Adults. *Depress. Anxiety*.2016; 33: 323–331. doi: 10.1002/da.22466
- Sigman A. Virtually addicted: why general practice must now confront screen dependency. *Br J Gen Pract* 2014;64(629):610-11. DOI: 10.3399/bjgp14X682597
- Jin C, Zhang T, Cai C, et al. Abnormal prefrontal cortex resting state functional connectivity and severity of internet gaming disorder. *Brain imaging and behavior*. 2015 Aug 27:1-1.
- Carter, B, et al. "Association Between Portable Screen-Based Media Device Access or Use and Sleep Outcomes: A Systematic Review and Meta-analysis." *JAMA pediatrics* 170.12 (2016): 1202-1208.
- Sigman A. Risks to children's brain development today: screen dependency. Plenary lecture, International Congress of Child Neurology. Amsterdam, 4 May 2016. <http://icnc2016.org/plenary-speakers-2/>
- Kuss DJ, Lopez-Fernandez O. Internet addiction and problematic Internet use: A systematic review of clinical research. *World journal of psychiatry*. 2016 Mar 22;6(1):143. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4804263/>
- Pontes, H.M., Andreassen, C.S. & Griffiths, M.D. *Int J Ment Health Addiction* (2016) 14: 1062. doi:10.1007/s11469-016-9694-y
- Andreassen CS, Pallesen S. Social network site addiction - an overview. *Curr Pharm Des*. 2014;20(25):4053-61.
- Kuhn S, Gallinat J. Brain Structure and Functional Connectivity Associated With Pornography Consumption. *JAMA Psychiatry*. 2014;71(7):827-834. doi:10.1001/jamapsychiatry.2014.93
- Love T, Laier C, Brand M, Hatch L, Hajela R. Neuroscience of Internet Pornography Addiction: A Review and Update. *Behavioral Sciences*. 2015 Sep 18;5(3):388-433. <http://www.mdpi.com/2076-328X/5/3/388/html>
- Brand M, Snagowski J, Laier C, Maderwald S. Ventral striatum activity when watching preferred pornographic pictures is correlated with symptoms of Internet pornography addiction. *NeuroImage*. 2016 Apr 1;129:224-32.
- Clark L. Disordered gambling: the evolving concept of behavioral addiction. *Ann. N.Y. Acad. Sci.* 1327 (2014) 46–61. doi: 10.1111/nyas.125582014
- Fauth-Bühler M, Mann K. Neurobiological correlates of internet gaming disorder: Similarities to pathological gambling. *Addict Behav*. 2015 Nov 24. pii: S0306-4603(15)30055-1. doi: 10.1016/j.addbeh.2015.11.004.
- Wen T and Hsieh S. Network-Based Analysis Reveals Functional Connectivity Related to Internet Addiction Tendency. *Front. Hum. Neurosci*. 2016;10:6. doi: 10.3389/fnhum.2016.00006
- American Psychiatric Association. Internet Gaming Disorder Fact Sheet. 2013.<http://www.dsm5.org/Documents/Internet%20Gaming%20Disorder%20Fact%20Sheet.pdf>
- Brand M, Young KS, Laier C, Wölfling K, Potenza MN. Integrating psychological and neurobiological considerations regarding the development and maintenance of specific Internet-use disorders: An Interaction of Person-Affect-Cognition-Execution (I-PACE) model. *Neuroscience & Biobehavioral Reviews*. 2016 Dec 31;71:252-66. <http://dx.doi.org/10.1016/j.neubiorev.2016.08.033>
- Du X, Qi X, Yang Y, et al. Altered Structural Correlates of Impulsivity in Adolescents with Internet Gaming Disorder. *Frontiers in Human Neuroscience*. 2016;10:4. doi:10.3389/fnhum.2016.00004.

24. Sepede, G., Tavino, M., Santacroce, R, et al. Functional magnetic resonance imaging of internet addiction in young adults. *World J Radiol.*2016, 8(2):210–225. <http://doi.org/10.4329/wjr.v8.i2.210>
25. Gentile DA. Pathological video game use among youth ages 8 to 18: a national study. *Psychol Sci.* 2009;20(5):594 – 602
26. Gentile DA, Choo H, Liau A, et al. Pathological Video Game Use Among Youths: A Two-Year Longitudinal Study. *Pediatrics* 2011;127(2):e319-29. doi: 10.1542/peds.2010-1353.
27. Groves CL, Gentile D, Tapscott RL, Lynch PJ. Testing the Predictive Validity and Construct of Pathological Video Game Use. Doan A, ed. *Behavioral Sciences.* 2015;5(4):602-625. doi:10.3390/bs5040602.
28. Kim NR, Hwang SS-H, Choi J-S, et al. Characteristics and Psychiatric Symptoms of Internet Gaming Disorder among Adults Using Self-Reported DSM-5 Criteria. *Psychiatry Investigation.* 2016;13(1):58-66. doi:10.4306/pi.2016.13.1.58.
29. Muller KW, Janikian M, Dreier M, et al. Regular gaming behavior and internet gaming disorder in European adolescents: results from a cross-national representative survey of prevalence, predictors, and psychopathological correlates. *Eur Child Adolesc Psychiatry* (2015) 24:565–574 DOI 10.1007/s00787-014-0611-2
30. Kühn S., Gleich T., Lorenz R. C., Lindenberger U., Gallinat J. Playing super mario induces structural brain plasticity: gray matter changes resulting from training with a commercial video game. *Molecular Psychiatry.* 2014;19(2):265–271. doi: 10.1038/mp.2013.120. [PubMed]
31. Lorenz RC, Gleich T, Galat J, Kühn S. Video game training and the reward system. *Front. Hum. Neurosci.*2015, 9:40.doi: 10.3389/fnhum.2015.00040
32. Takeuchi H, Taki Y, Nouchi R, et al. Effects of Multitasking-Training on Gray Matter Structure and Resting State Neural Mechanisms. *Human Brain Mapping.*2014,35:3646–3660
33. Rapoport JL, Gogtay N. Brain Neuroplasticity in Healthy, Hyperactive and Psychotic Children: Insights from Neuroimaging. *Neuropsychopharmacology Reviews.*2008,33:181 – 197 doi:10.1038/sj.npp.1301553
34. Kuss, D. J., & Griffiths, M. D. Internet and gaming addiction: A systematic literature review of neuroimaging studies. *Brain Sci.*2012, 2(3):347-374. doi: 10.3390/brainsci2030347
35. Hou H, Jia S, Hu S, et al. Reduced Striatal Dopamine Transporters in People with Internet Addiction Disorder. *J Biomed Biotechnol* 2012; 2012:854524. doi:10.1155/2012/854524.
36. Lin F, Zhou Y, Du Y, et al. Abnormal white matter integrity in adolescents with internet addiction disorder: a tract-based spatial statistics study. *PLoS ONE.* 2012,7:e30253. DOI:10.1371/journal.pone.0030253
37. Takeuchi H, Taki Y, Hashizume H, Asano K, Asano M, Sassa Y, Yokota S, Kotozaki Y, Nouchi R, Kawashima R. Impact of videogame play on the brain's microstructural properties: cross-sectional and longitudinal analyses. *Molecular psychiatry.* 2016.Jan 5. 21, 1781–1789. doi:10.1038/mp.2015.193
38. Zhang, J.-T., Ma, S.-S., Li, C.-S. R., Liu, L., Xia, C.-C., Lan, J., Wang, L.-J., Liu, B., Yao, Y.-W., and Fang, X.-Y. Craving behavioral intervention for internet gaming disorder: remediation of functional connectivity of the ventral striatum. *Addiction Biology.*2016 doi: 10.1111/adb.12474
39. Weinstein A, Lejoyeux M. New developments on the neurobiological and pharmaco-genetic mechanisms underlying internet and videogame addiction. *Am J Addict.*2015, 24: 117–125. doi: 10.1111/ajad.12110
40. Zhu Y, Zhang H, Tian M. Molecular and Functional Imaging of Internet Addiction. *BioMed Research International.* 2015, Article ID 378675. <http://dx.doi.org/10.1155/2015/378675>
41. Kim SH, Baik SH, Park CS, et al. Reduced striatal dopamine D2 receptors in people with Internet addiction. *Neuroreport.* 2011, 22(8):407– 411 doi: 10.1097/WNR.0b013e328346e16e.
42. Tian M, Chen Q, Zhang Y, et al. PET imaging reveals brain functional changes in internet gaming disorder. *Eur J Nucl Med Mol Imaging.* 2014 Jul;41(7):1388-97. doi: 10.1007/s00259-014-2708-8
43. Villarán RF et al. Endogenous dopamine enhances the neurotoxicity of 3-nitropropionic acid in the striatum through the increase of mitochondrial respiratory inhibition and free radicals production. *Neurotoxicology.* 2008,29(2):244-58. DOI: 10.1016/j.neuro.2007.11.001
44. Kuhn DM, Francescutti-Verbeem DM, Thomas DM. Dopamine Disposition in the Presynaptic Process Regulates the Severity of Methamphetamine-induced Neurotoxicity. *Ann N Y Acad Sci.* 2008, October,1139:118–126. doi:10.1196/annals.1432.026
45. Cheng NN, Maeda T, Kume T, Kaneko S, Kochiyama H, Akaike A, Goshima Y, Misu Y. Differential neurotoxicity induced by L-DOPA and dopamine in cultured striatal neurons. *Brain research.* 1996 Dec 16;743(1):278-83. [http://dx.doi.org/10.1016/S0006-8993\(96\)01056-6](http://dx.doi.org/10.1016/S0006-8993(96)01056-6)
46. Febo M, Blum K, Badgaiyan RD, Baron D, Thanos PK, Colon-Perez LM, Demortrovcis Z, Gold MS. Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome. *Frontiers in bioscience (Landmark edition).* 2017 Jan 1;22:669-691.
47. Mick, I., Ramos, A. C., Myers, J., Stokes, P. R., Chandrasekera, S., Erritzoe, D., Mendez, M. A., Gunn, R. N., Rabiner, E. A., Searle, G. E., Galduróz, J. C. F., Waldman, A. D., Bowden-Jones, H., Clark, L., Nutt, D. J., and Lingford-Hughes, A. R. (2016) Evidence for GABA-A receptor dysregulation in gambling disorder: correlation with impulsivity. *Addiction Biology,* doi: 10.1111/adb.12457
48. Olsen, C. M. Natural Rewards, Neuroplasticity, and Non-Drug Addictions. *Neuropharmacology.*2011, 61(7):109–1122. <http://doi.org/10.1016/j.neuropharm.2011.03.010>
49. Pitchers, K. K., Vialou, V., Nestler, E. J. et al. Natural and Drug Rewards Act on Common Neural Plasticity Mechanisms with FosB as a Key Mediator. *The Journal of Neuroscience.*2013, 33(8):3434–3442. <http://doi.org/10.1523/JNEUROSCI.4881-12.2013>
50. Lin F, Zhou Y, Du Y. Aberrant corticostriatal functional circuits in adolescents with Internet addiction disorder. *Front. Hum. Neurosci.*2015, 9:356. doi: 10.3389/fnhum.2015.00356
51. Hong SB, Kim JW, Cho EJ, et al. Reduced orbitofrontal cortical thickness in male adolescents with internet addiction. *Behav Brain Funct.*2013, 9:11. doi: 10.1186/1744-9081-9-11
52. Weng CB, Qian RB, Fu XM, et al. Gray matter and white matter abnormalities in online game addiction. *Eur J*

- Radiology. 2013,82(8):1308 – 1312. DOI: <http://dx.doi.org/10.1016/j.ejrad.2013.01.031>
53. Wang H, Jin C, Yuan K, et al. The alteration of gray matter volume and cognitive control in adolescents with internet gaming disorder. *Front. Behav. Neurosci.* 2015,9:64. doi: 10.3389/fnbeh.2015a.00064
 54. Yuan K, Qin W, Wang G, Zeng F, Zhao, L, Yang X, et al. Microstructure abnormalities in adolescents with internet addiction disorder. *PLoS One.* 2011, 6:e20708. doi: 10.1371/journal.pone.0020708
 55. Kühn S, Gallinat J. Brains online: structural and functional correlates of habitual internet use. *Addict. Biol.* 2015, 20:415–422. doi: 10.1111/adb.12128
 56. Sun Y, Sun J, Zhou Y, et al. Assessment of in vivo microstructure alterations in gray matter using DKI in internet gaming addiction. *Behav. Brain Funct.* 2014,10:37. doi: 10.1186/1744-9081-10-37
 57. Ko, C. H., Hsieh, T. J., Wang et al. (2015). Altered gray matter density and disrupted functional connectivity of the amygdala in adults with internet gaming disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2015, 57:185–192. doi: 10.1016/j.pnpbp. 2014.11.003
 58. Yuan, K., Cheng, P., Dong, T., et al. Cortical thickness abnormalities in late adolescence with online gaming addiction. *PLoS One.* 2013, 8(1):e53055. doi: 10.1371/journal.pone.0053055
 59. Li W, Li Y, Yang, W, et al. Brain structures and functional connectivity associated with individual differences in Internet tendency in healthy young adults. *Neuropsychologia.* 2015, Apr(70):134–144. doi: 10.1016/j.neuropsychologia.2015.02.019
 60. Cai C, Yuan K, Yin J, et al. Cai, Chenxi, et al. "Striatum morphometry is associated with cognitive control deficits and symptom severity in internet gaming disorder." *Brain imaging and behavior* 10.1 (2016): 12-20. <http://link.springer.com/article/10.1007/s11682-015-9358-8>
 61. Wang Y, Zou Z, Song H, Xu X, Wang H, Uquillas FD, Huang X. Altered gray matter volume and white matter integrity in college students with mobile phone dependence. *Frontiers in psychology.* 2016;7. doi: 10.3389/fpsyg.2016.00597
 62. Yuan K, Yu D, Cai C, Feng D, Li Y, Bi Y, Liu J, Zhang Y, Jin C, Li L, Qin W. Frontostriatal circuits, resting state functional connectivity and cognitive control in internet gaming disorder. *Addiction biology.* 2016 Jan 1.
 63. Xing L. Yuan K, Bi Y, et al. Reduced fiber integrity and cognitive control in adolescents with Internet gaming disorder. *Brain Res.* 2014.Oct 24,1586: 109-117
 64. Yuan K, Qin W, Yu D, et al. Core brain networks interactions and cognitive control in internet gaming disorder individuals in late adolescence/early adulthood. *Brain Struct Funct.* 2016, 221(3):1427-1442. DOI 10.1007/s00429-014-0982-7 <http://link.springer.com/article/10.1007/s00429-014-0982-7>
 65. Zhai J, Luo L, Qiu L, Kang Y, Liu B, Yu D, Lu X, Yuan K. The topological organization of white matter network in internet gaming disorder individuals. *Brain Imaging and Behavior.* 2016 Nov 4:1-0.
 66. Wang L, Wu L, Lin X, Zhang Y, Zhou H, Du X, Dong G. Altered brain functional networks in people with Internet gaming disorder: Evidence from resting-state fMRI. *Psychiatry Research: Neuroimaging.* 2016 Aug 30;254:156-63. <http://dx.doi.org/10.1016/j.pscychresns.2016.07.001>
 67. Wang Y, Yin Y, Sun Y, et al. Decreased Prefrontal Lobe Interhemispheric Functional Connectivity in Adolescents with Internet Gaming Disorder: A Primary Study Using Resting-State fMRI. *PLoS ONE.* 2015, 10(3): e0118733. doi:10.1371/journal.pone.0118733
 68. Zhang JT, Ma SS, Yip SW, et al. Decreased functional connectivity between ventral tegmental area and nucleus accumbens in Internet gaming disorder: evidence from resting state functional magnetic resonance imaging. *Behav Brain Funct.* 2015,11:37. DOI: 10.1186/s12993-015-0082-8
 69. Zhang JT, Yao YW, Zang YF, et al. Altered resting-state functional connectivity of the insula in young adults with Internet gaming disorder. 2016, *Addict Biol.* 21(3): 743–751. doi: 10.1111/adb.12247
 70. Zhang Y, Mei W, Zhang JX, Wu Q, Zhang W. Decreased functional connectivity of insula-based network in young adults with internet gaming disorder. *Experimental brain research.* 2016 Apr 27:1-8.
 71. D'Hondt F, Maurage P. Electrophysiological studies in Internet addiction: A review within the dual-process framework. *Addictive behaviors.* 2015 Oct 9.
 72. Duven ECP, Müller KW, Beutel ME, et al. Altered reward processing in pathological computer gamers – ERP-results from a semi-natural Gaming-Design. *Brain Behav.* 2015, 5(1): e00293. doi: 10.1002/brb3.293
 73. Li W, O'Brien JE, Snyder SM, et al. Diagnostic Criteria for Problematic Internet Use among U.S. University Students: A MixedMethods Evaluation. *PLoS ONE.* 2016, 11(1): e0145981. doi:10.1371/journal.pone.0145981
 74. Costigan J, Barnett L, Plotnikoff RC, et al. The health indicators associated with screen-based sedentary behavior among adolescent girls: a systematic review. *Adolesc Health.* 2013 Apr;52(4):382-92. doi: 10.1016/j.jadohealth.2012.07.018.
 75. Chaddock-Heyman L, Erickson KI, Holtrop JL, et al. Aerobic fitness is associated with greater white matter integrity in children. *Front. Hum Neurosci.* 2014;8:584 doi: 10.3389/fnhum.2014.00584
 76. Hillman CH et al. Effects of the FITKids Randomized Controlled Trial on Executive Control and Brain Function. *Pediatrics.* 2014 Oct 1;134(4):e1063-71. DOI: 10.1542/peds.2013-3219
 77. Reis RS, Salvo D, Ogilvie D, Lambert EV, Goenka S, Brownson RC, for the Lancet Physical Activity Series 2 Executive Committee. Scaling up physical activity interventions worldwide: stepping up to larger and smarter approaches to get people moving. *Lancet.* 2016; . Volume 388 , Issue 10051 , 1337 - 1348
 78. Tremblay, Mark S., et al. Global Matrix 2.0: report card grades on the physical activity of children and youth comparing 38 countries. *Journal of physical activity and health* 13.11 Suppl 2 (2016): S343-S366.
 79. Vink JM, Beijsterveldt TC, Huppertz C, Bartels M, Boomsma DI. Heritability of compulsive Internet use in adolescents. *Addiction biology.* 2015 Feb 1. <http://onlinelibrary.wiley.com/store/10.1111/adb.12218/asset/adb12218.pdf?v=1&t=ixmbd674&s=c992e6f8141035795a8aeb5ee051a2f0b49044ca>
 80. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychological medicine.* 2015 Apr 1;45(05):1061-72. DOI: <https://doi.org/10.1017/S0033291714002165>

81. Kornhuber J, Zenses E-M, Lenz B, et al. Low 2D:4D Values Are Associated with Video Game Addiction. *PLoS ONE* 2013;8(11): e79539. doi:10.1371/journal.pone.0079539
82. Nikkelen S, Vossen H, Valkenburg P. Media Violence and Children's ADHD-Related Behaviors: A Genetic Susceptibility Perspective. *J Communication*.2014, 64(1):42-60. doi: 10.1111/jcom.12073.
83. Demers CH, Bogdan R, Agrawal A. The Genetics, Neurogenetics and Pharmacogenetics of Addiction. *Curr Behav Neurosci Rep*. 2014; 1(1):33-44. doi:10.1007/s40473-013-0004-8.
84. Han DH, Lee YS, Yang KC, et al. Dopamine genes and reward dependence in adolescents with excessive internet video game play. *J Addict Med*.2007,1(3):133-138. doi: 10.1097/ADM.0b013e31811f465f.
85. Montag C, Kirsch P, Sauer C, et al. The Role of the CHRNA4 Gene in Internet Addiction: A Case-control Study. *Journal of Addiction Medicine*.2012, 6(3):191-195. doi: 10.1097/ADM.0b013e31825ba7e7
86. Blum K, Oscar-Berman M, Demetrovics Z, et al. Genetic Addiction Risk Score (GARS): Molecular Neurogenetic Evidence for Predisposition to Reward Deficiency Syndrome (RDS). *Mol Neurobiol*.2014,50:765-796 DOI 10.1007/s12035-014-8726-5
87. Archer T, Oscar-Berman M, Blum K, et al. Neurogenetics and Epigenetics in Impulsive Behaviour: Impact on Reward Circuitry. *J Genet Syndr Gene Ther*.2012; 3(3):1000115. doi:10.4172/2157-7412.1000115.
88. Vassoler FM, Sadri-Vakili G. Mechanisms of transgenerational inheritance of addictive-like behaviors. *Neuroscience*. 2014, April 4; 0: 198-206. doi:10.1016/j.neuroscience.2013.07.064.
89. Zhou Z, Enoch MA, Goldman D. Gene Expression in the Addicted Brain, In: Hitzemann R, Mcweeney S, Eds, *International Review of Neurobiology*, Academic Press. 2014, Volume 116, Pages 251-273, ISSN 0074-7742, ISBN 9780128011058, <http://dx.doi.org/10.1016/B978-0-12-801105-8.00010-2>.
90. Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. *Nature reviews neuroscience*. 2011 Nov 1;12(11):623-37. doi:10.1038/nrn3111
91. Agrawal A, Verweij KJH, Gillespie NA, et al. The genetics of addiction—a translational perspective. *Transl Psychiatry*. 2012,2, e140. doi:10.1038/tp.2012.54
92. Dick DM, Purcell S, Viken R, et al. Parental monitoring moderates the importance of genetic and environmental influences on adolescent smoking. *J Abnor Psychology*. 2007; 116:213-218. [PubMed: 17324032]
93. Dick DM, Latendresse SJ, Lansford JE, et al. Role of GABRA2 in trajectories of externalizing behavior across development and evidence of moderation by parental monitoring. *Arch Gen Psychiatry*. 2009; 66: 649-657.
94. Dick DM, Meyers JL, Latendresse SJ, et al. CHRM2, parental monitoring, and adolescent externalizing behavior: evidence for gene-environment interaction. *Psychol Sci*. 2011; 22: 481-489. doi:10.1177/0956797611403318.
95. Marceau, K., Narusyte, J., Lichtenstein, P., et al. Parental knowledge is an environmental influence on adolescent externalizing. *J Child Psychology Psychiatry*.2015,56:130-137. doi: 10.1111/jcpp.12288
96. Ge Y, Liu J. Psychometric Analysis on Neurotransmitter Deficiency of Internet Addicted Urban Left-behind Children. *J Alcohol Drug Depend*.2015, 3:221. doi:10.4172/2329-6488.1000221
97. Lin CH, Lin SL, Wu CP. The effects of parental monitoring and leisure boredom on adolescents' Internet addiction. *Adolescence*. 2009;44:993-1004.
98. Shah FA, Pike F, Alvarez K, et al. Bidirectional Relationship between Cognitive Function and Pneumonia. *American Journal of Respiratory and Critical Care Medicine* 2013 188:5, 586-592.
99. Smith L, Gardner B, Hamer M. Life course and long-term influences on health: Childhood correlates of adult TV viewing time: a 32-year follow-up of the 1970 British Cohort Study. *J Epidemiol Community Health*. 2015;69(4):309-313. doi:10.1136/jech-2014-204365
100. Lin CH, Lin SL, Wu CP. The effects of parental monitoring and leisure boredom on adolescents' Internet addiction. *Adolescence*. 2009;44:993-1004.
101. Tiberio SS, Kerr DR, Capaldi DM, et al. Parental Monitoring of Children's Media Consumption: The Long-term Influences on Body Mass Index in Children . *JAMA Pediatr*. 2014; May 1;168(5):414-21. doi:10.1001/jamapediatrics.2013.5483.
102. Jago R, Thompson JL, Sebire SJ, et al. Cross-sectional associations between the screen-time of parents and young children: differences by parent and child gender and day of the week. *Int J Beh Nutrition Phys Activ*. 2014, 11:54 doi:10.1186/1479-5868-11-54
103. U.S. Department of Health and Human Services. Healthy People 2020, Objective PA-8: Increase the proportion of children and adolescents who do not exceed recommended limits for screen time. <https://www.healthypeople.gov/2020/topics-objectives/topic/physical-activity/objectives>
104. AAP Council On Communications And Media. Media and Young Minds. *Pediatrics*. 2016;138(5):e20162591
105. Smith MA, Lynch WJ. Exercise as a potential treatment for drug abuse: evidence from preclinical studies. *Front Psychiatry*. 2012, Article 82. doi: 10.3389/fpsyt.2011.00082
106. Lynch WJ, Peterson AB, Sanchez V, et al. Exercise as a novel treatment for drug addiction: A neurobiological and stage-dependent hypothesis. *Neurosci Biobehav Rev*.2013, 37(8):1622-1644. <http://dx.doi.org/10.1016/j.neubiorev.2013.06.011>.
107. Zhou Y, Zhao M, Zhou C et al. Sex differences in drug addiction and response to exercise intervention: From human to animal studies, *Front Neuroendocrinology*. 2016, 40, January:24-41 <http://dx.doi.org/10.1016/j.yfrne.2015.07.001>.
108. Park S. Associations of physical activity with sleep satisfaction, perceived stress, and problematic Internet use in Korean adolescents. *BMC Pub Health*. 2014 14:1143. doi:10.1186/1471-2458-14-1143
109. Carlson SA, Fulton JE, Lee SM, et al. Influence of limit-setting and participation in physical activity on youth screen time. *Pediatrics* 2010;126:e89-96.
110. Fisher BE, Li Q, Nacca A. Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *Neuroreport*. 2013 Jul 10;24(10):509-14. doi: 10.1097/WNR.0b013e328361dc13.
111. Toy WA, Petzinger GM, Leyshon BJ. Treadmill exercise reverses dendritic spine loss in direct and indirect striatal medium spiny neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. *Neurobiol Dis*. 2014 Mar;63:201-9. doi: 10.1016/j.nbd.2013.11.017.

112. Statista. Digital Market Outlook (2015a). Statista.com <http://www.statista.com/statistics/237749/value-of-the-global-entertainment-and-media-market/>
113. Newzoo (2016) Global Games Market Report 2016, Quarterly update Q2. April 21 2016. <https://newzoo.com/insights/articles/global-games-market-reaches-99-6-billion-2016-mobile-generating-37/>
114. Statista (2015b) Digital Market Outlook: Social Media Advertising. <https://www.statista.com/outlook/220/100/social-media-advertising/worldwide#market-revenue>
115. South China Morning Post. Midnight bans and rehab centres on the cards for China's underage gamers. Jane Li Viola Zhou. PUBLISHED : Friday, 07 October, 2016. <http://www.scmp.com/news/china/policies-politics/article/2025821/china-mulls-midnight-ban-children-playing-online-games>
116. Simons DJ et al. Do "Brain-Training" Programs Work?. *Psychological Science in the Public Interest*. October 2016 17(3): 103-186, doi:10.1177/1529100616661983
117. Tufte ER. *The Cognitive Style of PowerPoint: Pitching Out Corrupts Within* (2nd ed.) 2006. p4. Cheshire, Connecticut: Graphics Press. ISBN 0-9613921-5-0.
118. Verloigne V, Van Lippevelde W, Bere E. Individual and family environmental correlates of television and computer time in 10- to 12-year-old European children: the ENERGY-project. *BMC Pub Health*. 2015, 15:912 DOI: 10.1186/s12889-015-2276-2