Reliability of methylphenidate as a cognitive enhancer

Methylphenidate (amphetamine), an inhibitor which acts on the noradrenergic and dopaminergic systems used in the treatment of attention deficit hyperactivity disorder (ADHD), has been widely cited in Bioethicist literature as having the capability to improve cognitive ability in healthy individuals (Husain & Mehta, 2011). Methylphenidate is widely used a wake promoting agent during training, in students to in the aim to increase their grades and in many academic professionals to maintain their performance. However, the effects of cognitive enhancement by methylphenidate are somewhat modest and large amount of variability exists between individuals.

In patients with ADHD methylphenidate drugs such as Ritalin, perform well promoting attention; similarly, in healthy individuals an improvement is seen as Ritalin aids spatial working memory performance and improves executive functions in novel tasks (Mehta et al., 2000; Elliot et al., 1997). In the analysis of the effects of Ritalin through PET scans Mehta et al., (2000) conveyed that methylphenidate induced a reduction of blood flow in the left and right dorsolateral prefrontal cortex, increasing performance accuracy in spatial working memory tasks (SWM) (Owen et al., 1996). SWM is localised in the prefrontal cortex, where damage to this area will lead to impairment in SWM tasks (Murphy et al., 1996). This suggests the increase of visual attention and improvement on visual working memory tasks may be due to the selective modulation effects of methylphenidate on the parietal, frontal and extra striate occipital regions- a finding synonymous with early research into monkeys and monoaminergic modulation of cognitive functions (Bernardi et al., 1982). However, recent exploration into fMRI and DCM studies on the brain show noradrenergic systems can influence neuronal

excitability in regions engaged in sensory processing and visuospatial attention, thus suggesting that perhaps methylphenidate is less specific and affects functional connectivity across the brain network (Grefkes, 2010).

The neural mechanisms by which, methylphenidate effects are primarily evident in the CNS; where the concentration of dopamine and norepinephrine in the brain is caused by the blocking their reuptakes-thus increasing the expression of the dopamine transporter DAT and blocking of the monoamine transporter 2. By doing so reducing activity of monoamine oxidase and increasing the expression of tyrosine hydroxylase is inhibited (Fibiger et al., 1971). Where levels of DAT are high in ADHD patients, inducing Ritalin restores catecholamine and alters dopaminergic firing systems, subsequently reducing synaptic transmission on the D2 and D3 dopamine receptors (Goldstein et al., 2000). Thus dopamine levels would be reduced and normalise deficiencies and improve concentration. A clear example of this is shown in Volkow et al., (2012) , where methylphenidate given orally blocks 60% of DAT sites whilst increasing dopamine concentrations in the striatum (by 8% to 16%) reducing hyperactivity in in ADHD patients. However, in normal patients the intake of methamphetamine could result in a DAT overexpression or hypo-dopaminergic activity and could possibly lead to enhanced cognition. Additionally, the prolonged use of methylphenidate could result in the downward regulation of dopamine D2 receptors and uptake sites, similar to the reinforcement effects in amphetamines like cocaine, emphasizing impulsive behaviour like gambling and hyper sexuality (Voltz, 2008 & Cools., 2007). Additionally,

hypodopemenergic activity within the basal ganglia could lead to involuntary movements (Dyskinesia)

it is often difficult to test the neuro-enhancement in healthy individuals caused by methylphenidate. In general cognitive processes one would subsume an enhancement would be on the emotional, motivational and cognitive functions within healthy individuals. Unlike other drugs such as AChEI (used in the treatment of the neurodegenerative disease Alzheimer's) where Emre etal., (2004) and McKeith et al.,(2000) convey positive effects of AChEI on cognition and neuropsychiatric measures such as mood , anxiety and visual hallucinations- the use of methylphenidate conveys quite modest results on cognitive enhancement (Mehta et al., 2011). Although previous research by Rependatis (2010), found the use of methylphenidate increases memory, there was no consistent evidence to support a substantial effect. Additionally, though Mehta et al ., (2000) did convey that Ritalin did improve spatial working memory, a finding supported by Elliot et al., (1997). However, in a recent analysis Mehta et al (2011) attributes previous findings to the variance of baseline ability. The plethora of research surround the effect of methylphenidate is largely inconsistent and there is little evidence to suggest methylphenidate can be used as a cognitive enhancer. Contrariwise to popular belief, there has been evidence to suggest that methylphenidate could actually impair previous cognitive abilities (Schaaf et al.,, 2013). In testing the effects of Ritalin on reward and punishment learning in healthy students, Schaaf et al., (2013), conveyed that the effect of Ritalin on baseline spatial working memory tasks varied in terms of tasks and demand between individuals. Although, methylphenidate improved

reward and punishment behaviour in high working memory subjects, it impaired those with low working memory . These inconsistent results may be partially due to the inverted U shape, whereby dopamine D1 antagonist can selectively modulate cognitive processes, such as SWM. Excessive levels of D1 in the prefrontal cortex can impair working memory (Vijayraghavan et al., 2007). However, adverse effects of methylphenidate can also been seen in repeated use (Lapworth et al., 2009). Lapworth et al., (2009) suggest that methylphenidate is associated with hostility, aggression, and psychotic symptoms in repeated users, where the repeated use of methylphenidate increases “ positive psychotic symptoms that contribute to a perception of the environment as a hostile and threatening place as well as by increasing impulsivity”.

The reliability and validity of the aforementioned research comes into context when looking at the methods for testing the cognitive effects of methylphenidate on healthy individuals. A large body of research lacks substance and is largely inconclusive do to the variability in methods, additionally the generalizability attributed to methylphenidate be taken with a reasonable amount of judicious concern (Tucha O, 2006) . So far there have been no comprehensive studied in normal subjects showing a fair effect of methylphenidate as a cognitive enhancer. A fundamental flaw in research is largely evident in a lack of standardized testing methods. For example, In ADHD patients there is a clear deficiency which one is able to target and improve to normalise baseline levels of hyperactivity however, in normal individuals there is no baseline. How one compare against a “ standard of enhancement” when there does is no standard for which to compare.

Additionally, when using methods such as SWM It's difficult to subsume that the change in cognition is due to methylphenidate rather than other cognitive processes. A researcher is yet to be able to pinpoint the source of effect as the brain involves a process of complex, interlinked networks. A classic example of this exists in Mehta et al (2000) research to test the effects of methylphenidate. Participants were presented with a spatial working memory task, tested with the Cambridge Neuropsychological Automated Battery Test (CANTAB). Results showed the dependent variables like spatial memory were enhanced by the IV (Mehta et al 2001). However, in a later study Mehta et al (2011), attributed the findings to the effect sizes, where average ratings for the effect of ADHD are produced by caregiver and parent responses, thus they are not correct methods of analysis for cognitive effects rather they convey behavioural effects. Furthermore, the majority of research presented on methylphenidate does not fairly analyse the negative effects with inducing methylphenidate, instead Elliot et al., (1979) purely focus on the positive effects and do not report any negative side effects, thus resulting in a bias portrayal of the overall cognitive effects of methylphenidate. Moreover on further analysis of the literature it is also evident that there is a large disparity in the duration of the trials presented and the dosages of methylphenidate given. For instance Mehta et al.,(2000) uses almost 20 mg more than Elliot et al., (1979) and Reprantis et al., (2000).

In a larger context the reliability of methylphenidate as a cognitive enhancers is somewhat limited due to a complete lack of evidence and dubious testing methods. Research would benefit from further analysis to

improve standard baselines and methods of comparison within pharmacology.

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