The wonderful 5-HT2a agonist. A case for (re)introducing psychedelic drugs into cognitive neuroscientific research

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ABSTRACT

Using psychedelic drugs to reach altered states of consciousness is a practice that has been around for thousands of years. Due to the infamous *'war on drugs'* led by the Nixon administration, researchers and governments around the globe were reluctant to investigate further into the nature of psychedelic substances and their influence on the human brain, leaving the research area dormant for decades. In this discussion paper, it is argued that psychedelic substances, instead of being shunned, can function as an effective experimental condition in order to investigate human cognition.The paper focusses on three research areas within cognitive neuroscience, namely time, multisensory integration and consciousness. The scope of this paper is to investigate whether psychedelic drugs could be seen as useful in investigating the brain regions that give rise to these phenomena. On a side note, it is investigated whether psychedelic drugs are safe enough to use on humans in experimental settings. After evaluation of the literature, it can be concluded that psychedelic drugs offer a unique insight in the workings of the human brain, especially for the selected research areas. Safety issues do not have to arise when special constructed guidelines are followed, which makes cognitive neuroscientific research with psychedelics a very compelling alternative to other interventions and is likely to keep on growing in the future.

A case for (re)introducing psychedelic drugs into cognitive neuroscientific research

> "It does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation." (Grof, 1980)

Ingesting psychedelic substances to reach altered states of consciousness (ASC) is a practice that has been around for thousands of years. Ancient civilizations in South America readily used it in order to transcend physical boundaries. Up to the 70's, psychedelics were widely used in the Western world in order to understand mental faculties, as well as the search for a truth serum. Due to the infamous *'war on drugs'* led by the Nixon administration, researchers and governments around the globe were reluctant to investigate further into the nature of psychedelic substances and their influence on the human brain. From the scientific point of view, this could be seen as an utter waste, as it has long been known that consuming psychedelic drugs, in particular 5-HT2a agonists like psilocybin and LSD, produce big distortions in everyday waking consciousness, time perception and multisensory integration. This psychedelic state is often accompanied by unconstrained, explorative thinking decoupled from reality, and unconstrained explorative cognition, much unlike normal waking consciousness.

5-HT2a agonists are molecules that bind to the 5-HT2a receptor, which belongs to the serotonin receptor family. These receptors are found in most areas of the neocortex, but are specially highly concentrated in the apical dendrites of pyramidal cells in layer V of the cortex. This high concentration may indicate that these receptors are responsible for modulating cognitive processes in the brain (Lambe et al., 2000). They would do so by

enhancing glutamate release, followed by a not yet completely understood reaction with the 5-HT1a, adenosine A1, GABAA, AMPA and OX2 receptors (Amargós-Bosch et al., 2004; Feng et al., 2001; Marek, 2009; Zhang & Marek, 2008; Lambe et al., 2004). Following, a profound alteration in brain activity occurs, which hints at a broad desynchronization of higher cortical areas (Tagliazucchi et al. 2014). Besides the neocortex, 5-HT2a receptors are found in a variety of places, ranging from the midbrain, olfactory systems, the brainstem and intestines to smooth muscles and cardiovascular systems throughout the body (Kent, 2012).

This wide distribution of 5-HT2a receptors, it's possible role in modulating cognitive processes and the profound effects of 5-HT2a agonists like psilocybin on this modulation show countless research possibilities. In the past 5 years, multiple fMRI studies have been carried out in order to discover the effects of psilocybin on the brain. In most cases, a decrease in cerebral blood flow (CBF) and BOLD signals of higher association areas is seen, including key regions of the Default Mode Network (DMN) and subcortical structures as the thalamus and putamen (Carhart-Harris et al., 2014). Moreover, a MEG study showed a decrease in broadband oscillatory power, with the biggest decrease again seen in association cortices and DMN (Muthukumaraswamy et al., 2013). All these findings suggest a very important role for the 5-HT2a receptor pathways and thus makes an extremely compelling area for cognitive neuroscientific research, as no other intervention that provides such extreme alterations in the human state exist to date. Transcranial direct current stimulation (Utz et al., 2010) and transcranial magnetic stimulation are only able to disrupt or enhance either small brain regions or limit themselves to the neocortex alone, which is not sufficient.

In this discussion paper it is therefore argued that psychedelic substances, instead of being shunned by many researchers, can function as an effective experimental condition in order to investigate human cognition, and should be a standard tool in discovering the underlying mechanisms of many cognitive domains. Due to the previous findings, this paper

will briefly focus on three research areas within cognitive neuroscience, namely time, multisensory integration and consciousness, where psychedelics, could add novel information when used correctly within sound experimental settings. These subjects are not chosen arbitrarily, as they are all interlinked concepts that are closely related in both nature and mystery. The scope of this paper is to investigate whether psychedelic drugs could be seen as useful in investigating the brain regions that give rise to these phenomena. On a side note, it is investigated whether psychedelic drugs are safe enough to use on humans in experimental settings. Due to the magnitude of these questions and the body of literature around them, not everything known will be discussed, and the further study of literature is advised.

Time Perception

Time is the very fabric that binds most of our conscious experience together and attributes to the subjective sense of extended self that we all experience, yet it's neural basis is still badly understood (Wittman, 2009). Variations in time perception and temporal judgement have been studied extensively by psychologists, where it is often noted that time can *flow* fast or slow, depending on the psychological state of the observer. Attention, emotions (Droit-volet & Meck, 2007) and personality traits all seem to influence time duration estimates. In light of the cognitive models describing time, we perceive signals from the sensory modalities that create the sense of a material me, has subjective feelings and is self-aware. The ascending pathways that feed into the insular cortex present information about the ongoing status of the body. An accumulation of physiological states over time would be registered in the insula, thus representing an internal measure of time and self (Wittmann et al., 2010) . Time perception and performance in humans has also primarily been linked to the dopamine system , with the cortico-basal ganglia–thalamic–cortical loop in particular (Meck, 1996). Dopaminergic agonists and antagonists have shown to influence the perception of time, where respectively an increase and decrease of clock speed is seen.

Although informative, no theory to date has found conclusive evidence for a neural mechanism that lies at the basis of time perception. Interestingly, 5-HT2a agonists have a strong influence on the perception of time, where there usually is a slowing effect, or at higher doses, an entire loss of perceived time. Wittmann et al. (2007) demonstrated an impairment in temporal related tasks while subjects were given psilocybin, such as synchronizing to a beat and reproducing time intervals. Curiously, at high doses, people preferred to tap at a slower rate when asked to tap at a preferred speed, which might indicate that 5-HT2a agonists decrease the clock speed of the brain. Maximum tapping speed was not impaired however, indicating that this is not due to impairment of the motor area. Furthermore, the impairment of the earlier described tasks only occurred when the time intervals were longer than 2 seconds, indicating conflicting interactions between different temporal cognitive dimensions instead of the classic dopaminergic pace-maker loop described by Meck (1996). Deficits in time perception have also been found in schizophrenia (Lee et al., 2009), a state that closely resembles many factors of the psychedelic state brought on by psilocybin, and also shows abnormalities in regards to 5-HT2a receptors. For this reason, we can say that there is some evidence of the serotonergic system involvement in temporal cognitive processes in the brain. Since there exists a great shortage on research regarding temporal processing and the serotonergic system, it could be useful to tackle the time issue by using different temporal experimental set-ups that include 5-HT2a agonists.

The influences of dopaminergic and serotonergic agonists on time perception might indicate an interlinked time-keeping system based on both serotonergic as dopaminergic receptors throughout the brain, or distinct systems that operate on a separate level. Wittman et al. (2007) only saw impairment of temporal judgement starting from intervals longer than 2 seconds, with intact judgment underneath this threshold. This might indicate that the dopaminergic system is responsible for keeping track of short time intervals, while the

serotonergic system is mainly responsible for longer intervals, and is therefore impaired through psilocybin. The fact that 5-HT2a receptors can be found throughout the entire body, while dopaminergic receptors are only found in the central nervous system, might also indicate that the 5-HT2a pathways are indeed responsible for sending bodily information through the insular cortex and thus updating the physical presence and sense of self. This would be in line with the subjective findings of psychedelic drugs and psychosis, where one often has the feeling of 'losing yourself' or 'losing time'. The option of two distinct systems was also proposed by Lewis et al., (2003), who stated an automatic and cognitively controlled time keeping system, resembling the dopaminergic - serotonergic division.

As shown by the presented studies, there are ample opportunities to investigate temporal processing and time perception by means of psychedelic drugs. Next, the effect of 5-HT2a agonists on multisensory integration is examined.

Multisensory Integration

The binding problem of multisensory information has been a bottleneck for centuries. Since everyday life is characterized by the seemingly effortless integration of multisensory information that fills up our conscious experience, it is very interesting to see what the neural effects of 5-HT2a agonists on this system actually are, as subjective accounts report multisensory destabilization. As earlier noted, 5-HT2a receptors are found throughout the entire human organism, and tracking of 5-HT2a modulated signalling makes it possible to say that the psychedelic state induced through 5-HT2a agonists is not only caused by disrupting sensory modalities, attention and time perception, but can be seen as a complex multi-layered experience integrated throughout the entire body, thus a good candidate for full body multisensory integration.

The cortical layer V neurons, extremely rich in 5-HT2a receptors, are thought to bind coherent sensory information from all the different sensory modalities together, which also

provides evidence that multisensory (de)stabilization is mediated by the 5-HT2a pathways (Jones, 2002). Muthukumaraswamy et al. (2013) found broadband cortical desynchronization of oscillatory rhythms in an fMRI study through 5-HT2a agonist, originating in the increased excitability of 5-HT2a receptors in the deep layer V neurons..

More evidence for the modulation of 5-HT2a pathways arise when the spatial and temporal rules of multisensory integration are kept in mind. The spatial rule states that integration is more likely or stronger when the constituent uni-sensory stimuli arise from approximately the same location**.** This however, holds for different aspects of visual sensory data as well. Curiously, binocular rivalry has been shown to increase by 5-HT2a agonist administration (Carter et al., 2007, Carter et al., 2005), which is known to produce brief unstable composites of different visual frames. Subjective accounts support this view, as slowly moving or crawling objects, creeping walls, flickering objects and breathing carpets are reported. With very high doses, a total frame loss and resulting ego death, a (temporarily) loss of the sense of self, can occur, where there is nothing left in conscious experience but a swirling vortex of time and space. This effect is explained in the Psychedelic Information Theory by Kent (2010), where it is defined as ‘frame stacking’, and might be a possible explanation for the phenomena.

The temporal rule of multisensory integration states that multisensory integration is more likely or stronger when the constituent uni-sensory stimuli arise at approximately the same time. As discussed earlier, 5-HT2a agonists cause a clear disturbance in time perception and performance in time related tasks, presumably through conflicts between different temporal cognitive dimensions (Witman et al., 2007). This could imply that top-down interference of lower level sensory stimuli through 5-HT2a agonist-mediation interrupts normal binding of multisensory information. Alonso et al. (2015) also found that that frontal brain regions decrease their influence over lower areas of the brain, indicating

less top down control on information transfer, thus destabilizing strong integration.

Stable multisensory integration is often given as a perquisite of human consciousness. Interestingly, humans are still very much aware and conscious in a psychedelic state, even with malfunctioning multisensory integration. This shows us that there are probably distinctive but interlinked networks that give rise to both multisensory perception and conscious experience, and that multisensory integration is merely a perquisite for normal waking consciousness. In the next paragraph, the notion of consciousness and it's altered states regarding to 5-HT2a pathways will be further examined.

Consciousness

Understanding human consciousness has been philosophy's quest for thousands of years, but a uniform and clear answer from philosophy never came. Neuroscience has long avoided the topic, as the concept of consciousness goes by many definitions and the experimental tools to search for it were absent. However, the study of subliminal perception, denial of impairment and blind sight have caused a stir in the scientific research of consciousness. On top of that, the study of ASC has seen an incredible increase in publications throughout the years, with special interest going to the similarities between the psychedelic state and psychotic state, as it could provide a useful insights in treating psychopathology (Vollenweider & Geyer, 2001). Schizophrenic people are considered humanly conscious by most standards, yet their conscious experience is profoundly different than ours. Normal waking consciousness of healthy adults is characterized by stable multisensory perception, a sense of selfhood and the notion of executive control over the mind. Interestingly, all three premises for normal waking consciousness are influenced by 5-HT2a agonists, and are affected in both the psychotic as psychedelic state. As noted before, the sense of self is strongly tied to ones perception of time. 5-HT2a agonists alter this perception, lowering the clock speed, and presumably disrupting temporal processing as well.

Furthermore, the changes in executive control over the mind can be explained by the decrease of CBF, BOLD signals, oscillatory power and functional connectivity in the DMN (Tagliazucchi et al., 2014). The DMN, to some extent, can be seen as a physical substrate of the self or ego, as it is heavily involved in self-dialogue, the construction of a life narrative and activates when accessing autobiographical memories (Carhart-Harris & Friston, 2010). Confusingly, when looked at the classical DMN theory, you would expect activity within the network to increase, as subjective accounts report stronger autobiographical memories (Carhart-Harris et al., 2012). Luckily, another study investigating the neural basis of psychosis and consciousness by means of psilocybin, and showed an increased functional connectivity between the DMN and task positive network (Carhart-Harris et al., 2013). This same increase has been found in states of early psychosis (Wortruba et al., 2013) and meditation, indicating that all three ASC rely on a vagueness between internal and external states, hinting at disruption of full body integrated multisensory information as well. This however, is a very novel theory, and more research is needed to establish it's relations. All of the evidence described above hint at a 5-HT2a agonist-mediated multisensory destabilization that lies at the root of ASC that is experienced when taking psychedelics. Subjective accounts, where extreme doses of 5-HT2a agonists produce a complete disruption of consciousness, provide proof for this assumption, as explained in the psychedelic information theory (Kent, 2010). Another state known to everybody, deep sleep, is characterized by an almost complete lack of consciousness. Through fMRI measures, Horovitz et al. (2009) found that this might rely on the decoupling of many DMN components, especially the connectivity with frontal cortex areas. This is a very interesting finding, as fMRI studies on the effects of psilocybin as earlier discussed, described the same findings regarding the DMN. In short – all these studies present intriguing findings - but have only been made possible by one of the most important factors within psychedelic research, namely safety.

Safety

Most critique regarding the use of psychedelic drugs in research arise from the potential safety issues. However, most of these supposed issues are not based on sound research and can be seen as folk truths, originating in the sensationalism that has formed in popular media around psychedelic drugs throughout the years. On top of that, there is a range of psychedelic drugs effective in creating psychedelic states like LSD, mescaline, psilocybin and DMT that are being used both recreationally and medically. Psilocybin could be seen as the most research friendly psychedelic, as it's duration is far shorter than LSD, respectively 4-6 hours to 8-12 hours, and studies describe it to be relatively safe (Studerus et al., 2011) Since psychedelic drug research was dormant for two decades, most data known about the safety of the drugs come from clinical accounts instead of randomized controlled trials. Johnson et al. (2008) wrote an extensive guideline for safety regarding the use of psychedelic drugs in research, which leaves little risks for the safety of subjects when followed. The biggest safety issue would be overwhelming distress or even a triggered state of psychosis. To safeguard against these risks exclusion of subjects who have a (family) history of psychotic disorders is needed. There should be focus on establishing trust with the subject and a safe physical session environment with interpersonal support is required. Long term adverse effects are very rare, although hallucinogenic persistent perception disorder should be checked for in a follow up. To study the acute effects of psilocybin, Hasler et al. (2004) conducted a double blind, placebo controlled dose-effect study which showed that psilocybin affects core dimensions of ASC and physiological parameters in a dose-dependent manner. They could not find any acute hazards for the subjects health, providing proof that psilocybin is indeed safe to use. They did state that it might not be wise to use subjects with cardiovascular problems as psilocybin slightly raises blood pressure. Together, these studies,

and many individual accounts, show that it is possible to use psilocybin safely in an experimental setting when safety guidelines are followed.

Conclusion

The scope of this paper was to investigate whether or not psychedelic drugs could be seen as useful in investigating the concepts of time, multisensory integration and consciousness. With safety issues dismissed, it has become clear that the use of psychedelic drugs has a lot of potential within cognitive neuroscientific research. There simply is no other type of intervention, that causes a profound, but entirely reversible effect on key brain systems that give rise to human cognition and consciousness. The chosen concepts, time, multisensory integration and consciousness all proved to be good candidates for investigation with the help of psychedelic drugs. Besides the chosen concepts, one could think of other domains worthy of investigation like the psychology of spirituality (Richards, 2008) and morality, different aspects of memory and psychopathology. The downside to the psychedelic drug approach is the amount of extra knowledge required in order to successfully carry out the experiments as to safeguard the subjects and the possibility to carry out research in the future.

Discussion

Due to the magnitude of the concepts investigated in this paper, a somewhat unidimensional positive view is present throughout, with little room for discussion. The same could be said for the choice to mainly focus on the 5-HT2a agonist psilocybin, as there are many other psychedelic drugs with very interesting reaction sites and interactions. This choice was thus primarily made due to the relatively scarceness of neuroscientific research on psychedelics.

When one sees the profound effects this drug has on the brain and it’s neural

processes, it is exciting to keep in mind that there are many others out there with slightly or entirely different mechanisms and effects. If future research continues within the noticeable positive trend that is currently present, data from many different fMRI, EEG and physiological studies can be combined, guided by the subjective accounts of subjects. Put together, the psychedelic neuroscience movement could have paradigm breaking effects, and redefine what we know about human cognition and consciousness.

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