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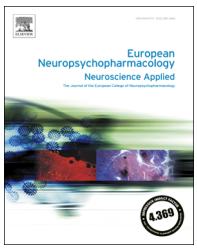

LSD modulates music-induced imagery via changes in parahippocampal connectivity

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Abstract
Psychedelic drugs such as lysergic acid diethylamide (LSD) were used extensively in psychiatry in the past and their therapeutic potential is beginning to be re-examined today. Psychedelic psychotherapy typically involves a patient lying with their eyes-closed during peak drug effects, while listening to music and being supervised by trained psychotherapists. In this context, music is considered to be a key element in the therapeutic model; working in synergy with the drug to evoke therapeutically meaningful thoughts, emotions and imagery. The underlying mechanisms involved in this process have, however, never been formally investigated. Here we studied the interaction between LSD and music-listening on eyes-closed imagery by means of a placebo-controlled, functional magnetic resonance imaging (fMRI) study. Twelve healthy volunteers received intravenously administered LSD (75 μg) and, on a separate occasion, placebo, before

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being scanned under eyes-closed resting conditions with and without music-listening. The parahippocampal cortex (PHC) has previously been linked with (1) music-evoked emotion, (2) the action of psychedelics, and (3) mental imagery. Imaging analyses therefore focused on changes in the connectivity profile of this particular structure. Results revealed increased PHC-visual cortex (VC) functional connectivity and PHC to VC information flow in the interaction between music and LSD. This latter result correlated positively with ratings of enhanced eyes-closed visual imagery, including imagery of an autobiographical nature. These findings suggest a plausible mechanism by which LSD works in combination with music listening to enhance certain subjective experiences that may be useful in a therapeutic context.

1. Introduction

Humans have chosen to alter their consciousness via psychedelic drugs for millennia, and often in combination with music (Nettl, 1956). In the 1950s and 1960s, psychedelic drugs such as lysergic acid diethylamide (LSD) were used in psychotherapy, and modern clinical trials are re-examining their therapeutic potential (Bogenschutz et al., 2015; Gasser et al., 2014; Grob et al., 2011; Johnson et al., 2014). Since the inception of psychedelic-assisted psychotherapy, music-listening has been considered an important component in the therapeutic model (Bonny and Pahnke, 1972). It is believed that music acts synergistically with the drug to enhance emotionality, mental imagery, and access to personal memories (Bonny and Pahnke, 1972; Grof, 1980; Kaelen et al., 2015).[1] The main aim of the present study was to investigate the brain mechanisms underlying the effects of LSD and music on mental imagery.

The characteristic subjective effects of LSD and other psychedelics such as psilocybin are thought to depend on agonist actions at the serotonin 2A receptor (Glennon et al., 1984; Vollenweider et al., 1998). The serotonin 2A receptor is expressed on "excitatory" deep layer pyramidal cells, as well as on a smaller proportion of "inhibitory" interneurons (Andrade, 2011; Celada et al., 2013). Its activation depolarises the cell membrane of the host neuron, increasing its likelihood of firing (Aghajanian and Marek, 1999). Although expressed throughout the neocortex (Pazos et al., 1987), the serotonin 2A receptor is especially highly expressed in high-level association cortices, including the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and insula, but also in the visual cortex (VC) and, to a lesser extent, the entorhinal cortex (Erritzoe et al., 2009; Ettrup et al., 2014; Pazos et al., 1987). Not surprisingly, functional neuroimaging studies revealed altered activity in these brain regions during serotonin 2A receptor agonist-induced psychedelic states (Carhart-Harris et al., 2012a; Muthukumaraswamy et al., 2013; Riba et al., 2002; Vollenweider et al., 1997).

Of particular interest to the present study are the effects of psychedelics and music-listening on activity in the parahippocampal cortex (PHC). The PHC is an important hub within the medial temporal lobe (MTL) (Burwell, 2000; Eichenbaum and Lipton, 2008), and it's acute functioning is appreciably altered by psychedelics as determined by fMRI (Kometer et al., 2015; Tagliazucchi et al., 2014), depth EEG (Monroe et al., 1957; Schwarz et al., 1956) and PET (Vollenweider et al., 1997). Furthermore, attenuation of the subjective and behavioural effects of LSD were observed after resection of the MTLs in humans (Serafetinides, 1965) and chimpanzees (Ramey and O'Doherty, 1960).

Activation of the PHC is found during spatial navigation (Aguirre and D'Esposito, 1999; Epstein, 2008), imagining scenes (Spreng et al., 2009), emotional arousal (LaBar and Cabeza, 2006; Smith et al., 2004) and personal memory recall (Fink et al., 1996). Importantly, the PHC is also implicated in music-evoked emotion (Baumgartner et al., 2006; Gosselin et al., 2006; Koelsch, 2014) and music-evoked personal memories (Janata, 2009). Damage to the PHC can result in impaired music-evoked emotion (Gosselin et al., 2006) and visual deficits (Harding et al., 2002; Hensley-Judge et al., 2013), whereas direct stimulation of the PHC can produce visual hallucinations of scenes (Mégevand et al., 2014), autobiographical memories (Vignal et al., 2007) and dream-like states (Bancaud et al., 1994; Barbeau et al., 2005; Bartolomei et al., 2004), accompanied by enhanced coupling between the PHC and the VC (Barbeau et al., 2005).

These insights motivated the present hypothesis that LSD, in combination with music-listening, modulates PHC functional connectivity. This hypothesis was tested using functional magnetic resonance imaging (fMRI) and a balanced-order, placebo-controlled design. Participants completed ratings of eye-closed visual imagery and spontaneous autobiographical memory recollection. Acute changes in PHC functional connectivity informed a subsequent Dynamic Causal Modelling (DCM) analysis that assessed how music and LSD interact to change the direction of information flow between the PHC and the VC (i.e. effective connectivity).

[1] By the late 1960s there existed, broadly speaking, two schools of thoughts around the therapeutic use of psychedelics – and these differed in the significance they attributed to music. In the United States, higher dosages of psychedelics were administered, with the goal to facilitate a peak- or mystical-type experience to promote long lasting change in personality traits and behaviour. Here, music was typically played for the entire duration of the drug effects, with intermittent periods of silence. In Europe, *psycholytic therapy* became more widely practiced. This method involved more frequent administration of lower dosages of a psychedelic, and with more interaction between therapist and patient. Music was played for to help with relaxation, or to support intermittent periods of introspection.